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Dossier zur Nutzenbewertung gemäß § 35a SGB V

Ublituximab (Briumvi®)

Neuraxpharm Arzneimittel GmbH

Modul 4 A - Anhang 4-M

Behandlung von erwachsenen Patienten mit schubförmiger Multipler Sklerose (RMS) mit aktiver Erkrankung, definiert durch klinischen Befund oder Bildgebung

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Stand: 26.01.2024

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4 Ultimate 1: Treatment Emergent Adverse events by SOC/PT

4.1 Any TEAE

4.1.1 Cardiac disorders - any

Tabelle 1: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	12	8.00	146	7	4.79	1,67 [0,68 ; 4,12]	1,73 [0,66 ; 4,52];	3,21 [-2,35 ; 8,76]; 0,344	0,344	0,5085
	>= 38 years	123	15	12.20	129	14	10.85	1,12 [0,57 ; 2,23]	1,14 [0,53 ; 2,47];	1,34 [-6,55 ; 9,23]; 0,844	0,844	
Disease Severity at baseline (EDSS)	<=3.5	201	20	9.95	208	15	7.21	1,38 [0,73 ; 2,62]	1,42 [0,71 ; 2,86];	2,74 [-2,69 ; 8,17]; 0,378	0,378	0,7032
	>3.5	72	7	9.72	67	6	8.96	1,09 [0,38 ; 3,07]	1,09 [0,35 ; 3,44];	0,77 [-8,91 ; 10,44]; 1	1	
Gender	Female	167	13	7.78	180	13	7.22	1,08 [0,51 ; 2,26]	1,08 [0,49 ; 2,41];	0,56 [-4,99 ; 6,11]; 0,842	0,842	0,494
	Male	106	14	13.21	95	8	8.42	1,57 [0,69 ; 3,57]	1,65 [0,66 ; 4,14];	4,79 [-3,74 ; 13,31]; 0,366	0,366	
Number of baseline Gd-enhancing lesions	>=1	117	14	11.97	116	5	4.31	2,78 [1,03 ; 7,46]	3,02 [1,05 ; 8,67];	7,66 [0,71 ; 14,6]; 0,053	0,053	0,0409
	0	155	13	8.39	157	16	10.19	0,82 [0,41 ; 1,65]	0,81 [0,37 ; 1,74];	-1,8 [-8,24 ; 4,63]; 0,697	0,697	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	12	11.11	92	3	3.26	3,41 [0,99 ; 11,71]	3,71 [1,01 ; 13,57];	7,85 [0,9 ; 14,8]; 0,057	0,057	0,1436
	>=3	42	4	9.52	58	7	12.07	0,79 [0,25 ; 2,52]	0,77 [0,21 ; 2,81];	-2,55 [-14,76 ; 9,67]; 0,757	0,757	
	2	123	11	8.94	125	11	8.80	1,02 [0,46 ; 2,26]	1,02 [0,42 ; 2,44];	0,14 [-6,93 ; 7,22]; 1	1	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Race	Other	7	1	14.29	8	0	0.00	3,38 [0,16 ; 71,67]	3,92 [0,14 ; 112,9];	13,19 [-17,72 ; 44,11]; 0,467	0,467	0,2463
	White	266	26	9.77	267	21	7.87	1,24 [0,72 ; 2,15]	1,27 [0,7 ; 2,32];	1,91 [-2,9 ; 6,72]; 0,45	0,45	
Received approved disease modifying MS drug prior to enrollment	No	181	19	10.50	193	19	9.84	1,07 [0,58 ; 1,95]	1,07 [0,55 ; 2,1];	0,65 [-5,48 ; 6,79]; 0,865	0,865	0,121
	Yes	92	8	8.70	82	2	2.44	3,57 [0,78 ; 16,31]	3,81 [0,79 ; 18,48];	6,26 [-0,4 ; 12,91]; 0,105	0,105	
Region	Eastern Europe	247	21	8.50	244	18	7.38	1,15 [0,63 ; 2,11]	1,17 [0,61 ; 2,25];	1,12 [-3,66 ; 5,91]; 0,739	0,739	0,2853
	USA and Western Europe	26	6	23.08	31	3	9.68	2,38 [0,66 ; 8,61]	2,8 [0,62 ; 12,55];	13,4 [-5,85 ; 32,65]; 0,275	0,275	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Cardiac disorders | any

4.1.2 Gastrointestinal disorders - any

Tabelle 2: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	52	34.67	146	43	29.45	1,18 [0,84 ; 1,64]	1,27 [0,78 ; 2,07];	5,21 [-5,4 ; 15,83]; 0,384	0,384	0,0839
	>= 38 years	123	29	23.58	129	41	31.78	0,74 [0,49 ; 1,11]	0,66 [0,38 ; 1,16];	-8,21 [-19,2 ; 2,79]; 0,161	0,161	
Disease Severity at baseline (EDSS)	<=3.5	201	60	29.85	208	63	30.29	0,99 [0,73 ; 1,32]	0,98 [0,64 ; 1,49];	-0,44 [-9,33 ; 8,45]; 1	1	0,8474
	>3.5	72	21	29.17	67	21	31.34	0,93 [0,56 ; 1,54]	0,9 [0,44 ; 1,86];	-2,18 [-17,46 ; 13,11]; 0,854	0,854	
Gender	Female	167	55	32.93	180	62	34.44	0,96 [0,71 ; 1,29]	0,93 [0,6 ; 1,46];	-1,51 [-11,46 ; 8,44]; 0,82	0,82	0,7219
	Male	106	26	24.53	95	22	23.16	1,06 [0,65 ; 1,74]	1,08 [0,56 ; 2,07];	1,37 [-10,42 ; 13,16]; 0,869	0,869	
Number of baseline Gd-enhancing lesions	>=1	117	38	32.48	116	38	32.76	0,99 [0,69 ; 1,43]	0,99 [0,57 ; 1,71];	-0,28 [-12,32 ; 11,76]; 1	1	0,8654
	0	155	43	27.74	157	46	29.30	0,95 [0,67 ; 1,35]	0,93 [0,57 ; 1,51];	-1,56 [-11,58 ; 8,46]; 0,803	0,803	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	34	31.48	92	24	26.09	1,21 [0,78 ; 1,88]	1,3 [0,7 ; 2,41];	5,39 [-7,14 ; 17,93]; 0,437	0,437	0,502
	>=3	42	13	30.95	58	20	34.48	0,9 [0,51 ; 1,59]	0,85 [0,36 ; 1,99];	-3,53 [-22,11 ; 15,05]; 0,83	0,83	
	2	123	34	27.64	125	40	32.00	0,86 [0,59 ; 1,27]	0,81 [0,47 ; 1,4];	-4,36 [-15,73 ; 7,02]; 0,489	0,489	
Race	Other	7	2	28.57	8	3	37.50	0,76 [0,17 ; 3,33]	0,67 [0,08 ; 5,88];	-8,93 [-56,31 ; 38,46]; 1	1	0,738
	White	266	79	29.70	267	81	30.34	0,98 [0,76 ; 1,27]	0,97 [0,67 ; 1,41];	-0,64 [-8,42 ; 7,14]; 0,925	0,925	
	No	181	46	25.41	193	53	27.46	0,93 [0,66 ; 1,3]	0,9 [0,57 ; 1,43];	-2,05 [-10,98 ; 6,89]; 0,725	0,725	0,768

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	35	38.04	82	31	37.80	1,01 [0,69 ; 1,47]	1,01 [0,55 ; 1,87];	0,24 [-14,2 ; 14,68]; 1	1	
Region	Eastern Europe	247	72	29.15	244	74	30.33	0,96 [0,73 ; 1,26]	0,95 [0,64 ; 1,39];	-1,18 [-9,26 ; 6,91]; 0,844	0,844	0,7858
	USA and Western Europe	26	9	34.62	31	10	32.26	1,07 [0,51 ; 2,24]	1,11 [0,37 ; 3,35];	2,36 [-22,24 ; 26,96]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Gastrointestinal disorders | any

4.1.3 General disorders and administration site conditions - any

Tabelle 3: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	68	45.33	146	16	10.96	4,14 [2,52 ; 6,78]	6,74 [3,66 ; 12,41];	34,37 [24,93 ; 43,82]; 0	0	0,0004
	>= 38 years	123	39	31.71	129	30	23.26	1,36 [0,91 ; 2,05]	1,53 [0,88 ; 2,68];	8,45 [-2,54 ; 19,44]; 0,158	0,158	
Disease Severity at baseline (EDSS)	<=3.5	201	83	41.29	208	35	16.83	2,45 [1,74 ; 3,46]	3,48 [2,2 ; 5,5];	24,47 [15,97 ; 32,96]; 0	0	0,5148
	>3.5	72	24	33.33	67	11	16.42	2,03 [1,08 ; 3,82]	2,55 [1,13 ; 5,73];	16,92 [2,87 ; 30,96]; 0,031	0,031	
Gender	Female	167	70	41.92	180	33	18.33	2,29 [1,6 ; 3,26]	3,21 [1,98 ; 5,23];	23,58 [14,2 ; 32,96]; 0	0	0,9076
	Male	106	37	34.91	95	13	13.68	2,55 [1,45 ; 4,5]	3,38 [1,67 ; 6,87];	21,22 [9,82 ; 32,63]; 0,001	0,001	
Number of baseline Gd-enhancing lesions	>=1	117	49	41.88	116	19	16.38	2,56 [1,61 ; 4,06]	3,68 [1,99 ; 6,8];	25,5 [14,31 ; 36,69]; 0	0	0,5518
	0	155	58	37.42	157	27	17.20	2,18 [1,46 ; 3,24]	2,88 [1,7 ; 4,88];	20,22 [10,58 ; 29,86]; 0	0	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	39	36.11	92	17	18.48	1,95 [1,19 ; 3,21]	2,49 [1,29 ; 4,81];	17,63 [5,59 ; 29,67]; 0,007	0,007	0,2105
	>=3	42	19	45.24	58	6	10.34	4,37 [1,91 ; 10]	7,16 [2,53 ; 20,27];	34,89 [17,92 ; 51,86]; 0	0	
	2	123	49	39.84	125	23	18.40	2,17 [1,41 ; 3,32]	2,94 [1,65 ; 5,24];	21,44 [10,44 ; 32,44]; 0	0	
Race	Other	7	4	57.14	8	3	37.50	1,52 [0,51 ; 4,58]	2,22 [0,28 ; 17,63];	19,64 [-30,05 ; 69,34]; 0,619	0,619	0,717
	White	266	103	38.72	267	43	16.10	2,4 [1,76 ; 3,29]	3,29 [2,19 ; 4,96];	22,62 [15,29 ; 29,95]; 0	0	
	No	181	63	34.81	193	32	16.58	2,1 [1,44 ; 3,05]	2,69 [1,65 ; 4,37];	18,23 [9,53 ; 26,93]; 0	0	0,2443

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	44	47.83	82	14	17.07	2,8 [1,66 ; 4,72]	4,45 [2,2 ; 9,02];	30,75 [17,69 ; 43,81]; 0	0	
Region	Eastern Europe	247	93	37.65	244	35	14.34	2,62 [1,86 ; 3,71]	3,61 [2,32 ; 5,6];	23,31 [15,83 ; 30,78]; 0	0	0,3701
	USA and Western Europe	26	14	53.85	31	11	35.48	1,52 [0,84 ; 2,75]	2,12 [0,73 ; 6,16];	18,36 [-7,15 ; 43,87]; 0,19	0,19	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - General disorders and administration site conditions | any

4.1.4 Infections and infestations - any

Tabelle 4: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	89	59.33	146	76	52.05	1,14 [0,93 ; 1,4]	1,34 [0,85 ; 2,13];	7,28 [-4,01 ; 18,57]; 0,242	0,242	0,0969
	>= 38 years	123	46	37.40	129	57	44.19	0,85 [0,63 ; 1,14]	0,75 [0,46 ; 1,25];	-6,79 [-18,89 ; 5,32]; 0,306	0,306	
Disease Severity at baseline (EDSS)	<=3.5	201	105	52.24	208	111	53.37	0,98 [0,81 ; 1,18]	0,96 [0,65 ; 1,41];	-1,13 [-10,8 ; 8,55]; 0,843	0,843	0,2937
	>3.5	72	30	41.67	67	22	32.84	1,27 [0,82 ; 1,97]	1,46 [0,73 ; 2,92];	8,83 [-7,17 ; 24,83]; 0,298	0,298	
Gender	Female	167	90	53.89	180	92	51.11	1,05 [0,86 ; 1,29]	1,12 [0,73 ; 1,7];	2,78 [-7,73 ; 13,29]; 0,667	0,667	0,6947
	Male	106	45	42.45	95	41	43.16	0,98 [0,71 ; 1,35]	0,97 [0,56 ; 1,7];	-0,71 [-14,41 ; 13]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	117	62	52.99	116	62	53.45	0,99 [0,78 ; 1,26]	0,98 [0,59 ; 1,64];	-0,46 [-13,27 ; 12,36]; 1	1	0,7871
	0	155	73	47.10	157	71	45.22	1,04 [0,82 ; 1,32]	1,08 [0,69 ; 1,68];	1,87 [-9,19 ; 12,94]; 0,82	0,82	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	45	41.67	92	40	43.48	0,96 [0,69 ; 1,32]	0,93 [0,53 ; 1,63];	-1,81 [-15,56 ; 11,94]; 0,886	0,886	0,7851
	>=3	42	23	54.76	58	28	48.28	1,13 [0,77 ; 1,66]	1,3 [0,58 ; 2,88];	6,49 [-13,31 ; 26,28]; 0,549	0,549	
	2	123	67	54.47	125	65	52.00	1,05 [0,83 ; 1,32]	1,1 [0,67 ; 1,82];	2,47 [-9,94 ; 14,89]; 0,705	0,705	
Race	Other	7	6	85.71	8	5	62.50	1,37 [0,74 ; 2,54]	3,6 [0,28 ; 46,36];	23,21 [-19,18 ; 65,61]; 0,569	0,569	0,3146
	White	266	129	48.50	267	128	47.94	1,01 [0,85 ; 1,21]	1,02 [0,73 ; 1,44];	0,56 [-7,93 ; 9,04]; 0,931	0,931	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	No	181	79	43.65	193	94	48.70	0,9 [0,72 ; 1,12]	0,82 [0,54 ; 1,23];	-5,06 [-15,15 ; 5,04]; 0,351	0,351	0,0446
	Yes	92	56	60.87	82	39	47.56	1,28 [0,97 ; 1,69]	1,72 [0,94 ; 3,13];	13,31 [-1,4 ; 28,02]; 0,094	0,094	
Region	Eastern Europe	247	117	47.37	244	111	45.49	1,04 [0,86 ; 1,26]	1,08 [0,76 ; 1,54];	1,88 [-6,94 ; 10,7]; 0,718	0,718	0,7947
	USA and Western Europe	26	18	69.23	31	22	70.97	0,98 [0,69 ; 1,37]	0,92 [0,29 ; 2,87];	-1,74 [-25,61 ; 22,14]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | any

4.1.5 Musculoskeletal and connective tissue disorders - any

Tabelle 5: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	31	20.67	146	25	17.12	1,21 [0,75 ; 1,94]	1,26 [0,7 ; 2,26];	3,54 [-5,36 ; 12,45]; 0,461	0,461	0,0793
	>= 38 years	123	24	19.51	129	37	28.68	0,68 [0,43 ; 1,07]	0,6 [0,34 ; 1,08];	-9,17 [-19,66 ; 1,32]; 0,106	0,106	
Disease Severity at baseline (EDSS)	<=3.5	201	41	20.40	208	43	20.67	0,99 [0,67 ; 1,44]	0,98 [0,61 ; 1,59];	-0,28 [-8,11 ; 7,56]; 1	1	0,3092
	>3.5	72	14	19.44	67	19	28.36	0,69 [0,37 ; 1,26]	0,61 [0,28 ; 1,34];	-8,91 [-23,06 ; 5,23]; 0,237	0,237	
Gender	Female	167	35	20.96	180	41	22.78	0,92 [0,62 ; 1,37]	0,9 [0,54 ; 1,5];	-1,82 [-10,52 ; 6,88]; 0,699	0,699	0,8321
	Male	106	20	18.87	95	21	22.11	0,85 [0,49 ; 1,47]	0,82 [0,41 ; 1,63];	-3,24 [-14,42 ; 7,95]; 0,602	0,602	
Number of baseline Gd-enhancing lesions	>=1	117	27	23.08	116	28	24.14	0,96 [0,6 ; 1,52]	0,94 [0,51 ; 1,73];	-1,06 [-11,97 ; 9,84]; 0,878	0,878	0,6903
	0	155	28	18.06	157	34	21.66	0,83 [0,53 ; 1,31]	0,8 [0,46 ; 1,39];	-3,59 [-12,43 ; 5,25]; 0,479	0,479	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	21	19.44	92	18	19.57	0,99 [0,56 ; 1,75]	0,99 [0,49 ; 2];	-0,12 [-11,14 ; 10,9]; 1	1	0,2962
	>=3	42	11	26.19	58	11	18.97	1,38 [0,66 ; 2,88]	1,52 [0,59 ; 3,92];	7,22 [-9,47 ; 23,92]; 0,466	0,466	
	2	123	23	18.70	125	33	26.40	0,71 [0,44 ; 1,13]	0,64 [0,35 ; 1,17];	-7,7 [-18,05 ; 2,65]; 0,172	0,172	
Race	Other	7	5	71.43	8	5	62.50	1,14 [0,56 ; 2,33]	1,5 [0,17 ; 13,23];	8,93 [-38,46 ; 56,31]; 1	1	0,6157
	White	266	50	18.80	267	57	21.35	0,88 [0,63 ; 1,24]	0,85 [0,56 ; 1,3];	-2,55 [-9,35 ; 4,25]; 0,517	0,517	
	No	181	29	16.02	193	45	23.32	0,69 [0,45 ; 1,05]	0,63 [0,37 ; 1,05];	-7,29 [-15,3 ; 0,72]; 0,091	0,091	0,0473

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	26	28.26	82	17	20.73	1,36 [0,8 ; 2,33]	1,51 [0,75 ; 3,04];	7,53 [-5,18 ; 20,24]; 0,293	0,293	
Region	Eastern Europe	247	41	16.60	244	46	18.85	0,88 [0,6 ; 1,29]	0,86 [0,54 ; 1,36];	-2,25 [-9,01 ; 4,5]; 0,555	0,555	0,6751
	USA and Western Europe	26	14	53.85	31	16	51.61	1,04 [0,64 ; 1,71]	1,09 [0,38 ; 3,11];	2,23 [-23,78 ; 28,25]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Musculoskeletal and connective tissue disorders | any

4.1.6 Nervous system disorders - any

Tabelle 6: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	72	48.00	146	52	35.62	1,35 [1,02 ; 1,77]	1,67 [1,05 ; 2,66];	12,38 [1,24 ; 23,53]; 0,034	0,034	0,1256
	>= 38 years	123	41	33.33	129	44	34.11	0,98 [0,69 ; 1,38]	0,97 [0,57 ; 1,63];	-0,78 [-12,45 ; 10,9]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	201	83	41.29	208	75	36.06	1,15 [0,9 ; 1,46]	1,25 [0,84 ; 1,86];	5,24 [-4,19 ; 14,67]; 0,31	0,31	0,5796
	>3.5	72	30	41.67	67	21	31.34	1,33 [0,85 ; 2,08]	1,56 [0,78 ; 3,14];	10,32 [-5,58 ; 26,23]; 0,223	0,223	
Gender	Female	167	74	44.31	180	70	38.89	1,14 [0,89 ; 1,46]	1,25 [0,82 ; 1,92];	5,42 [-4,94 ; 15,79]; 0,328	0,328	0,5731
	Male	106	39	36.79	95	26	27.37	1,34 [0,89 ; 2,03]	1,54 [0,85 ; 2,81];	9,42 [-3,41 ; 22,26]; 0,175	0,175	
Number of baseline Gd-enhancing lesions	>=1	117	51	43.59	116	52	44.83	0,97 [0,73 ; 1,3]	0,95 [0,57 ; 1,6];	-1,24 [-13,99 ; 11,52]; 0,895	0,895	0,0834
	0	155	62	40.00	157	43	27.39	1,46 [1,06 ; 2,01]	1,77 [1,1 ; 2,84];	12,61 [2,21 ; 23,01]; 0,023	0,023	
	NA	1	0	0.00	2	1	50.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	42	38.89	92	36	39.13	0,99 [0,7 ; 1,41]	0,99 [0,56 ; 1,75];	-0,24 [-13,81 ; 13,32]; 1	1	0,4866
	>=3	42	17	40.48	58	18	31.03	1,3 [0,77 ; 2,22]	1,51 [0,66 ; 3,47];	9,44 [-9,59 ; 28,47]; 0,397	0,397	
	2	123	54	43.90	125	42	33.60	1,31 [0,95 ; 1,79]	1,55 [0,92 ; 2,59];	10,3 [-1,76 ; 22,36]; 0,118	0,118	
Race	Other	7	5	71.43	8	5	62.50	1,14 [0,56 ; 2,33]	1,5 [0,17 ; 13,23];	8,93 [-38,46 ; 56,31]; 1	1	0,9105
	White	266	108	40.60	267	91	34.08	1,19 [0,95 ; 1,49]	1,32 [0,93 ; 1,88];	6,52 [-1,68 ; 14,71]; 0,128	0,128	
	No	181	68	37.57	193	67	34.72	1,08 [0,83 ; 1,42]	1,13 [0,74 ; 1,73];	2,85 [-6,89 ; 12,6]; 0,591	0,591	0,2485

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	45	48.91	82	29	35.37	1,38 [0,97 ; 1,98]	1,75 [0,95 ; 3,22];	13,55 [-0,99 ; 28,09]; 0,091	0,091	
Region	Eastern Europe	247	97	39.27	244	76	31.15	1,26 [0,99 ; 1,61]	1,43 [0,99 ; 2,07];	8,12 [-0,29 ; 16,54]; 0,073	0,073	0,4056
	USA and Western Europe	26	16	61.54	31	20	64.52	0,95 [0,64 ; 1,42]	0,88 [0,3 ; 2,59];	-2,98 [-28,14 ; 22,19]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Nervous system disorders | any

4.1.7 Renal and urinary disorders - any

Tabelle 7: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	7	4.67	146	8	5.48	0,85 [0,32 ; 2,29]	0,84 [0,3 ; 2,39];	-0,81 [-5,81 ; 4,19]; 0,796	0,796	0,8813
	>= 38 years	123	9	7.32	129	10	7.75	0,94 [0,4 ; 2,24]	0,94 [0,37 ; 2,4];	-0,43 [-6,95 ; 6,08]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	201	11	5.47	208	12	5.77	0,95 [0,43 ; 2,1]	0,95 [0,41 ; 2,2];	-0,3 [-4,76 ; 4,17]; 1	1	0,7728
	>3.5	72	5	6.94	67	6	8.96	0,78 [0,25 ; 2,42]	0,76 [0,22 ; 2,61];	-2,01 [-11,02 ; 7]; 0,758	0,758	
Gender	Female	167	12	7.19	180	8	4.44	1,62 [0,68 ; 3,86]	1,66 [0,66 ; 4,18];	2,74 [-2,2 ; 7,68]; 0,358	0,358	0,0306
	Male	106	4	3.77	95	10	10.53	0,36 [0,12 ; 1,11]	0,33 [0,1 ; 1,1];	-6,75 [-13,91 ; 0,41]; 0,094	0,094	
Number of baseline Gd-enhancing lesions	>=1	117	7	5.98	116	7	6.03	0,99 [0,36 ; 2,74]	0,99 [0,34 ; 2,92];	-0,05 [-6,15 ; 6,05]; 1	1	0,7904
	0	155	9	5.81	157	11	7.01	0,83 [0,35 ; 1,94]	0,82 [0,33 ; 2,03];	-1,2 [-6,63 ; 4,23]; 0,818	0,818	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	5	4.63	92	5	5.43	0,85 [0,25 ; 2,85]	0,84 [0,24 ; 3,01];	-0,81 [-6,9 ; 5,29]; 1	1	0,9732
	>=3	42	1	2.38	58	2	3.45	0,69 [0,06 ; 7,37]	0,68 [0,06 ; 7,79];	-1,07 [-7,65 ; 5,51]; 1	1	
	2	123	10	8.13	125	11	8.80	0,92 [0,41 ; 2,1]	0,92 [0,37 ; 2,24];	-0,67 [-7,6 ; 6,26]; 1	1	
Race	Other	7	0	0.00	8	1	12.50	0,38 [0,02 ; 7,96]	0,33 [0,01 ; 9,57];	-10,42 [-39,98 ; 19,15]; 0,477	0,477	0,2658
	White	266	16	6.02	267	17	6.37	0,94 [0,49 ; 1,83]	0,94 [0,47 ; 1,9];	-0,35 [-4,44 ; 3,74]; 1	1	
	No	181	11	6.08	193	12	6.22	0,98 [0,44 ; 2,16]	0,98 [0,42 ; 2,27];	-0,14 [-5,01 ; 4,73]; 1	1	0,6992

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	5	5.43	82	6	7.32	0,74 [0,24 ; 2,34]	0,73 [0,21 ; 2,48];	-1,88 [-9,18 ; 5,41]; 0,758	0,758	
Region	Eastern Europe	247	14	5.67	244	14	5.74	0,99 [0,48 ; 2,03]	0,99 [0,46 ; 2,12];	-0,07 [-4,17 ; 4,03]; 1	1	0,564
	USA and Western Europe	26	2	7.69	31	4	12.90	0,6 [0,12 ; 3]	0,56 [0,09 ; 3,35];	-5,21 [-20,84 ; 10,42]; 0,678	0,678	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Renal and urinary disorders | any

4.1.8 Reproductive system and breast disorders - any

Tabelle 8: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	12	8.00	146	14	9.59	0,83 [0,4 ; 1,74]	0,82 [0,37 ; 1,84];	-1,59 [-8,04 ; 4,87]; 0,685	0,685	0,9025
	>= 38 years	123	6	4.88	129	7	5.43	0,9 [0,31 ; 2,6]	0,89 [0,29 ; 2,74];	-0,55 [-6 ; 4,91]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	201	14	6.97	208	18	8.65	0,8 [0,41 ; 1,57]	0,79 [0,38 ; 1,63];	-1,69 [-6,88 ; 3,51]; 0,583	0,583	0,5919
	>3.5	72	4	5.56	67	3	4.48	1,24 [0,29 ; 5,34]	1,25 [0,27 ; 5,83];	1,08 [-6,17 ; 8,32]; 1	1	
Gender	Female	167	18	10.78	180	19	10.56	1,02 [0,56 ; 1,88]	1,02 [0,52 ; 2,02];	0,22 [-6,28 ; 6,72]; 1	1	0,0864
	Male	106	0	0.00	95	2	2.11	0,18 [0,01 ; 3,69]	0,18 [0,01 ; 3,7];	-2,14 [-5,57 ; 1,3]; 0,225	0,225	
Number of baseline Gd-enhancing lesions	>=1	117	9	7.69	116	7	6.03	1,27 [0,49 ; 3,31]	1,3 [0,47 ; 3,61];	1,66 [-4,83 ; 8,15]; 0,797	0,797	0,288
	0	155	9	5.81	157	14	8.92	0,65 [0,29 ; 1,46]	0,63 [0,26 ; 1,5];	-3,11 [-8,89 ; 2,67]; 0,387	0,387	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	8	7.41	92	9	9.78	0,76 [0,3 ; 1,88]	0,74 [0,27 ; 2];	-2,38 [-10,2 ; 5,45]; 0,616	0,616	0,893
	>=3	42	4	9.52	58	5	8.62	1,1 [0,32 ; 3,87]	1,12 [0,28 ; 4,43];	0,9 [-10,54 ; 12,35]; 1	1	
	2	123	6	4.88	125	7	5.60	0,87 [0,3 ; 2,52]	0,86 [0,28 ; 2,65];	-0,72 [-6,27 ; 4,82]; 1	1	
Race	Other	7	2	28.57	8	1	12.50	2,29 [0,26 ; 20,13]	2,8 [0,2 ; 40,06];	16,07 [-24,49 ; 56,63]; 0,569	0,569	0,3533
	White	266	16	6.02	267	20	7.49	0,8 [0,43 ; 1,52]	0,79 [0,4 ; 1,56];	-1,48 [-5,73 ; 2,78]; 0,605	0,605	
	No	181	14	7.73	193	15	7.77	1 [0,49 ; 2]	0,99 [0,47 ; 2,12];	-0,04 [-5,46 ; 5,39]; 1	1	0,4739

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	4	4.35	82	6	7.32	0,59 [0,17 ; 2,03]	0,58 [0,16 ; 2,12];	-2,97 [-9,98 ; 4,04]; 0,519	0,519	
Region	Eastern Europe	247	14	5.67	244	16	6.56	0,86 [0,43 ; 1,73]	0,86 [0,41 ; 1,79];	-0,89 [-5,13 ; 3,35]; 0,71	0,71	0,9041
	USA and Western Europe	26	4	15.38	31	5	16.13	0,95 [0,29 ; 3,19]	0,95 [0,23 ; 3,96];	-0,74 [-19,72 ; 18,23]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Reproductive system and breast disorders | any

4.1.9 Skin and subcutaneous tissue disorders - any

Tabelle 9: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	19	12.67	146	31	21.23	0,6 [0,35 ; 1,01]	0,54 [0,29 ; 1];	-8,57 [-17,07 ; -0,06]; 0,062	0,062	0,8046
	>= 38 years	123	15	12.20	129	29	22.48	0,54 [0,31 ; 0,96]	0,48 [0,24 ; 0,95];	-10,29 [-19,52 ; -1,05]; 0,046	0,046	
Disease Severity at baseline (EDSS)	<=3.5	201	26	12.94	208	53	25.48	0,51 [0,33 ; 0,78]	0,43 [0,26 ; 0,73];	-12,55 [-20,07 ; -5,02]; 0,002	0,002	0,1377
	>3.5	72	8	11.11	67	7	10.45	1,06 [0,41 ; 2,77]	1,07 [0,37 ; 3,14];	0,66 [-9,65 ; 10,98]; 1	1	
Gender	Female	167	24	14.37	180	49	27.22	0,53 [0,34 ; 0,82]	0,45 [0,26 ; 0,77];	-12,85 [-21,25 ; -4,45]; 0,004	0,004	0,2889
	Male	106	10	9.43	95	11	11.58	0,81 [0,36 ; 1,83]	0,8 [0,32 ; 1,97];	-2,14 [-10,65 ; 6,36]; 0,651	0,651	
Number of baseline Gd-enhancing lesions	>=1	117	14	11.97	116	26	22.41	0,53 [0,29 ; 0,97]	0,47 [0,23 ; 0,96];	-10,45 [-20,05 ; -0,85]; 0,038	0,038	0,7235
	0	155	20	12.90	157	33	21.02	0,61 [0,37 ; 1,02]	0,56 [0,3 ; 1,02];	-8,12 [-16,39 ; 0,16]; 0,07	0,07	
	NA	1	0	0.00	2	1	50.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	14	12.96	92	20	21.74	0,6 [0,32 ; 1,11]	0,54 [0,25 ; 1,13];	-8,78 [-19,32 ; 1,77]; 0,13	0,13	0,4731
	>=3	42	4	9.52	58	16	27.59	0,35 [0,12 ; 0,96]	0,28 [0,08 ; 0,9];	-18,06 [-32,59 ; -3,53]; 0,041	0,041	
	2	123	16	13.01	125	24	19.20	0,68 [0,38 ; 1,21]	0,63 [0,32 ; 1,25];	-6,19 [-15,3 ; 2,92]; 0,227	0,227	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Race	Other	7	3	42.86	8	5	62.50	0,69 [0,25 ; 1,88]	0,45 [0,06 ; 3,57];	-19,64 [-69,34 ; 30,05]; 0,619	0,619	0,9102
	White	266	31	11.65	267	55	20.60	0,57 [0,38 ; 0,85]	0,51 [0,32 ; 0,82];	-8,95 [-15,14 ; -2,75]; 0,007	0,007	
Received approved disease modifying MS drug prior to enrollment	No	181	20	11.05	193	38	19.69	0,56 [0,34 ; 0,93]	0,51 [0,28 ; 0,91];	-8,64 [-15,87 ; -1,41]; 0,023	0,023	0,9433
	Yes	92	14	15.22	82	22	26.83	0,57 [0,31 ; 1,03]	0,49 [0,23 ; 1,04];	-11,61 [-23,69 ; 0,46]; 0,064	0,064	
Region	Eastern Europe	247	27	10.93	244	48	19.67	0,56 [0,36 ; 0,86]	0,5 [0,3 ; 0,83];	-8,74 [-15,07 ; -2,41]; 0,008	0,008	0,8104
	USA and Western Europe	26	7	26.92	31	12	38.71	0,7 [0,32 ; 1,51]	0,58 [0,19 ; 1,8];	-11,79 [-35,97 ; 12,39]; 0,407	0,407	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Skin and subcutaneous tissue disorders | any

4.1.10 Respiratory, thoracic and mediastinal disorders - any

Tabelle 10: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	27	18.00	146	19	13.01	1,38 [0,81 ; 2,38]	1,47 [0,78 ; 2,77];	4,99 [-3,23 ; 13,21]; 0,264	0,264	0,6716
	>= 38 years	123	20	16.26	129	18	13.95	1,17 [0,65 ; 2,1]	1,2 [0,6 ; 2,39];	2,31 [-6,54 ; 11,15]; 0,725	0,725	
Disease Severity at baseline (EDSS)	<=3.5	201	38	18.91	208	30	14.42	1,31 [0,85 ; 2,03]	1,38 [0,82 ; 2,34];	4,48 [-2,74 ; 11,7]; 0,235	0,235	0,8388
	>3.5	72	9	12.50	67	7	10.45	1,2 [0,47 ; 3,03]	1,22 [0,43 ; 3,5];	2,05 [-8,53 ; 12,64]; 0,794	0,794	
Gender	Female	167	32	19.16	180	27	15.00	1,28 [0,8 ; 2,04]	1,34 [0,77 ; 2,36];	4,16 [-3,77 ; 12,09]; 0,32	0,32	0,9354
	Male	106	15	14.15	95	10	10.53	1,34 [0,63 ; 2,85]	1,4 [0,6 ; 3,29];	3,62 [-5,44 ; 12,69]; 0,523	0,523	
Number of baseline Gd-enhancing lesions	>=1	117	23	19.66	116	12	10.34	1,9 [0,99 ; 3,64]	2,12 [1 ; 4,5];	9,31 [0,23 ; 18,4]; 0,066	0,066	0,1088
	0	155	24	15.48	157	25	15.92	0,97 [0,58 ; 1,63]	0,97 [0,53 ; 1,78];	-0,44 [-8,51 ; 7,63]; 1	1	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	21	19.44	92	10	10.87	1,79 [0,89 ; 3,6]	1,98 [0,88 ; 4,45];	8,57 [-1,23 ; 18,38]; 0,118	0,118	0,4568
	>=3	42	6	14.29	58	7	12.07	1,18 [0,43 ; 3,27]	1,21 [0,38 ; 3,92];	2,22 [-11,28 ; 15,72]; 0,771	0,771	
	2	123	20	16.26	125	20	16.00	1,02 [0,58 ; 1,79]	1,02 [0,52 ; 2,01];	0,26 [-8,9 ; 9,42]; 1	1	
Race	Other	7	2	28.57	8	4	50.00	0,57 [0,15 ; 2,23]	0,4 [0,05 ; 3,42];	-21,43 [-69,6 ; 26,74]; 0,608	0,608	0,2437
	White	266	45	16.92	267	33	12.36	1,37 [0,9 ; 2,07]	1,44 [0,89 ; 2,35];	4,56 [-1,43 ; 10,55]; 0,143	0,143	
	No	181	24	13.26	193	24	12.44	1,07 [0,63 ; 1,81]	1,08 [0,59 ; 1,97];	0,82 [-5,96 ; 7,61]; 0,878	0,878	0,3132

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	23	25.00	82	13	15.85	1,58 [0,86 ; 2,91]	1,77 [0,83 ; 3,77];	9,15 [-2,72 ; 21,01]; 0,189	0,189	
Region	Eastern Europe	247	39	15.79	244	28	11.48	1,38 [0,88 ; 2,16]	1,45 [0,86 ; 2,44];	4,31 [-1,74 ; 10,37]; 0,189	0,189	0,6539
	USA and Western Europe	26	8	30.77	31	9	29.03	1,06 [0,48 ; 2,35]	1,09 [0,35 ; 3,39];	1,74 [-22,14 ; 25,61]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Respiratory, thoracic and mediastinal disorders | any

4.1.11 Injury, poisoning and procedural complications - any

Tabelle 11: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	11	7.33	146	15	10.27	0,71 [0,34 ; 1,5]	0,69 [0,31 ; 1,56];	-2,94 [-9,39 ; 3,51]; 0,416	0,416	0,2081
	>= 38 years	123	19	15.45	129	15	11.63	1,33 [0,71 ; 2,5]	1,39 [0,67 ; 2,87];	3,82 [-4,63 ; 12,27]; 0,461	0,461	
Disease Severity at baseline (EDSS)	<=3.5	201	21	10.45	208	20	9.62	1,09 [0,61 ; 1,94]	1,1 [0,58 ; 2,09];	0,83 [-4,99 ; 6,66]; 0,87	0,87	0,6161
	>3.5	72	9	12.50	67	10	14.93	0,84 [0,36 ; 1,93]	0,81 [0,31 ; 2,15];	-2,43 [-13,88 ; 9,03]; 0,806	0,806	
Gender	Female	167	18	10.78	180	20	11.11	0,97 [0,53 ; 1,77]	0,97 [0,49 ; 1,9];	-0,33 [-6,91 ; 6,24]; 1	1	0,8387
	Male	106	12	11.32	95	10	10.53	1,08 [0,49 ; 2,37]	1,09 [0,45 ; 2,64];	0,79 [-7,83 ; 9,42]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	117	17	14.53	116	14	12.07	1,2 [0,62 ; 2,33]	1,24 [0,58 ; 2,65];	2,46 [-6,25 ; 11,17]; 0,7	0,7	0,4356
	0	155	13	8.39	157	16	10.19	0,82 [0,41 ; 1,65]	0,81 [0,37 ; 1,74];	-1,8 [-8,24 ; 4,63]; 0,697	0,697	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	14	12.96	92	12	13.04	0,99 [0,48 ; 2,04]	0,99 [0,43 ; 2,27];	-0,08 [-9,43 ; 9,27]; 1	1	0,8704
	>=3	42	3	7.14	58	3	5.17	1,38 [0,29 ; 6,51]	1,41 [0,27 ; 7,36];	1,97 [-7,68 ; 11,62]; 0,694	0,694	
	2	123	13	10.57	125	15	12.00	0,88 [0,44 ; 1,77]	0,87 [0,39 ; 1,91];	-1,43 [-9,3 ; 6,44]; 0,842	0,842	
Race	Other	7	2	28.57	8	2	25.00	1,14 [0,21 ; 6,11]	1,2 [0,12 ; 11,87];	3,57 [-41,38 ; 48,52]; 1	1	0,8823
	White	266	28	10.53	267	28	10.49	1 [0,61 ; 1,65]	1 [0,58 ; 1,75];	0,04 [-5,17 ; 5,25]; 1	1	
	No	181	16	8.84	193	23	11.92	0,74 [0,41 ; 1,36]	0,72 [0,37 ; 1,4];	-3,08 [-9,24 ; 3,09]; 0,398	0,398	0,0934

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	14	15.22	82	7	8.54	1,78 [0,76 ; 4,2]	1,92 [0,74 ; 5,03];	6,68 [-2,83 ; 16,19]; 0,244	0,244	
Region	Eastern Europe	247	19	7.69	244	24	9.84	0,78 [0,44 ; 1,39]	0,76 [0,41 ; 1,43];	-2,14 [-7,14 ; 2,86]; 0,428	0,428	0,0391
	USA and Western Europe	26	11	42.31	31	6	19.35	2,19 [0,94 ; 5,1]	3,06 [0,94 ; 9,97];	22,95 [-0,59 ; 46,49]; 0,083	0,083	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Injury, poisoning and procedural complications | any

4.1.12 Investigations - any

Tabelle 12: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	56	37.33	146	42	28.77	1,3 [0,93 ; 1,8]	1,48 [0,91 ; 2,4];	8,57 [-2,1 ; 19,24]; 0,138	0,138	0,4443
	>= 38 years	123	39	31.71	129	38	29.46	1,08 [0,74 ; 1,56]	1,11 [0,65 ; 1,9];	2,25 [-9,13 ; 13,63]; 0,785	0,785	
Disease Severity at baseline (EDSS)	<=3.5	201	73	36.32	208	60	28.85	1,26 [0,95 ; 1,67]	1,41 [0,93 ; 2,13];	7,47 [-1,59 ; 16,53]; 0,114	0,114	0,4704
	>3.5	72	22	30.56	67	20	29.85	1,02 [0,62 ; 1,7]	1,03 [0,5 ; 2,13];	0,7 [-14,57 ; 15,98]; 1	1	
Gender	Female	167	57	34.13	180	47	26.11	1,31 [0,95 ; 1,81]	1,47 [0,92 ; 2,33];	8,02 [-1,62 ; 17,66]; 0,127	0,127	0,3769
	Male	106	38	35.85	95	33	34.74	1,03 [0,71 ; 1,5]	1,05 [0,59 ; 1,87];	1,11 [-12,12 ; 14,34]; 0,884	0,884	
Number of baseline Gd-enhancing lesions	>=1	117	42	35.90	116	35	30.17	1,19 [0,82 ; 1,72]	1,3 [0,75 ; 2,24];	5,73 [-6,33 ; 17,78]; 0,404	0,404	0,9373
	0	155	53	34.19	157	44	28.03	1,22 [0,87 ; 1,7]	1,33 [0,82 ; 2,16];	6,17 [-4,08 ; 16,42]; 0,271	0,271	
	NA	1	0	0.00	2	1	50.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	35	32.41	92	23	25.00	1,3 [0,83 ; 2,03]	1,44 [0,77 ; 2,68];	7,41 [-5,09 ; 19,91]; 0,276	0,276	0,2589
	>=3	42	23	54.76	58	20	34.48	1,59 [1,01 ; 2,49]	2,3 [1,02 ; 5,19];	20,28 [0,88 ; 39,68]; 0,065	0,065	
	2	123	37	30.08	125	37	29.60	1,02 [0,69 ; 1,49]	1,02 [0,59 ; 1,76];	0,48 [-10,91 ; 11,87]; 1	1	
Race	Other	7	3	42.86	8	3	37.50	1,14 [0,33 ; 3,94]	1,25 [0,16 ; 9,92];	5,36 [-44,34 ; 55,05]; 1	1	0,9682
	White	266	92	34.59	267	77	28.84	1,2 [0,93 ; 1,54]	1,3 [0,9 ; 1,88];	5,75 [-2,14 ; 13,63]; 0,163	0,163	
	No	181	65	35.91	193	52	26.94	1,33 [0,98 ; 1,8]	1,52 [0,98 ; 2,36];	8,97 [-0,41 ; 18,35]; 0,074	0,074	0,2143

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	30	32.61	82	28	34.15	0,95 [0,63 ; 1,45]	0,93 [0,5 ; 1,75];	-1,54 [-15,58 ; 12,5]; 0,873	0,873	
Region	Eastern Europe	247	87	35.22	244	71	29.10	1,21 [0,93 ; 1,57]	1,32 [0,91 ; 1,94];	6,12 [-2,12 ; 14,37]; 0,149	0,149	0,7457
	USA and Western Europe	26	8	30.77	31	9	29.03	1,06 [0,48 ; 2,35]	1,09 [0,35 ; 3,39];	1,74 [-22,14 ; 25,61]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Investigations | any

4.1.13 Metabolism and nutrition disorders - any

Tabelle 13: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	3	2.00	146	6	4.11	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>= 38 years	123	3	2.44	129	6	4.65	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	201	5	2.49	208	7	3.37	0,74 [0,24 ; 2,29]	0,73 [0,23 ; 2,35];	-0,88 [-4,14 ; 2,38]; 0,771	0,771	0,2205
	>3.5	72	1	1.39	67	5	7.46	0,19 [0,02 ; 1,55]	0,17 [0,02 ; 1,54];	-6,07 [-12,92 ; 0,77]; 0,106	0,106	
Gender	Female	167	4	2.40	180	6	3.33	0,72 [0,21 ; 2,5]	0,71 [0,2 ; 2,57];	-0,94 [-4,44 ; 2,56]; 0,752	0,752	0,3786
	Female	167	4	2.40	180	5	2.78	0,72 [0,21 ; 2,5]	0,71 [0,2 ; 2,57];	-0,94 [-4,44 ; 2,56]; 0,752	0,752	
	Female	167	3	1.80	180	6	3.33	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Female	167	3	1.80	180	5	2.78	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Male	106	2	1.89	95	6	6.32	0,3 [0,06 ; 1,44]	0,29 [0,06 ; 1,45];	-4,43 [-9,96 ; 1,11]; 0,152	0,152	
	Male	106	2	1.89	95	5	5.26	0,3 [0,06 ; 1,44]	0,29 [0,06 ; 1,45];	-4,43 [-9,96 ; 1,11]; 0,152	0,152	
	Male	106	2	1.89	95	6	6.32	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Male	106	2	1.89	95	5	5.26	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of baseline Gd-enhancing lesions	>=1	117	3	2.56	116	5	4.31	0,59 [0,15 ; 2,43]	0,58 [0,14 ; 2,5];	-1,75 [-6,42 ; 2,93]; 0,499	0,499	0,7514
	0	155	3	1.94	157	7	4.46	0,43 [0,11 ; 1,65]	0,42 [0,11 ; 1,67];	-2,52 [-6,41 ; 1,37]; 0,336	0,336	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Number of relapses experienced in the 2 years prior to study start	<=1	108	4	3.70	92	7	7.61	0,49 [0,15 ; 1,61]	0,47 [0,13 ; 1,65];	-3,9 [-10,39 ; 2,58]; 0,351	0,351	0,3034
	>=3	42	0	0.00	58	3	5.17	0,2 [0,01 ; 3,7]	0,19 [0,01 ; 3,71];	-4,77 [-11,6 ; 2,06]; 0,141	0,141	
	2	123	2	1.63	125	2	1.60	1,02 [0,15 ; 7,1]	1,02 [0,14 ; 7,33];	0,03 [-3,11 ; 3,16]; 1	1	
Race	Other	7	1	14.29	8	1	12.50	1,14 [0,09 ; 15,08]	1,17 [0,06 ; 22,94];	1,79 [-32,81 ; 36,39]; 1	1	0,5545
	White	266	5	1.88	267	11	4.12	0,46 [0,16 ; 1,3]	0,45 [0,15 ; 1,3];	-2,24 [-5,13 ; 0,65]; 0,203	0,203	
Received approved disease modifying MS drug prior to enrollment	No	181	5	2.76	193	9	4.66	0,59 [0,2 ; 1,73]	0,58 [0,19 ; 1,77];	-1,9 [-5,72 ; 1,91]; 0,418	0,418	0,5793
	Yes	92	1	1.09	82	3	3.66	0,3 [0,03 ; 2,8]	0,29 [0,03 ; 2,84];	-2,57 [-7,15 ; 2,01]; 0,344	0,344	
Region	Eastern Europe	247	4	1.62	244	9	3.69	0,44 [0,14 ; 1,41]	0,43 [0,13 ; 1,41];	-2,07 [-4,91 ; 0,77]; 0,172	0,172	0,603
	USA and Western Europe	26	2	7.69	31	3	9.68	0,79 [0,14 ; 4,4]	0,78 [0,12 ; 5,05];	-1,99 [-16,59 ; 12,62]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Metabolism and nutrition disorders | any

4.1.14 Eye disorders - any

Tabelle 14: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	8	5.33	146	7	4.79	1,11 [0,41 ; 2,99]	1,12 [0,4 ; 3,17];	0,54 [-4,46 ; 5,53]; 1	1	0,5152
	>= 38 years	123	6	4.88	129	9	6.98	0,7 [0,26 ; 1,91]	0,68 [0,24 ; 1,98];	-2,1 [-7,91 ; 3,72]; 0,598	0,598	
Disease Severity at baseline (EDSS)	<=3.5	201	11	5.47	208	13	6.25	0,88 [0,4 ; 1,91]	0,87 [0,38 ; 1,99];	-0,78 [-5,33 ; 3,77]; 0,834	0,834	0,9439
	>3.5	72	3	4.17	67	3	4.48	0,93 [0,19 ; 4,45]	0,93 [0,18 ; 4,76];	-0,31 [-7,08 ; 6,46]; 1	1	
Gender	Female	167	6	3.59	180	7	3.89	0,92 [0,32 ; 2,69]	0,92 [0,3 ; 2,8];	-0,3 [-4,29 ; 3,7]; 1	1	0,8273
	Male	106	8	7.55	95	9	9.47	0,8 [0,32 ; 1,98]	0,78 [0,29 ; 2,11];	-1,93 [-9,67 ; 5,82]; 0,8	0,8	
Number of baseline Gd-enhancing lesions	>=1	117	5	4.27	116	6	5.17	0,83 [0,26 ; 2,63]	0,82 [0,24 ; 2,76];	-0,9 [-6,35 ; 4,55]; 0,768	0,768	0,7857
	0	155	9	5.81	157	9	5.73	1,01 [0,41 ; 2,48]	1,01 [0,39 ; 2,63];	0,07 [-5,1 ; 5,25]; 1	1	
	NA	1	0	0.00	2	1	50.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	9	8.33	92	1	1.09	7,67 [0,99 ; 59,39]	8,27 [1,03 ; 66,58];	7,25 [1,62 ; 12,87]; 0,022	0,022	0,0022
	>=3	42	2	4.76	58	3	5.17	0,92 [0,16 ; 5,27]	0,92 [0,15 ; 5,74];	-0,41 [-9,01 ; 8,19]; 1	1	
	2	123	3	2.44	125	12	9.60	0,25 [0,07 ; 0,88]	0,24 [0,06 ; 0,86];	-7,16 [-13 ; -1,32]; 0,03	0,03	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	1
	White	266	14	5.26	267	16	5.99	0,88 [0,44 ; 1,76]	0,87 [0,42 ; 1,82];	-0,73 [-4,64 ; 3,18]; 0,851	0,851	
	No	181	6	3.31	193	7	3.63	0,91 [0,31 ; 2,67]	0,91 [0,3 ; 2,76];	-0,31 [-4,02 ; 3,4]; 1	1	0,8289

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	8	8.70	82	9	10.98	0,79 [0,32 ; 1,96]	0,77 [0,28 ; 2,11];	-2,28 [-11,16 ; 6,6]; 0,621	0,621	
Region	Eastern Europe	247	12	4.86	244	12	4.92	0,99 [0,45 ; 2,16]	0,99 [0,43 ; 2,24];	-0,06 [-3,87 ; 3,75]; 1	1	0,5688
	USA and Western Europe	26	2	7.69	31	4	12.90	0,6 [0,12 ; 3]	0,56 [0,09 ; 3,35];	-5,21 [-20,84 ; 10,42]; 0,678	0,678	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Eye disorders | any

4.1.15 Psychiatric disorders - any

Tabelle 15: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	21	14.00	146	10	6.85	2,04 [1 ; 4,19]	2,21 [1 ; 4,88];	7,15 [0,25 ; 14,05]; 0,057	0,057	0,0234
	>= 38 years	123	13	10.57	129	20	15.50	0,68 [0,35 ; 1,31]	0,64 [0,31 ; 1,36];	-4,93 [-13,21 ; 3,34]; 0,267	0,267	
Disease Severity at baseline (EDSS)	<=3.5	201	28	13.93	208	21	10.10	1,38 [0,81 ; 2,35]	1,44 [0,79 ; 2,63];	3,83 [-2,46 ; 10,13]; 0,286	0,286	0,1531
	>3.5	72	6	8.33	67	9	13.43	0,62 [0,23 ; 1,65]	0,59 [0,2 ; 1,75];	-5,1 [-15,46 ; 5,27]; 0,416	0,416	
Gender	Female	167	21	12.57	180	22	12.22	1,03 [0,59 ; 1,8]	1,03 [0,55 ; 1,96];	0,35 [-6,59 ; 7,29]; 1	1	0,4993
	Male	106	13	12.26	95	8	8.42	1,46 [0,63 ; 3,36]	1,52 [0,6 ; 3,85];	3,84 [-4,53 ; 12,22]; 0,49	0,49	
Number of baseline Gd-enhancing lesions	>=1	117	23	19.66	116	12	10.34	1,9 [0,99 ; 3,64]	2,12 [1 ; 4,5];	9,31 [0,23 ; 18,4]; 0,066	0,066	0,0189
	0	155	11	7.10	157	18	11.46	0,62 [0,3 ; 1,27]	0,59 [0,27 ; 1,29];	-4,37 [-10,79 ; 2,05]; 0,242	0,242	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	18	16.67	92	9	9.78	1,7 [0,8 ; 3,61]	1,84 [0,79 ; 4,33];	6,88 [-2,4 ; 16,17]; 0,213	0,213	0,2258
	>=3	42	4	9.52	58	4	6.90	1,38 [0,37 ; 5,21]	1,42 [0,33 ; 6,04];	2,63 [-8,39 ; 13,64]; 0,717	0,717	
	2	123	12	9.76	125	17	13.60	0,72 [0,36 ; 1,44]	0,69 [0,31 ; 1,51];	-3,84 [-11,82 ; 4,13]; 0,43	0,43	
Race	Other	7	3	42.86	8	2	25.00	1,71 [0,39 ; 7,48]	2,25 [0,25 ; 20,13];	17,86 [-29,52 ; 65,23]; 0,608	0,608	0,5443
	White	266	31	11.65	267	28	10.49	1,11 [0,69 ; 1,8]	1,13 [0,65 ; 1,94];	1,17 [-4,16 ; 6,49]; 0,681	0,681	
	No	181	20	11.05	193	18	9.33	1,18 [0,65 ; 2,17]	1,21 [0,62 ; 2,36];	1,72 [-4,42 ; 7,86]; 0,611	0,611	0,7942

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	14	15.22	82	12	14.63	1,04 [0,51 ; 2,12]	1,05 [0,45 ; 2,42];	0,58 [-10,02 ; 11,18]; 1	1	
Region	Eastern Europe	247	26	10.53	244	23	9.43	1,12 [0,66 ; 1,9]	1,13 [0,63 ; 2,04];	1,1 [-4,2 ; 6,4]; 0,764	0,764	0,6581
	USA and Western Europe	26	8	30.77	31	7	22.58	1,36 [0,57 ; 3,25]	1,52 [0,47 ; 4,98];	8,19 [-14,86 ; 31,24]; 0,554	0,554	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Psychiatric disorders | any

4.1.16 Vascular disorders - any

Tabelle 16: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	12	8.00	146	10	6.85	1,17 [0,52 ; 2,62]	1,18 [0,49 ; 2,83];	1,15 [-4,82 ; 7,12]; 0,826	0,826	0,1621
	>= 38 years	123	8	6.50	129	16	12.40	0,52 [0,23 ; 1,18]	0,49 [0,2 ; 1,19];	-5,9 [-13,06 ; 1,27]; 0,135	0,135	
Disease Severity at baseline (EDSS)	<=3.5	201	17	8.46	208	21	10.10	0,84 [0,46 ; 1,54]	0,82 [0,42 ; 1,61];	-1,64 [-7,26 ; 3,98]; 0,612	0,612	0,6054
	>3.5	72	3	4.17	67	5	7.46	0,56 [0,14 ; 2,25]	0,54 [0,12 ; 2,35];	-3,3 [-11,1 ; 4,51]; 0,482	0,482	
Gender	Female	167	15	8.98	180	16	8.89	1,01 [0,52 ; 1,98]	1,01 [0,48 ; 2,12];	0,09 [-5,91 ; 6,1]; 1	1	0,1908
	Male	106	5	4.72	95	10	10.53	0,45 [0,16 ; 1,26]	0,42 [0,14 ; 1,28];	-5,81 [-13,18 ; 1,56]; 0,178	0,178	
Number of baseline Gd-enhancing lesions	>=1	117	10	8.55	116	12	10.34	0,83 [0,37 ; 1,84]	0,81 [0,34 ; 1,96];	-1,8 [-9,31 ; 5,71]; 0,661	0,661	0,8225
	0	155	10	6.45	157	14	8.92	0,72 [0,33 ; 1,58]	0,7 [0,3 ; 1,64];	-2,47 [-8,37 ; 3,44]; 0,525	0,525	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	9	8.33	92	9	9.78	0,85 [0,35 ; 2,06]	0,84 [0,32 ; 2,21];	-1,45 [-9,45 ; 6,55]; 0,806	0,806	0,9469
	>=3	42	2	4.76	58	4	6.90	0,69 [0,13 ; 3,6]	0,68 [0,12 ; 3,87];	-2,13 [-11,3 ; 7,03]; 1	1	
	2	123	9	7.32	125	13	10.40	0,7 [0,31 ; 1,59]	0,68 [0,28 ; 1,65];	-3,08 [-10,14 ; 3,98]; 0,504	0,504	
Race	Other	7	1	14.29	8	0	0.00	3,38 [0,16 ; 71,67]	3,92 [0,14 ; 112,9];	13,19 [-17,72 ; 44,11]; 0,467	0,467	0,1618
	White	266	19	7.14	267	26	9.74	0,73 [0,42 ; 1,29]	0,71 [0,38 ; 1,32];	-2,59 [-7,31 ; 2,12]; 0,35	0,35	
	No	181	8	4.42	193	19	9.84	0,45 [0,2 ; 1]	0,42 [0,18 ; 0,99];	-5,42 [-10,59 ; -0,26]; 0,047	0,047	0,0399

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	12	13.04	82	7	8.54	1,53 [0,63 ; 3,7]	1,61 [0,6 ; 4,3];	4,51 [-4,65 ; 13,67]; 0,466	0,466	
Region	Eastern Europe	247	17	6.88	244	22	9.02	0,76 [0,42 ; 1,4]	0,75 [0,39 ; 1,44];	-2,13 [-6,92 ; 2,65]; 0,408	0,408	0,8511
	USA and Western Europe	26	3	11.54	31	4	12.90	0,89 [0,22 ; 3,64]	0,88 [0,18 ; 4,35];	-1,36 [-18,4 ; 15,67]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Vascular disorders | any

4.1.17 Blood and lymphatic system disorders - any

Tabelle 17: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	34	22.67	146	22	15.07	1,5 [0,93 ; 2,44]	1,65 [0,91 ; 2,99];	7,6 [-1,27 ; 16,46]; 0,104	0,104	0,2245
	>= 38 years	123	13	10.57	129	15	11.63	0,91 [0,45 ; 1,83]	0,9 [0,41 ; 1,97];	-1,06 [-8,81 ; 6,69]; 0,843	0,843	
Disease Severity at baseline (EDSS)	<=3.5	201	38	18.91	208	28	13.46	1,4 [0,9 ; 2,2]	1,5 [0,88 ; 2,55];	5,44 [-1,68 ; 12,57]; 0,141	0,141	0,3961
	>3.5	72	9	12.50	67	9	13.43	0,93 [0,39 ; 2,2]	0,92 [0,34 ; 2,48];	-0,93 [-12,11 ; 10,25]; 1	1	
Gender	Female	167	29	17.37	180	26	14.44	1,2 [0,74 ; 1,95]	1,24 [0,7 ; 2,22];	2,92 [-4,79 ; 10,63]; 0,466	0,466	0,653
	Male	106	18	16.98	95	11	11.58	1,47 [0,73 ; 2,94]	1,56 [0,7 ; 3,5];	5,4 [-4,21 ; 15,02]; 0,318	0,318	
Number of baseline Gd-enhancing lesions	>=1	117	21	17.95	116	14	12.07	1,49 [0,8 ; 2,78]	1,59 [0,77 ; 3,31];	5,88 [-3,26 ; 15,02]; 0,271	0,271	0,603
	0	155	26	16.77	157	22	14.01	1,2 [0,71 ; 2,02]	1,24 [0,67 ; 2,29];	2,76 [-5,24 ; 10,77]; 0,533	0,533	
	NA	1	0	0.00	2	1	50.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	14	12.96	92	9	9.78	1,33 [0,6 ; 2,92]	1,37 [0,57 ; 3,34];	3,18 [-5,59 ; 11,95]; 0,514	0,514	0,9858
	>=3	42	11	26.19	58	11	18.97	1,38 [0,66 ; 2,88]	1,52 [0,59 ; 3,92];	7,22 [-9,47 ; 23,92]; 0,466	0,466	
	2	123	22	17.89	125	17	13.60	1,32 [0,73 ; 2,35]	1,38 [0,7 ; 2,76];	4,29 [-4,77 ; 13,34]; 0,387	0,387	
Race	Other	7	0	0.00	8	2	25.00	0,22 [0,01 ; 4,02]	0,17 [0,01 ; 4,31];	-21,53 [-55,26 ; 12,2]; 0,467	0,467	0,0641
	White	266	47	17.67	267	35	13.11	1,35 [0,9 ; 2,02]	1,42 [0,88 ; 2,29];	4,56 [-1,55 ; 10,68]; 0,151	0,151	
	No	181	28	15.47	193	22	11.40	1,36 [0,81 ; 2,28]	1,42 [0,78 ; 2,59];	4,07 [-2,85 ; 10,99]; 0,288	0,288	0,6816

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	19	20.65	82	15	18.29	1,13 [0,61 ; 2,07]	1,16 [0,55 ; 2,47];	2,36 [-9,41 ; 14,13]; 0,707	0,707	
Region	Eastern Europe	247	46	18.62	244	34	13.93	1,34 [0,89 ; 2,01]	1,41 [0,87 ; 2,29];	4,69 [-1,83 ; 11,2]; 0,179	0,179	0,2395
	USA and Western Europe	26	1	3.85	31	3	9.68	0,4 [0,04 ; 3,6]	0,37 [0,04 ; 3,82];	-5,83 [-18,6 ; 6,93]; 0,617	0,617	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Blood and lymphatic system disorders | any

4.1.18 Immune system disorders - any

Tabelle 18: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	8	5.33	146	2	1.37	3,89 [0,84 ; 18,03]	4,06 [0,85 ; 19,43];	3,96 [-0,1 ; 8,02]; 0,104	0,104	0,0664
	>= 38 years	123	2	1.63	129	4	3.10	0,52 [0,1 ; 2,81]	0,52 [0,09 ; 2,87];	-1,47 [-5,21 ; 2,26]; 0,684	0,684	
Disease Severity at baseline (EDSS)	<=3.5	201	9	4.48	208	4	1.92	2,33 [0,73 ; 7,44]	2,39 [0,72 ; 7,89];	2,55 [-0,86 ; 5,97]; 0,166	0,166	0,2146
	>3.5	72	1	1.39	67	2	2.99	0,47 [0,04 ; 5,01]	0,46 [0,04 ; 5,17];	-1,6 [-6,49 ; 3,29]; 0,609	0,609	
Gender	Female	167	8	4.79	180	5	2.78	1,72 [0,58 ; 5,17]	1,76 [0,56 ; 5,49];	2,01 [-2,02 ; 6,04]; 0,401	0,401	0,9847
	Male	106	2	1.89	95	1	1.05	1,79 [0,17 ; 19,45]	1,81 [0,16 ; 20,26];	0,83 [-2,47 ; 4,14]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	117	5	4.27	116	3	2.59	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	155	5	3.23	157	3	1.91	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	3	2.78	92	2	2.17	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	2	4.76	58	1	1.72	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	5	4.07	125	3	2.40	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	0	0.00	8	1	12.50	0,38 [0,02 ; 7,96]	0,33 [0,01 ; 9,57];	-10,42 [-39,98 ; 19,15]; 0,477	0,477	0,1579
	White	266	10	3.76	267	5	1.87	2,01 [0,7 ; 5,79]	2,05 [0,69 ; 6,07];	1,89 [-0,92 ; 4,69]; 0,203	0,203	
	No	181	7	3.87	193	2	1.04	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	3	3.26	82	4	4.88	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Region	Eastern Europe	247	10	4.05	244	5	2.05	1,98 [0,69 ; 5,7]	2,02 [0,68 ; 5,99];	2 [-1,03 ; 5,03]; 0,294	0,294	0,1701
	USA and Western Europe	26	0	0.00	31	1	3.23	0,4 [0,02 ; 9,31]	0,38 [0,01 ; 9,82];	-2,84 [-11,75 ; 6,08]; 0,497	0,497	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Immune system disorders | any

4.1.19 Gastrointestinal disorders - Abdominal pain upper

Tabelle 19: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	6	4.00	146	6	4.11	0,97 [0,32 ; 2,95]	0,97 [0,31 ; 3,09];	-0,11 [-4,6 ; 4,39]; 1	1	0,0569
	>= 38 years	123	1	0.81	129	8	6.20	0,13 [0,02 ; 1,03]	0,12 [0,02 ; 1,01];	-5,39 [-9,84 ; -0,93]; 0,036	0,036	
Disease Severity at baseline (EDSS)	<=3.5	201	7	3.48	208	14	6.73	0,52 [0,21 ; 1,26]	0,5 [0,2 ; 1,27];	-3,25 [-7,49 ; 1]; 0,179	0,179	0,9999
	>3.5	72	0	0.00	67	0	0.00	0,93 [0,02 ; 46,29]	0,93 [0,02 ; 47,58];	-0,05 [-2,83 ; 2,73]; 1	1	
Gender	Female	167	6	3.59	180	12	6.67	0,54 [0,21 ; 1,4]	0,52 [0,19 ; 1,42];	-3,07 [-7,68 ; 1,54]; 0,232	0,232	0,9017
	Male	106	1	0.94	95	2	2.11	0,45 [0,04 ; 4,86]	0,44 [0,04 ; 4,96];	-1,16 [-4,59 ; 2,26]; 0,603	0,603	
Number of baseline Gd-enhancing lesions	>=1	117	3	2.56	116	8	6.90	0,37 [0,1 ; 1,37]	0,36 [0,09 ; 1,37];	-4,33 [-9,76 ; 1,1]; 0,136	0,136	0,5062
	0	155	4	2.58	157	6	3.82	0,68 [0,19 ; 2,35]	0,67 [0,18 ; 2,41];	-1,24 [-5,14 ; 2,66]; 0,75	0,75	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	4	3.70	92	6	6.52	0,57 [0,17 ; 1,95]	0,55 [0,15 ; 2,02];	-2,82 [-8,99 ; 3,36]; 0,518	0,518	0,5887
	>=3	42	1	2.38	58	1	1.72	1,38 [0,09 ; 21,46]	1,39 [0,08 ; 22,88];	0,66 [-5,04 ; 6,36]; 1	1	
	2	123	2	1.63	125	7	5.60	0,29 [0,06 ; 1,37]	0,28 [0,06 ; 1,37];	-3,97 [-8,58 ; 0,63]; 0,172	0,172	
Race	Other	7	1	14.29	8	1	12.50	1,14 [0,09 ; 15,08]	1,17 [0,06 ; 22,94];	1,79 [-32,81 ; 36,39]; 1	1	0,5558
	White	266	6	2.26	267	13	4.87	0,46 [0,18 ; 1,2]	0,45 [0,17 ; 1,2];	-2,61 [-5,75 ; 0,52]; 0,159	0,159	
	No	181	6	3.31	193	9	4.66	0,71 [0,26 ; 1,96]	0,7 [0,24 ; 2,01];	-1,35 [-5,3 ; 2,61]; 0,603	0,603	0,2107

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	1	1.09	82	5	6.10	0,18 [0,02 ; 1,49]	0,17 [0,02 ; 1,48];	-5,01 [-10,61 ; 0,59]; 0,101	0,101	
Region	Eastern Europe	247	6	2.43	244	12	4.92	0,49 [0,19 ; 1,3]	0,48 [0,18 ; 1,3];	-2,49 [-5,81 ; 0,83]; 0,157	0,157	0,8912
	USA and Western Europe	26	1	3.85	31	2	6.45	0,6 [0,06 ; 6,21]	0,58 [0,05 ; 6,78];	-2,61 [-13,98 ; 8,77]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Gastrointestinal disorders | Abdominal pain upper

4.1.20 General disorders and administration site conditions - Fatigue

Tabelle 20: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	8	5.33	146	2	1.37	3,89 [0,84 ; 18,03]	4,06 [0,85 ; 19,43];	3,96 [-0,1 ; 8,02]; 0,104	0,104	0,0441
	>= 38 years	123	4	3.25	129	7	5.43	0,6 [0,18 ; 2]	0,59 [0,17 ; 2,05];	-2,17 [-7,19 ; 2,84]; 0,541	0,541	
Disease Severity at baseline (EDSS)	<=3.5	201	12	5.97	208	7	3.37	1,77 [0,71 ; 4,41]	1,82 [0,7 ; 4,73];	2,6 [-1,49 ; 6,7]; 0,245	0,245	0,0454
	>3.5	72	0	0.00	67	2	2.99	0,19 [0,01 ; 3,81]	0,18 [0,01 ; 3,83];	-2,99 [-7,85 ; 1,86]; 0,234	0,234	
Gender	Female	167	8	4.79	180	6	3.33	1,44 [0,51 ; 4,06]	1,46 [0,5 ; 4,3];	1,46 [-2,71 ; 5,62]; 0,589	0,589	0,8395
	Male	106	4	3.77	95	3	3.16	1,19 [0,27 ; 5,2]	1,2 [0,26 ; 5,52];	0,62 [-4,44 ; 5,67]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	117	7	5.98	116	5	4.31	1,39 [0,45 ; 4,25]	1,41 [0,44 ; 4,59];	1,67 [-4 ; 7,34]; 0,768	0,768	0,91
	0	155	5	3.23	157	4	2.55	1,27 [0,35 ; 4,63]	1,27 [0,34 ; 4,84];	0,68 [-3,04 ; 4,39]; 0,749	0,749	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	4	3.70	92	2	2.17	1,7 [0,32 ; 9,09]	1,73 [0,31 ; 9,67];	1,53 [-3,11 ; 6,17]; 0,689	0,689	0,8132
	>=3	42	1	2.38	58	2	3.45	0,69 [0,06 ; 7,37]	0,68 [0,06 ; 7,79];	-1,07 [-7,65 ; 5,51]; 1	1	
	2	123	7	5.69	125	5	4.00	1,42 [0,46 ; 4,36]	1,45 [0,45 ; 4,69];	1,69 [-3,65 ; 7,04]; 0,569	0,569	
Race	Other	7	1	14.29	8	1	12.50	1,14 [0,09 ; 15,08]	1,17 [0,06 ; 22,94];	1,79 [-32,81 ; 36,39]; 1	1	0,9101
	White	266	11	4.14	267	8	3.00	1,38 [0,56 ; 3,38]	1,4 [0,55 ; 3,53];	1,14 [-2,01 ; 4,29]; 0,495	0,495	
	No	181	7	3.87	193	6	3.11	1,24 [0,43 ; 3,63]	1,25 [0,41 ; 3,8];	0,76 [-2,97 ; 4,48]; 0,781	0,781	0,8405

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	5	5.43	82	3	3.66	1,49 [0,37 ; 6,02]	1,51 [0,35 ; 6,54];	1,78 [-4,39 ; 7,94]; 0,724	0,724	
Region	Eastern Europe	247	9	3.64	244	5	2.05	1,78 [0,6 ; 5,23]	1,81 [0,6 ; 5,47];	1,59 [-1,34 ; 4,53]; 0,417	0,417	0,4652
	USA and Western Europe	26	3	11.54	31	4	12.90	0,89 [0,22 ; 3,64]	0,88 [0,18 ; 4,35];	-1,36 [-18,4 ; 15,67]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - General disorders and administration site conditions | Fatigue

4.1.21 Infections and infestations - Influenza

Tabelle 21: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	7	4.67	146	6	4.11	1,14 [0,39 ; 3,3]	1,14 [0,37 ; 3,48];	0,56 [-4,11 ; 5,22]; 1	1	0,9228
	>= 38 years	123	5	4.07	129	5	3.88	1,05 [0,31 ; 3,53]	1,05 [0,3 ; 3,72];	0,19 [-4,64 ; 5,01]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	201	10	4.98	208	8	3.85	1,29 [0,52 ; 3,21]	1,31 [0,51 ; 3,39];	1,13 [-2,85 ; 5,11]; 0,635	0,635	0,4614
	>3.5	72	2	2.78	67	3	4.48	0,62 [0,11 ; 3,6]	0,61 [0,1 ; 3,77];	-1,7 [-7,94 ; 4,54]; 0,672	0,672	
Gender	Female	167	6	3.59	180	8	4.44	0,81 [0,29 ; 2,28]	0,8 [0,27 ; 2,36];	-0,85 [-4,98 ; 3,28]; 0,788	0,788	0,3523
	Male	106	6	5.66	95	3	3.16	1,79 [0,46 ; 6,97]	1,84 [0,45 ; 7,57];	2,5 [-3,13 ; 8,13]; 0,504	0,504	
Number of baseline Gd-enhancing lesions	>=1	117	6	5.13	116	6	5.17	0,99 [0,33 ; 2,98]	0,99 [0,31 ; 3,17];	-0,04 [-5,72 ; 5,63]; 1	1	0,8047
	0	155	6	3.87	157	5	3.18	1,22 [0,38 ; 3,9]	1,22 [0,37 ; 4,1];	0,69 [-3,41 ; 4,78]; 0,769	0,769	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	9	8.33	92	0	0.00	16,21 [0,96 ; 274,79]	17,66 [1,01 ; 307,77];	8,18 [2,68 ; 13,68]; 0,002	0,002	0,0002
	>=3	42	1	2.38	58	1	1.72	1,38 [0,09 ; 21,46]	1,39 [0,08 ; 22,88];	0,66 [-5,04 ; 6,36]; 1	1	
	2	123	2	1.63	125	10	8.00	0,2 [0,05 ; 0,91]	0,19 [0,04 ; 0,89];	-6,37 [-11,63 ; -1,12]; 0,034	0,034	
Race	Other	7	1	14.29	8	0	0.00	3,38 [0,16 ; 71,67]	3,92 [0,14 ; 112,9];	13,19 [-17,72 ; 44,11]; 0,467	0,467	0,213
	White	266	11	4.14	267	11	4.12	1 [0,44 ; 2,28]	1 [0,43 ; 2,36];	0,02 [-3,36 ; 3,39]; 1	1	
	No	181	8	4.42	193	7	3.63	1,22 [0,45 ; 3,29]	1,23 [0,44 ; 3,46];	0,79 [-3,2 ; 4,78]; 0,795	0,795	0,7156

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	4	4.35	82	4	4.88	0,89 [0,23 ; 3,45]	0,89 [0,21 ; 3,66];	-0,53 [-6,78 ; 5,72]; 1	1	
Region	Eastern Europe	247	7	2.83	244	8	3.28	0,86 [0,32 ; 2,35]	0,86 [0,31 ; 2,41];	-0,44 [-3,49 ; 2,6]; 0,8	0,8	0,3101
	USA and Western Europe	26	5	19.23	31	3	9.68	1,99 [0,52 ; 7,54]	2,22 [0,48 ; 10,36];	9,55 [-8,83 ; 27,93]; 0,448	0,448	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Influenza

4.1.22 Gastrointestinal disorders - Nausea

Tabelle 22: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	18	12.00	146	6	4.11	2,92 [1,19 ; 7,15]	3,18 [1,23 ; 8,26];	7,89 [1,77 ; 14,01]; 0,018	0,018	0,1841
	>= 38 years	123	11	8.94	129	9	6.98	1,28 [0,55 ; 2,99]	1,31 [0,52 ; 3,28];	1,97 [-4,72 ; 8,66]; 0,644	0,644	
Disease Severity at baseline (EDSS)	<=3.5	201	20	9.95	208	11	5.29	1,88 [0,93 ; 3,83]	1,98 [0,92 ; 4,24];	4,66 [-0,47 ; 9,8]; 0,093	0,093	0,8614
	>3.5	72	9	12.50	67	4	5.97	2,09 [0,68 ; 6,48]	2,25 [0,66 ; 7,69];	6,53 [-2,99 ; 16,05]; 0,248	0,248	
Gender	Female	167	24	14.37	180	12	6.67	2,16 [1,11 ; 4,17]	2,35 [1,13 ; 4,87];	7,7 [1,26 ; 14,15]; 0,022	0,022	0,6039
	Male	106	5	4.72	95	3	3.16	1,49 [0,37 ; 6,08]	1,52 [0,35 ; 6,53];	1,56 [-3,79 ; 6,91]; 0,724	0,724	
Number of baseline Gd-enhancing lesions	>=1	117	14	11.97	116	5	4.31	2,78 [1,03 ; 7,46]	3,02 [1,05 ; 8,67];	7,66 [0,71 ; 14,6]; 0,053	0,053	0,3376
	0	155	15	9.68	157	10	6.37	1,52 [0,7 ; 3,28]	1,57 [0,68 ; 3,62];	3,31 [-2,71 ; 9,33]; 0,304	0,304	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	14	12.96	92	4	4.35	2,98 [1,02 ; 8,74]	3,28 [1,04 ; 10,33];	8,62 [1,03 ; 16,2]; 0,046	0,046	0,5421
	>=3	42	4	9.52	58	3	5.17	1,84 [0,43 ; 7,8]	1,93 [0,41 ; 9,12];	4,35 [-6,2 ; 14,9]; 0,449	0,449	
	2	123	11	8.94	125	8	6.40	1,4 [0,58 ; 3,36]	1,44 [0,56 ; 3,7];	2,54 [-4,08 ; 9,16]; 0,483	0,483	
Race	Other	7	2	28.57	8	1	12.50	2,29 [0,26 ; 20,13]	2,8 [0,2 ; 40,06];	16,07 [-24,49 ; 56,63]; 0,569	0,569	0,8198
	White	266	27	10.15	267	14	5.24	1,94 [1,04 ; 3,61]	2,04 [1,05 ; 3,99];	4,91 [0,4 ; 9,41]; 0,036	0,036	
	No	181	17	9.39	193	10	5.18	1,81 [0,85 ; 3,85]	1,9 [0,84 ; 4,26];	4,21 [-1,07 ; 9,49]; 0,161	0,161	0,7752

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	12	13.04	82	5	6.10	2,14 [0,79 ; 5,81]	2,31 [0,78 ; 6,86];	6,95 [-1,67 ; 15,56]; 0,135	0,135	
Region	Eastern Europe	247	24	9.72	244	11	4.51	2,16 [1,08 ; 4,3]	2,28 [1,09 ; 4,76];	5,21 [0,69 ; 9,73]; 0,034	0,034	0,6716
	USA and Western Europe	26	5	19.23	31	4	12.90	1,49 [0,45 ; 4,98]	1,61 [0,38 ; 6,74];	6,33 [-12,88 ; 25,53]; 0,718	0,718	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Gastrointestinal disorders | Nausea

4.1.23 Musculoskeletal and connective tissue disorders - Back pain

Tabelle 23: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	7	4.67	146	12	8.22	0,57 [0,23 ; 1,4]	0,55 [0,21 ; 1,43];	-3,55 [-9,14 ; 2,04]; 0,242	0,242	0,8591
	>= 38 years	123	9	7.32	129	18	13.95	0,52 [0,24 ; 1,12]	0,49 [0,21 ; 1,13];	-6,64 [-14,18 ; 0,91]; 0,105	0,105	
Disease Severity at baseline (EDSS)	<=3.5	201	9	4.48	208	21	10.10	0,44 [0,21 ; 0,94]	0,42 [0,19 ; 0,93];	-5,62 [-10,61 ; -0,62]; 0,036	0,036	0,4517
	>3.5	72	7	9.72	67	9	13.43	0,72 [0,29 ; 1,83]	0,69 [0,24 ; 1,98];	-3,71 [-14,36 ; 6,94]; 0,598	0,598	
Gender	Female	167	12	7.19	180	19	10.56	0,68 [0,34 ; 1,36]	0,66 [0,31 ; 1,4];	-3,37 [-9,33 ; 2,59]; 0,347	0,347	0,2628
	Male	106	4	3.77	95	11	11.58	0,33 [0,11 ; 0,99]	0,3 [0,09 ; 0,97];	-7,81 [-15,19 ; -0,42]; 0,057	0,057	
Number of baseline Gd-enhancing lesions	>=1	117	9	7.69	116	18	15.52	0,5 [0,23 ; 1,06]	0,45 [0,19 ; 1,06];	-7,82 [-15,99 ; 0,34]; 0,068	0,068	0,7239
	0	155	7	4.52	157	12	7.64	0,59 [0,24 ; 1,46]	0,57 [0,22 ; 1,49];	-3,13 [-8,41 ; 2,16]; 0,344	0,344	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	8	7.41	92	10	10.87	0,68 [0,28 ; 1,65]	0,66 [0,25 ; 1,74];	-3,46 [-11,52 ; 4,59]; 0,461	0,461	0,3122
	>=3	42	4	9.52	58	6	10.34	0,92 [0,28 ; 3,06]	0,91 [0,24 ; 3,46];	-0,82 [-12,66 ; 11,02]; 1	1	
	2	123	4	3.25	125	14	11.20	0,29 [0,1 ; 0,86]	0,27 [0,09 ; 0,83];	-7,95 [-14,3 ; -1,59]; 0,025	0,025	
Race	Other	7	3	42.86	8	3	37.50	1,14 [0,33 ; 3,94]	1,25 [0,16 ; 9,92];	5,36 [-44,34 ; 55,05]; 1	1	0,3664
	White	266	13	4.89	267	27	10.11	0,48 [0,25 ; 0,92]	0,46 [0,23 ; 0,91];	-5,23 [-9,67 ; -0,78]; 0,031	0,031	
	No	181	9	4.97	193	25	12.95	0,38 [0,18 ; 0,8]	0,35 [0,16 ; 0,78];	-7,98 [-13,68 ; -2,28]; 0,011	0,011	0,0744

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	7	7.61	82	5	6.10	1,25 [0,41 ; 3,78]	1,27 [0,39 ; 4,16];	1,51 [-5,98 ; 9,01]; 0,771	0,771	
Region	Eastern Europe	247	11	4.45	244	24	9.84	0,45 [0,23 ; 0,9]	0,43 [0,2 ; 0,89];	-5,38 [-9,92 ; -0,85]; 0,023	0,023	0,2779
	USA and Western Europe	26	5	19.23	31	6	19.35	0,99 [0,34 ; 2,89]	0,99 [0,26 ; 3,72];	-0,12 [-20,69 ; 20,44]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Musculoskeletal and connective tissue disorders | Back pain

4.1.24 Musculoskeletal and connective tissue disorders - Pain in extremity

Tabelle 24: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	8	5.33	146	3	2.05	2,6 [0,7 ; 9,59]	2,69 [0,7 ; 10,33];	3,28 [-0,99 ; 7,55]; 0,218	0,218	0,1498
	>= 38 years	123	7	5.69	129	9	6.98	0,82 [0,31 ; 2,12]	0,8 [0,29 ; 2,23];	-1,29 [-7,29 ; 4,72]; 0,798	0,798	
Disease Severity at baseline (EDSS)	<=3.5	201	10	4.98	208	8	3.85	1,29 [0,52 ; 3,21]	1,31 [0,51 ; 3,39];	1,13 [-2,85 ; 5,11]; 0,635	0,635	0,8989
	>3.5	72	5	6.94	67	4	5.97	1,16 [0,33 ; 4,15]	1,18 [0,3 ; 4,58];	0,97 [-7,19 ; 9,14]; 1	1	
Gender	Female	167	7	4.19	180	10	5.56	0,75 [0,29 ; 1,94]	0,74 [0,28 ; 2];	-1,36 [-5,88 ; 3,16]; 0,625	0,625	0,0669
	Male	106	8	7.55	95	2	2.11	3,58 [0,78 ; 16,47]	3,8 [0,79 ; 18,34];	5,44 [-0,36 ; 11,24]; 0,106	0,106	
Number of baseline Gd-enhancing lesions	>=1	117	10	8.55	116	2	1.72	4,96 [1,11 ; 22,13]	5,33 [1,14 ; 24,87];	6,82 [1,23 ; 12,42]; 0,034	0,034	0,0065
	0	155	5	3.23	157	10	6.37	0,51 [0,18 ; 1,45]	0,49 [0,16 ; 1,47];	-3,14 [-7,87 ; 1,58]; 0,29	0,29	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	6	5.56	92	4	4.35	1,28 [0,37 ; 4,39]	1,29 [0,35 ; 4,73];	1,21 [-4,79 ; 7,21]; 0,756	0,756	0,7365
	>=3	42	2	4.76	58	1	1.72	2,76 [0,26 ; 29,47]	2,85 [0,25 ; 32,51];	3,04 [-4,22 ; 10,3]; 0,571	0,571	
	2	123	7	5.69	125	7	5.60	1,02 [0,37 ; 2,81]	1,02 [0,35 ; 2,99];	0,09 [-5,65 ; 5,84]; 1	1	
Race	Other	7	3	42.86	8	0	0.00	7,88 [0,48 ; 130,28]	13,22 [0,55 ; 316,64];	38,19 [0,7 ; 75,69]; 0,077	0,077	0,0248
	White	266	12	4.51	267	12	4.49	1 [0,46 ; 2,19]	1 [0,44 ; 2,28];	0,02 [-3,5 ; 3,54]; 1	1	
	No	181	7	3.87	193	11	5.70	0,68 [0,27 ; 1,71]	0,67 [0,25 ; 1,76];	-1,83 [-6,14 ; 2,48]; 0,474	0,474	0,0143

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	8	8.70	82	1	1.22	7,13 [0,91 ; 55,8]	7,71 [0,94 ; 63,07];	7,48 [1,25 ; 13,7]; 0,037	0,037	
Region	Eastern Europe	247	8	3.24	244	11	4.51	0,72 [0,29 ; 1,76]	0,71 [0,28 ; 1,79];	-1,27 [-4,68 ; 2,14]; 0,493	0,493	0,0076
	USA and Western Europe	26	7	26.92	31	1	3.23	8,35 [1,1 ; 63,51]	11,05 [1,26 ; 97,06];	23,7 [5,55 ; 41,85]; 0,018	0,018	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Musculoskeletal and connective tissue disorders | Pain in extremity

4.1.25 Nervous system disorders - Headache

Tabelle 25: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	52	34.67	146	33	22.60	1,53 [1,06 ; 2,22]	1,82 [1,09 ; 3,04];	12,06 [1,86 ; 22,26]; 0,029	0,029	0,5053
	>= 38 years	123	32	26.02	129	26	20.16	1,29 [0,82 ; 2,03]	1,39 [0,77 ; 2,51];	5,86 [-4,53 ; 16,26]; 0,297	0,297	
Disease Severity at baseline (EDSS)	<=3.5	201	62	30.85	208	49	23.56	1,31 [0,95 ; 1,8]	1,45 [0,93 ; 2,24];	7,29 [-1,32 ; 15,89]; 0,119	0,119	0,2492
	>3.5	72	22	30.56	67	10	14.93	2,05 [1,05 ; 4]	2,51 [1,08 ; 5,8];	15,63 [1,99 ; 29,27]; 0,043	0,043	
Gender	Female	167	57	34.13	180	49	27.22	1,25 [0,91 ; 1,72]	1,39 [0,88 ; 2,19];	6,91 [-2,79 ; 16,6]; 0,199	0,199	0,1043
	Male	106	27	25.47	95	10	10.53	2,42 [1,24 ; 4,73]	2,91 [1,32 ; 6,39];	14,95 [4,61 ; 25,28]; 0,007	0,007	
Number of baseline Gd-enhancing lesions	>=1	117	36	30.77	116	32	27.59	1,12 [0,75 ; 1,67]	1,17 [0,66 ; 2,05];	3,18 [-8,48 ; 14,85]; 0,666	0,666	0,1207
	0	155	48	30.97	157	27	17.20	1,8 [1,19 ; 2,73]	2,16 [1,26 ; 3,69];	13,77 [4,4 ; 23,14]; 0,005	0,005	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	30	27.78	92	22	23.91	1,16 [0,72 ; 1,87]	1,22 [0,65 ; 2,32];	3,86 [-8,27 ; 16]; 0,628	0,628	0,4745
	>=3	42	13	30.95	58	9	15.52	1,99 [0,94 ; 4,23]	2,44 [0,93 ; 6,41];	15,44 [-1,37 ; 32,24]; 0,088	0,088	
	2	123	41	33.33	125	28	22.40	1,49 [0,99 ; 2,24]	1,73 [0,99 ; 3,04];	10,93 [-0,15 ; 22,02]; 0,066	0,066	
Race	Other	7	4	57.14	8	1	12.50	4,57 [0,66 ; 31,89]	9,33 [0,71 ; 122,57];	44,64 [1,41 ; 87,88]; 0,119	0,119	0,1436
	White	266	80	30.08	267	58	21.72	1,38 [1,03 ; 1,85]	1,55 [1,05 ; 2,29];	8,35 [0,95 ; 15,76]; 0,03	0,03	
	No	181	56	30.94	193	46	23.83	1,3 [0,93 ; 1,81]	1,43 [0,91 ; 2,26];	7,11 [-1,92 ; 16,13]; 0,132	0,132	0,272

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	28	30.43	82	13	15.85	1,92 [1,07 ; 3,45]	2,32 [1,11 ; 4,87];	14,58 [2,3 ; 26,87]; 0,031	0,031	
Region	Eastern Europe	247	75	30.36	244	53	21.72	1,4 [1,03 ; 1,89]	1,57 [1,05 ; 2,36];	8,64 [0,92 ; 16,37]; 0,031	0,031	0,5989
	USA and Western Europe	26	9	34.62	31	6	19.35	1,79 [0,73 ; 4,36]	2,21 [0,66 ; 7,34];	15,26 [-7,71 ; 38,23]; 0,236	0,236	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Nervous system disorders | Headache

4.1.26 Musculoskeletal and connective tissue disorders - Neck pain

Tabelle 26: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	4	2.67	146	5	3.42	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>= 38 years	123	6	4.88	129	1	0.78	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	201	8	3.98	208	4	1.92	2,07 [0,63 ; 6,77]	2,11 [0,63 ; 7,13];	2,06 [-1,23 ; 5,34]; 0,253	0,253	0,4901
	>3.5	72	2	2.78	67	2	2.99	0,93 [0,13 ; 6,42]	0,93 [0,13 ; 6,79];	-0,21 [-5,78 ; 5,36]; 1	1	
Gender	Female	167	8	4.79	180	3	1.67	2,87 [0,78 ; 10,65]	2,97 [0,77 ; 11,38];	3,12 [-0,62 ; 6,86]; 0,128	0,128	0,1518
	Male	106	2	1.89	95	3	3.16	0,6 [0,1 ; 3,5]	0,59 [0,1 ; 3,61];	-1,27 [-5,64 ; 3,1]; 0,669	0,669	
Number of baseline Gd-enhancing lesions	>=1	117	6	5.13	116	2	1.72	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	155	4	2.58	157	4	2.55	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	3	2.78	92	3	3.26	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	1	2.38	58	1	1.72	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	6	4.88	125	2	1.60	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	0	0.00	8	2	25.00	0,22 [0,01 ; 4,02]	0,17 [0,01 ; 4,31];	-21,53 [-55,26 ; 12,2]; 0,467	0,467	0,0361
	White	266	10	3.76	267	4	1.50	2,51 [0,8 ; 7,9]	2,57 [0,8 ; 8,29];	2,26 [-0,45 ; 4,97]; 0,113	0,113	
	No	181	7	3.87	193	3	1.55	2,49 [0,65 ; 9,48]	2,55 [0,65 ; 10,01];	2,31 [-0,99 ; 5,62]; 0,208	0,208	0,3287

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	3	3.26	82	3	3.66	0,89 [0,18 ; 4,29]	0,89 [0,17 ; 4,52];	-0,4 [-5,85 ; 5,05]; 1	1	
Region	Eastern Europe	247	8	3.24	244	3	1.23	2,63 [0,71 ; 9,81]	2,69 [0,7 ; 10,26];	2,01 [-0,6 ; 4,61]; 0,221	0,221	0,2821
	USA and Western Europe	26	2	7.69	31	3	9.68	0,79 [0,14 ; 4,4]	0,78 [0,12 ; 5,05];	-1,99 [-16,59 ; 12,62]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Musculoskeletal and connective tissue disorders | Neck pain

4.1.27 Cardiac disorders - Tachycardia

Tabelle 27: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	6	4.00	146	2	1.37	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>= 38 years	123	4	3.25	129	4	3.10	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	201	7	3.48	208	5	2.40	1,45 [0,47 ; 4,49]	1,46 [0,46 ; 4,69];	1,08 [-2,2 ; 4,36]; 0,57	0,57	0,5973
	>3.5	72	3	4.17	67	1	1.49	2,79 [0,3 ; 26,19]	2,87 [0,29 ; 28,29];	2,67 [-2,78 ; 8,13]; 0,621	0,621	
Gender	Female	167	2	1.20	180	5	2.78	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	Male	106	8	7.55	95	1	1.05	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of baseline Gd-enhancing lesions	>=1	117	6	5.13	116	1	0.86	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	155	4	2.58	157	5	3.18	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	5	4.63	92	1	1.09	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	1	2.38	58	2	3.45	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	4	3.25	125	3	2.40	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	1	14.29	8	0	0.00	3,38 [0,16 ; 71,67]	3,92 [0,14 ; 112,9];	13,19 [-17,72 ; 44,11]; 0,467	0,467	0,2841
	White	266	9	3.38	267	6	2.25	1,51 [0,54 ; 4,17]	1,52 [0,53 ; 4,34];	1,14 [-1,67 ; 3,94]; 0,448	0,448	
	No	181	6	3.31	193	4	2.07	1,6 [0,46 ; 5,58]	1,62 [0,45 ; 5,84];	1,24 [-2,05 ; 4,54]; 0,532	0,532	0,916

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	4	4.35	82	2	2.44	1,78 [0,34 ; 9,48]	1,82 [0,32 ; 10,2];	1,91 [-3,43 ; 7,25]; 0,685	0,685	
Region	Eastern Europe	247	7	2.83	244	5	2.05	1,38 [0,45 ; 4,3]	1,39 [0,44 ; 4,45];	0,78 [-1,94 ; 3,51]; 0,772	0,772	0,4187
	USA and Western Europe	26	3	11.54	31	1	3.23	3,58 [0,4 ; 32,36]	3,91 [0,38 ; 40,12];	8,31 [-5,45 ; 22,08]; 0,322	0,322	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Cardiac disorders | Tachycardia

4.1.28 Infections and infestations - Nasopharyngitis

Tabelle 28: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	23	15.33	146	26	17.81	0,86 [0,52 ; 1,44]	0,84 [0,45 ; 1,54];	-2,47 [-10,95 ; 6]; 0,64	0,64	0,5282
	>= 38 years	123	11	8.94	129	18	13.95	0,64 [0,32 ; 1,3]	0,61 [0,27 ; 1,34];	-5,01 [-12,83 ; 2,81]; 0,24	0,24	
Disease Severity at baseline (EDSS)	<=3.5	201	26	12.94	208	37	17.79	0,73 [0,46 ; 1,15]	0,69 [0,4 ; 1,18];	-4,85 [-11,82 ; 2,11]; 0,217	0,217	0,4682
	>3.5	72	8	11.11	67	7	10.45	1,06 [0,41 ; 2,77]	1,07 [0,37 ; 3,14];	0,66 [-9,65 ; 10,98]; 1	1	
Gender	Female	167	21	12.57	180	29	16.11	0,78 [0,46 ; 1,31]	0,75 [0,41 ; 1,37];	-3,54 [-10,89 ; 3,82]; 0,363	0,363	0,9929
	Male	106	13	12.26	95	15	15.79	0,78 [0,39 ; 1,55]	0,75 [0,33 ; 1,66];	-3,53 [-13,16 ; 6,11]; 0,543	0,543	
Number of baseline Gd-enhancing lesions	>=1	117	18	15.38	116	23	19.83	0,78 [0,44 ; 1,36]	0,74 [0,37 ; 1,45];	-4,44 [-14,21 ; 5,32]; 0,395	0,395	0,9776
	0	155	16	10.32	157	21	13.38	0,77 [0,42 ; 1,42]	0,75 [0,37 ; 1,49];	-3,05 [-10,22 ; 4,11]; 0,484	0,484	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	14	12.96	92	17	18.48	0,7 [0,37 ; 1,34]	0,66 [0,3 ; 1,42];	-5,52 [-15,67 ; 4,64]; 0,329	0,329	0,354
	>=3	42	1	2.38	58	6	10.34	0,23 [0,03 ; 1,84]	0,21 [0,02 ; 1,83];	-7,96 [-17,06 ; 1,13]; 0,234	0,234	
	2	123	19	15.45	125	21	16.80	0,92 [0,52 ; 1,62]	0,9 [0,46 ; 1,78];	-1,35 [-10,5 ; 7,8]; 0,863	0,863	
Race	Other	7	1	14.29	8	4	50.00	0,29 [0,04 ; 1,99]	0,17 [0,01 ; 2,09];	-35,71 [-78,99 ; 7,56]; 0,282	0,282	0,2004
	White	266	33	12.41	267	40	14.98	0,83 [0,54 ; 1,27]	0,8 [0,49 ; 1,32];	-2,58 [-8,41 ; 3,26]; 0,45	0,45	
	No	181	19	10.50	193	33	17.10	0,61 [0,36 ; 1,04]	0,57 [0,31 ; 1,04];	-6,6 [-13,54 ; 0,34]; 0,073	0,073	0,1311

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	15	16.30	82	11	13.41	1,22 [0,59 ; 2,49]	1,26 [0,54 ; 2,92];	2,89 [-7,66 ; 13,44]; 0,673	0,673	
Region	Eastern Europe	247	29	11.74	244	37	15.16	0,77 [0,49 ; 1,22]	0,74 [0,44 ; 1,25];	-3,42 [-9,45 ; 2,61]; 0,291	0,291	0,8964
	USA and Western Europe	26	5	19.23	31	7	22.58	0,85 [0,31 ; 2,37]	0,82 [0,23 ; 2,96];	-3,35 [-24,47 ; 17,77]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Nasopharyngitis

4.1.29 Infections and infestations - Urinary tract infection

Tabelle 29: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	5	3.33	146	8	5.48	0,61 [0,2 ; 1,82]	0,59 [0,19 ; 1,86];	-2,15 [-6,82 ; 2,53]; 0,408	0,408	0,861
	>= 38 years	123	6	4.88	129	9	6.98	0,7 [0,26 ; 1,91]	0,68 [0,24 ; 1,98];	-2,1 [-7,91 ; 3,72]; 0,598	0,598	
Disease Severity at baseline (EDSS)	<=3.5	201	6	2.99	208	11	5.29	0,56 [0,21 ; 1,5]	0,55 [0,2 ; 1,52];	-2,3 [-6,15 ; 1,54]; 0,323	0,323	0,695
	>3.5	72	5	6.94	67	6	8.96	0,78 [0,25 ; 2,42]	0,76 [0,22 ; 2,61];	-2,01 [-11,02 ; 7]; 0,758	0,758	
Gender	Female	167	10	5.99	180	15	8.33	0,72 [0,33 ; 1,55]	0,7 [0,31 ; 1,61];	-2,35 [-7,75 ; 3,06]; 0,416	0,416	0,7204
	Male	106	1	0.94	95	2	2.11	0,45 [0,04 ; 4,86]	0,44 [0,04 ; 4,96];	-1,16 [-4,59 ; 2,26]; 0,603	0,603	
Number of baseline Gd-enhancing lesions	>=1	117	4	3.42	116	4	3.45	0,99 [0,25 ; 3,87]	0,99 [0,24 ; 4,06];	-0,03 [-4,71 ; 4,65]; 1	1	0,462
	0	155	7	4.52	157	13	8.28	0,55 [0,22 ; 1,33]	0,52 [0,2 ; 1,35];	-3,76 [-9,17 ; 1,65]; 0,248	0,248	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	4	3.70	92	7	7.61	0,49 [0,15 ; 1,61]	0,47 [0,13 ; 1,65];	-3,9 [-10,39 ; 2,58]; 0,351	0,351	0,7358
	>=3	42	1	2.38	58	3	5.17	0,46 [0,05 ; 4,27]	0,45 [0,04 ; 4,46];	-2,79 [-10,12 ; 4,54]; 0,637	0,637	
	2	123	6	4.88	125	7	5.60	0,87 [0,3 ; 2,52]	0,86 [0,28 ; 2,65];	-0,72 [-6,27 ; 4,82]; 1	1	
Race	Other	7	1	14.29	8	1	12.50	1,14 [0,09 ; 15,08]	1,17 [0,06 ; 22,94];	1,79 [-32,81 ; 36,39]; 1	1	0,6839
	White	266	10	3.76	267	16	5.99	0,63 [0,29 ; 1,36]	0,61 [0,27 ; 1,38];	-2,23 [-5,88 ; 1,42]; 0,315	0,315	
	No	181	6	3.31	193	10	5.18	0,64 [0,24 ; 1,72]	0,63 [0,22 ; 1,76];	-1,87 [-5,94 ; 2,21]; 0,448	0,448	0,9814

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	5	5.43	82	7	8.54	0,64 [0,21 ; 1,93]	0,62 [0,19 ; 2,02];	-3,1 [-10,72 ; 4,52]; 0,552	0,552	
Region	Eastern Europe	247	7	2.83	244	10	4.10	0,69 [0,27 ; 1,79]	0,68 [0,26 ; 1,82];	-1,26 [-4,5 ; 1,97]; 0,471	0,471	0,9155
	USA and Western Europe	26	4	15.38	31	7	22.58	0,68 [0,22 ; 2,07]	0,62 [0,16 ; 2,42];	-7,2 [-27,42 ; 13,03]; 0,738	0,738	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Urinary tract infection

4.1.30 Investigations - Lipase increased

Tabelle 30: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	3	2.00	146	6	4.11	0,49 [0,12 ; 1,91]	0,48 [0,12 ; 1,94];	-2,11 [-6,03 ; 1,81]; 0,331	0,331	0,829
	>= 38 years	123	4	3.25	129	7	5.43	0,6 [0,18 ; 2]	0,59 [0,17 ; 2,05];	-2,17 [-7,19 ; 2,84]; 0,541	0,541	
Disease Severity at baseline (EDSS)	<=3.5	201	4	1.99	208	9	4.33	0,46 [0,14 ; 1,47]	0,45 [0,14 ; 1,48];	-2,34 [-5,71 ; 1,04]; 0,26	0,26	0,6709
	>3.5	72	3	4.17	67	4	5.97	0,7 [0,16 ; 3]	0,68 [0,15 ; 3,18];	-1,8 [-9,12 ; 5,51]; 0,711	0,711	
Gender	Female	167	3	1.80	180	6	3.33	0,54 [0,14 ; 2,12]	0,53 [0,13 ; 2,16];	-1,54 [-4,84 ; 1,77]; 0,505	0,505	0,9393
	Male	106	4	3.77	95	7	7.37	0,51 [0,15 ; 1,69]	0,49 [0,14 ; 1,74];	-3,59 [-9,98 ; 2,79]; 0,355	0,355	
Number of baseline Gd-enhancing lesions	>=1	117	4	3.42	116	1	0.86	3,97 [0,45 ; 34,95]	4,07 [0,45 ; 36,98];	2,56 [-1,14 ; 6,25]; 0,37	0,37	0,0142
	0	155	3	1.94	157	12	7.64	0,25 [0,07 ; 0,88]	0,24 [0,07 ; 0,86];	-5,71 [-10,4 ; -1,02]; 0,031	0,031	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	1	0.93	92	4	4.35	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	2	4.76	58	4	6.90	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	4	3.25	125	5	4.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	0	0.00	8	1	12.50	0,38 [0,02 ; 7,96]	0,33 [0,01 ; 9,57];	-10,42 [-39,98 ; 19,15]; 0,477	0,477	0,3578
	White	266	7	2.63	267	12	4.49	0,59 [0,23 ; 1,46]	0,57 [0,22 ; 1,48];	-1,86 [-5,01 ; 1,28]; 0,35	0,35	
	No	181	2	1.10	193	8	4.15	0,27 [0,06 ; 1,24]	0,26 [0,05 ; 1,23];	-3,04 [-6,24 ; 0,16]; 0,106	0,106	0,2162

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	5	5.43	82	5	6.10	0,89 [0,27 ; 2,97]	0,89 [0,25 ; 3,17];	-0,66 [-7,61 ; 6,29]; 1	1	
Region	Eastern Europe	247	5	2.02	244	11	4.51	0,45 [0,16 ; 1,27]	0,44 [0,15 ; 1,28];	-2,48 [-5,62 ; 0,66]; 0,135	0,135	0,3893
	USA and Western Europe	26	2	7.69	31	2	6.45	1,19 [0,18 ; 7,89]	1,21 [0,16 ; 9,23];	1,24 [-12,16 ; 14,65]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Investigations | Lipase increased

4.1.31 Psychiatric disorders - Anxiety

Tabelle 31: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	5	3.33	146	3	2.05	1,62 [0,39 ; 6,67]	1,64 [0,39 ; 7,01];	1,28 [-2,4 ; 4,96]; 0,723	0,723	0,1345
	>= 38 years	123	3	2.44	129	8	6.20	0,39 [0,11 ; 1,45]	0,38 [0,1 ; 1,46];	-3,76 [-8,74 ; 1,21]; 0,218	0,218	
Disease Severity at baseline (EDSS)	<=3.5	201	7	3.48	208	8	3.85	0,91 [0,33 ; 2,45]	0,9 [0,32 ; 2,54];	-0,36 [-4 ; 3,28]; 1	1	0,3678
	>3.5	72	1	1.39	67	3	4.48	0,31 [0,03 ; 2,91]	0,3 [0,03 ; 2,96];	-3,09 [-8,73 ; 2,55]; 0,352	0,352	
Gender	Female	167	6	3.59	180	10	5.56	0,65 [0,24 ; 1,74]	0,63 [0,23 ; 1,78];	-1,96 [-6,34 ; 2,42]; 0,449	0,449	0,421
	Male	106	2	1.89	95	1	1.05	1,79 [0,17 ; 19,45]	1,81 [0,16 ; 20,26];	0,83 [-2,47 ; 4,14]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	117	6	5.13	116	4	3.45	1,49 [0,43 ; 5,13]	1,51 [0,42 ; 5,51];	1,68 [-3,52 ; 6,88]; 0,748	0,748	0,0901
	0	155	2	1.29	157	7	4.46	0,29 [0,06 ; 1,37]	0,28 [0,06 ; 1,37];	-3,17 [-6,85 ; 0,52]; 0,173	0,173	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	5	4.63	92	3	3.26	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	2	4.76	58	2	3.45	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	1	0.81	125	6	4.80	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	1	14.29	8	0	0.00	3,38 [0,16 ; 71,67]	3,92 [0,14 ; 112,9];	13,19 [-17,72 ; 44,11]; 0,467	0,467	0,1515
	White	266	7	2.63	267	11	4.12	0,64 [0,25 ; 1,62]	0,63 [0,24 ; 1,65];	-1,49 [-4,55 ; 1,58]; 0,473	0,473	
	No	181	2	1.10	193	8	4.15	0,27 [0,06 ; 1,24]	0,26 [0,05 ; 1,23];	-3,04 [-6,24 ; 0,16]; 0,106	0,106	0,0529

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	6	6.52	82	3	3.66	1,78 [0,46 ; 6,9]	1,84 [0,44 ; 7,59];	2,86 [-3,62 ; 9,34]; 0,503	0,503	
Region	Eastern Europe	247	5	2.02	244	9	3.69	0,55 [0,19 ; 1,61]	0,54 [0,18 ; 1,63];	-1,66 [-4,61 ; 1,28]; 0,292	0,292	0,2522
	USA and Western Europe	26	3	11.54	31	2	6.45	1,79 [0,32 ; 9,9]	1,89 [0,29 ; 12,28];	5,09 [-9,93 ; 20,11]; 0,651	0,651	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Psychiatric disorders | Anxiety

4.1.32 Skin and subcutaneous tissue disorders - Alopecia

Tabelle 32: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	5	3.33	146	21	14.38	0,23 [0,09 ; 0,6]	0,21 [0,08 ; 0,56];	-11,05 [-17,43 ; -4,67]; 0,001	0,001	0,26
	>= 38 years	123	1	0.81	129	15	11.63	0,07 [0,01 ; 0,52]	0,06 [0,01 ; 0,48];	-10,81 [-16,57 ; -5,06]; 0	0	
Disease Severity at baseline (EDSS)	<=3.5	201	3	1.49	208	34	16.35	0,09 [0,03 ; 0,29]	0,08 [0,02 ; 0,26];	-14,85 [-20,15 ; -9,56]; 0	0	0,0081
	>3.5	72	3	4.17	67	2	2.99	1,4 [0,24 ; 8,1]	1,41 [0,23 ; 8,73];	1,18 [-4,98 ; 7,34]; 1	1	
Gender	Female	167	5	2.99	180	30	16.67	0,18 [0,07 ; 0,45]	0,15 [0,06 ; 0,41];	-13,67 [-19,7 ; -7,65]; 0	0	0,9408
	Male	106	1	0.94	95	6	6.32	0,15 [0,02 ; 1,22]	0,14 [0,02 ; 1,2];	-5,37 [-10,6 ; -0,15]; 0,054	0,054	
Number of baseline Gd-enhancing lesions	>=1	117	2	1.71	116	16	13.79	0,12 [0,03 ; 0,53]	0,11 [0,02 ; 0,48];	-12,08 [-18,78 ; -5,38]; 0	0	0,5393
	0	155	4	2.58	157	19	12.10	0,21 [0,07 ; 0,61]	0,19 [0,06 ; 0,58];	-9,52 [-15,2 ; -3,84]; 0,002	0,002	
	NA	1	0	0.00	2	1	50.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	3	2.78	92	10	10.87	0,26 [0,07 ; 0,9]	0,23 [0,06 ; 0,88];	-8,09 [-15,17 ; -1,02]; 0,04	0,04	0,2404
	>=3	42	0	0.00	58	10	17.24	0,07 [0 ; 1,08]	0,05 [0 ; 0,96];	-16,63 [-26,91 ; -6,36]; 0,005	0,005	
	2	123	3	2.44	125	16	12.80	0,19 [0,06 ; 0,64]	0,17 [0,05 ; 0,6];	-10,36 [-16,82 ; -3,9]; 0,003	0,003	
Race	Other	7	0	0.00	8	1	12.50	0,38 [0,02 ; 7,96]	0,33 [0,01 ; 9,57];	-10,42 [-39,98 ; 19,15]; 0,477	0,477	0,599
	White	266	6	2.26	267	35	13.11	0,17 [0,07 ; 0,4]	0,15 [0,06 ; 0,37];	-10,85 [-15,28 ; -6,43]; 0	0	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	No	181	2	1.10	193	26	13.47	0,08 [0,02 ; 0,34]	0,07 [0,02 ; 0,31];	-12,37 [-17,42 ; -7,31]; 0	0	0,1027
	Yes	92	4	4.35	82	10	12.20	0,36 [0,12 ; 1,09]	0,33 [0,1 ; 1,09];	-7,85 [-16,06 ; 0,37]; 0,091	0,091	
Region	Eastern Europe	247	6	2.43	244	31	12.70	0,19 [0,08 ; 0,45]	0,17 [0,07 ; 0,42];	-10,28 [-14,87 ; -5,68]; 0	0	0,229
	USA and Western Europe	26	0	0.00	31	5	16.13	0,11 [0,01 ; 1,86]	0,09 [0 ; 1,73];	-15,34 [-29,36 ; -1,31]; 0,028	0,028	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Skin and subcutaneous tissue disorders | Alopecia

4.1.33 Infections and infestations - Sinusitis

Tabelle 33: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	4	2.67	146	8	5.48	0,49 [0,15 ; 1,58]	0,47 [0,14 ; 1,6];	-2,81 [-7,32 ; 1,69]; 0,251	0,251	0,1104
	>= 38 years	123	0	0.00	129	4	3.10	0,12 [0,01 ; 2,14]	0,11 [0,01 ; 2,12];	-3,06 [-6,39 ; 0,28]; 0,122	0,122	
Disease Severity at baseline (EDSS)	<=3.5	201	2	1.00	208	10	4.81	0,21 [0,05 ; 0,93]	0,2 [0,04 ; 0,92];	-3,81 [-7,03 ; -0,6]; 0,036	0,036	0,2262
	>3.5	72	2	2.78	67	2	2.99	0,93 [0,13 ; 6,42]	0,93 [0,13 ; 6,79];	-0,21 [-5,78 ; 5,36]; 1	1	
Gender	Female	167	2	1.20	180	6	3.33	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	Male	106	2	1.89	95	6	6.32	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of baseline Gd-enhancing lesions	>=1	117	1	0.85	116	5	4.31	0,2 [0,02 ; 1,67]	0,19 [0,02 ; 1,66];	-3,46 [-7,51 ; 0,6]; 0,119	0,119	0,5302
	0	155	3	1.94	157	7	4.46	0,43 [0,11 ; 1,65]	0,42 [0,11 ; 1,67];	-2,52 [-6,41 ; 1,37]; 0,336	0,336	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	2	1.85	92	2	2.17	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	1	2.38	58	2	3.45	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	1	0.81	125	8	6.40	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	1	14.29	8	0	0.00	3,38 [0,16 ; 71,67]	3,92 [0,14 ; 112,9];	13,19 [-17,72 ; 44,11]; 0,467	0,467	0,0695
	White	266	3	1.13	267	12	4.49	0,25 [0,07 ; 0,88]	0,24 [0,07 ; 0,87];	-3,37 [-6,16 ; -0,58]; 0,033	0,033	
	No	181	2	1.10	193	9	4.66	0,24 [0,05 ; 1,08]	0,23 [0,05 ; 1,07];	-3,56 [-6,9 ; -0,22]; 0,063	0,063	0,4391

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	2	2.17	82	3	3.66	0,59 [0,1 ; 3,47]	0,59 [0,1 ; 3,59];	-1,48 [-6,52 ; 3,55]; 0,667	0,667	
Region	Eastern Europe	247	3	1.21	244	10	4.10	0,3 [0,08 ; 1,06]	0,29 [0,08 ; 1,06];	-2,88 [-5,72 ; -0,05]; 0,053	0,053	0,6295
	USA and Western Europe	26	1	3.85	31	2	6.45	0,6 [0,06 ; 6,21]	0,58 [0,05 ; 6,78];	-2,61 [-13,98 ; 8,77]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Sinusitis

4.1.34 Infections and infestations - Upper respiratory tract infection

Tabelle 34: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	9	6.00	146	10	6.85	0,88 [0,37 ; 2,09]	0,87 [0,34 ; 2,2];	-0,85 [-6,44 ; 4,74]; 0,816	0,816	0,3584
	>= 38 years	123	8	6.50	129	5	3.88	1,68 [0,56 ; 4,99]	1,73 [0,55 ; 5,43];	2,63 [-2,86 ; 8,11]; 0,402	0,402	
Disease Severity at baseline (EDSS)	<=3.5	201	15	7.46	208	13	6.25	1,19 [0,58 ; 2,45]	1,21 [0,56 ; 2,61];	1,21 [-3,69 ; 6,11]; 0,697	0,697	0,8081
	>3.5	72	2	2.78	67	2	2.99	0,93 [0,13 ; 6,42]	0,93 [0,13 ; 6,79];	-0,21 [-5,78 ; 5,36]; 1	1	
Gender	Female	167	13	7.78	180	11	6.11	1,27 [0,59 ; 2,76]	1,3 [0,56 ; 2,98];	1,67 [-3,69 ; 7,04]; 0,673	0,673	0,6553
	Male	106	4	3.77	95	4	4.21	0,9 [0,23 ; 3,48]	0,89 [0,22 ; 3,67];	-0,44 [-5,87 ; 4,99]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	117	5	4.27	116	9	7.76	0,55 [0,19 ; 1,59]	0,53 [0,17 ; 1,63];	-3,49 [-9,58 ; 2,61]; 0,286	0,286	0,0663
	0	155	12	7.74	157	6	3.82	2,03 [0,78 ; 5,26]	2,11 [0,77 ; 5,78];	3,92 [-1,25 ; 9,09]; 0,153	0,153	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	7	6.48	92	4	4.35	1,49 [0,45 ; 4,93]	1,52 [0,43 ; 5,38];	2,13 [-4,11 ; 8,37]; 0,552	0,552	0,3478
	>=3	42	2	4.76	58	6	10.34	0,46 [0,1 ; 2,17]	0,43 [0,08 ; 2,26];	-5,58 [-15,73 ; 4,56]; 0,462	0,462	
	2	123	8	6.50	125	5	4.00	1,63 [0,55 ; 4,83]	1,67 [0,53 ; 5,25];	2,5 [-3,05 ; 8,05]; 0,408	0,408	
Race	Other	7	2	28.57	8	0	0.00	5,62 [0,31 ; 100,52]	7,73 [0,31 ; 193,44];	25,69 [-9,74 ; 61,13]; 0,467	0,467	0,0716
	White	266	15	5.64	267	15	5.62	1 [0,5 ; 2,01]	1 [0,48 ; 2,1];	0,02 [-3,89 ; 3,93]; 1	1	
	No	181	10	5.52	193	12	6.22	0,89 [0,39 ; 2,01]	0,88 [0,37 ; 2,09];	-0,69 [-5,46 ; 4,07]; 0,829	0,829	0,2693

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	7	7.61	82	3	3.66	2,08 [0,56 ; 7,78]	2,17 [0,54 ; 8,68];	3,95 [-2,82 ; 10,72]; 0,338	0,338	
Region	Eastern Europe	247	11	4.45	244	12	4.92	0,91 [0,41 ; 2,01]	0,9 [0,39 ; 2,08];	-0,46 [-4,2 ; 3,27]; 0,834	0,834	0,187
	USA and Western Europe	26	6	23.08	31	3	9.68	2,38 [0,66 ; 8,61]	2,8 [0,62 ; 12,55];	13,4 [-5,85 ; 32,65]; 0,275	0,275	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Upper respiratory tract infection

4.1.35 Infections and infestations - Bronchitis

Tabelle 35: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	8	5.33	146	5	3.42	1,56 [0,52 ; 4,65]	1,59 [0,51 ; 4,97];	1,91 [-2,74 ; 6,56]; 0,573	0,573	0,0636
	>= 38 years	123	4	3.25	129	0	0.00	9,44 [0,51 ; 173,44]	9,75 [0,52 ; 183,07];	3,24 [-0,21 ; 6,7]; 0,055	0,055	
Disease Severity at baseline (EDSS)	<=3.5	201	12	5.97	208	5	2.40	2,48 [0,89 ; 6,92]	2,58 [0,89 ; 7,45];	3,57 [-0,31 ; 7,45]; 0,085	0,085	0,9999
	>3.5	72	0	0.00	67	0	0.00	0,93 [0,02 ; 46,29]	0,93 [0,02 ; 47,58];	-0,05 [-2,83 ; 2,73]; 1	1	
Gender	Female	167	10	5.99	180	3	1.67	3,59 [1,01 ; 12,83]	3,76 [1,02 ; 13,9];	4,32 [0,27 ; 8,38]; 0,046	0,046	0,2381
	Male	106	2	1.89	95	2	2.11	0,9 [0,13 ; 6,24]	0,89 [0,12 ; 6,48];	-0,22 [-4,1 ; 3,66]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	117	7	5.98	116	3	2.59	2,31 [0,61 ; 8,73]	2,4 [0,6 ; 9,51];	3,4 [-1,78 ; 8,57]; 0,333	0,333	0,9456
	0	155	5	3.23	157	2	1.27	2,53 [0,5 ; 12,86]	2,58 [0,49 ; 13,52];	1,95 [-1,34 ; 5,24]; 0,281	0,281	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	6	5.56	92	2	2.17	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	1	2.38	58	2	3.45	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	5	4.07	125	1	0.80	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9999
	White	266	12	4.51	267	5	1.87	2,41 [0,86 ; 6,74]	2,48 [0,86 ; 7,13];	2,64 [-0,34 ; 5,62]; 0,091	0,091	
	No	181	8	4.42	193	4	2.07	2,13 [0,65 ; 6,96]	2,18 [0,65 ; 7,38];	2,35 [-1,26 ; 5,95]; 0,247	0,247	0,6777

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	4	4.35	82	1	1.22	3,57 [0,41 ; 31,26]	3,68 [0,4 ; 33,63];	3,13 [-1,67 ; 7,93]; 0,372	0,372	
Region	Eastern Europe	247	11	4.45	244	3	1.23	3,62 [1,02 ; 12,82]	3,74 [1,03 ; 13,59];	3,22 [0,3 ; 6,14]; 0,054	0,054	0,172
	USA and Western Europe	26	1	3.85	31	2	6.45	0,6 [0,06 ; 6,21]	0,58 [0,05 ; 6,78];	-2,61 [-13,98 ; 8,77]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Bronchitis

4.1.36 Investigations - Lymphocyte count decreased

Tabelle 36: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	23	15.33	146	4	2.74	5,6 [1,98 ; 15,79]	6,43 [2,16 ; 19,09];	12,59 [6,25 ; 18,94]; 0	0	0,3665
	>= 38 years	123	11	8.94	129	4	3.10	2,88 [0,94 ; 8,82]	3,07 [0,95 ; 9,91];	5,84 [-0,02 ; 11,71]; 0,063	0,063	
Disease Severity at baseline (EDSS)	<=3.5	201	23	11.44	208	7	3.37	3,4 [1,49 ; 7,75]	3,71 [1,55 ; 8,85];	8,08 [3,04 ; 13,11]; 0,002	0,002	0,2631
	>3.5	72	11	15.28	67	1	1.49	10,24 [1,36 ; 77,16]	11,9 [1,49 ; 94,93];	13,79 [4,98 ; 22,59]; 0,005	0,005	
Gender	Female	167	22	13.17	180	5	2.78	4,74 [1,84 ; 12,24]	5,31 [1,96 ; 14,37];	10,4 [4,73 ; 16,06]; 0	0	0,717
	Male	106	12	11.32	95	3	3.16	3,58 [1,04 ; 12,32]	3,91 [1,07 ; 14,33];	8,16 [1,18 ; 15,14]; 0,032	0,032	
Number of baseline Gd-enhancing lesions	>=1	117	12	10.26	116	3	2.59	3,97 [1,15 ; 13,69]	4,3 [1,18 ; 15,68];	7,67 [1,46 ; 13,88]; 0,03	0,03	0,8526
	0	155	22	14.19	157	5	3.18	4,46 [1,73 ; 11,47]	5,03 [1,85 ; 13,65];	11,01 [4,87 ; 17,15]; 0,001	0,001	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	11	10.19	92	2	2.17	4,69 [1,07 ; 20,6]	5,1 [1,1 ; 23,65];	8,01 [1,58 ; 14,45]; 0,023	0,023	0,332
	>=3	42	9	21.43	58	1	1.72	12,43 [1,64 ; 94,39]	15,55 [1,88 ; 128,22];	19,7 [6,85 ; 32,56]; 0,002	0,002	
	2	123	14	11.38	125	5	4.00	2,85 [1,06 ; 7,66]	3,08 [1,07 ; 8,84];	7,38 [0,8 ; 13,96]; 0,033	0,033	
Race	Other	7	1	14.29	8	0	0.00	3,38 [0,16 ; 71,67]	3,92 [0,14 ; 112,9];	13,19 [-17,72 ; 44,11]; 0,467	0,467	0,4843
	White	266	33	12.41	267	8	3.00	4,14 [1,95 ; 8,8]	4,59 [2,08 ; 10,13];	9,41 [4,95 ; 13,87]; 0	0	
	No	181	26	14.36	193	6	3.11	4,62 [1,95 ; 10,97]	5,23 [2,1 ; 13,03];	11,26 [5,59 ; 16,92]; 0	0	0,7378

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	8	8.70	82	2	2.44	3,57 [0,78 ; 16,31]	3,81 [0,79 ; 18,48];	6,26 [-0,4 ; 12,91]; 0,105	0,105	
Region	Eastern Europe	247	33	13.36	244	6	2.46	5,43 [2,32 ; 12,73]	6,12 [2,51 ; 14,88];	10,9 [6,23 ; 15,57]; 0	0	0,0687
	USA and Western Europe	26	1	3.85	31	2	6.45	0,6 [0,06 ; 6,21]	0,58 [0,05 ; 6,78];	-2,61 [-13,98 ; 8,77]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Investigations | Lymphocyte count decreased

4.1.37 Investigations - White blood cell count decreased

Tabelle 37: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	4	2.67	146	9	6.16	0,43 [0,14 ; 1,37]	0,42 [0,13 ; 1,39];	-3,5 [-8,17 ; 1,18]; 0,165	0,165	0,2649
	>= 38 years	123	0	0.00	129	2	1.55	0,21 [0,01 ; 4,32]	0,21 [0,01 ; 4,34];	-1,52 [-4,13 ; 1,09]; 0,498	0,498	
Disease Severity at baseline (EDSS)	<=3.5	201	4	1.99	208	9	4.33	0,46 [0,14 ; 1,47]	0,45 [0,14 ; 1,48];	-2,34 [-5,71 ; 1,04]; 0,26	0,26	0,2268
	>3.5	72	0	0.00	67	2	2.99	0,19 [0,01 ; 3,81]	0,18 [0,01 ; 3,83];	-2,99 [-7,85 ; 1,86]; 0,234	0,234	
Gender	Female	167	1	0.60	180	7	3.89	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	Male	106	2	1.89	95	4	4.21	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of baseline Gd-enhancing lesions	>=1	117	2	1.71	116	7	6.03	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	155	2	1.29	157	4	2.55	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	0	0.00	92	5	5.43	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	3	7.14	58	3	5.17	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	1	0.81	125	3	2.40	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9999
	White	266	4	1.50	267	11	4.12	0,37 [0,12 ; 1,13]	0,36 [0,11 ; 1,13];	-2,62 [-5,41 ; 0,18]; 0,113	0,113	
	No	181	3	1.66	193	6	3.11	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	1	1.09	82	5	6.10	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Region	Eastern Europe	247	4	1.62	244	9	3.69	0,44 [0,14 ; 1,41]	0,43 [0,13 ; 1,41];	-2,07 [-4,91 ; 0,77]; 0,172	0,172	0,2763
	USA and Western Europe	26	0	0.00	31	2	6.45	0,24 [0,01 ; 4,73]	0,22 [0,01 ; 4,85];	-5,96 [-16,56 ; 4,64]; 0,497	0,497	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Investigations | White blood cell count decreased

4.1.38 General disorders and administration site conditions - Pyrexia

Tabelle 38: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	28	18.67	146	7	4.79	3,89 [1,76 ; 8,63]	4,56 [1,92 ; 10,8];	13,87 [6,74 ; 21,01]; 0	0	0,3508
	>= 38 years	123	13	10.57	129	6	4.65	2,27 [0,89 ; 5,79]	2,42 [0,89 ; 6,59];	5,92 [-0,62 ; 12,45]; 0,095	0,095	
Disease Severity at baseline (EDSS)	<=3.5	201	33	16.42	208	10	4.81	3,41 [1,73 ; 6,74]	3,89 [1,86 ; 8,13];	11,61 [5,72 ; 17,5]; 0	0	0,6397
	>3.5	72	8	11.11	67	3	4.48	2,48 [0,69 ; 8,97]	2,67 [0,68 ; 10,51];	6,63 [-2,15 ; 15,42]; 0,211	0,211	
Gender	Female	167	29	17.37	180	10	5.56	3,13 [1,57 ; 6,21]	3,57 [1,68 ; 7,59];	11,81 [5,16 ; 18,46]; 0,001	0,001	0,9044
	Male	106	12	11.32	95	3	3.16	3,58 [1,04 ; 12,32]	3,91 [1,07 ; 14,33];	8,16 [1,18 ; 15,14]; 0,032	0,032	
Number of baseline Gd-enhancing lesions	>=1	117	16	13.68	116	4	3.45	3,97 [1,37 ; 11,51]	4,44 [1,44 ; 13,71];	10,23 [3,17 ; 17,28]; 0,009	0,009	0,6278
	0	155	25	16.13	157	9	5.73	2,81 [1,36 ; 5,83]	3,16 [1,42 ; 7,02];	10,4 [3,56 ; 17,23]; 0,003	0,003	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	13	12.04	92	6	6.52	1,85 [0,73 ; 4,66]	1,96 [0,71 ; 5,39];	5,52 [-2,43 ; 13,46]; 0,23	0,23	0,3087
	>=3	42	7	16.67	58	3	5.17	3,22 [0,88 ; 11,74]	3,67 [0,89 ; 15,13];	11,49 [-1,14 ; 24,12]; 0,09	0,09	
	2	123	21	17.07	125	4	3.20	5,34 [1,89 ; 15,09]	6,23 [2,07 ; 18,73];	13,87 [6,54 ; 21,2]; 0	0	
Race	Other	7	1	14.29	8	1	12.50	1,14 [0,09 ; 15,08]	1,17 [0,06 ; 22,94];	1,79 [-32,81 ; 36,39]; 1	1	0,4595
	White	266	40	15.04	267	12	4.49	3,35 [1,8 ; 6,23]	3,76 [1,93 ; 7,35];	10,54 [5,58 ; 15,51]; 0	0	
	No	181	26	14.36	193	10	5.18	2,77 [1,38 ; 5,59]	3,07 [1,44 ; 6,56];	9,18 [3,19 ; 15,17]; 0,003	0,003	0,4887

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	15	16.30	82	3	3.66	4,46 [1,34 ; 14,85]	5,13 [1,43 ; 18,43];	12,65 [4,07 ; 21,22]; 0,006	0,006	
Region	Eastern Europe	247	38	15.38	244	10	4.10	3,75 [1,91 ; 7,36]	4,25 [2,07 ; 8,75];	11,29 [6,14 ; 16,43]; 0	0	0,1879
	USA and Western Europe	26	3	11.54	31	3	9.68	1,19 [0,26 ; 5,41]	1,22 [0,22 ; 6,62];	1,86 [-14,24 ; 17,96]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - General disorders and administration site conditions | Pyrexia

4.1.39 Psychiatric disorders - Insomnia

Tabelle 39: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	9	6.00	146	3	2.05	2,92 [0,81 ; 10,57]	3,04 [0,81 ; 11,47];	3,95 [-0,5 ; 8,39]; 0,138	0,138	0,1017
	>= 38 years	123	3	2.44	129	5	3.88	0,63 [0,15 ; 2,58]	0,62 [0,14 ; 2,65];	-1,44 [-5,74 ; 2,87]; 0,723	0,723	
Disease Severity at baseline (EDSS)	<=3.5	201	10	4.98	208	6	2.88	1,72 [0,64 ; 4,66]	1,76 [0,63 ; 4,94];	2,09 [-1,68 ; 5,86]; 0,316	0,316	0,5761
	>3.5	72	2	2.78	67	2	2.99	0,93 [0,13 ; 6,42]	0,93 [0,13 ; 6,79];	-0,21 [-5,78 ; 5,36]; 1	1	
Gender	Female	167	9	5.39	180	4	2.22	2,43 [0,76 ; 7,73]	2,51 [0,76 ; 8,3];	3,17 [-0,88 ; 7,21]; 0,159	0,159	0,1727
	Male	106	3	2.83	95	4	4.21	0,67 [0,15 ; 2,93]	0,66 [0,14 ; 3,04];	-1,38 [-6,51 ; 3,75]; 0,709	0,709	
Number of baseline Gd-enhancing lesions	>=1	117	8	6.84	116	3	2.59	2,64 [0,72 ; 9,72]	2,76 [0,71 ; 10,69];	4,25 [-1,16 ; 9,66]; 0,215	0,215	0,1942
	0	155	4	2.58	157	5	3.18	0,81 [0,22 ; 2,96]	0,81 [0,21 ; 3,06];	-0,6 [-4,32 ; 3,11]; 1	1	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	7	6.48	92	1	1.09	5,96 [0,75 ; 47,58]	6,31 [0,76 ; 52,25];	5,39 [0,29 ; 10,5]; 0,072	0,072	0,1355
	>=3	42	1	2.38	58	1	1.72	1,38 [0,09 ; 21,46]	1,39 [0,08 ; 22,88];	0,66 [-5,04 ; 6,36]; 1	1	
	2	123	4	3.25	125	6	4.80	0,68 [0,2 ; 2,34]	0,67 [0,18 ; 2,42];	-1,55 [-6,43 ; 3,34]; 0,749	0,749	
Race	Other	7	1	14.29	8	0	0.00	3,38 [0,16 ; 71,67]	3,92 [0,14 ; 112,9];	13,19 [-17,72 ; 44,11]; 0,467	0,467	0,2671
	White	266	11	4.14	267	8	3.00	1,38 [0,56 ; 3,38]	1,4 [0,55 ; 3,53];	1,14 [-2,01 ; 4,29]; 0,495	0,495	
	No	181	7	3.87	193	5	2.59	1,49 [0,48 ; 4,62]	1,51 [0,47 ; 4,85];	1,28 [-2,32 ; 4,87]; 0,565	0,565	0,9996

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	5	5.43	82	3	3.66	1,49 [0,37 ; 6,02]	1,51 [0,35 ; 6,54];	1,78 [-4,39 ; 7,94]; 0,724	0,724	
Region	Eastern Europe	247	9	3.64	244	8	3.28	1,11 [0,44 ; 2,83]	1,12 [0,42 ; 2,94];	0,37 [-2,87 ; 3,6]; 1	1	0,0441
	USA and Western Europe	26	3	11.54	31	0	0.00	8,3 [0,45 ; 153,61]	9,38 [0,46 ; 190,54];	11,4 [-1,98 ; 24,78]; 0,042	0,042	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Psychiatric disorders | Insomnia

4.1.40 Respiratory, thoracic and mediastinal disorders - Cough

Tabelle 40: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	6	4.00	146	5	3.42	1,17 [0,36 ; 3,74]	1,17 [0,35 ; 3,94];	0,58 [-3,73 ; 4,88]; 1	1	0,311
	>= 38 years	123	6	4.88	129	2	1.55	3,15 [0,65 ; 15,29]	3,26 [0,64 ; 16,45];	3,33 [-1,04 ; 7,69]; 0,164	0,164	
Disease Severity at baseline (EDSS)	<=3.5	201	10	4.98	208	7	3.37	1,48 [0,57 ; 3,81]	1,5 [0,56 ; 4,03];	1,61 [-2,27 ; 5,49]; 0,465	0,465	0,1775
	>3.5	72	2	2.78	67	0	0.00	4,66 [0,23 ; 95,28]	4,79 [0,23 ; 101,56];	2,69 [-1,95 ; 7,33]; 0,497	0,497	
Gender	Female	167	10	5.99	180	6	3.33	1,8 [0,67 ; 4,83]	1,85 [0,66 ; 5,2];	2,65 [-1,8 ; 7,11]; 0,308	0,308	0,9872
	Male	106	2	1.89	95	1	1.05	1,79 [0,17 ; 19,45]	1,81 [0,16 ; 20,26];	0,83 [-2,47 ; 4,14]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	117	7	5.98	116	3	2.59	2,31 [0,61 ; 8,73]	2,4 [0,6 ; 9,51];	3,4 [-1,78 ; 8,57]; 0,333	0,333	0,5165
	0	155	5	3.23	157	4	2.55	1,27 [0,35 ; 4,63]	1,27 [0,34 ; 4,84];	0,68 [-3,04 ; 4,39]; 0,749	0,749	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	9	8.33	92	3	3.26	2,56 [0,71 ; 9,16]	2,7 [0,71 ; 10,28];	5,07 [-1,28 ; 11,42]; 0,149	0,149	0,2904
	>=3	42	0	0.00	58	1	1.72	0,46 [0,02 ; 10,96]	0,45 [0,02 ; 11,34];	-1,38 [-6,52 ; 3,76]; 0,511	0,511	
	2	123	3	2.44	125	3	2.40	1,02 [0,21 ; 4,94]	1,02 [0,2 ; 5,14];	0,04 [-3,79 ; 3,86]; 1	1	
Race	Other	7	1	14.29	8	0	0.00	3,38 [0,16 ; 71,67]	3,92 [0,14 ; 112,9];	13,19 [-17,72 ; 44,11]; 0,467	0,467	0,2913
	White	266	11	4.14	267	7	2.62	1,58 [0,62 ; 4,01]	1,6 [0,61 ; 4,2];	1,51 [-1,55 ; 4,58]; 0,35	0,35	
	No	181	7	3.87	193	6	3.11	1,24 [0,43 ; 3,63]	1,25 [0,41 ; 3,8];	0,76 [-2,97 ; 4,48]; 0,781	0,781	0,2561

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	5	5.43	82	1	1.22	4,46 [0,53 ; 37,36]	4,66 [0,53 ; 40,7];	4,22 [-0,99 ; 9,42]; 0,215	0,215	
Region	Eastern Europe	247	8	3.24	244	6	2.46	1,32 [0,46 ; 3,74]	1,33 [0,45 ; 3,88];	0,78 [-2,16 ; 3,72]; 0,788	0,788	0,2372
	USA and Western Europe	26	4	15.38	31	1	3.23	4,77 [0,57 ; 40,07]	5,45 [0,57 ; 52,24];	12,16 [-3,04 ; 27,36]; 0,167	0,167	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Respiratory, thoracic and mediastinal disorders | Cough

4.1.41 General disorders and administration site conditions - Chills

Tabelle 41: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	14	9.33	146	1	0.68	13,63 [1,82 ; 102,3]	14,93 [1,94 ; 115,05];	8,65 [3,8 ; 13,49]; 0,001	0,001	0,4373
	>= 38 years	123	5	4.07	129	0	0.00	11,53 [0,64 ; 206,38]	12,02 [0,66 ; 219,74];	4,05 [0,27 ; 7,83]; 0,013	0,013	
Disease Severity at baseline (EDSS)	<=3.5	201	15	7.46	208	1	0.48	15,52 [2,07 ; 116,42]	16,69 [2,18 ; 127,6];	6,98 [3,23 ; 10,73]; 0	0	0,5212
	>3.5	72	4	5.56	67	0	0.00	8,38 [0,46 ; 152,82]	8,87 [0,47 ; 167,93];	5,43 [-0,45 ; 11,31]; 0,12	0,12	
Gender	Female	167	7	4.19	180	0	0.00	16,16 [0,93 ; 280,78]	16,87 [0,96 ; 297,7];	4,19 [0,97 ; 7,4]; 0,003	0,003	0,3245
	Male	106	12	11.32	95	1	1.05	10,75 [1,43 ; 81,16]	12 [1,53 ; 94,15];	10,27 [3,9 ; 16,64]; 0,003	0,003	
Number of baseline Gd-enhancing lesions	>=1	117	6	5.13	116	1	0.86	5,95 [0,73 ; 48,64]	6,22 [0,74 ; 52,47];	4,27 [-0,07 ; 8,6]; 0,119	0,119	0,1318
	0	155	13	8.39	157	0	0.00	27,35 [1,64 ; 456,03]	29,84 [1,76 ; 506,57];	8,34 [3,84 ; 12,84]; 0	0	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	6	5.56	92	0	0.00	11,09 [0,63 ; 194,28]	11,73 [0,65 ; 211,12];	5,43 [0,74 ; 10,11]; 0,032	0,032	0,4756
	>=3	42	4	9.52	58	0	0.00	12,35 [0,68 ; 223,35]	13,68 [0,72 ; 261,26];	9,62 [0,17 ; 19,06]; 0,029	0,029	
	2	123	9	7.32	125	1	0.80	9,15 [1,18 ; 71,11]	9,79 [1,22 ; 78,48];	6,52 [1,66 ; 11,38]; 0,01	0,01	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9997
	White	266	19	7.14	267	1	0.37	19,07 [2,57 ; 141,44]	20,46 [2,72 ; 153,99];	6,77 [3,59 ; 9,95]; 0	0	
	No	181	14	7.73	193	1	0.52	14,93 [1,98 ; 112,38]	16,1 [2,09 ; 123,7];	7,22 [3,2 ; 11,24]; 0	0	0,4801

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	5	5.43	82	0	0.00	9,82 [0,55 ; 174,87]	10,37 [0,56 ; 190,51];	5,31 [0,24 ; 10,39]; 0,031	0,031	
Region	Eastern Europe	247	17	6.88	244	1	0.41	16,79 [2,25 ; 125,21]	17,96 [2,37 ; 136,05];	6,47 [3,22 ; 9,73]; 0	0	0,6107
	USA and Western Europe	26	2	7.69	31	0	0.00	5,93 [0,3 ; 118,18]	6,43 [0,29 ; 140,14];	7,7 [-4,05 ; 19,44]; 0,197	0,197	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - General disorders and administration site conditions | Chills

4.1.42 Gastrointestinal disorders - Abdominal pain

Tabelle 42: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	10	6.67	146	8	5.48	1,22 [0,49 ; 3]	1,23 [0,47 ; 3,21];	1,19 [-4,25 ; 6,62]; 0,809	0,809	0,1782
	>= 38 years	123	5	4.07	129	1	0.78	5,24 [0,62 ; 44,25]	5,42 [0,62 ; 47,1];	3,29 [-0,51 ; 7,09]; 0,113	0,113	
Disease Severity at baseline (EDSS)	<=3.5	201	9	4.48	208	8	3.85	1,16 [0,46 ; 2,96]	1,17 [0,44 ; 3,1];	0,63 [-3,24 ; 4,51]; 0,808	0,808	0,1312
	>3.5	72	6	8.33	67	1	1.49	5,58 [0,69 ; 45,17]	6 [0,7 ; 51,22];	6,84 [-0,17 ; 13,85]; 0,117	0,117	
Gender	Female	167	10	5.99	180	7	3.89	1,54 [0,6 ; 3,95]	1,57 [0,59 ; 4,24];	2,1 [-2,48 ; 6,67]; 0,458	0,458	0,6969
	Male	106	5	4.72	95	2	2.11	2,24 [0,45 ; 11,28]	2,3 [0,44 ; 12,15];	2,61 [-2,35 ; 7,57]; 0,45	0,45	
Number of baseline Gd-enhancing lesions	>=1	117	7	5.98	116	2	1.72	3,47 [0,74 ; 16,35]	3,63 [0,74 ; 17,84];	4,26 [-0,65 ; 9,17]; 0,171	0,171	0,2242
	0	155	8	5.16	157	7	4.46	1,16 [0,43 ; 3,11]	1,17 [0,41 ; 3,3];	0,7 [-4,05 ; 5,45]; 0,798	0,798	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	4	3.70	92	4	4.35	0,85 [0,22 ; 3,31]	0,85 [0,21 ; 3,48];	-0,64 [-6,13 ; 4,84]; 1	1	0,1905
	>=3	42	5	11.90	58	1	1.72	6,9 [0,84 ; 56,95]	7,7 [0,87 ; 68,59];	10,18 [-0,17 ; 20,53]; 0,08	0,08	
	2	123	6	4.88	125	4	3.20	1,52 [0,44 ; 5,27]	1,55 [0,43 ; 5,64];	1,68 [-3,22 ; 6,58]; 0,538	0,538	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9999
	White	266	15	5.64	267	9	3.37	1,67 [0,75 ; 3,76]	1,71 [0,74 ; 3,99];	2,27 [-1,25 ; 5,79]; 0,218	0,218	
	No	181	8	4.42	193	7	3.63	1,22 [0,45 ; 3,29]	1,23 [0,44 ; 3,46];	0,79 [-3,2 ; 4,78]; 0,795	0,795	0,294

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	7	7.61	82	2	2.44	3,12 [0,67 ; 14,6]	3,29 [0,66 ; 16,33];	5,17 [-1,19 ; 11,53]; 0,175	0,175	
Region	Eastern Europe	247	15	6.07	244	8	3.28	1,85 [0,8 ; 4,29]	1,91 [0,79 ; 4,58];	2,79 [-0,93 ; 6,52]; 0,199	0,199	0,1734
	USA and Western Europe	26	0	0.00	31	1	3.23	0,4 [0,02 ; 9,31]	0,38 [0,01 ; 9,82];	-2,84 [-11,75 ; 6,08]; 0,497	0,497	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Gastrointestinal disorders | Abdominal pain

4.1.43 Gastrointestinal disorders - Diarrhoea

Tabelle 43: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	8	5.33	146	14	9.59	0,56 [0,24 ; 1,29]	0,53 [0,22 ; 1,31];	-4,26 [-10,23 ; 1,72]; 0,188	0,188	0,3512
	>= 38 years	123	11	8.94	129	12	9.30	0,96 [0,44 ; 2,1]	0,96 [0,41 ; 2,26];	-0,36 [-7,47 ; 6,75]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	201	12	5.97	208	18	8.65	0,69 [0,34 ; 1,4]	0,67 [0,31 ; 1,43];	-2,68 [-7,72 ; 2,35]; 0,345	0,345	0,8001
	>3.5	72	7	9.72	67	8	11.94	0,81 [0,31 ; 2,12]	0,79 [0,27 ; 2,32];	-2,22 [-12,57 ; 8,13]; 0,787	0,787	
Gender	Female	167	14	8.38	180	23	12.78	0,66 [0,35 ; 1,23]	0,62 [0,31 ; 1,26];	-4,39 [-10,83 ; 2,04]; 0,224	0,224	0,2745
	Male	106	5	4.72	95	3	3.16	1,49 [0,37 ; 6,08]	1,52 [0,35 ; 6,53];	1,56 [-3,79 ; 6,91]; 0,724	0,724	
Number of baseline Gd-enhancing lesions	>=1	117	7	5.98	116	13	11.21	0,53 [0,22 ; 1,29]	0,5 [0,19 ; 1,31];	-5,22 [-12,39 ; 1,95]; 0,169	0,169	0,338
	0	155	12	7.74	157	13	8.28	0,93 [0,44 ; 1,98]	0,93 [0,41 ; 2,11];	-0,54 [-6,56 ; 5,49]; 1	1	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	5	4.63	92	8	8.70	0,53 [0,18 ; 1,57]	0,51 [0,16 ; 1,62];	-4,07 [-11,06 ; 2,92]; 0,265	0,265	0,3554
	>=3	42	1	2.38	58	5	8.62	0,28 [0,03 ; 2,28]	0,26 [0,03 ; 2,3];	-6,24 [-14,81 ; 2,33]; 0,396	0,396	
	2	123	13	10.57	125	13	10.40	1,02 [0,49 ; 2,1]	1,02 [0,45 ; 2,29];	0,17 [-7,46 ; 7,8]; 1	1	
Race	Other	7	1	14.29	8	0	0.00	3,38 [0,16 ; 71,67]	3,92 [0,14 ; 112,9];	13,19 [-17,72 ; 44,11]; 0,467	0,467	0,1546
	White	266	18	6.77	267	26	9.74	0,69 [0,39 ; 1,24]	0,67 [0,36 ; 1,26];	-2,97 [-7,64 ; 1,69]; 0,27	0,27	
	No	181	14	7.73	193	18	9.33	0,83 [0,43 ; 1,62]	0,82 [0,39 ; 1,69];	-1,59 [-7,25 ; 4,06]; 0,712	0,712	0,5388

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	5	5.43	82	8	9.76	0,56 [0,19 ; 1,64]	0,53 [0,17 ; 1,7];	-4,32 [-12,24 ; 3,6]; 0,388	0,388	
Region	Eastern Europe	247	17	6.88	244	23	9.43	0,73 [0,4 ; 1,33]	0,71 [0,37 ; 1,37];	-2,54 [-7,38 ; 2,29]; 0,326	0,326	0,9285
	USA and Western Europe	26	2	7.69	31	3	9.68	0,79 [0,14 ; 4,4]	0,78 [0,12 ; 5,05];	-1,99 [-16,59 ; 12,62]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Gastrointestinal disorders | Diarrhoea

4.1.44 Blood and lymphatic system disorders - Leukopenia

Tabelle 44: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	3	2.00	146	10	6.85	0,29 [0,08 ; 1,04]	0,28 [0,07 ; 1,03];	-4,85 [-9,52 ; -0,18]; 0,049	0,049	0,4255
	>= 38 years	123	2	1.63	129	3	2.33	0,7 [0,12 ; 4,11]	0,69 [0,11 ; 4,23];	-0,7 [-4,13 ; 2,73]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	201	3	1.49	208	12	5.77	0,26 [0,07 ; 0,9]	0,25 [0,07 ; 0,89];	-4,28 [-7,86 ; -0,69]; 0,032	0,032	0,1314
	>3.5	72	2	2.78	67	1	1.49	1,86 [0,17 ; 20,05]	1,89 [0,17 ; 21,29];	1,29 [-3,49 ; 6,06]; 1	1	
Gender	Female	167	2	1.20	180	9	5.00	0,24 [0,05 ; 1,09]	0,23 [0,05 ; 1,08];	-3,8 [-7,39 ; -0,22]; 0,063	0,063	0,3331
	Male	106	3	2.83	95	4	4.21	0,67 [0,15 ; 2,93]	0,66 [0,14 ; 3,04];	-1,38 [-6,51 ; 3,75]; 0,709	0,709	
Number of baseline Gd-enhancing lesions	>=1	117	1	0.85	116	5	4.31	0,2 [0,02 ; 1,67]	0,19 [0,02 ; 1,66];	-3,46 [-7,51 ; 0,6]; 0,119	0,119	0,3684
	0	155	4	2.58	157	7	4.46	0,58 [0,17 ; 1,94]	0,57 [0,16 ; 1,98];	-1,88 [-5,96 ; 2,2]; 0,542	0,542	
	NA	1	0	0.00	2	1	50.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	1	0.93	92	3	3.26	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	1	2.38	58	6	10.34	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	3	2.44	125	4	3.20	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	0	0.00	8	1	12.50	0,38 [0,02 ; 7,96]	0,33 [0,01 ; 9,57];	-10,42 [-39,98 ; 19,15]; 0,477	0,477	0,4239
	White	266	5	1.88	267	12	4.49	0,42 [0,15 ; 1,17]	0,41 [0,14 ; 1,17];	-2,61 [-5,59 ; 0,36]; 0,137	0,137	
	No	181	4	2.21	193	5	2.59	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	1	1.09	82	8	9.76	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Region	Eastern Europe	247	5	2.02	244	12	4.92	0,41 [0,15 ; 1,15]	0,4 [0,14 ; 1,15];	-2,89 [-6,13 ; 0,34]; 0,089	0,089	0,4495
	USA and Western Europe	26	0	0.00	31	1	3.23	0,4 [0,02 ; 9,31]	0,38 [0,01 ; 9,82];	-2,84 [-11,75 ; 6,08]; 0,497	0,497	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Blood and lymphatic system disorders | Leukopenia

4.1.45 Blood and lymphatic system disorders - Neutropenia

Tabelle 45: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	9	6.00	146	9	6.16	0,97 [0,4 ; 2,38]	0,97 [0,37 ; 2,52];	-0,16 [-5,61 ; 5,28]; 1	1	0,7457
	>= 38 years	123	2	1.63	129	3	2.33	0,7 [0,12 ; 4,11]	0,69 [0,11 ; 4,23];	-0,7 [-4,13 ; 2,73]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	201	10	4.98	208	11	5.29	0,94 [0,41 ; 2,17]	0,94 [0,39 ; 2,26];	-0,31 [-4,59 ; 3,96]; 1	1	0,9954
	>3.5	72	1	1.39	67	1	1.49	0,93 [0,06 ; 14,58]	0,93 [0,06 ; 15,16];	-0,1 [-4,07 ; 3,86]; 1	1	
Gender	Female	167	7	4.19	180	9	5.00	0,84 [0,32 ; 2,2]	0,83 [0,3 ; 2,28];	-0,81 [-5,21 ; 3,59]; 0,801	0,801	0,6911
	Male	106	4	3.77	95	3	3.16	1,19 [0,27 ; 5,2]	1,2 [0,26 ; 5,52];	0,62 [-4,44 ; 5,67]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	117	3	2.56	116	6	5.17	0,5 [0,13 ; 1,94]	0,48 [0,12 ; 1,98];	-2,61 [-7,55 ; 2,34]; 0,333	0,333	0,2413
	0	155	8	5.16	157	6	3.82	1,35 [0,48 ; 3,8]	1,37 [0,46 ; 4,04];	1,34 [-3,26 ; 5,94]; 0,597	0,597	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	5	4.63	92	3	3.26	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	2	4.76	58	5	8.62	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	4	3.25	125	4	3.20	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	0	0.00	8	1	12.50	0,38 [0,02 ; 7,96]	0,33 [0,01 ; 9,57];	-10,42 [-39,98 ; 19,15]; 0,477	0,477	0,2572
	White	266	11	4.14	267	11	4.12	1 [0,44 ; 2,28]	1 [0,43 ; 2,36];	0,02 [-3,36 ; 3,39]; 1	1	
	No	181	5	2.76	193	7	3.63	0,76 [0,25 ; 2,36]	0,75 [0,24 ; 2,42];	-0,86 [-4,42 ; 2,69]; 0,772	0,772	0,6818

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	6	6.52	82	5	6.10	1,07 [0,34 ; 3,37]	1,07 [0,32 ; 3,66];	0,42 [-6,81 ; 7,65]; 1	1	
Region	Eastern Europe	247	10	4.05	244	11	4.51	0,9 [0,39 ; 2,08]	0,89 [0,37 ; 2,14];	-0,46 [-4,04 ; 3,12]; 0,827	0,827	0,8452
	USA and Western Europe	26	1	3.85	31	1	3.23	1,19 [0,08 ; 18,14]	1,2 [0,07 ; 20,18];	0,62 [-9,04 ; 10,28]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Blood and lymphatic system disorders | Neutropenia

4.1.46 Respiratory, thoracic and mediastinal disorders - Oropharyngeal pain

Tabelle 46: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	9	6.00	146	5	3.42	1,75 [0,6 ; 5,1]	1,8 [0,59 ; 5,5];	2,58 [-2,24 ; 7,39]; 0,413	0,413	0,3835
	>= 38 years	123	4	3.25	129	5	3.88	0,84 [0,23 ; 3,05]	0,83 [0,22 ; 3,18];	-0,62 [-5,2 ; 3,95]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	201	10	4.98	208	9	4.33	1,15 [0,48 ; 2,77]	1,16 [0,46 ; 2,91];	0,65 [-3,44 ; 4,73]; 0,817	0,817	0,4507
	>3.5	72	3	4.17	67	1	1.49	2,79 [0,3 ; 26,19]	2,87 [0,29 ; 28,29];	2,67 [-2,78 ; 8,13]; 0,621	0,621	
Gender	Female	167	9	5.39	180	10	5.56	0,97 [0,4 ; 2,33]	0,97 [0,38 ; 2,45];	-0,17 [-4,95 ; 4,62]; 1	1	0,0313
	Male	106	4	3.77	95	0	0.00	8,07 [0,44 ; 148,04]	8,39 [0,45 ; 157,83];	3,68 [-0,38 ; 7,75]; 0,123	0,123	
Number of baseline Gd-enhancing lesions	>=1	117	6	5.13	116	2	1.72	2,97 [0,61 ; 14,43]	3,08 [0,61 ; 15,59];	3,4 [-1,24 ; 8,05]; 0,281	0,281	0,1848
	0	155	7	4.52	157	8	5.10	0,89 [0,33 ; 2,38]	0,88 [0,31 ; 2,49];	-0,58 [-5,32 ; 4,17]; 1	1	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	4	3.70	92	2	2.17	1,7 [0,32 ; 9,09]	1,73 [0,31 ; 9,67];	1,53 [-3,11 ; 6,17]; 0,689	0,689	0,9501
	>=3	42	3	7.14	58	3	5.17	1,38 [0,29 ; 6,51]	1,41 [0,27 ; 7,36];	1,97 [-7,68 ; 11,62]; 0,694	0,694	
	2	123	6	4.88	125	5	4.00	1,22 [0,38 ; 3,89]	1,23 [0,37 ; 4,14];	0,88 [-4,25 ; 6,01]; 0,768	0,768	
Race	Other	7	0	0.00	8	2	25.00	0,22 [0,01 ; 4,02]	0,17 [0,01 ; 4,31];	-21,53 [-55,26 ; 12,2]; 0,467	0,467	0,058
	White	266	13	4.89	267	8	3.00	1,63 [0,69 ; 3,87]	1,66 [0,68 ; 4,08];	1,89 [-1,41 ; 5,19]; 0,276	0,276	
	No	181	6	3.31	193	7	3.63	0,91 [0,31 ; 2,67]	0,91 [0,3 ; 2,76];	-0,31 [-4,02 ; 3,4]; 1	1	0,3303

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	7	7.61	82	3	3.66	2,08 [0,56 ; 7,78]	2,17 [0,54 ; 8,68];	3,95 [-2,82 ; 10,72]; 0,338	0,338	
Region	Eastern Europe	247	12	4.86	244	8	3.28	1,48 [0,62 ; 3,56]	1,51 [0,6 ; 3,75];	1,58 [-1,91 ; 5,07]; 0,495	0,495	0,4637
	USA and Western Europe	26	1	3.85	31	2	6.45	0,6 [0,06 ; 6,21]	0,58 [0,05 ; 6,78];	-2,61 [-13,98 ; 8,77]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Respiratory, thoracic and mediastinal disorders | Oropharyngeal pain

4.1.47 Infections and infestations - Respiratory tract infection

Tabelle 47: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	8	5.33	146	7	4.79	1,11 [0,41 ; 2,99]	1,12 [0,4 ; 3,17];	0,54 [-4,46 ; 5,53]; 1	1	0,804
	>= 38 years	123	4	3.25	129	3	2.33	1,4 [0,32 ; 6,12]	1,41 [0,31 ; 6,44];	0,93 [-3,15 ; 5]; 0,717	0,717	
Disease Severity at baseline (EDSS)	<=3.5	201	9	4.48	208	10	4.81	0,93 [0,39 ; 2,24]	0,93 [0,37 ; 2,33];	-0,33 [-4,41 ; 3,75]; 1	1	0,0513
	>3.5	72	3	4.17	67	0	0.00	6,52 [0,34 ; 123,92]	6,8 [0,34 ; 134,12];	4,06 [-1,25 ; 9,36]; 0,121	0,121	
Gender	Female	167	8	4.79	180	7	3.89	1,23 [0,46 ; 3,32]	1,24 [0,44 ; 3,51];	0,9 [-3,4 ; 5,2]; 0,794	0,794	0,9717
	Male	106	4	3.77	95	3	3.16	1,19 [0,27 ; 5,2]	1,2 [0,26 ; 5,52];	0,62 [-4,44 ; 5,67]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	117	5	4.27	116	5	4.31	0,99 [0,29 ; 3,33]	0,99 [0,28 ; 3,52];	-0,04 [-5,24 ; 5,17]; 1	1	0,6719
	0	155	7	4.52	157	5	3.18	1,42 [0,46 ; 4,37]	1,44 [0,45 ; 4,63];	1,33 [-2,94 ; 5,6]; 0,572	0,572	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	1	0.93	92	0	0.00	2,56 [0,11 ; 62,08]	2,58 [0,1 ; 64,13];	0,84 [-1,81 ; 3,48]; 0,502	0,502	0,4997
	>=3	42	5	11.90	58	4	6.90	1,73 [0,49 ; 6,05]	1,82 [0,46 ; 7,25];	5,01 [-6,76 ; 16,77]; 0,486	0,486	
	2	123	6	4.88	125	6	4.80	1,02 [0,34 ; 3,06]	1,02 [0,32 ; 3,24];	0,08 [-5,26 ; 5,42]; 1	1	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	1
	White	266	12	4.51	267	10	3.75	1,2 [0,53 ; 2,74]	1,21 [0,52 ; 2,86];	0,77 [-2,61 ; 4,14]; 0,671	0,671	
	No	181	3	1.66	193	5	2.59	0,64 [0,16 ; 2,64]	0,63 [0,15 ; 2,69];	-0,93 [-3,85 ; 1,98]; 0,725	0,725	0,2942

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	9	9.78	82	5	6.10	1,6 [0,56 ; 4,59]	1,67 [0,54 ; 5,2];	3,69 [-4,29 ; 11,66]; 0,416	0,416	
Region	Eastern Europe	247	12	4.86	244	9	3.69	1,32 [0,57 ; 3,07]	1,33 [0,55 ; 3,22];	1,17 [-2,41 ; 4,74]; 0,657	0,657	0,2266
	USA and Western Europe	26	0	0.00	31	1	3.23	0,4 [0,02 ; 9,31]	0,38 [0,01 ; 9,82];	-2,84 [-11,75 ; 6,08]; 0,497	0,497	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Respiratory tract infection

4.1.48 Vascular disorders - Hypertension

Tabelle 48: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	7	4.67	146	9	6.16	0,76 [0,29 ; 1,98]	0,75 [0,27 ; 2,06];	-1,5 [-6,66 ; 3,66]; 0,615	0,615	0,2379
	>= 38 years	123	4	3.25	129	13	10.08	0,32 [0,11 ; 0,96]	0,3 [0,1 ; 0,95];	-6,83 [-12,89 ; -0,76]; 0,043	0,043	
Disease Severity at baseline (EDSS)	<=3.5	201	8	3.98	208	17	8.17	0,49 [0,21 ; 1,1]	0,47 [0,2 ; 1,1];	-4,19 [-8,79 ; 0,41]; 0,098	0,098	0,8668
	>3.5	72	3	4.17	67	5	7.46	0,56 [0,14 ; 2,25]	0,54 [0,12 ; 2,35];	-3,3 [-11,1 ; 4,51]; 0,482	0,482	
Gender	Female	167	8	4.79	180	14	7.78	0,62 [0,27 ; 1,43]	0,6 [0,24 ; 1,46];	-2,99 [-8,07 ; 2,09]; 0,278	0,278	0,4381
	Male	106	3	2.83	95	8	8.42	0,34 [0,09 ; 1,23]	0,32 [0,08 ; 1,23];	-5,59 [-12,01 ; 0,82]; 0,12	0,12	
Number of baseline Gd-enhancing lesions	>=1	117	5	4.27	116	11	9.48	0,45 [0,16 ; 1,26]	0,43 [0,14 ; 1,27];	-5,21 [-11,68 ; 1,26]; 0,129	0,129	0,766
	0	155	6	3.87	157	11	7.01	0,55 [0,21 ; 1,46]	0,53 [0,19 ; 1,48];	-3,14 [-8,15 ; 1,88]; 0,319	0,319	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	4	3.70	92	8	8.70	0,43 [0,13 ; 1,37]	0,4 [0,12 ; 1,39];	-4,99 [-11,76 ; 1,78]; 0,231	0,231	0,7576
	>=3	42	2	4.76	58	3	5.17	0,92 [0,16 ; 5,27]	0,92 [0,15 ; 5,74];	-0,41 [-9,01 ; 8,19]; 1	1	
	2	123	5	4.07	125	11	8.80	0,46 [0,17 ; 1,29]	0,44 [0,15 ; 1,3];	-4,73 [-10,8 ; 1,33]; 0,195	0,195	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9999
	White	266	11	4.14	267	22	8.24	0,5 [0,25 ; 1,01]	0,48 [0,23 ; 1,01];	-4,1 [-8,18 ; -0,03]; 0,071	0,071	
	No	181	5	2.76	193	16	8.29	0,33 [0,12 ; 0,89]	0,31 [0,11 ; 0,88];	-5,53 [-10,09 ; -0,96]; 0,024	0,024	0,189

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	6	6.52	82	6	7.32	0,89 [0,3 ; 2,66]	0,88 [0,27 ; 2,86];	-0,8 [-8,36 ; 6,77]; 1	1	
Region	Eastern Europe	247	11	4.45	244	21	8.61	0,52 [0,25 ; 1,05]	0,49 [0,23 ; 1,05];	-4,15 [-8,51 ; 0,21]; 0,069	0,069	0,4045
	USA and Western Europe	26	0	0.00	31	1	3.23	0,4 [0,02 ; 9,31]	0,38 [0,01 ; 9,82];	-2,84 [-11,75 ; 6,08]; 0,497	0,497	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Vascular disorders | Hypertension

4.1.49 General disorders and administration site conditions - Asthenia

Tabelle 49: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	10	6.67	146	4	2.74	2,43 [0,78 ; 7,59]	2,54 [0,78 ; 8,28];	3,93 [-0,86 ; 8,72]; 0,17	0,17	0,0022
	>= 38 years	123	0	0.00	129	5	3.88	0,1 [0,01 ; 1,71]	0,09 [0,01 ; 1,68];	-3,83 [-7,46 ; -0,19]; 0,03	0,03	
Disease Severity at baseline (EDSS)	<=3.5	201	8	3.98	208	8	3.85	1,03 [0,4 ; 2,7]	1,04 [0,38 ; 2,82];	0,13 [-3,63 ; 3,89]; 1	1	0,6482
	>3.5	72	2	2.78	67	1	1.49	1,86 [0,17 ; 20,05]	1,89 [0,17 ; 21,29];	1,29 [-3,49 ; 6,06]; 1	1	
Gender	Female	167	5	2.99	180	4	2.22	1,35 [0,37 ; 4,93]	1,36 [0,36 ; 5,14];	0,77 [-2,59 ; 4,14]; 0,743	0,743	0,6535
	Male	106	5	4.72	95	5	5.26	0,9 [0,27 ; 3]	0,89 [0,25 ; 3,18];	-0,55 [-6,58 ; 5,49]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	117	5	4.27	116	5	4.31	0,99 [0,29 ; 3,33]	0,99 [0,28 ; 3,52];	-0,04 [-5,24 ; 5,17]; 1	1	0,7882
	0	155	5	3.23	157	4	2.55	1,27 [0,35 ; 4,63]	1,27 [0,34 ; 4,84];	0,68 [-3,04 ; 4,39]; 0,749	0,749	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	3	2.78	92	1	1.09	2,56 [0,27 ; 24,15]	2,6 [0,27 ; 25,43];	1,69 [-2,06 ; 5,45]; 0,626	0,626	0,2224
	>=3	42	0	0.00	58	2	3.45	0,27 [0,01 ; 5,57]	0,27 [0,01 ; 5,68];	-3,07 [-9,13 ; 2,98]; 0,508	0,508	
	2	123	7	5.69	125	6	4.80	1,19 [0,41 ; 3,43]	1,2 [0,39 ; 3,67];	0,89 [-4,66 ; 6,44]; 0,784	0,784	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	1
	White	266	10	3.76	267	9	3.37	1,12 [0,46 ; 2,7]	1,12 [0,45 ; 2,8];	0,39 [-2,76 ; 3,54]; 0,82	0,82	
	No	181	6	3.31	193	6	3.11	1,07 [0,35 ; 3,25]	1,07 [0,34 ; 3,38];	0,21 [-3,37 ; 3,78]; 1	1	0,9073

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	4	4.35	82	3	3.66	1,19 [0,27 ; 5,15]	1,2 [0,26 ; 5,51];	0,69 [-5,13 ; 6,51]; 1	1	
Region	Eastern Europe	247	10	4.05	244	9	3.69	1,1 [0,45 ; 2,65]	1,1 [0,44 ; 2,76];	0,36 [-3,05 ; 3,77]; 1	1	1
	USA and Western Europe	26	0	0.00	31	0	0.00	1,19 [0,02 ; 57,76]	1,19 [0,02 ; 61,97];	0,29 [-6,37 ; 6,95]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - General disorders and administration site conditions | Asthenia

4.1.50 Blood and lymphatic system disorders - Lymphopenia

Tabelle 50: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	18	12.00	146	1	0.68	17,52 [2,37 ; 129,55]	19,77 [2,6 ; 150,16];	11,32 [5,95 ; 16,68]; 0	0	0,1191
	>= 38 years	123	9	7.32	129	3	2.33	3,15 [0,87 ; 11,35]	3,32 [0,88 ; 12,55];	4,99 [-0,29 ; 10,28]; 0,079	0,079	
Disease Severity at baseline (EDSS)	<=3.5	201	23	11.44	208	1	0.48	23,8 [3,24 ; 174,59]	26,75 [3,58 ; 200,05];	10,96 [6,46 ; 15,46]; 0	0	0,0097
	>3.5	72	4	5.56	67	3	4.48	1,24 [0,29 ; 5,34]	1,25 [0,27 ; 5,83];	1,08 [-6,17 ; 8,32]; 1	1	
Gender	Female	167	14	8.38	180	3	1.67	5,03 [1,47 ; 17,19]	5,4 [1,52 ; 19,14];	6,72 [2,12 ; 11,32]; 0,005	0,005	0,4482
	Male	106	13	12.26	95	1	1.05	11,65 [1,55 ; 87,39]	13,14 [1,68 ; 102,48];	11,21 [4,64 ; 17,78]; 0,002	0,002	
Number of baseline Gd-enhancing lesions	>=1	117	14	11.97	116	1	0.86	13,88 [1,86 ; 103,85]	15,63 [2,02 ; 120,95];	11,1 [4,99 ; 17,22]; 0,001	0,001	0,2992
	0	155	13	8.39	157	3	1.91	4,39 [1,28 ; 15,1]	4,7 [1,31 ; 16,83];	6,48 [1,62 ; 11,34]; 0,01	0,01	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	7	6.48	92	0	0.00	12,8 [0,74 ; 221,1]	13,67 [0,77 ; 242,68];	6,34 [1,36 ; 11,32]; 0,008	0,008	0,3831
	>=3	42	6	14.29	58	1	1.72	8,29 [1,04 ; 66,28]	9,5 [1,1 ; 82,19];	12,56 [1,46 ; 23,66]; 0,039	0,039	
	2	123	14	11.38	125	3	2.40	4,74 [1,4 ; 16,09]	5,22 [1,46 ; 18,66];	8,98 [2,76 ; 15,2]; 0,005	0,005	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9998
	White	266	27	10.15	267	4	1.50	6,78 [2,4 ; 19,1]	7,43 [2,56 ; 21,54];	8,65 [4,74 ; 12,56]; 0	0	
	No	181	14	7.73	193	2	1.04	7,46 [1,72 ; 32,39]	8,01 [1,79 ; 35,74];	6,7 [2,55 ; 10,84]; 0,001	0,001	0,8573

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	13	14.13	82	2	2.44	5,79 [1,35 ; 24,91]	6,58 [1,44 ; 30,12];	11,69 [3,83 ; 19,55]; 0,006	0,006	
Region	Eastern Europe	247	27	10.93	244	4	1.64	6,67 [2,37 ; 18,77]	7,36 [2,54 ; 21,38];	9,29 [5,09 ; 13,5]; 0	0	0,9997
	USA and Western Europe	26	0	0.00	31	0	0.00	1,19 [0,02 ; 57,76]	1,19 [0,02 ; 61,97];	0,29 [-6,37 ; 6,95]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Blood and lymphatic system disorders | Lymphopenia

4.1.51 Infections and infestations - Respiratory tract infection viral

Tabelle 51: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	17	11.33	146	6	4.11	2,76 [1,12 ; 6,8]	2,98 [1,14 ; 7,79];	7,22 [1,22 ; 13,23]; 0,028	0,028	0,5514
	>= 38 years	123	3	2.44	129	2	1.55	1,57 [0,27 ; 9,25]	1,59 [0,26 ; 9,67];	0,89 [-2,57 ; 4,35]; 0,678	0,678	
Disease Severity at baseline (EDSS)	<=3.5	201	16	7.96	208	8	3.85	2,07 [0,91 ; 4,73]	2,16 [0,9 ; 5,17];	4,11 [-0,45 ; 8,68]; 0,093	0,093	0,1004
	>3.5	72	4	5.56	67	0	0.00	8,38 [0,46 ; 152,82]	8,87 [0,47 ; 167,93];	5,43 [-0,45 ; 11,31]; 0,12	0,12	
Gender	Female	167	10	5.99	180	3	1.67	3,59 [1,01 ; 12,83]	3,76 [1,02 ; 13,9];	4,32 [0,27 ; 8,38]; 0,046	0,046	0,4224
	Male	106	10	9.43	95	5	5.26	1,79 [0,64 ; 5,06]	1,88 [0,62 ; 5,7];	4,17 [-2,98 ; 11,32]; 0,295	0,295	
Number of baseline Gd-enhancing lesions	>=1	117	7	5.98	116	3	2.59	2,31 [0,61 ; 8,73]	2,4 [0,6 ; 9,51];	3,4 [-1,78 ; 8,57]; 0,333	0,333	0,8664
	0	155	13	8.39	157	5	3.18	2,63 [0,96 ; 7,21]	2,78 [0,97 ; 8];	5,2 [0,05 ; 10,36]; 0,055	0,055	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	8	7.41	92	1	1.09	6,81 [0,87 ; 53,48]	7,28 [0,89 ; 59,34];	6,32 [0,95 ; 11,69]; 0,04	0,04	0,3197
	>=3	42	5	11.90	58	2	3.45	3,45 [0,7 ; 16,95]	3,78 [0,7 ; 20,54];	8,46 [-2,41 ; 19,32]; 0,127	0,127	
	2	123	7	5.69	125	5	4.00	1,42 [0,46 ; 4,36]	1,45 [0,45 ; 4,69];	1,69 [-3,65 ; 7,04]; 0,569	0,569	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9999
	White	266	20	7.52	267	8	3.00	2,51 [1,13 ; 5,6]	2,63 [1,14 ; 6,09];	4,52 [0,75 ; 8,29]; 0,02	0,02	
	No	181	7	3.87	193	6	3.11	1,24 [0,43 ; 3,63]	1,25 [0,41 ; 3,8];	0,76 [-2,97 ; 4,48]; 0,781	0,781	0,0674

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	13	14.13	82	2	2.44	5,79 [1,35 ; 24,91]	6,58 [1,44 ; 30,12];	11,69 [3,83 ; 19,55]; 0,006	0,006	
Region	Eastern Europe	247	20	8.10	244	8	3.28	2,47 [1,11 ; 5,5]	2,6 [1,12 ; 6,02];	4,82 [0,75 ; 8,89]; 0,031	0,031	0,9999
	USA and Western Europe	26	0	0.00	31	0	0.00	1,19 [0,02 ; 57,76]	1,19 [0,02 ; 61,97];	0,29 [-6,37 ; 6,95]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Respiratory tract infection viral

4.1.52 General disorders and administration site conditions - Hyperthermia

Tabelle 52: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	7	4.67	146	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>= 38 years	123	6	4.88	129	2	1.55	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	201	8	3.98	208	1	0.48	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>3.5	72	5	6.94	67	1	1.49	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Gender	Female	167	9	5.39	180	2	1.11	4,85 [1,06 ; 22,12]	5,07 [1,08 ; 23,82];	4,28 [0,53 ; 8,03]; 0,03	0,03	0,2833
	Male	106	4	3.77	95	0	0.00	8,07 [0,44 ; 148,04]	8,39 [0,45 ; 157,83];	3,68 [-0,38 ; 7,75]; 0,123	0,123	
Number of baseline Gd-enhancing lesions	>=1	117	6	5.13	116	1	0.86	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	155	7	4.52	157	1	0.64	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	5	4.63	92	2	2.17	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	6	14.29	58	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	2	1.63	125	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9995
	White	266	13	4.89	267	2	0.75	6,52 [1,49 ; 28,63]	6,81 [1,52 ; 30,47];	4,14 [1,35 ; 6,93]; 0,004	0,004	
	No	181	6	3.31	193	2	1.04	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	7	7.61	82	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Region	Eastern Europe	247	13	5.26	244	2	0.82	6,42 [1,46 ; 28,16]	6,72 [1,5 ; 30,11];	4,44 [1,44 ; 7,45]; 0,007	0,007	0,9999
	USA and Western Europe	26	0	0.00	31	0	0.00	1,19 [0,02 ; 57,76]	1,19 [0,02 ; 61,97];	0,29 [-6,37 ; 6,95]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - General disorders and administration site conditions | Hyperthermia

4.1.53 General disorders and administration site conditions - Influenza like illness

Tabelle 53: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	8	5.33	146	1	0.68	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>= 38 years	123	3	2.44	129	3	2.33	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	201	9	4.48	208	2	0.96	4,66 [1,02 ; 21,29]	4,83 [1,03 ; 22,63];	3,52 [0,36 ; 6,67]; 0,033	0,033	0,1972
	>3.5	72	2	2.78	67	2	2.99	0,93 [0,13 ; 6,42]	0,93 [0,13 ; 6,79];	-0,21 [-5,78 ; 5,36]; 1	1	
Gender	Female	167	7	4.19	180	4	2.22	1,89 [0,56 ; 6,33]	1,92 [0,55 ; 6,7];	1,97 [-1,76 ; 5,69]; 0,366	0,366	0,1064
	Male	106	4	3.77	95	0	0.00	8,07 [0,44 ; 148,04]	8,39 [0,45 ; 157,83];	3,68 [-0,38 ; 7,75]; 0,123	0,123	
Number of baseline Gd-enhancing lesions	>=1	117	3	2.56	116	2	1.72	1,49 [0,25 ; 8,74]	1,5 [0,25 ; 9,15];	0,84 [-2,88 ; 4,56]; 1	1	0,3972
	0	155	8	5.16	157	2	1.27	4,05 [0,87 ; 18,78]	4,22 [0,88 ; 20,19];	3,89 [-0,01 ; 7,79]; 0,06	0,06	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	5	4.63	92	2	2.17	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	2	4.76	58	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	4	3.25	125	2	1.60	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9999
	White	266	11	4.14	267	4	1.50	2,76 [0,89 ; 8,56]	2,84 [0,89 ; 9,02];	2,64 [-0,16 ; 5,44]; 0,072	0,072	
	No	181	5	2.76	193	2	1.04	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	6	6.52	82	2	2.44	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Region	Eastern Europe	247	11	4.45	244	4	1.64	2,72 [0,88 ; 8,41]	2,8 [0,88 ; 8,91];	2,81 [-0,21 ; 5,84]; 0,113	0,113	0,9999
	USA and Western Europe	26	0	0.00	31	0	0.00	1,19 [0,02 ; 57,76]	1,19 [0,02 ; 61,97];	0,29 [-6,37 ; 6,95]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - General disorders and administration site conditions | Influenza like illness

4.1.54 Investigations - Alanine aminotransferase increased

Tabelle 54: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	6	4.00	146	10	6.85	0,58 [0,22 ; 1,57]	0,57 [0,2 ; 1,6];	-2,85 [-8,01 ; 2,31]; 0,313	0,313	0,4588
	>= 38 years	123	5	4.07	129	5	3.88	1,05 [0,31 ; 3,53]	1,05 [0,3 ; 3,72];	0,19 [-4,64 ; 5,01]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	201	9	4.48	208	9	4.33	1,03 [0,42 ; 2,55]	1,04 [0,4 ; 2,67];	0,15 [-3,83 ; 4,13]; 1	1	0,1687
	>3.5	72	2	2.78	67	6	8.96	0,31 [0,06 ; 1,48]	0,29 [0,06 ; 1,49];	-6,18 [-14 ; 1,64]; 0,154	0,154	
Gender	Female	167	5	2.99	180	7	3.89	0,77 [0,25 ; 2,38]	0,76 [0,24 ; 2,45];	-0,89 [-4,72 ; 2,93]; 0,772	0,772	0,8485
	Male	106	6	5.66	95	8	8.42	0,67 [0,24 ; 1,87]	0,65 [0,22 ; 1,95];	-2,76 [-9,87 ; 4,35]; 0,581	0,581	
Number of baseline Gd-enhancing lesions	>=1	117	5	4.27	116	8	6.90	0,62 [0,21 ; 1,84]	0,6 [0,19 ; 1,9];	-2,62 [-8,51 ; 3,27]; 0,409	0,409	0,6596
	0	155	6	3.87	157	7	4.46	0,87 [0,3 ; 2,53]	0,86 [0,28 ; 2,63];	-0,59 [-5,02 ; 3,84]; 1	1	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	4	3.70	92	2	2.17	1,7 [0,32 ; 9,09]	1,73 [0,31 ; 9,67];	1,53 [-3,11 ; 6,17]; 0,689	0,689	0,4909
	>=3	42	2	4.76	58	6	10.34	0,46 [0,1 ; 2,17]	0,43 [0,08 ; 2,26];	-5,58 [-15,73 ; 4,56]; 0,462	0,462	
	2	123	5	4.07	125	7	5.60	0,73 [0,24 ; 2,23]	0,71 [0,22 ; 2,31];	-1,53 [-6,87 ; 3,8]; 0,769	0,769	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	1
	White	266	11	4.14	267	15	5.62	0,74 [0,34 ; 1,57]	0,72 [0,33 ; 1,61];	-1,48 [-5,14 ; 2,17]; 0,547	0,547	
	No	181	7	3.87	193	9	4.66	0,83 [0,32 ; 2,18]	0,82 [0,3 ; 2,26];	-0,8 [-4,89 ; 3,3]; 0,801	0,801	0,6705

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	4	4.35	82	6	7.32	0,59 [0,17 ; 2,03]	0,58 [0,16 ; 2,12];	-2,97 [-9,98 ; 4,04]; 0,519	0,519	
Region	Eastern Europe	247	11	4.45	244	15	6.15	0,72 [0,34 ; 1,55]	0,71 [0,32 ; 1,58];	-1,69 [-5,66 ; 2,27]; 0,427	0,427	1
	USA and Western Europe	26	0	0.00	31	0	0.00	1,19 [0,02 ; 57,76]	1,19 [0,02 ; 61,97];	0,29 [-6,37 ; 6,95]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Investigations | Alanine aminotransferase increased

4.1.55 Investigations - Body temperature increased

Tabelle 55: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	8	5.33	146	2	1.37	3,89 [0,84 ; 18,03]	4,06 [0,85 ; 19,43];	3,96 [-0,1 ; 8,02]; 0,104	0,104	0,9659
	>= 38 years	123	4	3.25	129	1	0.78	4,2 [0,48 ; 37,01]	4,3 [0,47 ; 39,04];	2,48 [-1 ; 5,96]; 0,204	0,204	
Disease Severity at baseline (EDSS)	<=3.5	201	10	4.98	208	3	1.44	3,45 [0,96 ; 12,35]	3,58 [0,97 ; 13,2];	3,53 [0,12 ; 6,95]; 0,05	0,05	0,35
	>3.5	72	2	2.78	67	0	0.00	4,66 [0,23 ; 95,28]	4,79 [0,23 ; 101,56];	2,69 [-1,95 ; 7,33]; 0,497	0,497	
Gender	Female	167	7	4.19	180	2	1.11	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	Male	106	5	4.72	95	1	1.05	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of baseline Gd-enhancing lesions	>=1	117	3	2.56	116	3	2.59	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	155	9	5.81	157	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	6	5.56	92	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	2	4.76	58	1	1.72	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	4	3.25	125	2	1.60	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9998
	White	266	12	4.51	267	3	1.12	4,02 [1,15 ; 14,07]	4,16 [1,16 ; 14,91];	3,39 [0,59 ; 6,18]; 0,019	0,019	
	No	181	6	3.31	193	2	1.04	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	6	6.52	82	1	1.22	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Region	Eastern Europe	247	12	4.86	244	3	1.23	3,95 [1,13 ; 13,83]	4,1 [1,14 ; 14,72];	3,63 [0,61 ; 6,65]; 0,033	0,033	0,9999
	USA and Western Europe	26	0	0.00	31	0	0.00	1,19 [0,02 ; 57,76]	1,19 [0,02 ; 61,97];	0,29 [-6,37 ; 6,95]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Investigations | Body temperature increased

4.1.56 Investigations - Aspartate aminotransferase increased

Tabelle 56: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	10	6.67	146	4	2.74	2,43 [0,78 ; 7,59]	2,54 [0,78 ; 8,28];	3,93 [-0,86 ; 8,72]; 0,17	0,17	0,1203
	>= 38 years	123	4	3.25	129	0	0.00	9,44 [0,51 ; 173,44]	9,75 [0,52 ; 183,07];	3,24 [-0,21 ; 6,7]; 0,055	0,055	
Disease Severity at baseline (EDSS)	<=3.5	201	10	4.98	208	3	1.44	3,45 [0,96 ; 12,35]	3,58 [0,97 ; 13,2];	3,53 [0,12 ; 6,95]; 0,05	0,05	0,9502
	>3.5	72	4	5.56	67	1	1.49	3,72 [0,43 ; 32,47]	3,88 [0,42 ; 35,65];	4,06 [-1,97 ; 10,1]; 0,368	0,368	
Gender	Female	167	8	4.79	180	2	1.11	4,31 [0,93 ; 20,01]	4,48 [0,94 ; 21,4];	3,68 [0,1 ; 7,26]; 0,054	0,054	0,6814
	Male	106	6	5.66	95	2	2.11	2,69 [0,56 ; 13]	2,79 [0,55 ; 14,17];	3,56 [-1,71 ; 8,82]; 0,285	0,285	
Number of baseline Gd-enhancing lesions	>=1	117	6	5.13	116	2	1.72	2,97 [0,61 ; 14,43]	3,08 [0,61 ; 15,59];	3,4 [-1,24 ; 8,05]; 0,281	0,281	
	0	155	8	5.16	157	2	1.27	4,05 [0,87 ; 18,78]	4,22 [0,88 ; 20,19];	3,89 [-0,01 ; 7,79]; 0,06	0,06	0,7849
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	4	3.70	92	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	>=3	42	4	9.52	58	2	3.45	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	2	123	6	4.88	125	2	1.60	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9999
	White	266	14	5.26	267	4	1.50	3,51 [1,17 ; 10,53]	3,65 [1,19 ; 11,25];	3,77 [0,71 ; 6,82]; 0,017	0,017	
	No	181	10	5.52	193	2	1.04	5,33 [1,18 ; 24]	5,58 [1,21 ; 25,85];	4,49 [0,87 ; 8,11]; 0,017	0,017	0,343

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	4	4.35	82	2	2.44	1,78 [0,34 ; 9,48]	1,82 [0,32 ; 10,2];	1,91 [-3,43 ; 7,25]; 0,685	0,685	
Region	Eastern Europe	247	14	5.67	244	4	1.64	3,46 [1,15 ; 10,36]	3,61 [1,17 ; 11,11];	4,03 [0,73 ; 7,32]; 0,028	0,028	0,9999
	USA and Western Europe	26	0	0.00	31	0	0.00	1,19 [0,02 ; 57,76]	1,19 [0,02 ; 61,97];	0,29 [-6,37 ; 6,95]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Investigations | Aspartate aminotransferase increased

4.1.57 Infections and infestations - Rhinitis

Tabelle 57: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	14	9.33	146	3	2.05	4,54 [1,33 ; 15,48]	4,91 [1,38 ; 17,45];	7,28 [2,09 ; 12,47]; 0,01	0,01	0,0281
	>= 38 years	123	3	2.44	129	5	3.88	0,63 [0,15 ; 2,58]	0,62 [0,14 ; 2,65];	-1,44 [-5,74 ; 2,87]; 0,723	0,723	
Disease Severity at baseline (EDSS)	<=3.5	201	12	5.97	208	7	3.37	1,77 [0,71 ; 4,41]	1,82 [0,7 ; 4,73];	2,6 [-1,49 ; 6,7]; 0,245	0,245	0,3815
	>3.5	72	5	6.94	67	1	1.49	4,65 [0,56 ; 38,81]	4,93 [0,56 ; 43,3];	5,45 [-1,1 ; 12]; 0,21	0,21	
Gender	Female	167	6	3.59	180	6	3.33	1,08 [0,35 ; 3,28]	1,08 [0,34 ; 3,42];	0,26 [-3,59 ; 4,11]; 1	1	0,0832
	Male	106	11	10.38	95	2	2.11	4,93 [1,12 ; 21,67]	5,38 [1,16 ; 24,95];	8,27 [1,79 ; 14,76]; 0,021	0,021	
Number of baseline Gd-enhancing lesions	>=1	117	8	6.84	116	5	4.31	1,59 [0,53 ; 4,71]	1,63 [0,52 ; 5,14];	2,53 [-3,35 ; 8,41]; 0,57	0,57	0,4538
	0	155	9	5.81	157	3	1.91	3,04 [0,84 ; 11,01]	3,16 [0,84 ; 11,92];	3,9 [-0,36 ; 8,15]; 0,085	0,085	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	1	0.93	92	4	4.35	0,21 [0,02 ; 1,87]	0,21 [0,02 ; 1,87];	-3,42 [-7,96 ; 1,12]; 0,182	0,182	0,0038
	>=3	42	1	2.38	58	2	3.45	0,69 [0,06 ; 7,37]	0,68 [0,06 ; 7,79];	-1,07 [-7,65 ; 5,51]; 1	1	
	2	123	15	12.20	125	2	1.60	7,62 [1,78 ; 32,63]	8,54 [1,91 ; 38,2];	10,6 [4,41 ; 16,78]; 0,001	0,001	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9999
	White	266	17	6.39	267	8	3.00	2,13 [0,94 ; 4,86]	2,21 [0,94 ; 5,21];	3,39 [-0,19 ; 6,98]; 0,068	0,068	
	No	181	11	6.08	193	7	3.63	1,68 [0,66 ; 4,23]	1,72 [0,65 ; 4,54];	2,45 [-1,92 ; 6,82]; 0,336	0,336	0,2818

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	6	6.52	82	1	1.22	5,35 [0,66 ; 43,5]	5,65 [0,67 ; 47,97];	5,3 [-0,27 ; 10,88]; 0,122	0,122	
Region	Eastern Europe	247	17	6.88	244	8	3.28	2,1 [0,92 ; 4,77]	2,18 [0,92 ; 5,15];	3,6 [-0,26 ; 7,47]; 0,099	0,099	0,9999
	USA and Western Europe	26	0	0.00	31	0	0.00	1,19 [0,02 ; 57,76]	1,19 [0,02 ; 61,97];	0,29 [-6,37 ; 6,95]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Rhinitis

4.2 Non-severe TEAE

4.2.1 Cardiac disorders - any

Tabelle 58: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	12	8.00	146	7	4.79	1,67 [0,68 ; 4,12]	1,73 [0,66 ; 4,52];	3,21 [-2,35 ; 8,76]; 0,344	0,344	0,5085
	>= 38 years	123	15	12.20	129	14	10.85	1,12 [0,57 ; 2,23]	1,14 [0,53 ; 2,47];	1,34 [-6,55 ; 9,23]; 0,844	0,844	
Disease Severity at baseline (EDSS)	<=3.5	201	20	9.95	208	15	7.21	1,38 [0,73 ; 2,62]	1,42 [0,71 ; 2,86];	2,74 [-2,69 ; 8,17]; 0,378	0,378	0,7032
	>3.5	72	7	9.72	67	6	8.96	1,09 [0,38 ; 3,07]	1,09 [0,35 ; 3,44];	0,77 [-8,91 ; 10,44]; 1	1	
Gender	Female	167	13	7.78	180	13	7.22	1,08 [0,51 ; 2,26]	1,08 [0,49 ; 2,41];	0,56 [-4,99 ; 6,11]; 0,842	0,842	0,494
	Male	106	14	13.21	95	8	8.42	1,57 [0,69 ; 3,57]	1,65 [0,66 ; 4,14];	4,79 [-3,74 ; 13,31]; 0,366	0,366	
Number of baseline Gd-enhancing lesions	>=1	117	14	11.97	116	5	4.31	2,78 [1,03 ; 7,46]	3,02 [1,05 ; 8,67];	7,66 [0,71 ; 14,6]; 0,053	0,053	0,0409
	0	155	13	8.39	157	16	10.19	0,82 [0,41 ; 1,65]	0,81 [0,37 ; 1,74];	-1,8 [-8,24 ; 4,63]; 0,697	0,697	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	12	11.11	92	3	3.26	3,41 [0,99 ; 11,71]	3,71 [1,01 ; 13,57];	7,85 [0,9 ; 14,8]; 0,057	0,057	0,1436
	>=3	42	4	9.52	58	7	12.07	0,79 [0,25 ; 2,52]	0,77 [0,21 ; 2,81];	-2,55 [-14,76 ; 9,67]; 0,757	0,757	
	2	123	11	8.94	125	11	8.80	1,02 [0,46 ; 2,26]	1,02 [0,42 ; 2,44];	0,14 [-6,93 ; 7,22]; 1	1	
Race	Other	7	1	14.29	8	0	0.00	3,38 [0,16 ; 71,67]	3,92 [0,14 ; 112,9];	13,19 [-17,72 ; 44,11]; 0,467	0,467	0,2463

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
	White	266	26	9.77	267	21	7.87	1,24 [0,72 ; 2,15]	1,27 [0,7 ; 2,32];	1,91 [-2,9 ; 6,72]; 0,45	0,45	
Received approved disease modifying MS drug prior to enrollment	No	181	19	10.50	193	19	9.84	1,07 [0,58 ; 1,95]	1,07 [0,55 ; 2,1];	0,65 [-5,48 ; 6,79]; 0,865	0,865	0,121
	Yes	92	8	8.70	82	2	2.44	3,57 [0,78 ; 16,31]	3,81 [0,79 ; 18,48];	6,26 [-0,4 ; 12,91]; 0,105	0,105	
Region	Eastern Europe	247	21	8.50	244	18	7.38	1,15 [0,63 ; 2,11]	1,17 [0,61 ; 2,25];	1,12 [-3,66 ; 5,91]; 0,739	0,739	0,2853
	USA and Western Europe	26	6	23.08	31	3	9.68	2,38 [0,66 ; 8,61]	2,8 [0,62 ; 12,55];	13,4 [-5,85 ; 32,65]; 0,275	0,275	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Cardiac disorders | any

4.2.2 Gastrointestinal disorders - any

Tabelle 59: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	52	34.67	146	42	28.77	1,21 [0,86 ; 1,69]	1,31 [0,8 ; 2,15];	5,9 [-4,68 ; 16,48]; 0,318	0,318	0,0863
	>= 38 years	123	29	23.58	129	40	31.01	0,76 [0,5 ; 1,14]	0,69 [0,39 ; 1,2];	-7,43 [-18,38 ; 3,52]; 0,205	0,205	
Disease Severity at baseline (EDSS)	<=3.5	201	60	29.85	208	61	29.33	1,02 [0,75 ; 1,37]	1,03 [0,67 ; 1,57];	0,52 [-8,32 ; 9,37]; 0,914	0,914	0,7645
	>3.5	72	21	29.17	67	21	31.34	0,93 [0,56 ; 1,54]	0,9 [0,44 ; 1,86];	-2,18 [-17,46 ; 13,11]; 0,854	0,854	
Gender	Female	167	55	32.93	180	62	34.44	0,96 [0,71 ; 1,29]	0,93 [0,6 ; 1,46];	-1,51 [-11,46 ; 8,44]; 0,82	0,82	0,5141
	Male	106	26	24.53	95	20	21.05	1,17 [0,7 ; 1,95]	1,22 [0,63 ; 2,36];	3,48 [-8,11 ; 15,06]; 0,616	0,616	
Number of baseline Gd-enhancing lesions	>=1	117	38	32.48	116	36	31.03	1,05 [0,72 ; 1,53]	1,07 [0,62 ; 1,86];	1,44 [-10,51 ; 13,4]; 0,888	0,888	0,7044
	0	155	43	27.74	157	46	29.30	0,95 [0,67 ; 1,35]	0,93 [0,57 ; 1,51];	-1,56 [-11,58 ; 8,46]; 0,803	0,803	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	34	31.48	92	24	26.09	1,21 [0,78 ; 1,88]	1,3 [0,7 ; 2,41];	5,39 [-7,14 ; 17,93]; 0,437	0,437	0,5853
	>=3	42	13	30.95	58	20	34.48	0,9 [0,51 ; 1,59]	0,85 [0,36 ; 1,99];	-3,53 [-22,11 ; 15,05]; 0,83	0,83	
	2	123	34	27.64	125	38	30.40	0,91 [0,62 ; 1,34]	0,87 [0,51 ; 1,51];	-2,76 [-14,05 ; 8,53]; 0,676	0,676	
Race	Other	7	2	28.57	8	3	37.50	0,76 [0,17 ; 3,33]	0,67 [0,08 ; 5,88];	-8,93 [-56,31 ; 38,46]; 1	1	0,7141
	White	266	79	29.70	267	79	29.59	1 [0,77 ; 1,3]	1,01 [0,69 ; 1,46];	0,11 [-7,64 ; 7,87]; 1	1	
	No	181	46	25.41	193	51	26.42	0,96 [0,68 ; 1,36]	0,95 [0,6 ; 1,51];	-1,01 [-9,89 ; 7,87]; 0,906	0,906	0,8728

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	35	38.04	82	31	37.80	1,01 [0,69 ; 1,47]	1,01 [0,55 ; 1,87];	0,24 [-14,2 ; 14,68]; 1	1	
Region	Eastern Europe	247	72	29.15	244	72	29.51	0,99 [0,75 ; 1,3]	0,98 [0,67 ; 1,45];	-0,36 [-8,41 ; 7,7]; 1	1	0,8366
	USA and Western Europe	26	9	34.62	31	10	32.26	1,07 [0,51 ; 2,24]	1,11 [0,37 ; 3,35];	2,36 [-22,24 ; 26,96]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Gastrointestinal disorders | any

4.2.3 General disorders and administration site conditions - any

Tabelle 60: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	67	44.67	146	16	10.96	4,08 [2,48 ; 6,69]	6,56 [3,56 ; 12,08];	33,71 [24,28 ; 43,14]; 0	0	0,0005
	>= 38 years	123	39	31.71	129	30	23.26	1,36 [0,91 ; 2,05]	1,53 [0,88 ; 2,68];	8,45 [-2,54 ; 19,44]; 0,158	0,158	
Disease Severity at baseline (EDSS)	<=3.5	201	82	40.80	208	35	16.83	2,42 [1,72 ; 3,42]	3,41 [2,15 ; 5,39];	23,97 [15,48 ; 32,45]; 0	0	0,5428
	>3.5	72	24	33.33	67	11	16.42	2,03 [1,08 ; 3,82]	2,55 [1,13 ; 5,73];	16,92 [2,87 ; 30,96]; 0,031	0,031	
Gender	Female	167	69	41.32	180	33	18.33	2,25 [1,58 ; 3,22]	3,14 [1,93 ; 5,11];	22,98 [13,62 ; 32,35]; 0	0	0,8631
	Male	106	37	34.91	95	13	13.68	2,55 [1,45 ; 4,5]	3,38 [1,67 ; 6,87];	21,22 [9,82 ; 32,63]; 0,001	0,001	
Number of baseline Gd-enhancing lesions	>=1	117	48	41.03	116	19	16.38	2,5 [1,57 ; 3,99]	3,55 [1,92 ; 6,57];	24,65 [13,48 ; 35,82]; 0	0	0,6107
	0	155	58	37.42	157	27	17.20	2,18 [1,46 ; 3,24]	2,88 [1,7 ; 4,88];	20,22 [10,58 ; 29,86]; 0	0	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	39	36.11	92	17	18.48	1,95 [1,19 ; 3,21]	2,49 [1,29 ; 4,81];	17,63 [5,59 ; 29,67]; 0,007	0,007	0,2834
	>=3	42	18	42.86	58	6	10.34	4,14 [1,8 ; 9,54]	6,5 [2,29 ; 18,44];	32,51 [15,62 ; 49,41]; 0	0	
	2	123	49	39.84	125	23	18.40	2,17 [1,41 ; 3,32]	2,94 [1,65 ; 5,24];	21,44 [10,44 ; 32,44]; 0	0	
Race	Other	7	4	57.14	8	3	37.50	1,52 [0,51 ; 4,58]	2,22 [0,28 ; 17,63];	19,64 [-30,05 ; 69,34]; 0,619	0,619	0,7279
	White	266	102	38.35	267	43	16.10	2,38 [1,74 ; 3,26]	3,24 [2,15 ; 4,88];	22,24 [14,92 ; 29,56]; 0	0	
	No	181	63	34.81	193	32	16.58	2,1 [1,44 ; 3,05]	2,69 [1,65 ; 4,37];	18,23 [9,53 ; 26,93]; 0	0	0,2879

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	43	46.74	82	14	17.07	2,74 [1,62 ; 4,63]	4,26 [2,1 ; 8,64];	29,67 [16,62 ; 42,71]; 0	0	
Region	Eastern Europe	247	92	37.25	244	35	14.34	2,6 [1,84 ; 3,67]	3,54 [2,28 ; 5,51];	22,9 [15,44 ; 30,37]; 0	0	0,3858
	USA and Western Europe	26	14	53.85	31	11	35.48	1,52 [0,84 ; 2,75]	2,12 [0,73 ; 6,16];	18,36 [-7,15 ; 43,87]; 0,19	0,19	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - General disorders and administration site conditions | any

4.2.4 Infections and infestations - any

Tabelle 61: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	88	58.67	146	76	52.05	1,13 [0,92 ; 1,38]	1,31 [0,83 ; 2,07];	6,61 [-4,69 ; 17,92]; 0,293	0,293	0,1138
	>= 38 years	123	46	37.40	129	57	44.19	0,85 [0,63 ; 1,14]	0,75 [0,46 ; 1,25];	-6,79 [-18,89 ; 5,32]; 0,306	0,306	
Disease Severity at baseline (EDSS)	<=3.5	201	104	51.74	208	111	53.37	0,97 [0,81 ; 1,17]	0,94 [0,64 ; 1,38];	-1,62 [-11,3 ; 8,05]; 0,767	0,767	0,2716
	>3.5	72	30	41.67	67	22	32.84	1,27 [0,82 ; 1,97]	1,46 [0,73 ; 2,92];	8,83 [-7,17 ; 24,83]; 0,298	0,298	
Gender	Female	167	89	53.29	180	92	51.11	1,04 [0,85 ; 1,28]	1,09 [0,72 ; 1,66];	2,18 [-8,33 ; 12,7]; 0,747	0,747	0,745
	Male	106	45	42.45	95	41	43.16	0,98 [0,71 ; 1,35]	0,97 [0,56 ; 1,7];	-0,71 [-14,41 ; 13]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	117	61	52.14	116	62	53.45	0,98 [0,77 ; 1,24]	0,95 [0,57 ; 1,59];	-1,31 [-14,13 ; 11,51]; 0,896	0,896	0,7122
	0	155	73	47.10	157	71	45.22	1,04 [0,82 ; 1,32]	1,08 [0,69 ; 1,68];	1,87 [-9,19 ; 12,94]; 0,82	0,82	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	45	41.67	92	40	43.48	0,96 [0,69 ; 1,32]	0,93 [0,53 ; 1,63];	-1,81 [-15,56 ; 11,94]; 0,886	0,886	0,7949
	>=3	42	23	54.76	58	28	48.28	1,13 [0,77 ; 1,66]	1,3 [0,58 ; 2,88];	6,49 [-13,31 ; 26,28]; 0,549	0,549	
	2	123	66	53.66	125	65	52.00	1,03 [0,82 ; 1,31]	1,07 [0,65 ; 1,76];	1,66 [-10,77 ; 14,08]; 0,801	0,801	
Race	Other	7	6	85.71	8	5	62.50	1,37 [0,74 ; 2,54]	3,6 [0,28 ; 46,36];	23,21 [-19,18 ; 65,61]; 0,569	0,569	0,3086
	White	266	128	48.12	267	128	47.94	1 [0,84 ; 1,2]	1,01 [0,72 ; 1,41];	0,18 [-8,3 ; 8,66]; 1	1	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	No	181	78	43.09	193	94	48.70	0,88 [0,71 ; 1,1]	0,8 [0,53 ; 1,2];	-5,61 [-15,7 ; 4,48]; 0,3	0,3	0,0385
	Yes	92	56	60.87	82	39	47.56	1,28 [0,97 ; 1,69]	1,72 [0,94 ; 3,13];	13,31 [-1,4 ; 28,02]; 0,094	0,094	
Region	Eastern Europe	247	116	46.96	244	111	45.49	1,03 [0,85 ; 1,25]	1,06 [0,74 ; 1,51];	1,47 [-7,35 ; 10,29]; 0,786	0,786	0,8154
	USA and Western Europe	26	18	69.23	31	22	70.97	0,98 [0,69 ; 1,37]	0,92 [0,29 ; 2,87];	-1,74 [-25,61 ; 22,14]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | any

4.2.5 Musculoskeletal and connective tissue disorders - any

Tabelle 62: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	30	20.00	146	25	17.12	1,17 [0,72 ; 1,89]	1,21 [0,67 ; 2,18];	2,88 [-5,97 ; 11,73]; 0,553	0,553	0,0987
	>= 38 years	123	24	19.51	129	37	28.68	0,68 [0,43 ; 1,07]	0,6 [0,34 ; 1,08];	-9,17 [-19,66 ; 1,32]; 0,106	0,106	
Disease Severity at baseline (EDSS)	<=3.5	201	40	19.90	208	43	20.67	0,96 [0,66 ; 1,41]	0,95 [0,59 ; 1,54];	-0,77 [-8,57 ; 7,02]; 0,902	0,902	0,3423
	>3.5	72	14	19.44	67	19	28.36	0,69 [0,37 ; 1,26]	0,61 [0,28 ; 1,34];	-8,91 [-23,06 ; 5,23]; 0,237	0,237	
Gender	Female	167	35	20.96	180	41	22.78	0,92 [0,62 ; 1,37]	0,9 [0,54 ; 1,5];	-1,82 [-10,52 ; 6,88]; 0,699	0,699	0,7235
	Male	106	19	17.92	95	21	22.11	0,81 [0,47 ; 1,41]	0,77 [0,38 ; 1,54];	-4,18 [-15,27 ; 6,91]; 0,484	0,484	
Number of baseline Gd-enhancing lesions	>=1	117	27	23.08	116	28	24.14	0,96 [0,6 ; 1,52]	0,94 [0,51 ; 1,73];	-1,06 [-11,97 ; 9,84]; 0,878	0,878	0,6156
	0	155	27	17.42	157	34	21.66	0,8 [0,51 ; 1,27]	0,76 [0,43 ; 1,34];	-4,24 [-13,02 ; 4,55]; 0,393	0,393	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	21	19.44	92	18	19.57	0,99 [0,56 ; 1,75]	0,99 [0,49 ; 2];	-0,12 [-11,14 ; 10,9]; 1	1	0,248
	>=3	42	11	26.19	58	11	18.97	1,38 [0,66 ; 2,88]	1,52 [0,59 ; 3,92];	7,22 [-9,47 ; 23,92]; 0,466	0,466	
	2	123	22	17.89	125	33	26.40	0,68 [0,42 ; 1,09]	0,61 [0,33 ; 1,12];	-8,51 [-18,79 ; 1,76]; 0,127	0,127	
Race	Other	7	5	71.43	8	5	62.50	1,14 [0,56 ; 2,33]	1,5 [0,17 ; 13,23];	8,93 [-38,46 ; 56,31]; 1	1	0,6002
	White	266	49	18.42	267	57	21.35	0,86 [0,61 ; 1,21]	0,83 [0,54 ; 1,27];	-2,93 [-9,7 ; 3,84]; 0,448	0,448	
	No	181	28	15.47	193	45	23.32	0,66 [0,43 ; 1,02]	0,6 [0,36 ; 1,02];	-7,85 [-15,81 ; 0,11]; 0,067	0,067	0,0382

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	26	28.26	82	17	20.73	1,36 [0,8 ; 2,33]	1,51 [0,75 ; 3,04];	7,53 [-5,18 ; 20,24]; 0,293	0,293	
Region	Eastern Europe	247	40	16.19	244	46	18.85	0,86 [0,58 ; 1,26]	0,83 [0,52 ; 1,33];	-2,66 [-9,38 ; 4,06]; 0,477	0,477	0,6388
	USA and Western Europe	26	14	53.85	31	16	51.61	1,04 [0,64 ; 1,71]	1,09 [0,38 ; 3,11];	2,23 [-23,78 ; 28,25]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Musculoskeletal and connective tissue disorders | any

4.2.6 Nervous system disorders - any

Tabelle 63: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	72	48.00	146	51	34.93	1,37 [1,04 ; 1,81]	1,72 [1,08 ; 2,74];	13,07 [1,95 ; 24,19]; 0,025	0,025	0,1894
	>= 38 years	123	41	33.33	129	41	31.78	1,05 [0,74 ; 1,5]	1,07 [0,63 ; 1,82];	1,55 [-10,02 ; 13,12]; 0,893	0,893	
Disease Severity at baseline (EDSS)	<=3.5	201	83	41.29	208	71	34.13	1,21 [0,94 ; 1,55]	1,36 [0,91 ; 2,03];	7,16 [-2,21 ; 16,53]; 0,153	0,153	0,7287
	>3.5	72	30	41.67	67	21	31.34	1,33 [0,85 ; 2,08]	1,56 [0,78 ; 3,14];	10,32 [-5,58 ; 26,23]; 0,223	0,223	
Gender	Female	167	74	44.31	180	69	38.33	1,16 [0,9 ; 1,49]	1,28 [0,83 ; 1,96];	5,98 [-4,38 ; 16,33]; 0,276	0,276	0,3534
	Male	106	39	36.79	95	23	24.21	1,52 [0,98 ; 2,35]	1,82 [0,99 ; 3,36];	12,58 [-0,01 ; 25,17]; 0,066	0,066	
Number of baseline Gd-enhancing lesions	>=1	117	51	43.59	116	49	42.24	1,03 [0,77 ; 1,39]	1,06 [0,63 ; 1,78];	1,35 [-11,36 ; 14,06]; 0,895	0,895	0,1282
	0	155	62	40.00	157	42	26.75	1,5 [1,08 ; 2,06]	1,83 [1,13 ; 2,94];	13,25 [2,88 ; 23,61]; 0,016	0,016	
	NA	1	0	0.00	2	1	50.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	42	38.89	92	33	35.87	1,08 [0,76 ; 1,56]	1,14 [0,64 ; 2,02];	3,02 [-10,42 ; 16,46]; 0,77	0,77	0,6773
	>=3	42	17	40.48	58	17	29.31	1,38 [0,8 ; 2,38]	1,64 [0,71 ; 3,78];	11,17 [-7,74 ; 30,08]; 0,288	0,288	
	2	123	54	43.90	125	42	33.60	1,31 [0,95 ; 1,79]	1,55 [0,92 ; 2,59];	10,3 [-1,76 ; 22,36]; 0,118	0,118	
Race	Other	7	5	71.43	8	5	62.50	1,14 [0,56 ; 2,33]	1,5 [0,17 ; 13,23];	8,93 [-38,46 ; 56,31]; 1	1	0,9582
	White	266	108	40.60	267	87	32.58	1,25 [0,99 ; 1,56]	1,41 [0,99 ; 2,02];	8,02 [-0,13 ; 16,17]; 0,059	0,059	
	No	181	68	37.57	193	64	33.16	1,13 [0,86 ; 1,49]	1,21 [0,79 ; 1,85];	4,41 [-5,28 ; 14,1]; 0,388	0,388	0,268

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	45	48.91	82	28	34.15	1,43 [0,99 ; 2,07]	1,85 [1 ; 3,41];	14,77 [0,29 ; 29,25]; 0,065	0,065	
Region	Eastern Europe	247	97	39.27	244	73	29.92	1,31 [1,03 ; 1,68]	1,51 [1,04 ; 2,2];	9,35 [0,98 ; 17,73]; 0,037	0,037	0,4851
	USA and Western Europe	26	16	61.54	31	19	61.29	1 [0,66 ; 1,52]	1,01 [0,35 ; 2,95];	0,25 [-25,12 ; 25,62]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Nervous system disorders | any

4.2.7 Renal and urinary disorders - any

Tabelle 64: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	7	4.67	146	8	5.48	0,85 [0,32 ; 2,29]	0,84 [0,3 ; 2,39];	-0,81 [-5,81 ; 4,19]; 0,796	0,796	0,8813
	>= 38 years	123	9	7.32	129	10	7.75	0,94 [0,4 ; 2,24]	0,94 [0,37 ; 2,4];	-0,43 [-6,95 ; 6,08]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	201	11	5.47	208	12	5.77	0,95 [0,43 ; 2,1]	0,95 [0,41 ; 2,2];	-0,3 [-4,76 ; 4,17]; 1	1	0,7728
	>3.5	72	5	6.94	67	6	8.96	0,78 [0,25 ; 2,42]	0,76 [0,22 ; 2,61];	-2,01 [-11,02 ; 7]; 0,758	0,758	
Gender	Female	167	12	7.19	180	8	4.44	1,62 [0,68 ; 3,86]	1,66 [0,66 ; 4,18];	2,74 [-2,2 ; 7,68]; 0,358	0,358	0,0306
	Male	106	4	3.77	95	10	10.53	0,36 [0,12 ; 1,11]	0,33 [0,1 ; 1,1];	-6,75 [-13,91 ; 0,41]; 0,094	0,094	
Number of baseline Gd-enhancing lesions	>=1	117	7	5.98	116	7	6.03	0,99 [0,36 ; 2,74]	0,99 [0,34 ; 2,92];	-0,05 [-6,15 ; 6,05]; 1	1	0,7904
	0	155	9	5.81	157	11	7.01	0,83 [0,35 ; 1,94]	0,82 [0,33 ; 2,03];	-1,2 [-6,63 ; 4,23]; 0,818	0,818	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	5	4.63	92	5	5.43	0,85 [0,25 ; 2,85]	0,84 [0,24 ; 3,01];	-0,81 [-6,9 ; 5,29]; 1	1	0,9732
	>=3	42	1	2.38	58	2	3.45	0,69 [0,06 ; 7,37]	0,68 [0,06 ; 7,79];	-1,07 [-7,65 ; 5,51]; 1	1	
	2	123	10	8.13	125	11	8.80	0,92 [0,41 ; 2,1]	0,92 [0,37 ; 2,24];	-0,67 [-7,6 ; 6,26]; 1	1	
Race	Other	7	0	0.00	8	1	12.50	0,38 [0,02 ; 7,96]	0,33 [0,01 ; 9,57];	-10,42 [-39,98 ; 19,15]; 0,477	0,477	0,2658
	White	266	16	6.02	267	17	6.37	0,94 [0,49 ; 1,83]	0,94 [0,47 ; 1,9];	-0,35 [-4,44 ; 3,74]; 1	1	
	No	181	11	6.08	193	12	6.22	0,98 [0,44 ; 2,16]	0,98 [0,42 ; 2,27];	-0,14 [-5,01 ; 4,73]; 1	1	0,6992

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	5	5.43	82	6	7.32	0,74 [0,24 ; 2,34]	0,73 [0,21 ; 2,48];	-1,88 [-9,18 ; 5,41]; 0,758	0,758	
Region	Eastern Europe	247	14	5.67	244	14	5.74	0,99 [0,48 ; 2,03]	0,99 [0,46 ; 2,12];	-0,07 [-4,17 ; 4,03]; 1	1	0,564
	USA and Western Europe	26	2	7.69	31	4	12.90	0,6 [0,12 ; 3]	0,56 [0,09 ; 3,35];	-5,21 [-20,84 ; 10,42]; 0,678	0,678	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Renal and urinary disorders | any

4.2.8 Reproductive system and breast disorders - any

Tabelle 65: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	12	8.00	146	14	9.59	0,83 [0,4 ; 1,74]	0,82 [0,37 ; 1,84];	-1,59 [-8,04 ; 4,87]; 0,685	0,685	0,7302
	>= 38 years	123	6	4.88	129	6	4.65	1,05 [0,35 ; 3,16]	1,05 [0,33 ; 3,35];	0,23 [-5,04 ; 5,49]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	201	14	6.97	208	17	8.17	0,85 [0,43 ; 1,68]	0,84 [0,4 ; 1,76];	-1,21 [-6,33 ; 3,92]; 0,711	0,711	0,6437
	>3.5	72	4	5.56	67	3	4.48	1,24 [0,29 ; 5,34]	1,25 [0,27 ; 5,83];	1,08 [-6,17 ; 8,32]; 1	1	
Gender	Female	167	18	10.78	180	19	10.56	1,02 [0,56 ; 1,88]	1,02 [0,52 ; 2,02];	0,22 [-6,28 ; 6,72]; 1	1	0,2213
	Male	106	0	0.00	95	1	1.05	0,3 [0,01 ; 7,25]	0,3 [0,01 ; 7,35];	-1,1 [-3,89 ; 1,7]; 0,225	0,225	
Number of baseline Gd-enhancing lesions	>=1	117	9	7.69	116	7	6.03	1,27 [0,49 ; 3,31]	1,3 [0,47 ; 3,61];	1,66 [-4,83 ; 8,15]; 0,797	0,797	0,3487
	0	155	9	5.81	157	13	8.28	0,7 [0,31 ; 1,59]	0,68 [0,28 ; 1,65];	-2,47 [-8,14 ; 3,2]; 0,508	0,508	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	8	7.41	92	9	9.78	0,76 [0,3 ; 1,88]	0,74 [0,27 ; 2];	-2,38 [-10,2 ; 5,45]; 0,616	0,616	0,8656
	>=3	42	4	9.52	58	5	8.62	1,1 [0,32 ; 3,87]	1,12 [0,28 ; 4,43];	0,9 [-10,54 ; 12,35]; 1	1	
	2	123	6	4.88	125	6	4.80	1,02 [0,34 ; 3,06]	1,02 [0,32 ; 3,24];	0,08 [-5,26 ; 5,42]; 1	1	
Race	Other	7	2	28.57	8	1	12.50	2,29 [0,26 ; 20,13]	2,8 [0,2 ; 40,06];	16,07 [-24,49 ; 56,63]; 0,569	0,569	0,3754
	White	266	16	6.02	267	19	7.12	0,85 [0,44 ; 1,61]	0,84 [0,42 ; 1,66];	-1,1 [-5,31 ; 3,1]; 0,727	0,727	
	No	181	14	7.73	193	15	7.77	1 [0,49 ; 2]	0,99 [0,47 ; 2,12];	-0,04 [-5,46 ; 5,39]; 1	1	0,6556

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	4	4.35	82	5	6.10	0,71 [0,2 ; 2,57]	0,7 [0,18 ; 2,7];	-1,75 [-8,4 ; 4,9]; 0,737	0,737	
Region	Eastern Europe	247	14	5.67	244	16	6.56	0,86 [0,43 ; 1,73]	0,86 [0,41 ; 1,79];	-0,89 [-5,13 ; 3,35]; 0,71	0,71	0,6727
	USA and Western Europe	26	4	15.38	31	4	12.90	1,19 [0,33 ; 4,31]	1,23 [0,27 ; 5,48];	2,48 [-15,73 ; 20,69]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Reproductive system and breast disorders | any

4.2.9 Skin and subcutaneous tissue disorders - any

Tabelle 66: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	19	12.67	146	31	21.23	0,6 [0,35 ; 1,01]	0,54 [0,29 ; 1];	-8,57 [-17,07 ; -0,06]; 0,062	0,062	0,8046
	>= 38 years	123	15	12.20	129	29	22.48	0,54 [0,31 ; 0,96]	0,48 [0,24 ; 0,95];	-10,29 [-19,52 ; -1,05]; 0,046	0,046	
Disease Severity at baseline (EDSS)	<=3.5	201	26	12.94	208	53	25.48	0,51 [0,33 ; 0,78]	0,43 [0,26 ; 0,73];	-12,55 [-20,07 ; -5,02]; 0,002	0,002	0,1377
	>3.5	72	8	11.11	67	7	10.45	1,06 [0,41 ; 2,77]	1,07 [0,37 ; 3,14];	0,66 [-9,65 ; 10,98]; 1	1	
Gender	Female	167	24	14.37	180	49	27.22	0,53 [0,34 ; 0,82]	0,45 [0,26 ; 0,77];	-12,85 [-21,25 ; -4,45]; 0,004	0,004	0,2889
	Male	106	10	9.43	95	11	11.58	0,81 [0,36 ; 1,83]	0,8 [0,32 ; 1,97];	-2,14 [-10,65 ; 6,36]; 0,651	0,651	
Number of baseline Gd-enhancing lesions	>=1	117	14	11.97	116	26	22.41	0,53 [0,29 ; 0,97]	0,47 [0,23 ; 0,96];	-10,45 [-20,05 ; -0,85]; 0,038	0,038	0,7235
	0	155	20	12.90	157	33	21.02	0,61 [0,37 ; 1,02]	0,56 [0,3 ; 1,02];	-8,12 [-16,39 ; 0,16]; 0,07	0,07	
	NA	1	0	0.00	2	1	50.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	14	12.96	92	20	21.74	0,6 [0,32 ; 1,11]	0,54 [0,25 ; 1,13];	-8,78 [-19,32 ; 1,77]; 0,13	0,13	0,4731
	>=3	42	4	9.52	58	16	27.59	0,35 [0,12 ; 0,96]	0,28 [0,08 ; 0,9];	-18,06 [-32,59 ; -3,53]; 0,041	0,041	
	2	123	16	13.01	125	24	19.20	0,68 [0,38 ; 1,21]	0,63 [0,32 ; 1,25];	-6,19 [-15,3 ; 2,92]; 0,227	0,227	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Race	Other	7	3	42.86	8	5	62.50	0,69 [0,25 ; 1,88]	0,45 [0,06 ; 3,57];	-19,64 [-69,34 ; 30,05]; 0,619	0,619	0,9102
	White	266	31	11.65	267	55	20.60	0,57 [0,38 ; 0,85]	0,51 [0,32 ; 0,82];	-8,95 [-15,14 ; -2,75]; 0,007	0,007	
Received approved disease modifying MS drug prior to enrollment	No	181	20	11.05	193	38	19.69	0,56 [0,34 ; 0,93]	0,51 [0,28 ; 0,91];	-8,64 [-15,87 ; -1,41]; 0,023	0,023	0,9433
	Yes	92	14	15.22	82	22	26.83	0,57 [0,31 ; 1,03]	0,49 [0,23 ; 1,04];	-11,61 [-23,69 ; 0,46]; 0,064	0,064	
Region	Eastern Europe	247	27	10.93	244	48	19.67	0,56 [0,36 ; 0,86]	0,5 [0,3 ; 0,83];	-8,74 [-15,07 ; -2,41]; 0,008	0,008	0,8104
	USA and Western Europe	26	7	26.92	31	12	38.71	0,7 [0,32 ; 1,51]	0,58 [0,19 ; 1,8];	-11,79 [-35,97 ; 12,39]; 0,407	0,407	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Skin and subcutaneous tissue disorders | any

4.2.10 Respiratory, thoracic and mediastinal disorders - any

Tabelle 67: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	27	18.00	146	19	13.01	1,38 [0,81 ; 2,38]	1,47 [0,78 ; 2,77];	4,99 [-3,23 ; 13,21]; 0,264	0,264	0,7764
	>= 38 years	123	20	16.26	129	17	13.18	1,23 [0,68 ; 2,24]	1,28 [0,64 ; 2,58];	3,08 [-5,67 ; 11,83]; 0,594	0,594	
Disease Severity at baseline (EDSS)	<=3.5	201	38	18.91	208	30	14.42	1,31 [0,85 ; 2,03]	1,38 [0,82 ; 2,34];	4,48 [-2,74 ; 11,7]; 0,235	0,235	0,937
	>3.5	72	9	12.50	67	6	8.96	1,4 [0,52 ; 3,71]	1,45 [0,49 ; 4,33];	3,54 [-6,71 ; 13,8]; 0,59	0,59	
Gender	Female	167	32	19.16	180	27	15.00	1,28 [0,8 ; 2,04]	1,34 [0,77 ; 2,36];	4,16 [-3,77 ; 12,09]; 0,32	0,32	0,764
	Male	106	15	14.15	95	9	9.47	1,49 [0,69 ; 3,25]	1,58 [0,66 ; 3,79];	4,68 [-4,19 ; 13,55]; 0,385	0,385	
Number of baseline Gd-enhancing lesions	>=1	117	23	19.66	116	12	10.34	1,9 [0,99 ; 3,64]	2,12 [1 ; 4,5];	9,31 [0,23 ; 18,4]; 0,066	0,066	0,134
	0	155	24	15.48	157	24	15.29	1,01 [0,6 ; 1,7]	1,02 [0,55 ; 1,88];	0,2 [-7,81 ; 8,2]; 1	1	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	21	19.44	92	9	9.78	1,99 [0,96 ; 4,12]	2,23 [0,96 ; 5,14];	9,66 [0,04 ; 19,28]; 0,073	0,073	0,3461
	>=3	42	6	14.29	58	7	12.07	1,18 [0,43 ; 3,27]	1,21 [0,38 ; 3,92];	2,22 [-11,28 ; 15,72]; 0,771	0,771	
	2	123	20	16.26	125	20	16.00	1,02 [0,58 ; 1,79]	1,02 [0,52 ; 2,01];	0,26 [-8,9 ; 9,42]; 1	1	
Race	Other	7	2	28.57	8	3	37.50	0,76 [0,17 ; 3,33]	0,67 [0,08 ; 5,88];	-8,93 [-56,31 ; 38,46]; 1	1	0,494
	White	266	45	16.92	267	33	12.36	1,37 [0,9 ; 2,07]	1,44 [0,89 ; 2,35];	4,56 [-1,43 ; 10,55]; 0,143	0,143	
	No	181	24	13.26	193	24	12.44	1,07 [0,63 ; 1,81]	1,08 [0,59 ; 1,97];	0,82 [-5,96 ; 7,61]; 0,878	0,878	0,235

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	23	25.00	82	12	14.63	1,71 [0,91 ; 3,21]	1,94 [0,9 ; 4,21];	10,37 [-1,33 ; 22,06]; 0,129	0,129	
Region	Eastern Europe	247	39	15.79	244	28	11.48	1,38 [0,88 ; 2,16]	1,45 [0,86 ; 2,44];	4,31 [-1,74 ; 10,37]; 0,189	0,189	0,8483
	USA and Western Europe	26	8	30.77	31	8	25.81	1,19 [0,52 ; 2,73]	1,28 [0,4 ; 4,07];	4,96 [-18,53 ; 28,46]; 0,771	0,771	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Respiratory, thoracic and mediastinal disorders | any

4.2.11 Injury, poisoning and procedural complications - any

Tabelle 68: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	10	6.67	146	15	10.27	0,65 [0,3 ; 1,4]	0,62 [0,27 ; 1,44];	-3,61 [-9,95 ; 2,73]; 0,3	0,3	0,1916
	>= 38 years	123	18	14.63	129	15	11.63	1,26 [0,66 ; 2,38]	1,3 [0,62 ; 2,72];	3,01 [-5,34 ; 11,35]; 0,576	0,576	
Disease Severity at baseline (EDSS)	<=3.5	201	20	9.95	208	20	9.62	1,03 [0,57 ; 1,86]	1,04 [0,54 ; 1,99];	0,33 [-5,42 ; 6,09]; 1	1	0,5342
	>3.5	72	8	11.11	67	10	14.93	0,74 [0,31 ; 1,77]	0,71 [0,26 ; 1,93];	-3,81 [-15,02 ; 7,39]; 0,615	0,615	
Gender	Female	167	17	10.18	180	20	11.11	0,92 [0,5 ; 1,69]	0,91 [0,46 ; 1,8];	-0,93 [-7,42 ; 5,56]; 0,862	0,862	0,8872
	Male	106	11	10.38	95	10	10.53	0,99 [0,44 ; 2,22]	0,98 [0,4 ; 2,43];	-0,15 [-8,62 ; 8,32]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	117	15	12.82	116	14	12.07	1,06 [0,54 ; 2,1]	1,07 [0,49 ; 2,33];	0,75 [-7,72 ; 9,23]; 1	1	0,6107
	0	155	13	8.39	157	16	10.19	0,82 [0,41 ; 1,65]	0,81 [0,37 ; 1,74];	-1,8 [-8,24 ; 4,63]; 0,697	0,697	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	13	12.04	92	12	13.04	0,92 [0,44 ; 1,92]	0,91 [0,39 ; 2,11];	-1,01 [-10,23 ; 8,21]; 0,834	0,834	0,8275
	>=3	42	3	7.14	58	3	5.17	1,38 [0,29 ; 6,51]	1,41 [0,27 ; 7,36];	1,97 [-7,68 ; 11,62]; 0,694	0,694	
	2	123	12	9.76	125	15	12.00	0,81 [0,4 ; 1,67]	0,79 [0,35 ; 1,77];	-2,24 [-9,99 ; 5,5]; 0,684	0,684	
Race	Other	7	1	14.29	8	2	25.00	0,57 [0,06 ; 5,03]	0,5 [0,04 ; 7,1];	-10,71 [-50,37 ; 28,94]; 1	1	0,6288
	White	266	27	10.15	267	28	10.49	0,97 [0,59 ; 1,6]	0,96 [0,55 ; 1,69];	-0,34 [-5,5 ; 4,83]; 1	1	
	No	181	14	7.73	193	23	11.92	0,65 [0,34 ; 1,22]	0,62 [0,31 ; 1,25];	-4,18 [-10,19 ; 1,82]; 0,225	0,225	0,0565

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	14	15.22	82	7	8.54	1,78 [0,76 ; 4,2]	1,92 [0,74 ; 5,03];	6,68 [-2,83 ; 16,19]; 0,244	0,244	
Region	Eastern Europe	247	18	7.29	244	24	9.84	0,74 [0,41 ; 1,33]	0,72 [0,38 ; 1,36];	-2,55 [-7,5 ; 2,4]; 0,336	0,336	0,0588
	USA and Western Europe	26	10	38.46	31	6	19.35	1,99 [0,83 ; 4,73]	2,6 [0,79 ; 8,57];	19,11 [-4,2 ; 42,41]; 0,144	0,144	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Injury, poisoning and procedural complications | any

4.2.12 Investigations - any

Tabelle 69: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	44	29.33	146	41	28.08	1,04 [0,73 ; 1,5]	1,06 [0,64 ; 1,76];	1,25 [-9,06 ; 11,56]; 0,898	0,898	0,5896
	>= 38 years	123	29	23.58	129	34	26.36	0,89 [0,58 ; 1,37]	0,86 [0,49 ; 1,53];	-2,78 [-13,46 ; 7,9]; 0,664	0,664	
Disease Severity at baseline (EDSS)	<=3.5	201	56	27.86	208	58	27.88	1 [0,73 ; 1,36]	1 [0,65 ; 1,54];	-0,02 [-8,72 ; 8,67]; 1	1	0,8351
	>3.5	72	17	23.61	67	17	25.37	0,93 [0,52 ; 1,67]	0,91 [0,42 ; 1,97];	-1,76 [-16,07 ; 12,55]; 0,845	0,845	
Gender	Female	167	41	24.55	180	43	23.89	1,03 [0,71 ; 1,49]	1,04 [0,63 ; 1,69];	0,66 [-8,36 ; 9,68]; 0,901	0,901	0,6166
	Male	106	32	30.19	95	32	33.68	0,9 [0,6 ; 1,34]	0,85 [0,47 ; 1,54];	-3,5 [-16,41 ; 9,42]; 0,65	0,65	
Number of baseline Gd-enhancing lesions	>=1	117	30	25.64	116	32	27.59	0,93 [0,61 ; 1,42]	0,91 [0,51 ; 1,62];	-1,95 [-13,29 ; 9,4]; 0,768	0,768	0,7018
	0	155	43	27.74	157	42	26.75	1,04 [0,72 ; 1,49]	1,05 [0,64 ; 1,73];	0,99 [-8,89 ; 10,87]; 0,899	0,899	
	NA	1	0	0.00	2	1	50.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	27	25.00	92	23	25.00	1 [0,62 ; 1,62]	1 [0,53 ; 1,9];	0 [-12,04 ; 12,04]; 1	1	0,9114
	>=3	42	16	38.10	58	20	34.48	1,1 [0,65 ; 1,87]	1,17 [0,51 ; 2,67];	3,61 [-15,5 ; 22,73]; 0,833	0,833	
	2	123	30	24.39	125	32	25.60	0,95 [0,62 ; 1,47]	0,94 [0,53 ; 1,67];	-1,21 [-11,99 ; 9,57]; 0,884	0,884	
Race	Other	7	3	42.86	8	2	25.00	1,71 [0,39 ; 7,48]	2,25 [0,25 ; 20,13];	17,86 [-29,52 ; 65,23]; 0,608	0,608	0,4422
	White	266	70	26.32	267	73	27.34	0,96 [0,73 ; 1,27]	0,95 [0,65 ; 1,39];	-1,03 [-8,55 ; 6,5]; 0,845	0,845	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	No	181	48	26.52	193	49	25.39	1,04 [0,74 ; 1,47]	1,06 [0,67 ; 1,68];	1,13 [-7,76 ; 10,02]; 0,814	0,814	0,4971
	Yes	92	25	27.17	82	26	31.71	0,86 [0,54 ; 1,36]	0,8 [0,42 ; 1,55];	-4,53 [-18,1 ; 9,03]; 0,617	0,617	
Region	Eastern Europe	247	65	26.32	244	68	27.87	0,94 [0,71 ; 1,26]	0,92 [0,62 ; 1,38];	-1,55 [-9,41 ; 6,31]; 0,761	0,761	0,4322
	USA and Western Europe	26	8	30.77	31	7	22.58	1,36 [0,57 ; 3,25]	1,52 [0,47 ; 4,98];	8,19 [-14,86 ; 31,24]; 0,554	0,554	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Investigations | any

4.2.13 Metabolism and nutrition disorders - any

Tabelle 70: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	3	2.00	146	4	2.74	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>= 38 years	123	2	1.63	129	6	4.65	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	201	5	2.49	208	6	2.88	0,86 [0,27 ; 2,78]	0,86 [0,26 ; 2,86];	-0,4 [-3,53 ; 2,73]; 1	1	0,0379
	>3.5	72	0	0.00	67	4	5.97	0,1 [0,01 ; 1,89]	0,1 [0,01 ; 1,84];	-5,93 [-12,14 ; 0,27]; 0,053	0,053	
Number of baseline Gd-enhancing lesions	>=1	117	3	2.56	116	5	4.31	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	155	2	1.29	157	5	3.18	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	3	2.78	92	6	6.52	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	0	0.00	58	2	3.45	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	2	1.63	125	2	1.60	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	1	14.29	8	1	12.50	1,14 [0,09 ; 15,08]	1,17 [0,06 ; 22,94];	1,79 [-32,81 ; 36,39]; 1	1	0,552
	White	266	4	1.50	267	9	3.37	0,45 [0,14 ; 1,43]	0,44 [0,13 ; 1,44];	-1,87 [-4,48 ; 0,75]; 0,261	0,261	
Received approved disease modifying MS drug prior to enrollment	No	181	4	2.21	193	7	3.63	0,61 [0,18 ; 2,05]	0,6 [0,17 ; 2,09];	-1,42 [-4,81 ; 1,98]; 0,545	0,545	0,5714
	Yes	92	1	1.09	82	3	3.66	0,3 [0,03 ; 2,8]	0,29 [0,03 ; 2,84];	-2,57 [-7,15 ; 2,01]; 0,344	0,344	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	247	3	1.21	244	7	2.87	0,42 [0,11 ; 1,62]	0,42 [0,11 ; 1,63];	-1,65 [-4,15 ; 0,85]; 0,219	0,219	0,5985
	USA and Western Europe	26	2	7.69	31	3	9.68	0,79 [0,14 ; 4,4]	0,78 [0,12 ; 5,05];	-1,99 [-16,59 ; 12,62]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Metabolism and nutrition disorders | any

4.2.14 Eye disorders - any

Tabelle 71: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	7	4.67	146	7	4.79	0,97 [0,35 ; 2,71]	0,97 [0,33 ; 2,84];	-0,13 [-4,97 ; 4,71]; 1	1	0,6476
	>= 38 years	123	6	4.88	129	9	6.98	0,7 [0,26 ; 1,91]	0,68 [0,24 ; 1,98];	-2,1 [-7,91 ; 3,72]; 0,598	0,598	
Disease Severity at baseline (EDSS)	<=3.5	201	10	4.98	208	13	6.25	0,8 [0,36 ; 1,77]	0,79 [0,34 ; 1,83];	-1,27 [-5,73 ; 3,18]; 0,67	0,67	0,8595
	>3.5	72	3	4.17	67	3	4.48	0,93 [0,19 ; 4,45]	0,93 [0,18 ; 4,76];	-0,31 [-7,08 ; 6,46]; 1	1	
Gender	Female	167	6	3.59	180	7	3.89	0,92 [0,32 ; 2,69]	0,92 [0,3 ; 2,8];	-0,3 [-4,29 ; 3,7]; 1	1	0,6886
	Male	106	7	6.60	95	9	9.47	0,7 [0,27 ; 1,8]	0,68 [0,24 ; 1,89];	-2,87 [-10,42 ; 4,68]; 0,603	0,603	
Number of baseline Gd-enhancing lesions	>=1	117	5	4.27	116	6	5.17	0,83 [0,26 ; 2,63]	0,82 [0,24 ; 2,76];	-0,9 [-6,35 ; 4,55]; 0,768	0,768	0,9107
	0	155	8	5.16	157	9	5.73	0,9 [0,36 ; 2,27]	0,89 [0,34 ; 2,38];	-0,57 [-5,61 ; 4,46]; 1	1	
	NA	1	0	0.00	2	1	50.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	9	8.33	92	1	1.09	7,67 [0,99 ; 59,39]	8,27 [1,03 ; 66,58];	7,25 [1,62 ; 12,87]; 0,022	0,022	0,0019
	>=3	42	1	2.38	58	3	5.17	0,46 [0,05 ; 4,27]	0,45 [0,04 ; 4,46];	-2,79 [-10,12 ; 4,54]; 0,637	0,637	
	2	123	3	2.44	125	12	9.60	0,25 [0,07 ; 0,88]	0,24 [0,06 ; 0,86];	-7,16 [-13 ; -1,32]; 0,03	0,03	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	1
	White	266	13	4.89	267	16	5.99	0,82 [0,4 ; 1,66]	0,81 [0,38 ; 1,71];	-1,11 [-4,95 ; 2,74]; 0,703	0,703	
	No	181	6	3.31	193	7	3.63	0,91 [0,31 ; 2,67]	0,91 [0,3 ; 2,76];	-0,31 [-4,02 ; 3,4]; 1	1	0,6888

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	7	7.61	82	9	10.98	0,69 [0,27 ; 1,78]	0,67 [0,24 ; 1,88];	-3,37 [-12,03 ; 5,3]; 0,6	0,6	
Region	Eastern Europe	247	11	4.45	244	12	4.92	0,91 [0,41 ; 2,01]	0,9 [0,39 ; 2,08];	-0,46 [-4,2 ; 3,27]; 0,834	0,834	0,6352
	USA and Western Europe	26	2	7.69	31	4	12.90	0,6 [0,12 ; 3]	0,56 [0,09 ; 3,35];	-5,21 [-20,84 ; 10,42]; 0,678	0,678	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Eye disorders | any

4.2.15 Psychiatric disorders - any

Tabelle 72: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	20	13.33	146	10	6.85	1,95 [0,94 ; 4,02]	2,09 [0,94 ; 4,64];	6,48 [-0,33 ; 13,29]; 0,083	0,083	0,0314
	>= 38 years	123	13	10.57	129	20	15.50	0,68 [0,35 ; 1,31]	0,64 [0,31 ; 1,36];	-4,93 [-13,21 ; 3,34]; 0,267	0,267	
Disease Severity at baseline (EDSS)	<=3.5	201	27	13.43	208	21	10.10	1,33 [0,78 ; 2,27]	1,38 [0,75 ; 2,53];	3,34 [-2,91 ; 9,58]; 0,357	0,357	0,1741
	>3.5	72	6	8.33	67	9	13.43	0,62 [0,23 ; 1,65]	0,59 [0,2 ; 1,75];	-5,1 [-15,46 ; 5,27]; 0,416	0,416	
Gender	Female	167	21	12.57	180	22	12.22	1,03 [0,59 ; 1,8]	1,03 [0,55 ; 1,96];	0,35 [-6,59 ; 7,29]; 1	1	0,6092
	Male	106	12	11.32	95	8	8.42	1,34 [0,57 ; 3,15]	1,39 [0,54 ; 3,56];	2,9 [-5,32 ; 11,12]; 0,638	0,638	
Number of baseline Gd-enhancing lesions	>=1	117	22	18.80	116	12	10.34	1,82 [0,94 ; 3,5]	2,01 [0,94 ; 4,28];	8,46 [-0,53 ; 17,45]; 0,094	0,094	0,0253
	0	155	11	7.10	157	18	11.46	0,62 [0,3 ; 1,27]	0,59 [0,27 ; 1,29];	-4,37 [-10,79 ; 2,05]; 0,242	0,242	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	17	15.74	92	9	9.78	1,61 [0,75 ; 3,44]	1,72 [0,73 ; 4,08];	5,96 [-3,21 ; 15,12]; 0,292	0,292	0,2728
	>=3	42	4	9.52	58	4	6.90	1,38 [0,37 ; 5,21]	1,42 [0,33 ; 6,04];	2,63 [-8,39 ; 13,64]; 0,717	0,717	
	2	123	12	9.76	125	17	13.60	0,72 [0,36 ; 1,44]	0,69 [0,31 ; 1,51];	-3,84 [-11,82 ; 4,13]; 0,43	0,43	
Race	Other	7	3	42.86	8	2	25.00	1,71 [0,39 ; 7,48]	2,25 [0,25 ; 20,13];	17,86 [-29,52 ; 65,23]; 0,608	0,608	0,523
	White	266	30	11.28	267	28	10.49	1,08 [0,66 ; 1,75]	1,09 [0,63 ; 1,87];	0,79 [-4,5 ; 6,08]; 0,783	0,783	
	No	181	19	10.50	193	18	9.33	1,13 [0,61 ; 2,08]	1,14 [0,58 ; 2,25];	1,17 [-4,89 ; 7,23]; 0,732	0,732	0,8766

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	14	15.22	82	12	14.63	1,04 [0,51 ; 2,12]	1,05 [0,45 ; 2,42];	0,58 [-10,02 ; 11,18]; 1	1	
Region	Eastern Europe	247	26	10.53	244	23	9.43	1,12 [0,66 ; 1,9]	1,13 [0,63 ; 2,04];	1,1 [-4,2 ; 6,4]; 0,764	0,764	0,8715
	USA and Western Europe	26	7	26.92	31	7	22.58	1,19 [0,48 ; 2,96]	1,26 [0,38 ; 4,23];	4,34 [-18,18 ; 26,87]; 0,764	0,764	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Psychiatric disorders | any

4.2.16 Vascular disorders - any

Tabelle 73: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	12	8.00	146	9	6.16	1,3 [0,56 ; 2,99]	1,32 [0,54 ; 3,24];	1,84 [-4 ; 7,67]; 0,652	0,652	0,1188
	>= 38 years	123	8	6.50	129	16	12.40	0,52 [0,23 ; 1,18]	0,49 [0,2 ; 1,19];	-5,9 [-13,06 ; 1,27]; 0,135	0,135	
Disease Severity at baseline (EDSS)	<=3.5	201	17	8.46	208	20	9.62	0,88 [0,47 ; 1,63]	0,87 [0,44 ; 1,71];	-1,16 [-6,71 ; 4,4]; 0,732	0,732	0,5603
	>3.5	72	3	4.17	67	5	7.46	0,56 [0,14 ; 2,25]	0,54 [0,12 ; 2,35];	-3,3 [-11,1 ; 4,51]; 0,482	0,482	
Gender	Female	167	15	8.98	180	16	8.89	1,01 [0,52 ; 1,98]	1,01 [0,48 ; 2,12];	0,09 [-5,91 ; 6,1]; 1	1	0,2643
	Male	106	5	4.72	95	9	9.47	0,5 [0,17 ; 1,43]	0,47 [0,15 ; 1,46];	-4,76 [-11,9 ; 2,38]; 0,267	0,267	
Number of baseline Gd-enhancing lesions	>=1	117	10	8.55	116	11	9.48	0,9 [0,4 ; 2,04]	0,89 [0,36 ; 2,19];	-0,94 [-8,29 ; 6,42]; 0,823	0,823	0,7069
	0	155	10	6.45	157	14	8.92	0,72 [0,33 ; 1,58]	0,7 [0,3 ; 1,64];	-2,47 [-8,37 ; 3,44]; 0,525	0,525	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	9	8.33	92	9	9.78	0,85 [0,35 ; 2,06]	0,84 [0,32 ; 2,21];	-1,45 [-9,45 ; 6,55]; 0,806	0,806	0,933
	>=3	42	2	4.76	58	3	5.17	0,92 [0,16 ; 5,27]	0,92 [0,15 ; 5,74];	-0,41 [-9,01 ; 8,19]; 1	1	
	2	123	9	7.32	125	13	10.40	0,7 [0,31 ; 1,59]	0,68 [0,28 ; 1,65];	-3,08 [-10,14 ; 3,98]; 0,504	0,504	
Race	Other	7	1	14.29	8	0	0.00	3,38 [0,16 ; 71,67]	3,92 [0,14 ; 112,9];	13,19 [-17,72 ; 44,11]; 0,467	0,467	0,1675
	White	266	19	7.14	267	25	9.36	0,76 [0,43 ; 1,35]	0,74 [0,4 ; 1,39];	-2,22 [-6,89 ; 2,45]; 0,432	0,432	
	No	181	8	4.42	193	18	9.33	0,47 [0,21 ; 1,06]	0,45 [0,19 ; 1,06];	-4,91 [-9,99 ; 0,17]; 0,069	0,069	0,0508

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	12	13.04	82	7	8.54	1,53 [0,63 ; 3,7]	1,61 [0,6 ; 4,3];	4,51 [-4,65 ; 13,67]; 0,466	0,466	
Region	Eastern Europe	247	17	6.88	244	21	8.61	0,8 [0,43 ; 1,48]	0,78 [0,4 ; 1,53];	-1,72 [-6,45 ; 3]; 0,503	0,503	0,8966
	USA and Western Europe	26	3	11.54	31	4	12.90	0,89 [0,22 ; 3,64]	0,88 [0,18 ; 4,35];	-1,36 [-18,4 ; 15,67]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Vascular disorders | any

4.2.17 Blood and lymphatic system disorders - any

Tabelle 74: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	25	16.67	146	19	13.01	1,28 [0,74 ; 2,22]	1,34 [0,7 ; 2,55];	3,65 [-4,43 ; 11,74]; 0,416	0,416	0,0949
	>= 38 years	123	8	6.50	129	15	11.63	0,56 [0,25 ; 1,27]	0,53 [0,22 ; 1,3];	-5,12 [-12,17 ; 1,92]; 0,192	0,192	
Disease Severity at baseline (EDSS)	<=3.5	201	26	12.94	208	25	12.02	1,08 [0,64 ; 1,8]	1,09 [0,6 ; 1,96];	0,92 [-5,49 ; 7,32]; 0,881	0,881	0,4626
	>3.5	72	7	9.72	67	9	13.43	0,72 [0,29 ; 1,83]	0,69 [0,24 ; 1,98];	-3,71 [-14,36 ; 6,94]; 0,598	0,598	
Gender	Female	167	21	12.57	180	23	12.78	0,98 [0,57 ; 1,71]	0,98 [0,52 ; 1,85];	-0,2 [-7,21 ; 6,8]; 1	1	0,9896
	Male	106	12	11.32	95	11	11.58	0,98 [0,45 ; 2,11]	0,97 [0,41 ; 2,33];	-0,26 [-9,08 ; 8,56]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	117	12	10.26	116	13	11.21	0,92 [0,44 ; 1,92]	0,91 [0,39 ; 2,08];	-0,95 [-8,9 ; 7]; 0,836	0,836	0,7527
	0	155	21	13.55	157	20	12.74	1,06 [0,6 ; 1,88]	1,07 [0,56 ; 2,07];	0,81 [-6,69 ; 8,31]; 0,868	0,868	
	NA	1	0	0.00	2	1	50.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	9	8.33	92	7	7.61	1,1 [0,42 ; 2,83]	1,1 [0,39 ; 3,09];	0,72 [-6,79 ; 8,24]; 1	1	0,99
	>=3	42	8	19.05	58	11	18.97	1 [0,44 ; 2,28]	1,01 [0,37 ; 2,77];	0,08 [-15,5 ; 15,66]; 1	1	
	2	123	16	13.01	125	16	12.80	1,02 [0,53 ; 1,94]	1,02 [0,48 ; 2,14];	0,21 [-8,14 ; 8,55]; 1	1	
Race	Other	7	0	0.00	8	2	25.00	0,22 [0,01 ; 4,02]	0,17 [0,01 ; 4,31];	-21,53 [-55,26 ; 12,2]; 0,467	0,467	0,0945
	White	266	33	12.41	267	32	11.99	1,04 [0,66 ; 1,63]	1,04 [0,62 ; 1,75];	0,42 [-5,14 ; 5,98]; 0,895	0,895	
	No	181	22	12.15	193	19	9.84	1,23 [0,69 ; 2,2]	1,27 [0,66 ; 2,43];	2,31 [-4,04 ; 8,66]; 0,511	0,511	0,1731

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	11	11.96	82	15	18.29	0,65 [0,32 ; 1,34]	0,61 [0,26 ; 1,41];	-6,34 [-17,01 ; 4,34]; 0,289	0,289	
Region	Eastern Europe	247	33	13.36	244	31	12.70	1,05 [0,67 ; 1,66]	1,06 [0,63 ; 1,79];	0,66 [-5,3 ; 6,61]; 0,894	0,894	0,0507
	USA and Western Europe	26	0	0.00	31	3	9.68	0,17 [0,01 ; 3,13]	0,15 [0,01 ; 3,12];	-9,09 [-21,04 ; 2,86]; 0,12	0,12	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Blood and lymphatic system disorders | any

4.2.18 Gastrointestinal disorders - Abdominal pain upper

Tabelle 75: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	6	4.00	146	6	4.11	0,97 [0,32 ; 2,95]	0,97 [0,31 ; 3,09];	-0,11 [-4,6 ; 4,39]; 1	1	0,0569
	>= 38 years	123	1	0.81	129	8	6.20	0,13 [0,02 ; 1,03]	0,12 [0,02 ; 1,01];	-5,39 [-9,84 ; -0,93]; 0,036	0,036	
Disease Severity at baseline (EDSS)	<=3.5	201	7	3.48	208	14	6.73	0,52 [0,21 ; 1,26]	0,5 [0,2 ; 1,27];	-3,25 [-7,49 ; 1]; 0,179	0,179	0,9999
	>3.5	72	0	0.00	67	0	0.00	0,93 [0,02 ; 46,29]	0,93 [0,02 ; 47,58];	-0,05 [-2,83 ; 2,73]; 1	1	
Gender	Female	167	6	3.59	180	12	6.67	0,54 [0,21 ; 1,4]	0,52 [0,19 ; 1,42];	-3,07 [-7,68 ; 1,54]; 0,232	0,232	0,9017
	Male	106	1	0.94	95	2	2.11	0,45 [0,04 ; 4,86]	0,44 [0,04 ; 4,96];	-1,16 [-4,59 ; 2,26]; 0,603	0,603	
Number of baseline Gd-enhancing lesions	>=1	117	3	2.56	116	8	6.90	0,37 [0,1 ; 1,37]	0,36 [0,09 ; 1,37];	-4,33 [-9,76 ; 1,1]; 0,136	0,136	0,5062
	0	155	4	2.58	157	6	3.82	0,68 [0,19 ; 2,35]	0,67 [0,18 ; 2,41];	-1,24 [-5,14 ; 2,66]; 0,75	0,75	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	4	3.70	92	6	6.52	0,57 [0,17 ; 1,95]	0,55 [0,15 ; 2,02];	-2,82 [-8,99 ; 3,36]; 0,518	0,518	0,5887
	>=3	42	1	2.38	58	1	1.72	1,38 [0,09 ; 21,46]	1,39 [0,08 ; 22,88];	0,66 [-5,04 ; 6,36]; 1	1	
	2	123	2	1.63	125	7	5.60	0,29 [0,06 ; 1,37]	0,28 [0,06 ; 1,37];	-3,97 [-8,58 ; 0,63]; 0,172	0,172	
Race	Other	7	1	14.29	8	1	12.50	1,14 [0,09 ; 15,08]	1,17 [0,06 ; 22,94];	1,79 [-32,81 ; 36,39]; 1	1	0,5558
	White	266	6	2.26	267	13	4.87	0,46 [0,18 ; 1,2]	0,45 [0,17 ; 1,2];	-2,61 [-5,75 ; 0,52]; 0,159	0,159	
	No	181	6	3.31	193	9	4.66	0,71 [0,26 ; 1,96]	0,7 [0,24 ; 2,01];	-1,35 [-5,3 ; 2,61]; 0,603	0,603	0,2107

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	1	1.09	82	5	6.10	0,18 [0,02 ; 1,49]	0,17 [0,02 ; 1,48];	-5,01 [-10,61 ; 0,59]; 0,101	0,101	
Region	Eastern Europe	247	6	2.43	244	12	4.92	0,49 [0,19 ; 1,3]	0,48 [0,18 ; 1,3];	-2,49 [-5,81 ; 0,83]; 0,157	0,157	0,8912
	USA and Western Europe	26	1	3.85	31	2	6.45	0,6 [0,06 ; 6,21]	0,58 [0,05 ; 6,78];	-2,61 [-13,98 ; 8,77]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Gastrointestinal disorders | Abdominal pain upper

4.2.19 General disorders and administration site conditions - Fatigue

Tabelle 76: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	8	5.33	146	2	1.37	3,89 [0,84 ; 18,03]	4,06 [0,85 ; 19,43];	3,96 [-0,1 ; 8,02]; 0,104	0,104	0,0441
	>= 38 years	123	4	3.25	129	7	5.43	0,6 [0,18 ; 2]	0,59 [0,17 ; 2,05];	-2,17 [-7,19 ; 2,84]; 0,541	0,541	
Disease Severity at baseline (EDSS)	<=3.5	201	12	5.97	208	7	3.37	1,77 [0,71 ; 4,41]	1,82 [0,7 ; 4,73];	2,6 [-1,49 ; 6,7]; 0,245	0,245	0,0454
	>3.5	72	0	0.00	67	2	2.99	0,19 [0,01 ; 3,81]	0,18 [0,01 ; 3,83];	-2,99 [-7,85 ; 1,86]; 0,234	0,234	
Gender	Female	167	8	4.79	180	6	3.33	1,44 [0,51 ; 4,06]	1,46 [0,5 ; 4,3];	1,46 [-2,71 ; 5,62]; 0,589	0,589	0,8395
	Male	106	4	3.77	95	3	3.16	1,19 [0,27 ; 5,2]	1,2 [0,26 ; 5,52];	0,62 [-4,44 ; 5,67]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	117	7	5.98	116	5	4.31	1,39 [0,45 ; 4,25]	1,41 [0,44 ; 4,59];	1,67 [-4 ; 7,34]; 0,768	0,768	0,91
	0	155	5	3.23	157	4	2.55	1,27 [0,35 ; 4,63]	1,27 [0,34 ; 4,84];	0,68 [-3,04 ; 4,39]; 0,749	0,749	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	4	3.70	92	2	2.17	1,7 [0,32 ; 9,09]	1,73 [0,31 ; 9,67];	1,53 [-3,11 ; 6,17]; 0,689	0,689	0,8132
	>=3	42	1	2.38	58	2	3.45	0,69 [0,06 ; 7,37]	0,68 [0,06 ; 7,79];	-1,07 [-7,65 ; 5,51]; 1	1	
	2	123	7	5.69	125	5	4.00	1,42 [0,46 ; 4,36]	1,45 [0,45 ; 4,69];	1,69 [-3,65 ; 7,04]; 0,569	0,569	
Race	Other	7	1	14.29	8	1	12.50	1,14 [0,09 ; 15,08]	1,17 [0,06 ; 22,94];	1,79 [-32,81 ; 36,39]; 1	1	0,9101
	White	266	11	4.14	267	8	3.00	1,38 [0,56 ; 3,38]	1,4 [0,55 ; 3,53];	1,14 [-2,01 ; 4,29]; 0,495	0,495	
	No	181	7	3.87	193	6	3.11	1,24 [0,43 ; 3,63]	1,25 [0,41 ; 3,8];	0,76 [-2,97 ; 4,48]; 0,781	0,781	0,8405

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	5	5.43	82	3	3.66	1,49 [0,37 ; 6,02]	1,51 [0,35 ; 6,54];	1,78 [-4,39 ; 7,94]; 0,724	0,724	
Region	Eastern Europe	247	9	3.64	244	5	2.05	1,78 [0,6 ; 5,23]	1,81 [0,6 ; 5,47];	1,59 [-1,34 ; 4,53]; 0,417	0,417	0,4652
	USA and Western Europe	26	3	11.54	31	4	12.90	0,89 [0,22 ; 3,64]	0,88 [0,18 ; 4,35];	-1,36 [-18,4 ; 15,67]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - General disorders and administration site conditions | Fatigue

4.2.20 Infections and infestations - Influenza

Tabelle 77: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	7	4.67	146	6	4.11	1,14 [0,39 ; 3,3]	1,14 [0,37 ; 3,48];	0,56 [-4,11 ; 5,22]; 1	1	0,9228
	>= 38 years	123	5	4.07	129	5	3.88	1,05 [0,31 ; 3,53]	1,05 [0,3 ; 3,72];	0,19 [-4,64 ; 5,01]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	201	10	4.98	208	8	3.85	1,29 [0,52 ; 3,21]	1,31 [0,51 ; 3,39];	1,13 [-2,85 ; 5,11]; 0,635	0,635	0,4614
	>3.5	72	2	2.78	67	3	4.48	0,62 [0,11 ; 3,6]	0,61 [0,1 ; 3,77];	-1,7 [-7,94 ; 4,54]; 0,672	0,672	
Gender	Female	167	6	3.59	180	8	4.44	0,81 [0,29 ; 2,28]	0,8 [0,27 ; 2,36];	-0,85 [-4,98 ; 3,28]; 0,788	0,788	0,3523
	Male	106	6	5.66	95	3	3.16	1,79 [0,46 ; 6,97]	1,84 [0,45 ; 7,57];	2,5 [-3,13 ; 8,13]; 0,504	0,504	
Number of baseline Gd-enhancing lesions	>=1	117	6	5.13	116	6	5.17	0,99 [0,33 ; 2,98]	0,99 [0,31 ; 3,17];	-0,04 [-5,72 ; 5,63]; 1	1	0,8047
	0	155	6	3.87	157	5	3.18	1,22 [0,38 ; 3,9]	1,22 [0,37 ; 4,1];	0,69 [-3,41 ; 4,78]; 0,769	0,769	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	9	8.33	92	0	0.00	16,21 [0,96 ; 274,79]	17,66 [1,01 ; 307,77];	8,18 [2,68 ; 13,68]; 0,002	0,002	0,0002
	>=3	42	1	2.38	58	1	1.72	1,38 [0,09 ; 21,46]	1,39 [0,08 ; 22,88];	0,66 [-5,04 ; 6,36]; 1	1	
	2	123	2	1.63	125	10	8.00	0,2 [0,05 ; 0,91]	0,19 [0,04 ; 0,89];	-6,37 [-11,63 ; -1,12]; 0,034	0,034	
Race	Other	7	1	14.29	8	0	0.00	3,38 [0,16 ; 71,67]	3,92 [0,14 ; 112,9];	13,19 [-17,72 ; 44,11]; 0,467	0,467	0,213
	White	266	11	4.14	267	11	4.12	1 [0,44 ; 2,28]	1 [0,43 ; 2,36];	0,02 [-3,36 ; 3,39]; 1	1	
	No	181	8	4.42	193	7	3.63	1,22 [0,45 ; 3,29]	1,23 [0,44 ; 3,46];	0,79 [-3,2 ; 4,78]; 0,795	0,795	0,7156

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	4	4.35	82	4	4.88	0,89 [0,23 ; 3,45]	0,89 [0,21 ; 3,66];	-0,53 [-6,78 ; 5,72]; 1	1	
Region	Eastern Europe	247	7	2.83	244	8	3.28	0,86 [0,32 ; 2,35]	0,86 [0,31 ; 2,41];	-0,44 [-3,49 ; 2,6]; 0,8	0,8	0,3101
	USA and Western Europe	26	5	19.23	31	3	9.68	1,99 [0,52 ; 7,54]	2,22 [0,48 ; 10,36];	9,55 [-8,83 ; 27,93]; 0,448	0,448	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Influenza

4.2.21 Gastrointestinal disorders - Nausea

Tabelle 78: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	18	12.00	146	6	4.11	2,92 [1,19 ; 7,15]	3,18 [1,23 ; 8,26];	7,89 [1,77 ; 14,01]; 0,018	0,018	0,1841
	>= 38 years	123	11	8.94	129	9	6.98	1,28 [0,55 ; 2,99]	1,31 [0,52 ; 3,28];	1,97 [-4,72 ; 8,66]; 0,644	0,644	
Disease Severity at baseline (EDSS)	<=3.5	201	20	9.95	208	11	5.29	1,88 [0,93 ; 3,83]	1,98 [0,92 ; 4,24];	4,66 [-0,47 ; 9,8]; 0,093	0,093	0,8614
	>3.5	72	9	12.50	67	4	5.97	2,09 [0,68 ; 6,48]	2,25 [0,66 ; 7,69];	6,53 [-2,99 ; 16,05]; 0,248	0,248	
Gender	Female	167	24	14.37	180	12	6.67	2,16 [1,11 ; 4,17]	2,35 [1,13 ; 4,87];	7,7 [1,26 ; 14,15]; 0,022	0,022	0,6039
	Male	106	5	4.72	95	3	3.16	1,49 [0,37 ; 6,08]	1,52 [0,35 ; 6,53];	1,56 [-3,79 ; 6,91]; 0,724	0,724	
Number of baseline Gd-enhancing lesions	>=1	117	14	11.97	116	5	4.31	2,78 [1,03 ; 7,46]	3,02 [1,05 ; 8,67];	7,66 [0,71 ; 14,6]; 0,053	0,053	0,3376
	0	155	15	9.68	157	10	6.37	1,52 [0,7 ; 3,28]	1,57 [0,68 ; 3,62];	3,31 [-2,71 ; 9,33]; 0,304	0,304	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	14	12.96	92	4	4.35	2,98 [1,02 ; 8,74]	3,28 [1,04 ; 10,33];	8,62 [1,03 ; 16,2]; 0,046	0,046	0,5421
	>=3	42	4	9.52	58	3	5.17	1,84 [0,43 ; 7,8]	1,93 [0,41 ; 9,12];	4,35 [-6,2 ; 14,9]; 0,449	0,449	
	2	123	11	8.94	125	8	6.40	1,4 [0,58 ; 3,36]	1,44 [0,56 ; 3,7];	2,54 [-4,08 ; 9,16]; 0,483	0,483	
Race	Other	7	2	28.57	8	1	12.50	2,29 [0,26 ; 20,13]	2,8 [0,2 ; 40,06];	16,07 [-24,49 ; 56,63]; 0,569	0,569	0,8198
	White	266	27	10.15	267	14	5.24	1,94 [1,04 ; 3,61]	2,04 [1,05 ; 3,99];	4,91 [0,4 ; 9,41]; 0,036	0,036	
	No	181	17	9.39	193	10	5.18	1,81 [0,85 ; 3,85]	1,9 [0,84 ; 4,26];	4,21 [-1,07 ; 9,49]; 0,161	0,161	0,7752

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	12	13.04	82	5	6.10	2,14 [0,79 ; 5,81]	2,31 [0,78 ; 6,86];	6,95 [-1,67 ; 15,56]; 0,135	0,135	
Region	Eastern Europe	247	24	9.72	244	11	4.51	2,16 [1,08 ; 4,3]	2,28 [1,09 ; 4,76];	5,21 [0,69 ; 9,73]; 0,034	0,034	0,6716
	USA and Western Europe	26	5	19.23	31	4	12.90	1,49 [0,45 ; 4,98]	1,61 [0,38 ; 6,74];	6,33 [-12,88 ; 25,53]; 0,718	0,718	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Gastrointestinal disorders | Nausea

4.2.22 Musculoskeletal and connective tissue disorders - Back pain

Tabelle 79: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	7	4.67	146	12	8.22	0,57 [0,23 ; 1,4]	0,55 [0,21 ; 1,43];	-3,55 [-9,14 ; 2,04]; 0,242	0,242	0,8591
	>= 38 years	123	9	7.32	129	18	13.95	0,52 [0,24 ; 1,12]	0,49 [0,21 ; 1,13];	-6,64 [-14,18 ; 0,91]; 0,105	0,105	
Disease Severity at baseline (EDSS)	<=3.5	201	9	4.48	208	21	10.10	0,44 [0,21 ; 0,94]	0,42 [0,19 ; 0,93];	-5,62 [-10,61 ; -0,62]; 0,036	0,036	0,4517
	>3.5	72	7	9.72	67	9	13.43	0,72 [0,29 ; 1,83]	0,69 [0,24 ; 1,98];	-3,71 [-14,36 ; 6,94]; 0,598	0,598	
Gender	Female	167	12	7.19	180	19	10.56	0,68 [0,34 ; 1,36]	0,66 [0,31 ; 1,4];	-3,37 [-9,33 ; 2,59]; 0,347	0,347	0,2628
	Male	106	4	3.77	95	11	11.58	0,33 [0,11 ; 0,99]	0,3 [0,09 ; 0,97];	-7,81 [-15,19 ; -0,42]; 0,057	0,057	
Number of baseline Gd-enhancing lesions	>=1	117	9	7.69	116	18	15.52	0,5 [0,23 ; 1,06]	0,45 [0,19 ; 1,06];	-7,82 [-15,99 ; 0,34]; 0,068	0,068	0,7239
	0	155	7	4.52	157	12	7.64	0,59 [0,24 ; 1,46]	0,57 [0,22 ; 1,49];	-3,13 [-8,41 ; 2,16]; 0,344	0,344	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	8	7.41	92	10	10.87	0,68 [0,28 ; 1,65]	0,66 [0,25 ; 1,74];	-3,46 [-11,52 ; 4,59]; 0,461	0,461	0,3122
	>=3	42	4	9.52	58	6	10.34	0,92 [0,28 ; 3,06]	0,91 [0,24 ; 3,46];	-0,82 [-12,66 ; 11,02]; 1	1	
	2	123	4	3.25	125	14	11.20	0,29 [0,1 ; 0,86]	0,27 [0,09 ; 0,83];	-7,95 [-14,3 ; -1,59]; 0,025	0,025	
Race	Other	7	3	42.86	8	3	37.50	1,14 [0,33 ; 3,94]	1,25 [0,16 ; 9,92];	5,36 [-44,34 ; 55,05]; 1	1	0,3664
	White	266	13	4.89	267	27	10.11	0,48 [0,25 ; 0,92]	0,46 [0,23 ; 0,91];	-5,23 [-9,67 ; -0,78]; 0,031	0,031	
	No	181	9	4.97	193	25	12.95	0,38 [0,18 ; 0,8]	0,35 [0,16 ; 0,78];	-7,98 [-13,68 ; -2,28]; 0,011	0,011	0,0744

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	7	7.61	82	5	6.10	1,25 [0,41 ; 3,78]	1,27 [0,39 ; 4,16];	1,51 [-5,98 ; 9,01]; 0,771	0,771	
Region	Eastern Europe	247	11	4.45	244	24	9.84	0,45 [0,23 ; 0,9]	0,43 [0,2 ; 0,89];	-5,38 [-9,92 ; -0,85]; 0,023	0,023	0,2779
	USA and Western Europe	26	5	19.23	31	6	19.35	0,99 [0,34 ; 2,89]	0,99 [0,26 ; 3,72];	-0,12 [-20,69 ; 20,44]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Musculoskeletal and connective tissue disorders | Back pain

4.2.23 Musculoskeletal and connective tissue disorders - Pain in extremity

Tabelle 80: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	8	5.33	146	3	2.05	2,6 [0,7 ; 9,59]	2,69 [0,7 ; 10,33];	3,28 [-0,99 ; 7,55]; 0,218	0,218	0,1498
	>= 38 years	123	7	5.69	129	9	6.98	0,82 [0,31 ; 2,12]	0,8 [0,29 ; 2,23];	-1,29 [-7,29 ; 4,72]; 0,798	0,798	
Disease Severity at baseline (EDSS)	<=3.5	201	10	4.98	208	8	3.85	1,29 [0,52 ; 3,21]	1,31 [0,51 ; 3,39];	1,13 [-2,85 ; 5,11]; 0,635	0,635	0,8989
	>3.5	72	5	6.94	67	4	5.97	1,16 [0,33 ; 4,15]	1,18 [0,3 ; 4,58];	0,97 [-7,19 ; 9,14]; 1	1	
Gender	Female	167	7	4.19	180	10	5.56	0,75 [0,29 ; 1,94]	0,74 [0,28 ; 2];	-1,36 [-5,88 ; 3,16]; 0,625	0,625	0,0669
	Male	106	8	7.55	95	2	2.11	3,58 [0,78 ; 16,47]	3,8 [0,79 ; 18,34];	5,44 [-0,36 ; 11,24]; 0,106	0,106	
Number of baseline Gd-enhancing lesions	>=1	117	10	8.55	116	2	1.72	4,96 [1,11 ; 22,13]	5,33 [1,14 ; 24,87];	6,82 [1,23 ; 12,42]; 0,034	0,034	0,0065
	0	155	5	3.23	157	10	6.37	0,51 [0,18 ; 1,45]	0,49 [0,16 ; 1,47];	-3,14 [-7,87 ; 1,58]; 0,29	0,29	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	6	5.56	92	4	4.35	1,28 [0,37 ; 4,39]	1,29 [0,35 ; 4,73];	1,21 [-4,79 ; 7,21]; 0,756	0,756	0,7365
	>=3	42	2	4.76	58	1	1.72	2,76 [0,26 ; 29,47]	2,85 [0,25 ; 32,51];	3,04 [-4,22 ; 10,3]; 0,571	0,571	
	2	123	7	5.69	125	7	5.60	1,02 [0,37 ; 2,81]	1,02 [0,35 ; 2,99];	0,09 [-5,65 ; 5,84]; 1	1	
Race	Other	7	3	42.86	8	0	0.00	7,88 [0,48 ; 130,28]	13,22 [0,55 ; 316,64];	38,19 [0,7 ; 75,69]; 0,077	0,077	0,0248
	White	266	12	4.51	267	12	4.49	1 [0,46 ; 2,19]	1 [0,44 ; 2,28];	0,02 [-3,5 ; 3,54]; 1	1	
	No	181	7	3.87	193	11	5.70	0,68 [0,27 ; 1,71]	0,67 [0,25 ; 1,76];	-1,83 [-6,14 ; 2,48]; 0,474	0,474	0,0143

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	8	8.70	82	1	1.22	7,13 [0,91 ; 55,8]	7,71 [0,94 ; 63,07];	7,48 [1,25 ; 13,7]; 0,037	0,037	
Region	Eastern Europe	247	8	3.24	244	11	4.51	0,72 [0,29 ; 1,76]	0,71 [0,28 ; 1,79];	-1,27 [-4,68 ; 2,14]; 0,493	0,493	0,0076
	USA and Western Europe	26	7	26.92	31	1	3.23	8,35 [1,1 ; 63,51]	11,05 [1,26 ; 97,06];	23,7 [5,55 ; 41,85]; 0,018	0,018	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Musculoskeletal and connective tissue disorders | Pain in extremity

4.2.24 Nervous system disorders - Headache

Tabelle 81: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	52	34.67	146	33	22.60	1,53 [1,06 ; 2,22]	1,82 [1,09 ; 3,04];	12,06 [1,86 ; 22,26]; 0,029	0,029	0,5053
	>= 38 years	123	32	26.02	129	26	20.16	1,29 [0,82 ; 2,03]	1,39 [0,77 ; 2,51];	5,86 [-4,53 ; 16,26]; 0,297	0,297	
Disease Severity at baseline (EDSS)	<=3.5	201	62	30.85	208	49	23.56	1,31 [0,95 ; 1,8]	1,45 [0,93 ; 2,24];	7,29 [-1,32 ; 15,89]; 0,119	0,119	0,2492
	>3.5	72	22	30.56	67	10	14.93	2,05 [1,05 ; 4]	2,51 [1,08 ; 5,8];	15,63 [1,99 ; 29,27]; 0,043	0,043	
Gender	Female	167	57	34.13	180	49	27.22	1,25 [0,91 ; 1,72]	1,39 [0,88 ; 2,19];	6,91 [-2,79 ; 16,6]; 0,199	0,199	0,1043
	Male	106	27	25.47	95	10	10.53	2,42 [1,24 ; 4,73]	2,91 [1,32 ; 6,39];	14,95 [4,61 ; 25,28]; 0,007	0,007	
Number of baseline Gd-enhancing lesions	>=1	117	36	30.77	116	32	27.59	1,12 [0,75 ; 1,67]	1,17 [0,66 ; 2,05];	3,18 [-8,48 ; 14,85]; 0,666	0,666	0,1207
	0	155	48	30.97	157	27	17.20	1,8 [1,19 ; 2,73]	2,16 [1,26 ; 3,69];	13,77 [4,4 ; 23,14]; 0,005	0,005	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	30	27.78	92	22	23.91	1,16 [0,72 ; 1,87]	1,22 [0,65 ; 2,32];	3,86 [-8,27 ; 16]; 0,628	0,628	0,4745
	>=3	42	13	30.95	58	9	15.52	1,99 [0,94 ; 4,23]	2,44 [0,93 ; 6,41];	15,44 [-1,37 ; 32,24]; 0,088	0,088	
	2	123	41	33.33	125	28	22.40	1,49 [0,99 ; 2,24]	1,73 [0,99 ; 3,04];	10,93 [-0,15 ; 22,02]; 0,066	0,066	
Race	Other	7	4	57.14	8	1	12.50	4,57 [0,66 ; 31,89]	9,33 [0,71 ; 122,57];	44,64 [1,41 ; 87,88]; 0,119	0,119	0,1436
	White	266	80	30.08	267	58	21.72	1,38 [1,03 ; 1,85]	1,55 [1,05 ; 2,29];	8,35 [0,95 ; 15,76]; 0,03	0,03	
	No	181	56	30.94	193	46	23.83	1,3 [0,93 ; 1,81]	1,43 [0,91 ; 2,26];	7,11 [-1,92 ; 16,13]; 0,132	0,132	0,272

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	28	30.43	82	13	15.85	1,92 [1,07 ; 3,45]	2,32 [1,11 ; 4,87];	14,58 [2,3 ; 26,87]; 0,031	0,031	
Region	Eastern Europe	247	75	30.36	244	53	21.72	1,4 [1,03 ; 1,89]	1,57 [1,05 ; 2,36];	8,64 [0,92 ; 16,37]; 0,031	0,031	0,5989
	USA and Western Europe	26	9	34.62	31	6	19.35	1,79 [0,73 ; 4,36]	2,21 [0,66 ; 7,34];	15,26 [-7,71 ; 38,23]; 0,236	0,236	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Nervous system disorders | Headache

4.2.25 Musculoskeletal and connective tissue disorders - Neck pain

Tabelle 82: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	4	2.67	146	5	3.42	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>= 38 years	123	6	4.88	129	1	0.78	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	201	8	3.98	208	4	1.92	2,07 [0,63 ; 6,77]	2,11 [0,63 ; 7,13];	2,06 [-1,23 ; 5,34]; 0,253	0,253	0,4901
	>3.5	72	2	2.78	67	2	2.99	0,93 [0,13 ; 6,42]	0,93 [0,13 ; 6,79];	-0,21 [-5,78 ; 5,36]; 1	1	
Gender	Female	167	8	4.79	180	3	1.67	2,87 [0,78 ; 10,65]	2,97 [0,77 ; 11,38];	3,12 [-0,62 ; 6,86]; 0,128	0,128	0,1518
	Female	167	8	4.79	180	5	2.78	2,87 [0,78 ; 10,65]	2,97 [0,77 ; 11,38];	3,12 [-0,62 ; 6,86]; 0,128	0,128	
	Female	167	2	1.20	180	3	1.67	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Female	167	2	1.20	180	5	2.78	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Male	106	2	1.89	95	3	3.16	0,6 [0,1 ; 3,5]	0,59 [0,1 ; 3,61];	-1,27 [-5,64 ; 3,1]; 0,669	0,669	
	Male	106	2	1.89	95	1	1.05	0,6 [0,1 ; 3,5]	0,59 [0,1 ; 3,61];	-1,27 [-5,64 ; 3,1]; 0,669	0,669	
	Male	106	8	7.55	95	3	3.16	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Male	106	8	7.55	95	1	1.05	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of baseline Gd-enhancing lesions	>=1	117	6	5.13	116	2	1.72	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	155	4	2.58	157	4	2.55	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Number of relapses experienced in the 2 years prior to study start	<=1	108	3	2.78	92	3	3.26	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	1	2.38	58	1	1.72	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	6	4.88	125	2	1.60	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	0	0.00	8	2	25.00	0,22 [0,01 ; 4,02]	0,17 [0,01 ; 4,31];	-21,53 [-55,26 ; 12,2]; 0,467	0,467	0,0361
	White	266	10	3.76	267	4	1.50	2,51 [0,8 ; 7,9]	2,57 [0,8 ; 8,29];	2,26 [-0,45 ; 4,97]; 0,113	0,113	
Received approved disease modifying MS drug prior to enrollment	No	181	7	3.87	193	3	1.55	2,49 [0,65 ; 9,48]	2,55 [0,65 ; 10,01];	2,31 [-0,99 ; 5,62]; 0,208	0,208	0,3287
	Yes	92	3	3.26	82	3	3.66	0,89 [0,18 ; 4,29]	0,89 [0,17 ; 4,52];	-0,4 [-5,85 ; 5,05]; 1	1	
Region	Eastern Europe	247	8	3.24	244	3	1.23	2,63 [0,71 ; 9,81]	2,69 [0,7 ; 10,26];	2,01 [-0,6 ; 4,61]; 0,221	0,221	0,2821
	USA and Western Europe	26	2	7.69	31	3	9.68	0,79 [0,14 ; 4,4]	0,78 [0,12 ; 5,05];	-1,99 [-16,59 ; 12,62]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Musculoskeletal and connective tissue disorders | Neck pain

4.2.26 Cardiac disorders - Tachycardia

Tabelle 83: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	6	4.00	146	2	1.37	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>= 38 years	123	4	3.25	129	4	3.10	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	201	7	3.48	208	5	2.40	1,45 [0,47 ; 4,49]	1,46 [0,46 ; 4,69];	1,08 [-2,2 ; 4,36]; 0,57	0,57	0,5973
	>3.5	72	3	4.17	67	1	1.49	2,79 [0,3 ; 26,19]	2,87 [0,29 ; 28,29];	2,67 [-2,78 ; 8,13]; 0,621	0,621	
Number of baseline Gd-enhancing lesions	>=1	117	6	5.13	116	1	0.86	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	155	4	2.58	157	5	3.18	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	5	4.63	92	1	1.09	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	1	2.38	58	2	3.45	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	4	3.25	125	3	2.40	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	1	14.29	8	0	0.00	3,38 [0,16 ; 71,67]	3,92 [0,14 ; 112,9];	13,19 [-17,72 ; 44,11]; 0,467	0,467	0,2841
	White	266	9	3.38	267	6	2.25	1,51 [0,54 ; 4,17]	1,52 [0,53 ; 4,34];	1,14 [-1,67 ; 3,94]; 0,448	0,448	
Received approved disease modifying MS drug prior to enrollment	No	181	6	3.31	193	4	2.07	1,6 [0,46 ; 5,58]	1,62 [0,45 ; 5,84];	1,24 [-2,05 ; 4,54]; 0,532	0,532	0,916
	Yes	92	4	4.35	82	2	2.44	1,78 [0,34 ; 9,48]	1,82 [0,32 ; 10,2];	1,91 [-3,43 ; 7,25]; 0,685	0,685	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	247	7	2.83	244	5	2.05	1,38 [0,45 ; 4,3]	1,39 [0,44 ; 4,45];	0,78 [-1,94 ; 3,51]; 0,772	0,772	0,4187
	USA and Western Europe	26	3	11.54	31	1	3.23	3,58 [0,4 ; 32,36]	3,91 [0,38 ; 40,12];	8,31 [-5,45 ; 22,08]; 0,322	0,322	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Cardiac disorders | Tachycardia

4.2.27 Infections and infestations - Nasopharyngitis

Tabelle 84: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	23	15.33	146	26	17.81	0,86 [0,52 ; 1,44]	0,84 [0,45 ; 1,54];	-2,47 [-10,95 ; 6]; 0,64	0,64	0,5282
	>= 38 years	123	11	8.94	129	18	13.95	0,64 [0,32 ; 1,3]	0,61 [0,27 ; 1,34];	-5,01 [-12,83 ; 2,81]; 0,24	0,24	
Disease Severity at baseline (EDSS)	<=3.5	201	26	12.94	208	37	17.79	0,73 [0,46 ; 1,15]	0,69 [0,4 ; 1,18];	-4,85 [-11,82 ; 2,11]; 0,217	0,217	0,4682
	>3.5	72	8	11.11	67	7	10.45	1,06 [0,41 ; 2,77]	1,07 [0,37 ; 3,14];	0,66 [-9,65 ; 10,98]; 1	1	
Gender	Female	167	21	12.57	180	29	16.11	0,78 [0,46 ; 1,31]	0,75 [0,41 ; 1,37];	-3,54 [-10,89 ; 3,82]; 0,363	0,363	0,9929
	Male	106	13	12.26	95	15	15.79	0,78 [0,39 ; 1,55]	0,75 [0,33 ; 1,66];	-3,53 [-13,16 ; 6,11]; 0,543	0,543	
Number of baseline Gd-enhancing lesions	>=1	117	18	15.38	116	23	19.83	0,78 [0,44 ; 1,36]	0,74 [0,37 ; 1,45];	-4,44 [-14,21 ; 5,32]; 0,395	0,395	0,9776
	0	155	16	10.32	157	21	13.38	0,77 [0,42 ; 1,42]	0,75 [0,37 ; 1,49];	-3,05 [-10,22 ; 4,11]; 0,484	0,484	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	14	12.96	92	17	18.48	0,7 [0,37 ; 1,34]	0,66 [0,3 ; 1,42];	-5,52 [-15,67 ; 4,64]; 0,329	0,329	0,354
	>=3	42	1	2.38	58	6	10.34	0,23 [0,03 ; 1,84]	0,21 [0,02 ; 1,83];	-7,96 [-17,06 ; 1,13]; 0,234	0,234	
	2	123	19	15.45	125	21	16.80	0,92 [0,52 ; 1,62]	0,9 [0,46 ; 1,78];	-1,35 [-10,5 ; 7,8]; 0,863	0,863	
Race	Other	7	1	14.29	8	4	50.00	0,29 [0,04 ; 1,99]	0,17 [0,01 ; 2,09];	-35,71 [-78,99 ; 7,56]; 0,282	0,282	0,2004
	White	266	33	12.41	267	40	14.98	0,83 [0,54 ; 1,27]	0,8 [0,49 ; 1,32];	-2,58 [-8,41 ; 3,26]; 0,45	0,45	
	No	181	19	10.50	193	33	17.10	0,61 [0,36 ; 1,04]	0,57 [0,31 ; 1,04];	-6,6 [-13,54 ; 0,34]; 0,073	0,073	0,1311

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	15	16.30	82	11	13.41	1,22 [0,59 ; 2,49]	1,26 [0,54 ; 2,92];	2,89 [-7,66 ; 13,44]; 0,673	0,673	
Region	Eastern Europe	247	29	11.74	244	37	15.16	0,77 [0,49 ; 1,22]	0,74 [0,44 ; 1,25];	-3,42 [-9,45 ; 2,61]; 0,291	0,291	0,8964
	USA and Western Europe	26	5	19.23	31	7	22.58	0,85 [0,31 ; 2,37]	0,82 [0,23 ; 2,96];	-3,35 [-24,47 ; 17,77]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Nasopharyngitis

4.2.28 Infections and infestations - Urinary tract infection

Tabelle 85: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	5	3.33	146	8	5.48	0,61 [0,2 ; 1,82]	0,59 [0,19 ; 1,86];	-2,15 [-6,82 ; 2,53]; 0,408	0,408	0,861
	>= 38 years	123	6	4.88	129	9	6.98	0,7 [0,26 ; 1,91]	0,68 [0,24 ; 1,98];	-2,1 [-7,91 ; 3,72]; 0,598	0,598	
Disease Severity at baseline (EDSS)	<=3.5	201	6	2.99	208	11	5.29	0,56 [0,21 ; 1,5]	0,55 [0,2 ; 1,52];	-2,3 [-6,15 ; 1,54]; 0,323	0,323	0,695
	>3.5	72	5	6.94	67	6	8.96	0,78 [0,25 ; 2,42]	0,76 [0,22 ; 2,61];	-2,01 [-11,02 ; 7]; 0,758	0,758	
Gender	Female	167	10	5.99	180	15	8.33	0,72 [0,33 ; 1,55]	0,7 [0,31 ; 1,61];	-2,35 [-7,75 ; 3,06]; 0,416	0,416	0,7204
	Male	106	1	0.94	95	2	2.11	0,45 [0,04 ; 4,86]	0,44 [0,04 ; 4,96];	-1,16 [-4,59 ; 2,26]; 0,603	0,603	
Number of baseline Gd-enhancing lesions	>=1	117	4	3.42	116	4	3.45	0,99 [0,25 ; 3,87]	0,99 [0,24 ; 4,06];	-0,03 [-4,71 ; 4,65]; 1	1	0,462
	0	155	7	4.52	157	13	8.28	0,55 [0,22 ; 1,33]	0,52 [0,2 ; 1,35];	-3,76 [-9,17 ; 1,65]; 0,248	0,248	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	4	3.70	92	7	7.61	0,49 [0,15 ; 1,61]	0,47 [0,13 ; 1,65];	-3,9 [-10,39 ; 2,58]; 0,351	0,351	0,7358
	>=3	42	1	2.38	58	3	5.17	0,46 [0,05 ; 4,27]	0,45 [0,04 ; 4,46];	-2,79 [-10,12 ; 4,54]; 0,637	0,637	
	2	123	6	4.88	125	7	5.60	0,87 [0,3 ; 2,52]	0,86 [0,28 ; 2,65];	-0,72 [-6,27 ; 4,82]; 1	1	
Race	Other	7	1	14.29	8	1	12.50	1,14 [0,09 ; 15,08]	1,17 [0,06 ; 22,94];	1,79 [-32,81 ; 36,39]; 1	1	0,6839
	White	266	10	3.76	267	16	5.99	0,63 [0,29 ; 1,36]	0,61 [0,27 ; 1,38];	-2,23 [-5,88 ; 1,42]; 0,315	0,315	
	No	181	6	3.31	193	10	5.18	0,64 [0,24 ; 1,72]	0,63 [0,22 ; 1,76];	-1,87 [-5,94 ; 2,21]; 0,448	0,448	0,9814

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	5	5.43	82	7	8.54	0,64 [0,21 ; 1,93]	0,62 [0,19 ; 2,02];	-3,1 [-10,72 ; 4,52]; 0,552	0,552	
Region	Eastern Europe	247	7	2.83	244	10	4.10	0,69 [0,27 ; 1,79]	0,68 [0,26 ; 1,82];	-1,26 [-4,5 ; 1,97]; 0,471	0,471	0,9155
	USA and Western Europe	26	4	15.38	31	7	22.58	0,68 [0,22 ; 2,07]	0,62 [0,16 ; 2,42];	-7,2 [-27,42 ; 13,03]; 0,738	0,738	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Urinary tract infection

4.2.29 Psychiatric disorders - Anxiety

Tabelle 86: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	5	3.33	146	3	2.05	1,62 [0,39 ; 6,67]	1,64 [0,39 ; 7,01];	1,28 [-2,4 ; 4,96]; 0,723	0,723	0,1345
	>= 38 years	123	3	2.44	129	8	6.20	0,39 [0,11 ; 1,45]	0,38 [0,1 ; 1,46];	-3,76 [-8,74 ; 1,21]; 0,218	0,218	
Disease Severity at baseline (EDSS)	<=3.5	201	7	3.48	208	8	3.85	0,91 [0,33 ; 2,45]	0,9 [0,32 ; 2,54];	-0,36 [-4 ; 3,28]; 1	1	0,3678
	>3.5	72	1	1.39	67	3	4.48	0,31 [0,03 ; 2,91]	0,3 [0,03 ; 2,96];	-3,09 [-8,73 ; 2,55]; 0,352	0,352	
Gender	Female	167	6	3.59	180	10	5.56	0,65 [0,24 ; 1,74]	0,63 [0,23 ; 1,78];	-1,96 [-6,34 ; 2,42]; 0,449	0,449	0,421
	Male	106	2	1.89	95	1	1.05	1,79 [0,17 ; 19,45]	1,81 [0,16 ; 20,26];	0,83 [-2,47 ; 4,14]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	117	6	5.13	116	4	3.45	1,49 [0,43 ; 5,13]	1,51 [0,42 ; 5,51];	1,68 [-3,52 ; 6,88]; 0,748	0,748	0,0901
	0	155	2	1.29	157	7	4.46	0,29 [0,06 ; 1,37]	0,28 [0,06 ; 1,37];	-3,17 [-6,85 ; 0,52]; 0,173	0,173	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	5	4.63	92	3	3.26	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	2	4.76	58	2	3.45	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	1	0.81	125	6	4.80	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	1	14.29	8	0	0.00	3,38 [0,16 ; 71,67]	3,92 [0,14 ; 112,9];	13,19 [-17,72 ; 44,11]; 0,467	0,467	0,1515
	White	266	7	2.63	267	11	4.12	0,64 [0,25 ; 1,62]	0,63 [0,24 ; 1,65];	-1,49 [-4,55 ; 1,58]; 0,473	0,473	
	No	181	2	1.10	193	8	4.15	0,27 [0,06 ; 1,24]	0,26 [0,05 ; 1,23];	-3,04 [-6,24 ; 0,16]; 0,106	0,106	0,0529

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	6	6.52	82	3	3.66	1,78 [0,46 ; 6,9]	1,84 [0,44 ; 7,59];	2,86 [-3,62 ; 9,34]; 0,503	0,503	
Region	Eastern Europe	247	5	2.02	244	9	3.69	0,55 [0,19 ; 1,61]	0,54 [0,18 ; 1,63];	-1,66 [-4,61 ; 1,28]; 0,292	0,292	0,2522
	USA and Western Europe	26	3	11.54	31	2	6.45	1,79 [0,32 ; 9,9]	1,89 [0,29 ; 12,28];	5,09 [-9,93 ; 20,11]; 0,651	0,651	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Psychiatric disorders | Anxiety

4.2.30 Skin and subcutaneous tissue disorders - Alopecia

Tabelle 87: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	5	3.33	146	21	14.38	0,23 [0,09 ; 0,6]	0,21 [0,08 ; 0,56];	-11,05 [-17,43 ; -4,67]; 0,001	0,001	0,26
	>= 38 years	123	1	0.81	129	15	11.63	0,07 [0,01 ; 0,52]	0,06 [0,01 ; 0,48];	-10,81 [-16,57 ; -5,06]; 0	0	
Disease Severity at baseline (EDSS)	<=3.5	201	3	1.49	208	34	16.35	0,09 [0,03 ; 0,29]	0,08 [0,02 ; 0,26];	-14,85 [-20,15 ; -9,56]; 0	0	0,0081
	>3.5	72	3	4.17	67	2	2.99	1,4 [0,24 ; 8,1]	1,41 [0,23 ; 8,73];	1,18 [-4,98 ; 7,34]; 1	1	
Gender	Female	167	5	2.99	180	30	16.67	0,18 [0,07 ; 0,45]	0,15 [0,06 ; 0,41];	-13,67 [-19,7 ; -7,65]; 0	0	0,9408
	Female	167	5	2.99	180	6	3.33	0,18 [0,07 ; 0,45]	0,15 [0,06 ; 0,41];	-13,67 [-19,7 ; -7,65]; 0	0	
	Female	167	2	1.20	180	30	16.67	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Female	167	2	1.20	180	6	3.33	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Male	106	1	0.94	95	6	6.32	0,15 [0,02 ; 1,22]	0,14 [0,02 ; 1,2];	-5,37 [-10,6 ; -0,15]; 0,054	0,054	
	Male	106	1	0.94	95	6	6.32	0,15 [0,02 ; 1,22]	0,14 [0,02 ; 1,2];	-5,37 [-10,6 ; -0,15]; 0,054	0,054	
	Male	106	2	1.89	95	6	6.32	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Male	106	2	1.89	95	6	6.32	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of baseline Gd-enhancing lesions	>=1	117	2	1.71	116	16	13.79	0,12 [0,03 ; 0,53]	0,11 [0,02 ; 0,48];	-12,08 [-18,78 ; -5,38]; 0	0	0,5393
	0	155	4	2.58	157	19	12.10	0,21 [0,07 ; 0,61]	0,19 [0,06 ; 0,58];	-9,52 [-15,2 ; -3,84]; 0,002	0,002	
	NA	1	0	0.00	2	1	50.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Number of relapses experienced in the 2 years prior to study start	<=1	108	3	2.78	92	10	10.87	0,26 [0,07 ; 0,9]	0,23 [0,06 ; 0,88];	-8,09 [-15,17 ; -1,02]; 0,04	0,04	0,2404
	>=3	42	0	0.00	58	10	17.24	0,07 [0 ; 1,08]	0,05 [0 ; 0,96];	-16,63 [-26,91 ; -6,36]; 0,005	0,005	
	2	123	3	2.44	125	16	12.80	0,19 [0,06 ; 0,64]	0,17 [0,05 ; 0,6];	-10,36 [-16,82 ; -3,9]; 0,003	0,003	
Race	Other	7	0	0.00	8	1	12.50	0,38 [0,02 ; 7,96]	0,33 [0,01 ; 9,57];	-10,42 [-39,98 ; 19,15]; 0,477	0,477	0,599
	White	266	6	2.26	267	35	13.11	0,17 [0,07 ; 0,4]	0,15 [0,06 ; 0,37];	-10,85 [-15,28 ; -6,43]; 0	0	
Received approved disease modifying MS drug prior to enrollment	No	181	2	1.10	193	26	13.47	0,08 [0,02 ; 0,34]	0,07 [0,02 ; 0,31];	-12,37 [-17,42 ; -7,31]; 0	0	0,1027
	Yes	92	4	4.35	82	10	12.20	0,36 [0,12 ; 1,09]	0,33 [0,1 ; 1,09];	-7,85 [-16,06 ; 0,37]; 0,091	0,091	
Region	Eastern Europe	247	6	2.43	244	31	12.70	0,19 [0,08 ; 0,45]	0,17 [0,07 ; 0,42];	-10,28 [-14,87 ; -5,68]; 0	0	0,229
	USA and Western Europe	26	0	0.00	31	5	16.13	0,11 [0,01 ; 1,86]	0,09 [0 ; 1,73];	-15,34 [-29,36 ; -1,31]; 0,028	0,028	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Skin and subcutaneous tissue disorders | Alopecia

4.2.31 Infections and infestations - Sinusitis

Tabelle 88: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	4	2.67	146	8	5.48	0,49 [0,15 ; 1,58]	0,47 [0,14 ; 1,6];	-2,81 [-7,32 ; 1,69]; 0,251	0,251	0,1104
	>= 38 years	123	0	0.00	129	4	3.10	0,12 [0,01 ; 2,14]	0,11 [0,01 ; 2,12];	-3,06 [-6,39 ; 0,28]; 0,122	0,122	
Disease Severity at baseline (EDSS)	<=3.5	201	2	1.00	208	10	4.81	0,21 [0,05 ; 0,93]	0,2 [0,04 ; 0,92];	-3,81 [-7,03 ; -0,6]; 0,036	0,036	0,2262
	>3.5	72	2	2.78	67	2	2.99	0,93 [0,13 ; 6,42]	0,93 [0,13 ; 6,79];	-0,21 [-5,78 ; 5,36]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	117	1	0.85	116	5	4.31	0,2 [0,02 ; 1,67]	0,19 [0,02 ; 1,66];	-3,46 [-7,51 ; 0,6]; 0,119	0,119	0,5302
	0	155	3	1.94	157	7	4.46	0,43 [0,11 ; 1,65]	0,42 [0,11 ; 1,67];	-2,52 [-6,41 ; 1,37]; 0,336	0,336	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	2	1.85	92	2	2.17	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	1	2.38	58	2	3.45	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	1	0.81	125	8	6.40	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	1	14.29	8	0	0.00	3,38 [0,16 ; 71,67]	3,92 [0,14 ; 112,9];	13,19 [-17,72 ; 44,11]; 0,467	0,467	0,0695
	White	266	3	1.13	267	12	4.49	0,25 [0,07 ; 0,88]	0,24 [0,07 ; 0,87];	-3,37 [-6,16 ; -0,58]; 0,033	0,033	
Received approved disease modifying MS drug prior to enrollment	No	181	2	1.10	193	9	4.66	0,24 [0,05 ; 1,08]	0,23 [0,05 ; 1,07];	-3,56 [-6,9 ; -0,22]; 0,063	0,063	0,4391
	Yes	92	2	2.17	82	3	3.66	0,59 [0,1 ; 3,47]	0,59 [0,1 ; 3,59];	-1,48 [-6,52 ; 3,55]; 0,667	0,667	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	247	3	1.21	244	10	4.10	0,3 [0,08 ; 1,06]	0,29 [0,08 ; 1,06];	-2,88 [-5,72 ; -0,05]; 0,053	0,053	0,6295
	USA and Western Europe	26	1	3.85	31	2	6.45	0,6 [0,06 ; 6,21]	0,58 [0,05 ; 6,78];	-2,61 [-13,98 ; 8,77]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Sinusitis

4.2.32 Infections and infestations - Upper respiratory tract infection

Tabelle 89: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	9	6.00	146	10	6.85	0,88 [0,37 ; 2,09]	0,87 [0,34 ; 2,2];	-0,85 [-6,44 ; 4,74]; 0,816	0,816	0,3584
	>= 38 years	123	8	6.50	129	5	3.88	1,68 [0,56 ; 4,99]	1,73 [0,55 ; 5,43];	2,63 [-2,86 ; 8,11]; 0,402	0,402	
Disease Severity at baseline (EDSS)	<=3.5	201	15	7.46	208	13	6.25	1,19 [0,58 ; 2,45]	1,21 [0,56 ; 2,61];	1,21 [-3,69 ; 6,11]; 0,697	0,697	0,8081
	>3.5	72	2	2.78	67	2	2.99	0,93 [0,13 ; 6,42]	0,93 [0,13 ; 6,79];	-0,21 [-5,78 ; 5,36]; 1	1	
Gender	Female	167	13	7.78	180	11	6.11	1,27 [0,59 ; 2,76]	1,3 [0,56 ; 2,98];	1,67 [-3,69 ; 7,04]; 0,673	0,673	0,6553
	Male	106	4	3.77	95	4	4.21	0,9 [0,23 ; 3,48]	0,89 [0,22 ; 3,67];	-0,44 [-5,87 ; 4,99]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	117	5	4.27	116	9	7.76	0,55 [0,19 ; 1,59]	0,53 [0,17 ; 1,63];	-3,49 [-9,58 ; 2,61]; 0,286	0,286	0,0663
	0	155	12	7.74	157	6	3.82	2,03 [0,78 ; 5,26]	2,11 [0,77 ; 5,78];	3,92 [-1,25 ; 9,09]; 0,153	0,153	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	7	6.48	92	4	4.35	1,49 [0,45 ; 4,93]	1,52 [0,43 ; 5,38];	2,13 [-4,11 ; 8,37]; 0,552	0,552	0,3478
	>=3	42	2	4.76	58	6	10.34	0,46 [0,1 ; 2,17]	0,43 [0,08 ; 2,26];	-5,58 [-15,73 ; 4,56]; 0,462	0,462	
	2	123	8	6.50	125	5	4.00	1,63 [0,55 ; 4,83]	1,67 [0,53 ; 5,25];	2,5 [-3,05 ; 8,05]; 0,408	0,408	
Race	Other	7	2	28.57	8	0	0.00	5,62 [0,31 ; 100,52]	7,73 [0,31 ; 193,44];	25,69 [-9,74 ; 61,13]; 0,467	0,467	0,0716
	White	266	15	5.64	267	15	5.62	1 [0,5 ; 2,01]	1 [0,48 ; 2,1];	0,02 [-3,89 ; 3,93]; 1	1	
	No	181	10	5.52	193	12	6.22	0,89 [0,39 ; 2,01]	0,88 [0,37 ; 2,09];	-0,69 [-5,46 ; 4,07]; 0,829	0,829	0,2693

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	7	7.61	82	3	3.66	2,08 [0,56 ; 7,78]	2,17 [0,54 ; 8,68];	3,95 [-2,82 ; 10,72]; 0,338	0,338	
Region	Eastern Europe	247	11	4.45	244	12	4.92	0,91 [0,41 ; 2,01]	0,9 [0,39 ; 2,08];	-0,46 [-4,2 ; 3,27]; 0,834	0,834	0,187
	USA and Western Europe	26	6	23.08	31	3	9.68	2,38 [0,66 ; 8,61]	2,8 [0,62 ; 12,55];	13,4 [-5,85 ; 32,65]; 0,275	0,275	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Upper respiratory tract infection

4.2.33 Infections and infestations - Bronchitis

Tabelle 90: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	8	5.33	146	5	3.42	1,56 [0,52 ; 4,65]	1,59 [0,51 ; 4,97];	1,91 [-2,74 ; 6,56]; 0,573	0,573	0,0636
	>= 38 years	123	4	3.25	129	0	0.00	9,44 [0,51 ; 173,44]	9,75 [0,52 ; 183,07];	3,24 [-0,21 ; 6,7]; 0,055	0,055	
Disease Severity at baseline (EDSS)	<=3.5	201	12	5.97	208	5	2.40	2,48 [0,89 ; 6,92]	2,58 [0,89 ; 7,45];	3,57 [-0,31 ; 7,45]; 0,085	0,085	0,9999
	>3.5	72	0	0.00	67	0	0.00	0,93 [0,02 ; 46,29]	0,93 [0,02 ; 47,58];	-0,05 [-2,83 ; 2,73]; 1	1	
Gender	Female	167	10	5.99	180	3	1.67	3,59 [1,01 ; 12,83]	3,76 [1,02 ; 13,9];	4,32 [0,27 ; 8,38]; 0,046	0,046	0,2381
	Male	106	2	1.89	95	2	2.11	0,9 [0,13 ; 6,24]	0,89 [0,12 ; 6,48];	-0,22 [-4,1 ; 3,66]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	117	7	5.98	116	3	2.59	2,31 [0,61 ; 8,73]	2,4 [0,6 ; 9,51];	3,4 [-1,78 ; 8,57]; 0,333	0,333	0,9456
	0	155	5	3.23	157	2	1.27	2,53 [0,5 ; 12,86]	2,58 [0,49 ; 13,52];	1,95 [-1,34 ; 5,24]; 0,281	0,281	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	6	5.56	92	2	2.17	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	1	2.38	58	2	3.45	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	5	4.07	125	1	0.80	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9999
	White	266	12	4.51	267	5	1.87	2,41 [0,86 ; 6,74]	2,48 [0,86 ; 7,13];	2,64 [-0,34 ; 5,62]; 0,091	0,091	
	No	181	8	4.42	193	4	2.07	2,13 [0,65 ; 6,96]	2,18 [0,65 ; 7,38];	2,35 [-1,26 ; 5,95]; 0,247	0,247	0,6777

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	4	4.35	82	1	1.22	3,57 [0,41 ; 31,26]	3,68 [0,4 ; 33,63];	3,13 [-1,67 ; 7,93]; 0,372	0,372	
Region	Eastern Europe	247	11	4.45	244	3	1.23	3,62 [1,02 ; 12,82]	3,74 [1,03 ; 13,59];	3,22 [0,3 ; 6,14]; 0,054	0,054	0,172
	USA and Western Europe	26	1	3.85	31	2	6.45	0,6 [0,06 ; 6,21]	0,58 [0,05 ; 6,78];	-2,61 [-13,98 ; 8,77]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Bronchitis

4.2.34 Investigations - Lymphocyte count decreased

Tabelle 91: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	12	8.00	146	4	2.74	2,92 [0,96 ; 8,85]	3,09 [0,97 ; 9,8];	5,26 [0,18 ; 10,35]; 0,069	0,069	0,2431
	>= 38 years	123	4	3.25	129	4	3.10	1,05 [0,27 ; 4,1]	1,05 [0,26 ; 4,3];	0,15 [-4,18 ; 4,48]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	201	10	4.98	208	7	3.37	1,48 [0,57 ; 3,81]	1,5 [0,56 ; 4,03];	1,61 [-2,27 ; 5,49]; 0,465	0,465	0,2088
	>3.5	72	6	8.33	67	1	1.49	5,58 [0,69 ; 45,17]	6 [0,7 ; 51,22];	6,84 [-0,17 ; 13,85]; 0,117	0,117	
Gender	Female	167	9	5.39	180	5	2.78	1,94 [0,66 ; 5,67]	1,99 [0,65 ; 6,07];	2,61 [-1,57 ; 6,79]; 0,278	0,278	0,926
	Female	167	9	5.39	180	7	3.89	1,94 [0,66 ; 5,67]	1,99 [0,65 ; 6,07];	2,61 [-1,57 ; 6,79]; 0,278	0,278	
	Female	167	1	0.60	180	5	2.78	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Female	167	1	0.60	180	7	3.89	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Male	106	7	6.60	95	3	3.16	2,09 [0,56 ; 7,86]	2,17 [0,54 ; 8,64];	3,45 [-2,45 ; 9,34]; 0,339	0,339	
	Male	106	7	6.60	95	4	4.21	2,09 [0,56 ; 7,86]	2,17 [0,54 ; 8,64];	3,45 [-2,45 ; 9,34]; 0,339	0,339	
	Male	106	3	2.83	95	3	3.16	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Male	106	3	2.83	95	4	4.21	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of baseline Gd-enhancing lesions	>=1	117	6	5.13	116	3	2.59	1,98 [0,51 ; 7,74]	2,04 [0,5 ; 8,34];	2,54 [-2,39 ; 7,47]; 0,499	0,499	0,9744
	0	155	10	6.45	157	5	3.18	2,03 [0,71 ; 5,79]	2,1 [0,7 ; 6,28];	3,27 [-1,48 ; 8,01]; 0,197	0,197	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Number of relapses experienced in the 2 years prior to study start	<=1	108	5	4.63	92	2	2.17	2,13 [0,42 ; 10,72]	2,18 [0,41 ; 11,54];	2,46 [-2,5 ; 7,41]; 0,456	0,456	0,7451
	>=3	42	3	7.14	58	1	1.72	4,14 [0,45 ; 38,45]	4,38 [0,44 ; 43,71];	5,42 [-3,06 ; 13,9]; 0,307	0,307	
	2	123	8	6.50	125	5	4.00	1,63 [0,55 ; 4,83]	1,67 [0,53 ; 5,25];	2,5 [-3,05 ; 8,05]; 0,408	0,408	
Race	Other	7	1	14.29	8	0	0.00	3,38 [0,16 ; 71,67]	3,92 [0,14 ; 112,9];	13,19 [-17,72 ; 44,11]; 0,467	0,467	0,3234
	White	266	15	5.64	267	8	3.00	1,88 [0,81 ; 4,36]	1,93 [0,81 ; 4,64];	2,64 [-0,8 ; 6,09]; 0,142	0,142	
Received approved disease modifying MS drug prior to enrollment	No	181	12	6.63	193	6	3.11	2,13 [0,82 ; 5,56]	2,21 [0,81 ; 6,03];	3,52 [-0,85 ; 7,9]; 0,147	0,147	0,8477
	Yes	92	4	4.35	82	2	2.44	1,78 [0,34 ; 9,48]	1,82 [0,32 ; 10,2];	1,91 [-3,43 ; 7,25]; 0,685	0,685	
Region	Eastern Europe	247	15	6.07	244	6	2.46	2,47 [0,97 ; 6,26]	2,56 [0,98 ; 6,72];	3,61 [0,06 ; 7,17]; 0,072	0,072	0,254
	USA and Western Europe	26	1	3.85	31	2	6.45	0,6 [0,06 ; 6,21]	0,58 [0,05 ; 6,78];	-2,61 [-13,98 ; 8,77]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Investigations | Lymphocyte count decreased

4.2.35 Investigations - White blood cell count decreased

Tabelle 92: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	3	2.00	146	9	6.16	0,32 [0,09 ; 1,17]	0,31 [0,08 ; 1,17];	-4,16 [-8,66 ; 0,33]; 0,082	0,082	0,3265
	>= 38 years	123	0	0.00	129	2	1.55	0,21 [0,01 ; 4,32]	0,21 [0,01 ; 4,34];	-1,52 [-4,13 ; 1,09]; 0,498	0,498	
Disease Severity at baseline (EDSS)	<=3.5	201	3	1.49	208	9	4.33	0,34 [0,09 ; 1,26]	0,34 [0,09 ; 1,26];	-2,83 [-6,07 ; 0,4]; 0,141	0,141	0,2858
	>3.5	72	0	0.00	67	2	2.99	0,19 [0,01 ; 3,81]	0,18 [0,01 ; 3,83];	-2,99 [-7,85 ; 1,86]; 0,234	0,234	
Number of baseline Gd-enhancing lesions	>=1	117	2	1.71	116	7	6.03	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	155	1	0.65	157	4	2.55	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	0	0.00	92	5	5.43	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	3	7.14	58	3	5.17	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	0	0.00	125	3	2.40	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9995
	White	266	3	1.13	267	11	4.12	0,27 [0,08 ; 0,97]	0,27 [0,07 ; 0,96];	-2,99 [-5,69 ; -0,29]; 0,054	0,054	
Received approved disease modifying MS drug prior to enrollment	No	181	2	1.10	193	6	3.11	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	Yes	92	1	1.09	82	5	6.10	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	247	3	1.21	244	9	3.69	0,33 [0,09 ; 1,2]	0,32 [0,09 ; 1,2];	-2,47 [-5,21 ; 0,26]; 0,087	0,087	0,3373
	USA and Western Europe	26	0	0.00	31	2	6.45	0,24 [0,01 ; 4,73]	0,22 [0,01 ; 4,85];	-5,96 [-16,56 ; 4,64]; 0,497	0,497	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Investigations | White blood cell count decreased

4.2.36 General disorders and administration site conditions - Pyrexia

Tabelle 93: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	27	18.00	146	7	4.79	3,75 [1,69 ; 8,35]	4,36 [1,83 ; 10,36];	13,21 [6,15 ; 20,26]; 0	0	0,3863
	>= 38 years	123	13	10.57	129	6	4.65	2,27 [0,89 ; 5,79]	2,42 [0,89 ; 6,59];	5,92 [-0,62 ; 12,45]; 0,095	0,095	
Disease Severity at baseline (EDSS)	<=3.5	201	32	15.92	208	10	4.81	3,31 [1,67 ; 6,56]	3,75 [1,79 ; 7,85];	11,11 [5,28 ; 16,95]; 0	0	0,6723
	>3.5	72	8	11.11	67	3	4.48	2,48 [0,69 ; 8,97]	2,67 [0,68 ; 10,51];	6,63 [-2,15 ; 15,42]; 0,211	0,211	
Gender	Female	167	28	16.77	180	10	5.56	3,02 [1,51 ; 6,02]	3,42 [1,61 ; 7,29];	11,21 [4,63 ; 17,79]; 0,001	0,001	0,8605
	Male	106	12	11.32	95	3	3.16	3,58 [1,04 ; 12,32]	3,91 [1,07 ; 14,33];	8,16 [1,18 ; 15,14]; 0,032	0,032	
Number of baseline Gd-enhancing lesions	>=1	117	15	12.82	116	4	3.45	3,72 [1,27 ; 10,87]	4,12 [1,32 ; 12,81];	9,37 [2,46 ; 16,28]; 0,015	0,015	
	0	155	25	16.13	157	9	5.73	2,81 [1,36 ; 5,83]	3,16 [1,42 ; 7,02];	10,4 [3,56 ; 17,23]; 0,003	0,003	0,707
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	13	12.04	92	6	6.52	1,85 [0,73 ; 4,66]	1,96 [0,71 ; 5,39];	5,52 [-2,43 ; 13,46]; 0,23	0,23	
	>=3	42	6	14.29	58	3	5.17	2,76 [0,73 ; 10,42]	3,06 [0,72 ; 13];	9,11 [-2,91 ; 21,13]; 0,16	0,16	0,3031
	2	123	21	17.07	125	4	3.20	5,34 [1,89 ; 15,09]	6,23 [2,07 ; 18,73];	13,87 [6,54 ; 21,2]; 0	0	
Race	Other	7	1	14.29	8	1	12.50	1,14 [0,09 ; 15,08]	1,17 [0,06 ; 22,94];	1,79 [-32,81 ; 36,39]; 1	1	0,4706
	White	266	39	14.66	267	12	4.49	3,26 [1,75 ; 6,09]	3,65 [1,87 ; 7,14];	10,17 [5,24 ; 15,09]; 0	0	
	No	181	26	14.36	193	10	5.18	2,77 [1,38 ; 5,59]	3,07 [1,44 ; 6,56];	9,18 [3,19 ; 15,17]; 0,003	0,003	0,5636

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	14	15.22	82	3	3.66	4,16 [1,24 ; 13,96]	4,73 [1,31 ; 17,09];	11,56 [3,17 ; 19,95]; 0,011	0,011	
Region	Eastern Europe	247	37	14.98	244	10	4.10	3,66 [1,86 ; 7,18]	4,12 [2 ; 8,5];	10,88 [5,78 ; 15,98]; 0	0	0,1991
	USA and Western Europe	26	3	11.54	31	3	9.68	1,19 [0,26 ; 5,41]	1,22 [0,22 ; 6,62];	1,86 [-14,24 ; 17,96]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - General disorders and administration site conditions | Pyrexia

4.2.37 Psychiatric disorders - Insomnia

Tabelle 94: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	9	6.00	146	3	2.05	2,92 [0,81 ; 10,57]	3,04 [0,81 ; 11,47];	3,95 [-0,5 ; 8,39]; 0,138	0,138	0,1017
	>= 38 years	123	3	2.44	129	5	3.88	0,63 [0,15 ; 2,58]	0,62 [0,14 ; 2,65];	-1,44 [-5,74 ; 2,87]; 0,723	0,723	
Disease Severity at baseline (EDSS)	<=3.5	201	10	4.98	208	6	2.88	1,72 [0,64 ; 4,66]	1,76 [0,63 ; 4,94];	2,09 [-1,68 ; 5,86]; 0,316	0,316	0,5761
	>3.5	72	2	2.78	67	2	2.99	0,93 [0,13 ; 6,42]	0,93 [0,13 ; 6,79];	-0,21 [-5,78 ; 5,36]; 1	1	
Gender	Female	167	9	5.39	180	4	2.22	2,43 [0,76 ; 7,73]	2,51 [0,76 ; 8,3];	3,17 [-0,88 ; 7,21]; 0,159	0,159	0,1727
	Male	106	3	2.83	95	4	4.21	0,67 [0,15 ; 2,93]	0,66 [0,14 ; 3,04];	-1,38 [-6,51 ; 3,75]; 0,709	0,709	
Number of baseline Gd-enhancing lesions	>=1	117	8	6.84	116	3	2.59	2,64 [0,72 ; 9,72]	2,76 [0,71 ; 10,69];	4,25 [-1,16 ; 9,66]; 0,215	0,215	0,1942
	0	155	4	2.58	157	5	3.18	0,81 [0,22 ; 2,96]	0,81 [0,21 ; 3,06];	-0,6 [-4,32 ; 3,11]; 1	1	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	7	6.48	92	1	1.09	5,96 [0,75 ; 47,58]	6,31 [0,76 ; 52,25];	5,39 [0,29 ; 10,5]; 0,072	0,072	0,1355
	>=3	42	1	2.38	58	1	1.72	1,38 [0,09 ; 21,46]	1,39 [0,08 ; 22,88];	0,66 [-5,04 ; 6,36]; 1	1	
	2	123	4	3.25	125	6	4.80	0,68 [0,2 ; 2,34]	0,67 [0,18 ; 2,42];	-1,55 [-6,43 ; 3,34]; 0,749	0,749	
Race	Other	7	1	14.29	8	0	0.00	3,38 [0,16 ; 71,67]	3,92 [0,14 ; 112,9];	13,19 [-17,72 ; 44,11]; 0,467	0,467	0,2671
	White	266	11	4.14	267	8	3.00	1,38 [0,56 ; 3,38]	1,4 [0,55 ; 3,53];	1,14 [-2,01 ; 4,29]; 0,495	0,495	
	No	181	7	3.87	193	5	2.59	1,49 [0,48 ; 4,62]	1,51 [0,47 ; 4,85];	1,28 [-2,32 ; 4,87]; 0,565	0,565	0,9996

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	5	5.43	82	3	3.66	1,49 [0,37 ; 6,02]	1,51 [0,35 ; 6,54];	1,78 [-4,39 ; 7,94]; 0,724	0,724	
Region	Eastern Europe	247	9	3.64	244	8	3.28	1,11 [0,44 ; 2,83]	1,12 [0,42 ; 2,94];	0,37 [-2,87 ; 3,6]; 1	1	0,0441
	USA and Western Europe	26	3	11.54	31	0	0.00	8,3 [0,45 ; 153,61]	9,38 [0,46 ; 190,54];	11,4 [-1,98 ; 24,78]; 0,042	0,042	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Psychiatric disorders | Insomnia

4.2.38 Respiratory, thoracic and mediastinal disorders - Cough

Tabelle 95: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	6	4.00	146	5	3.42	1,17 [0,36 ; 3,74]	1,17 [0,35 ; 3,94];	0,58 [-3,73 ; 4,88]; 1	1	0,311
	>= 38 years	123	6	4.88	129	2	1.55	3,15 [0,65 ; 15,29]	3,26 [0,64 ; 16,45];	3,33 [-1,04 ; 7,69]; 0,164	0,164	
Disease Severity at baseline (EDSS)	<=3.5	201	10	4.98	208	7	3.37	1,48 [0,57 ; 3,81]	1,5 [0,56 ; 4,03];	1,61 [-2,27 ; 5,49]; 0,465	0,465	0,1775
	>3.5	72	2	2.78	67	0	0.00	4,66 [0,23 ; 95,28]	4,79 [0,23 ; 101,56];	2,69 [-1,95 ; 7,33]; 0,497	0,497	
Gender	Female	167	10	5.99	180	6	3.33	1,8 [0,67 ; 4,83]	1,85 [0,66 ; 5,2];	2,65 [-1,8 ; 7,11]; 0,308	0,308	0,9872
	Male	106	2	1.89	95	1	1.05	1,79 [0,17 ; 19,45]	1,81 [0,16 ; 20,26];	0,83 [-2,47 ; 4,14]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	117	7	5.98	116	3	2.59	2,31 [0,61 ; 8,73]	2,4 [0,6 ; 9,51];	3,4 [-1,78 ; 8,57]; 0,333	0,333	0,5165
	0	155	5	3.23	157	4	2.55	1,27 [0,35 ; 4,63]	1,27 [0,34 ; 4,84];	0,68 [-3,04 ; 4,39]; 0,749	0,749	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	9	8.33	92	3	3.26	2,56 [0,71 ; 9,16]	2,7 [0,71 ; 10,28];	5,07 [-1,28 ; 11,42]; 0,149	0,149	0,2904
	>=3	42	0	0.00	58	1	1.72	0,46 [0,02 ; 10,96]	0,45 [0,02 ; 11,34];	-1,38 [-6,52 ; 3,76]; 0,511	0,511	
	2	123	3	2.44	125	3	2.40	1,02 [0,21 ; 4,94]	1,02 [0,2 ; 5,14];	0,04 [-3,79 ; 3,86]; 1	1	
Race	Other	7	1	14.29	8	0	0.00	3,38 [0,16 ; 71,67]	3,92 [0,14 ; 112,9];	13,19 [-17,72 ; 44,11]; 0,467	0,467	0,2913
	White	266	11	4.14	267	7	2.62	1,58 [0,62 ; 4,01]	1,6 [0,61 ; 4,2];	1,51 [-1,55 ; 4,58]; 0,35	0,35	
	No	181	7	3.87	193	6	3.11	1,24 [0,43 ; 3,63]	1,25 [0,41 ; 3,8];	0,76 [-2,97 ; 4,48]; 0,781	0,781	0,2561

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	5	5.43	82	1	1.22	4,46 [0,53 ; 37,36]	4,66 [0,53 ; 40,7];	4,22 [-0,99 ; 9,42]; 0,215	0,215	
Region	Eastern Europe	247	8	3.24	244	6	2.46	1,32 [0,46 ; 3,74]	1,33 [0,45 ; 3,88];	0,78 [-2,16 ; 3,72]; 0,788	0,788	0,2372
	USA and Western Europe	26	4	15.38	31	1	3.23	4,77 [0,57 ; 40,07]	5,45 [0,57 ; 52,24];	12,16 [-3,04 ; 27,36]; 0,167	0,167	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Respiratory, thoracic and mediastinal disorders | Cough

4.2.39 General disorders and administration site conditions - Chills

Tabelle 96: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	14	9.33	146	1	0.68	13,63 [1,82 ; 102,3]	14,93 [1,94 ; 115,05];	8,65 [3,8 ; 13,49]; 0,001	0,001	0,4373
	>= 38 years	123	5	4.07	129	0	0.00	11,53 [0,64 ; 206,38]	12,02 [0,66 ; 219,74];	4,05 [0,27 ; 7,83]; 0,013	0,013	
Disease Severity at baseline (EDSS)	<=3.5	201	15	7.46	208	1	0.48	15,52 [2,07 ; 116,42]	16,69 [2,18 ; 127,6];	6,98 [3,23 ; 10,73]; 0	0	0,5212
	>3.5	72	4	5.56	67	0	0.00	8,38 [0,46 ; 152,82]	8,87 [0,47 ; 167,93];	5,43 [-0,45 ; 11,31]; 0,12	0,12	
Gender	Female	167	7	4.19	180	0	0.00	16,16 [0,93 ; 280,78]	16,87 [0,96 ; 297,7];	4,19 [0,97 ; 7,4]; 0,003	0,003	0,3245
	Male	106	12	11.32	95	1	1.05	10,75 [1,43 ; 81,16]	12 [1,53 ; 94,15];	10,27 [3,9 ; 16,64]; 0,003	0,003	
Number of baseline Gd-enhancing lesions	>=1	117	6	5.13	116	1	0.86	5,95 [0,73 ; 48,64]	6,22 [0,74 ; 52,47];	4,27 [-0,07 ; 8,6]; 0,119	0,119	0,1318
	0	155	13	8.39	157	0	0.00	27,35 [1,64 ; 456,03]	29,84 [1,76 ; 506,57];	8,34 [3,84 ; 12,84]; 0	0	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	6	5.56	92	0	0.00	11,09 [0,63 ; 194,28]	11,73 [0,65 ; 211,12];	5,43 [0,74 ; 10,11]; 0,032	0,032	0,4756
	>=3	42	4	9.52	58	0	0.00	12,35 [0,68 ; 223,35]	13,68 [0,72 ; 261,26];	9,62 [0,17 ; 19,06]; 0,029	0,029	
	2	123	9	7.32	125	1	0.80	9,15 [1,18 ; 71,11]	9,79 [1,22 ; 78,48];	6,52 [1,66 ; 11,38]; 0,01	0,01	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9997
	White	266	19	7.14	267	1	0.37	19,07 [2,57 ; 141,44]	20,46 [2,72 ; 153,99];	6,77 [3,59 ; 9,95]; 0	0	
	No	181	14	7.73	193	1	0.52	14,93 [1,98 ; 112,38]	16,1 [2,09 ; 123,7];	7,22 [3,2 ; 11,24]; 0	0	0,4801

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	5	5.43	82	0	0.00	9,82 [0,55 ; 174,87]	10,37 [0,56 ; 190,51];	5,31 [0,24 ; 10,39]; 0,031	0,031	
Region	Eastern Europe	247	17	6.88	244	1	0.41	16,79 [2,25 ; 125,21]	17,96 [2,37 ; 136,05];	6,47 [3,22 ; 9,73]; 0	0	0,6107
	USA and Western Europe	26	2	7.69	31	0	0.00	5,93 [0,3 ; 118,18]	6,43 [0,29 ; 140,14];	7,7 [-4,05 ; 19,44]; 0,197	0,197	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - General disorders and administration site conditions | Chills

4.2.40 Gastrointestinal disorders - Abdominal pain

Tabelle 97: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	10	6.67	146	8	5.48	1,22 [0,49 ; 3]	1,23 [0,47 ; 3,21];	1,19 [-4,25 ; 6,62]; 0,809	0,809	0,1782
	>= 38 years	123	5	4.07	129	1	0.78	5,24 [0,62 ; 44,25]	5,42 [0,62 ; 47,1];	3,29 [-0,51 ; 7,09]; 0,113	0,113	
Disease Severity at baseline (EDSS)	<=3.5	201	9	4.48	208	8	3.85	1,16 [0,46 ; 2,96]	1,17 [0,44 ; 3,1];	0,63 [-3,24 ; 4,51]; 0,808	0,808	0,1312
	>3.5	72	6	8.33	67	1	1.49	5,58 [0,69 ; 45,17]	6 [0,7 ; 51,22];	6,84 [-0,17 ; 13,85]; 0,117	0,117	
Gender	Female	167	10	5.99	180	7	3.89	1,54 [0,6 ; 3,95]	1,57 [0,59 ; 4,24];	2,1 [-2,48 ; 6,67]; 0,458	0,458	0,6969
	Male	106	5	4.72	95	2	2.11	2,24 [0,45 ; 11,28]	2,3 [0,44 ; 12,15];	2,61 [-2,35 ; 7,57]; 0,45	0,45	
Number of baseline Gd-enhancing lesions	>=1	117	7	5.98	116	2	1.72	3,47 [0,74 ; 16,35]	3,63 [0,74 ; 17,84];	4,26 [-0,65 ; 9,17]; 0,171	0,171	0,2242
	0	155	8	5.16	157	7	4.46	1,16 [0,43 ; 3,11]	1,17 [0,41 ; 3,3];	0,7 [-4,05 ; 5,45]; 0,798	0,798	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	4	3.70	92	4	4.35	0,85 [0,22 ; 3,31]	0,85 [0,21 ; 3,48];	-0,64 [-6,13 ; 4,84]; 1	1	0,1905
	>=3	42	5	11.90	58	1	1.72	6,9 [0,84 ; 56,95]	7,7 [0,87 ; 68,59];	10,18 [-0,17 ; 20,53]; 0,08	0,08	
	2	123	6	4.88	125	4	3.20	1,52 [0,44 ; 5,27]	1,55 [0,43 ; 5,64];	1,68 [-3,22 ; 6,58]; 0,538	0,538	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9999
	White	266	15	5.64	267	9	3.37	1,67 [0,75 ; 3,76]	1,71 [0,74 ; 3,99];	2,27 [-1,25 ; 5,79]; 0,218	0,218	
	No	181	8	4.42	193	7	3.63	1,22 [0,45 ; 3,29]	1,23 [0,44 ; 3,46];	0,79 [-3,2 ; 4,78]; 0,795	0,795	0,294

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	7	7.61	82	2	2.44	3,12 [0,67 ; 14,6]	3,29 [0,66 ; 16,33];	5,17 [-1,19 ; 11,53]; 0,175	0,175	
Region	Eastern Europe	247	15	6.07	244	8	3.28	1,85 [0,8 ; 4,29]	1,91 [0,79 ; 4,58];	2,79 [-0,93 ; 6,52]; 0,199	0,199	0,1734
	USA and Western Europe	26	0	0.00	31	1	3.23	0,4 [0,02 ; 9,31]	0,38 [0,01 ; 9,82];	-2,84 [-11,75 ; 6,08]; 0,497	0,497	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Gastrointestinal disorders | Abdominal pain

4.2.41 Gastrointestinal disorders - Diarrhoea

Tabelle 98: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	8	5.33	146	14	9.59	0,56 [0,24 ; 1,29]	0,53 [0,22 ; 1,31];	-4,26 [-10,23 ; 1,72]; 0,188	0,188	0,3512
	>= 38 years	123	11	8.94	129	12	9.30	0,96 [0,44 ; 2,1]	0,96 [0,41 ; 2,26];	-0,36 [-7,47 ; 6,75]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	201	12	5.97	208	18	8.65	0,69 [0,34 ; 1,4]	0,67 [0,31 ; 1,43];	-2,68 [-7,72 ; 2,35]; 0,345	0,345	0,8001
	>3.5	72	7	9.72	67	8	11.94	0,81 [0,31 ; 2,12]	0,79 [0,27 ; 2,32];	-2,22 [-12,57 ; 8,13]; 0,787	0,787	
Gender	Female	167	14	8.38	180	23	12.78	0,66 [0,35 ; 1,23]	0,62 [0,31 ; 1,26];	-4,39 [-10,83 ; 2,04]; 0,224	0,224	0,2745
	Male	106	5	4.72	95	3	3.16	1,49 [0,37 ; 6,08]	1,52 [0,35 ; 6,53];	1,56 [-3,79 ; 6,91]; 0,724	0,724	
Number of baseline Gd-enhancing lesions	>=1	117	7	5.98	116	13	11.21	0,53 [0,22 ; 1,29]	0,5 [0,19 ; 1,31];	-5,22 [-12,39 ; 1,95]; 0,169	0,169	0,338
	0	155	12	7.74	157	13	8.28	0,93 [0,44 ; 1,98]	0,93 [0,41 ; 2,11];	-0,54 [-6,56 ; 5,49]; 1	1	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	5	4.63	92	8	8.70	0,53 [0,18 ; 1,57]	0,51 [0,16 ; 1,62];	-4,07 [-11,06 ; 2,92]; 0,265	0,265	0,3554
	>=3	42	1	2.38	58	5	8.62	0,28 [0,03 ; 2,28]	0,26 [0,03 ; 2,3];	-6,24 [-14,81 ; 2,33]; 0,396	0,396	
	2	123	13	10.57	125	13	10.40	1,02 [0,49 ; 2,1]	1,02 [0,45 ; 2,29];	0,17 [-7,46 ; 7,8]; 1	1	
Race	Other	7	1	14.29	8	0	0.00	3,38 [0,16 ; 71,67]	3,92 [0,14 ; 112,9];	13,19 [-17,72 ; 44,11]; 0,467	0,467	0,1546
	White	266	18	6.77	267	26	9.74	0,69 [0,39 ; 1,24]	0,67 [0,36 ; 1,26];	-2,97 [-7,64 ; 1,69]; 0,27	0,27	
	No	181	14	7.73	193	18	9.33	0,83 [0,43 ; 1,62]	0,82 [0,39 ; 1,69];	-1,59 [-7,25 ; 4,06]; 0,712	0,712	0,5388

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	5	5.43	82	8	9.76	0,56 [0,19 ; 1,64]	0,53 [0,17 ; 1,7];	-4,32 [-12,24 ; 3,6]; 0,388	0,388	
Region	Eastern Europe	247	17	6.88	244	23	9.43	0,73 [0,4 ; 1,33]	0,71 [0,37 ; 1,37];	-2,54 [-7,38 ; 2,29]; 0,326	0,326	0,9285
	USA and Western Europe	26	2	7.69	31	3	9.68	0,79 [0,14 ; 4,4]	0,78 [0,12 ; 5,05];	-1,99 [-16,59 ; 12,62]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Gastrointestinal disorders | Diarrhoea

4.2.42 Blood and lymphatic system disorders - Leukopenia

Tabelle 99: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	3	2.00	146	10	6.85	0,29 [0,08 ; 1,04]	0,28 [0,07 ; 1,03];	-4,85 [-9,52 ; -0,18]; 0,049	0,049	0,4255
	>= 38 years	123	2	1.63	129	3	2.33	0,7 [0,12 ; 4,11]	0,69 [0,11 ; 4,23];	-0,7 [-4,13 ; 2,73]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	201	3	1.49	208	12	5.77	0,26 [0,07 ; 0,9]	0,25 [0,07 ; 0,89];	-4,28 [-7,86 ; -0,69]; 0,032	0,032	0,1314
	>3.5	72	2	2.78	67	1	1.49	1,86 [0,17 ; 20,05]	1,89 [0,17 ; 21,29];	1,29 [-3,49 ; 6,06]; 1	1	
Gender	Female	167	2	1.20	180	9	5.00	0,24 [0,05 ; 1,09]	0,23 [0,05 ; 1,08];	-3,8 [-7,39 ; -0,22]; 0,063	0,063	0,3331
	Male	106	3	2.83	95	4	4.21	0,67 [0,15 ; 2,93]	0,66 [0,14 ; 3,04];	-1,38 [-6,51 ; 3,75]; 0,709	0,709	
Number of baseline Gd-enhancing lesions	>=1	117	1	0.85	116	5	4.31	0,2 [0,02 ; 1,67]	0,19 [0,02 ; 1,66];	-3,46 [-7,51 ; 0,6]; 0,119	0,119	0,3684
	0	155	4	2.58	157	7	4.46	0,58 [0,17 ; 1,94]	0,57 [0,16 ; 1,98];	-1,88 [-5,96 ; 2,2]; 0,542	0,542	
	NA	1	0	0.00	2	1	50.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	1	0.93	92	3	3.26	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	1	2.38	58	6	10.34	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	3	2.44	125	4	3.20	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	0	0.00	8	1	12.50	0,38 [0,02 ; 7,96]	0,33 [0,01 ; 9,57];	-10,42 [-39,98 ; 19,15]; 0,477	0,477	0,4239
	White	266	5	1.88	267	12	4.49	0,42 [0,15 ; 1,17]	0,41 [0,14 ; 1,17];	-2,61 [-5,59 ; 0,36]; 0,137	0,137	
	No	181	4	2.21	193	5	2.59	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	1	1.09	82	8	9.76	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Region	Eastern Europe	247	5	2.02	244	12	4.92	0,41 [0,15 ; 1,15]	0,4 [0,14 ; 1,15];	-2,89 [-6,13 ; 0,34]; 0,089	0,089	0,4495
	USA and Western Europe	26	0	0.00	31	1	3.23	0,4 [0,02 ; 9,31]	0,38 [0,01 ; 9,82];	-2,84 [-11,75 ; 6,08]; 0,497	0,497	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Blood and lymphatic system disorders | Leukopenia

4.2.43 Blood and lymphatic system disorders - Neutropenia

Tabelle 100: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	4	2.67	146	8	5.48	0,49 [0,15 ; 1,58]	0,47 [0,14 ; 1,6];	-2,81 [-7,32 ; 1,69]; 0,251	0,251	0,8075
	>= 38 years	123	1	0.81	129	3	2.33	0,35 [0,04 ; 3,32]	0,34 [0,04 ; 3,36];	-1,51 [-4,56 ; 1,53]; 0,622	0,622	
Disease Severity at baseline (EDSS)	<=3.5	201	5	2.49	208	10	4.81	0,52 [0,18 ; 1,49]	0,51 [0,17 ; 1,5];	-2,32 [-5,94 ; 1,3]; 0,294	0,294	0,3601
	>3.5	72	0	0.00	67	1	1.49	0,31 [0,01 ; 7,49]	0,31 [0,01 ; 7,64];	-1,52 [-5,49 ; 2,45]; 0,234	0,234	
Gender	Female	167	2	1.20	180	8	4.44	0,27 [0,06 ; 1,25]	0,26 [0,05 ; 1,25];	-3,25 [-6,68 ; 0,19]; 0,107	0,107	0,2755
	Male	106	3	2.83	95	3	3.16	0,9 [0,19 ; 4,33]	0,89 [0,18 ; 4,54];	-0,33 [-5,05 ; 4,4]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	117	1	0.85	116	5	4.31	0,2 [0,02 ; 1,67]	0,19 [0,02 ; 1,66];	-3,46 [-7,51 ; 0,6]; 0,119	0,119	0,3029
	0	155	4	2.58	157	6	3.82	0,68 [0,19 ; 2,35]	0,67 [0,18 ; 2,41];	-1,24 [-5,14 ; 2,66]; 0,75	0,75	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	1	0.93	92	2	2.17	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	1	2.38	58	5	8.62	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	3	2.44	125	4	3.20	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	0	0.00	8	1	12.50	0,38 [0,02 ; 7,96]	0,33 [0,01 ; 9,57];	-10,42 [-39,98 ; 19,15]; 0,477	0,477	0,3886
	White	266	5	1.88	267	10	3.75	0,5 [0,17 ; 1,45]	0,49 [0,17 ; 1,46];	-1,87 [-4,67 ; 0,94]; 0,295	0,295	
	No	181	3	1.66	193	6	3.11	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	2	2.17	82	5	6.10	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Region	Eastern Europe	247	5	2.02	244	10	4.10	0,49 [0,17 ; 1,42]	0,48 [0,16 ; 1,44];	-2,07 [-5,12 ; 0,97]; 0,201	0,201	0,4134
	USA and Western Europe	26	0	0.00	31	1	3.23	0,4 [0,02 ; 9,31]	0,38 [0,01 ; 9,82];	-2,84 [-11,75 ; 6,08]; 0,497	0,497	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Blood and lymphatic system disorders | Neutropenia

4.2.44 Respiratory, thoracic and mediastinal disorders - Oropharyngeal pain

Tabelle 101: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	9	6.00	146	5	3.42	1,75 [0,6 ; 5,1]	1,8 [0,59 ; 5,5];	2,58 [-2,24 ; 7,39]; 0,413	0,413	0,3835
	>= 38 years	123	4	3.25	129	5	3.88	0,84 [0,23 ; 3,05]	0,83 [0,22 ; 3,18];	-0,62 [-5,2 ; 3,95]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	201	10	4.98	208	9	4.33	1,15 [0,48 ; 2,77]	1,16 [0,46 ; 2,91];	0,65 [-3,44 ; 4,73]; 0,817	0,817	0,4507
	>3.5	72	3	4.17	67	1	1.49	2,79 [0,3 ; 26,19]	2,87 [0,29 ; 28,29];	2,67 [-2,78 ; 8,13]; 0,621	0,621	
Gender	Female	167	9	5.39	180	10	5.56	0,97 [0,4 ; 2,33]	0,97 [0,38 ; 2,45];	-0,17 [-4,95 ; 4,62]; 1	1	0,0313
	Male	106	4	3.77	95	0	0.00	8,07 [0,44 ; 148,04]	8,39 [0,45 ; 157,83];	3,68 [-0,38 ; 7,75]; 0,123	0,123	
Number of baseline Gd-enhancing lesions	>=1	117	6	5.13	116	2	1.72	2,97 [0,61 ; 14,43]	3,08 [0,61 ; 15,59];	3,4 [-1,24 ; 8,05]; 0,281	0,281	0,1848
	0	155	7	4.52	157	8	5.10	0,89 [0,33 ; 2,38]	0,88 [0,31 ; 2,49];	-0,58 [-5,32 ; 4,17]; 1	1	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	4	3.70	92	2	2.17	1,7 [0,32 ; 9,09]	1,73 [0,31 ; 9,67];	1,53 [-3,11 ; 6,17]; 0,689	0,689	0,9501
	>=3	42	3	7.14	58	3	5.17	1,38 [0,29 ; 6,51]	1,41 [0,27 ; 7,36];	1,97 [-7,68 ; 11,62]; 0,694	0,694	
	2	123	6	4.88	125	5	4.00	1,22 [0,38 ; 3,89]	1,23 [0,37 ; 4,14];	0,88 [-4,25 ; 6,01]; 0,768	0,768	
Race	Other	7	0	0.00	8	2	25.00	0,22 [0,01 ; 4,02]	0,17 [0,01 ; 4,31];	-21,53 [-55,26 ; 12,2]; 0,467	0,467	0,058
	White	266	13	4.89	267	8	3.00	1,63 [0,69 ; 3,87]	1,66 [0,68 ; 4,08];	1,89 [-1,41 ; 5,19]; 0,276	0,276	
	No	181	6	3.31	193	7	3.63	0,91 [0,31 ; 2,67]	0,91 [0,3 ; 2,76];	-0,31 [-4,02 ; 3,4]; 1	1	0,3303

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	7	7.61	82	3	3.66	2,08 [0,56 ; 7,78]	2,17 [0,54 ; 8,68];	3,95 [-2,82 ; 10,72]; 0,338	0,338	
Region	Eastern Europe	247	12	4.86	244	8	3.28	1,48 [0,62 ; 3,56]	1,51 [0,6 ; 3,75];	1,58 [-1,91 ; 5,07]; 0,495	0,495	0,4637
	USA and Western Europe	26	1	3.85	31	2	6.45	0,6 [0,06 ; 6,21]	0,58 [0,05 ; 6,78];	-2,61 [-13,98 ; 8,77]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Respiratory, thoracic and mediastinal disorders | Oropharyngeal pain

4.2.45 Infections and infestations - Respiratory tract infection

Tabelle 102: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	8	5.33	146	7	4.79	1,11 [0,41 ; 2,99]	1,12 [0,4 ; 3,17];	0,54 [-4,46 ; 5,53]; 1	1	0,804
	>= 38 years	123	4	3.25	129	3	2.33	1,4 [0,32 ; 6,12]	1,41 [0,31 ; 6,44];	0,93 [-3,15 ; 5]; 0,717	0,717	
Disease Severity at baseline (EDSS)	<=3.5	201	9	4.48	208	10	4.81	0,93 [0,39 ; 2,24]	0,93 [0,37 ; 2,33];	-0,33 [-4,41 ; 3,75]; 1	1	0,0513
	>3.5	72	3	4.17	67	0	0.00	6,52 [0,34 ; 123,92]	6,8 [0,34 ; 134,12];	4,06 [-1,25 ; 9,36]; 0,121	0,121	
Gender	Female	167	8	4.79	180	7	3.89	1,23 [0,46 ; 3,32]	1,24 [0,44 ; 3,51];	0,9 [-3,4 ; 5,2]; 0,794	0,794	0,9717
	Male	106	4	3.77	95	3	3.16	1,19 [0,27 ; 5,2]	1,2 [0,26 ; 5,52];	0,62 [-4,44 ; 5,67]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	117	5	4.27	116	5	4.31	0,99 [0,29 ; 3,33]	0,99 [0,28 ; 3,52];	-0,04 [-5,24 ; 5,17]; 1	1	0,6719
	0	155	7	4.52	157	5	3.18	1,42 [0,46 ; 4,37]	1,44 [0,45 ; 4,63];	1,33 [-2,94 ; 5,6]; 0,572	0,572	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	1	0.93	92	0	0.00	2,56 [0,11 ; 62,08]	2,58 [0,1 ; 64,13];	0,84 [-1,81 ; 3,48]; 0,502	0,502	0,4997
	>=3	42	5	11.90	58	4	6.90	1,73 [0,49 ; 6,05]	1,82 [0,46 ; 7,25];	5,01 [-6,76 ; 16,77]; 0,486	0,486	
	2	123	6	4.88	125	6	4.80	1,02 [0,34 ; 3,06]	1,02 [0,32 ; 3,24];	0,08 [-5,26 ; 5,42]; 1	1	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	1
	White	266	12	4.51	267	10	3.75	1,2 [0,53 ; 2,74]	1,21 [0,52 ; 2,86];	0,77 [-2,61 ; 4,14]; 0,671	0,671	
	No	181	3	1.66	193	5	2.59	0,64 [0,16 ; 2,64]	0,63 [0,15 ; 2,69];	-0,93 [-3,85 ; 1,98]; 0,725	0,725	0,2942

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	9	9.78	82	5	6.10	1,6 [0,56 ; 4,59]	1,67 [0,54 ; 5,2];	3,69 [-4,29 ; 11,66]; 0,416	0,416	
Region	Eastern Europe	247	12	4.86	244	9	3.69	1,32 [0,57 ; 3,07]	1,33 [0,55 ; 3,22];	1,17 [-2,41 ; 4,74]; 0,657	0,657	0,2266
	USA and Western Europe	26	0	0.00	31	1	3.23	0,4 [0,02 ; 9,31]	0,38 [0,01 ; 9,82];	-2,84 [-11,75 ; 6,08]; 0,497	0,497	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Respiratory tract infection

4.2.46 Vascular disorders - Hypertension

Tabelle 103: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	7	4.67	146	8	5.48	0,85 [0,32 ; 2,29]	0,84 [0,3 ; 2,39];	-0,81 [-5,81 ; 4,19]; 0,796	0,796	0,1834
	>= 38 years	123	4	3.25	129	13	10.08	0,32 [0,11 ; 0,96]	0,3 [0,1 ; 0,95];	-6,83 [-12,89 ; -0,76]; 0,043	0,043	
Disease Severity at baseline (EDSS)	<=3.5	201	8	3.98	208	16	7.69	0,52 [0,23 ; 1,18]	0,5 [0,21 ; 1,19];	-3,71 [-8,23 ; 0,81]; 0,141	0,141	0,9266
	>3.5	72	3	4.17	67	5	7.46	0,56 [0,14 ; 2,25]	0,54 [0,12 ; 2,35];	-3,3 [-11,1 ; 4,51]; 0,482	0,482	
Gender	Female	167	8	4.79	180	14	7.78	0,62 [0,27 ; 1,43]	0,6 [0,24 ; 1,46];	-2,99 [-8,07 ; 2,09]; 0,278	0,278	0,5568
	Male	106	3	2.83	95	7	7.37	0,38 [0,1 ; 1,44]	0,37 [0,09 ; 1,46];	-4,54 [-10,67 ; 1,59]; 0,196	0,196	
Number of baseline Gd-enhancing lesions	>=1	117	5	4.27	116	10	8.62	0,5 [0,17 ; 1,41]	0,47 [0,16 ; 1,43];	-4,35 [-10,63 ; 1,94]; 0,194	0,194	0,874
	0	155	6	3.87	157	11	7.01	0,55 [0,21 ; 1,46]	0,53 [0,19 ; 1,48];	-3,14 [-8,15 ; 1,88]; 0,319	0,319	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	4	3.70	92	8	8.70	0,43 [0,13 ; 1,37]	0,4 [0,12 ; 1,39];	-4,99 [-11,76 ; 1,78]; 0,231	0,231	0,5623
	>=3	42	2	4.76	58	2	3.45	1,38 [0,2 ; 9,41]	1,4 [0,19 ; 10,36];	1,31 [-6,66 ; 9,28]; 1	1	
	2	123	5	4.07	125	11	8.80	0,46 [0,17 ; 1,29]	0,44 [0,15 ; 1,3];	-4,73 [-10,8 ; 1,33]; 0,195	0,195	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9999
	White	266	11	4.14	267	21	7.87	0,53 [0,26 ; 1,07]	0,51 [0,24 ; 1,07];	-3,73 [-7,75 ; 0,29]; 0,099	0,099	
	No	181	5	2.76	193	15	7.77	0,36 [0,13 ; 0,96]	0,34 [0,12 ; 0,95];	-5,01 [-9,48 ; -0,54]; 0,038	0,038	0,2226

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	6	6.52	82	6	7.32	0,89 [0,3 ; 2,66]	0,88 [0,27 ; 2,86];	-0,8 [-8,36 ; 6,77]; 1	1	
Region	Eastern Europe	247	11	4.45	244	20	8.20	0,54 [0,27 ; 1,11]	0,52 [0,24 ; 1,11];	-3,74 [-8,04 ; 0,55]; 0,097	0,097	0,3942
	USA and Western Europe	26	0	0.00	31	1	3.23	0,4 [0,02 ; 9,31]	0,38 [0,01 ; 9,82];	-2,84 [-11,75 ; 6,08]; 0,497	0,497	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Vascular disorders | Hypertension

4.2.47 General disorders and administration site conditions - Asthenia

Tabelle 104: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	10	6.67	146	4	2.74	2,43 [0,78 ; 7,59]	2,54 [0,78 ; 8,28];	3,93 [-0,86 ; 8,72]; 0,17	0,17	0,0022
	>= 38 years	123	0	0.00	129	5	3.88	0,1 [0,01 ; 1,71]	0,09 [0,01 ; 1,68];	-3,83 [-7,46 ; -0,19]; 0,03	0,03	
Disease Severity at baseline (EDSS)	<=3.5	201	8	3.98	208	8	3.85	1,03 [0,4 ; 2,7]	1,04 [0,38 ; 2,82];	0,13 [-3,63 ; 3,89]; 1	1	0,6482
	>3.5	72	2	2.78	67	1	1.49	1,86 [0,17 ; 20,05]	1,89 [0,17 ; 21,29];	1,29 [-3,49 ; 6,06]; 1	1	
Gender	Female	167	5	2.99	180	4	2.22	1,35 [0,37 ; 4,93]	1,36 [0,36 ; 5,14];	0,77 [-2,59 ; 4,14]; 0,743	0,743	0,6535
	Male	106	5	4.72	95	5	5.26	0,9 [0,27 ; 3]	0,89 [0,25 ; 3,18];	-0,55 [-6,58 ; 5,49]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	117	5	4.27	116	5	4.31	0,99 [0,29 ; 3,33]	0,99 [0,28 ; 3,52];	-0,04 [-5,24 ; 5,17]; 1	1	0,7882
	0	155	5	3.23	157	4	2.55	1,27 [0,35 ; 4,63]	1,27 [0,34 ; 4,84];	0,68 [-3,04 ; 4,39]; 0,749	0,749	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	3	2.78	92	1	1.09	2,56 [0,27 ; 24,15]	2,6 [0,27 ; 25,43];	1,69 [-2,06 ; 5,45]; 0,626	0,626	0,2224
	>=3	42	0	0.00	58	2	3.45	0,27 [0,01 ; 5,57]	0,27 [0,01 ; 5,68];	-3,07 [-9,13 ; 2,98]; 0,508	0,508	
	2	123	7	5.69	125	6	4.80	1,19 [0,41 ; 3,43]	1,2 [0,39 ; 3,67];	0,89 [-4,66 ; 6,44]; 0,784	0,784	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	1
	White	266	10	3.76	267	9	3.37	1,12 [0,46 ; 2,7]	1,12 [0,45 ; 2,8];	0,39 [-2,76 ; 3,54]; 0,82	0,82	
	No	181	6	3.31	193	6	3.11	1,07 [0,35 ; 3,25]	1,07 [0,34 ; 3,38];	0,21 [-3,37 ; 3,78]; 1	1	0,9073

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	4	4.35	82	3	3.66	1,19 [0,27 ; 5,15]	1,2 [0,26 ; 5,51];	0,69 [-5,13 ; 6,51]; 1	1	
Region	Eastern Europe	247	10	4.05	244	9	3.69	1,1 [0,45 ; 2,65]	1,1 [0,44 ; 2,76];	0,36 [-3,05 ; 3,77]; 1	1	1
	USA and Western Europe	26	0	0.00	31	0	0.00	1,19 [0,02 ; 57,76]	1,19 [0,02 ; 61,97];	0,29 [-6,37 ; 6,95]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - General disorders and administration site conditions | Asthenia

4.2.48 Blood and lymphatic system disorders - Lymphopenia

Tabelle 105: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	10	6.67	146	0	0.00	20,44 [1,21 ; 345,71]	21,9 [1,27 ; 377,21];	6,61 [2,45 ; 10,78]; 0,002	0,002	0,026
	>= 38 years	123	3	2.44	129	2	1.55	1,57 [0,27 ; 9,25]	1,59 [0,26 ; 9,67];	0,89 [-2,57 ; 4,35]; 0,678	0,678	
Disease Severity at baseline (EDSS)	<=3.5	201	11	5.47	208	0	0.00	23,8 [1,41 ; 401,16]	25,17 [1,47 ; 430,1];	5,45 [2,19 ; 8,72]; 0	0	0,01
	>3.5	72	2	2.78	67	2	2.99	0,93 [0,13 ; 6,42]	0,93 [0,13 ; 6,79];	-0,21 [-5,78 ; 5,36]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	117	6	5.13	116	1	0.86	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	155	7	4.52	157	1	0.64	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	4	3.70	92	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	3	7.14	58	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	6	4.88	125	2	1.60	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9995
	White	266	13	4.89	267	2	0.75	6,52 [1,49 ; 28,63]	6,81 [1,52 ; 30,47];	4,14 [1,35 ; 6,93]; 0,004	0,004	
Received approved disease modifying MS drug prior to enrollment	No	181	6	3.31	193	1	0.52	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	Yes	92	7	7.61	82	1	1.22	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	247	13	5.26	244	2	0.82	6,42 [1,46 ; 28,16]	6,72 [1,5 ; 30,11];	4,44 [1,44 ; 7,45]; 0,007	0,007	0,9999
	USA and Western Europe	26	0	0.00	31	0	0.00	1,19 [0,02 ; 57,76]	1,19 [0,02 ; 61,97];	0,29 [-6,37 ; 6,95]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Blood and lymphatic system disorders | Lymphopenia

4.2.49 Infections and infestations - Respiratory tract infection viral

Tabelle 106: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	17	11.33	146	6	4.11	2,76 [1,12 ; 6,8]	2,98 [1,14 ; 7,79];	7,22 [1,22 ; 13,23]; 0,028	0,028	0,5514
	>= 38 years	123	3	2.44	129	2	1.55	1,57 [0,27 ; 9,25]	1,59 [0,26 ; 9,67];	0,89 [-2,57 ; 4,35]; 0,678	0,678	
Disease Severity at baseline (EDSS)	<=3.5	201	16	7.96	208	8	3.85	2,07 [0,91 ; 4,73]	2,16 [0,9 ; 5,17];	4,11 [-0,45 ; 8,68]; 0,093	0,093	0,1004
	>3.5	72	4	5.56	67	0	0.00	8,38 [0,46 ; 152,82]	8,87 [0,47 ; 167,93];	5,43 [-0,45 ; 11,31]; 0,12	0,12	
Gender	Female	167	10	5.99	180	3	1.67	3,59 [1,01 ; 12,83]	3,76 [1,02 ; 13,9];	4,32 [0,27 ; 8,38]; 0,046	0,046	0,4224
	Male	106	10	9.43	95	5	5.26	1,79 [0,64 ; 5,06]	1,88 [0,62 ; 5,7];	4,17 [-2,98 ; 11,32]; 0,295	0,295	
Number of baseline Gd-enhancing lesions	>=1	117	7	5.98	116	3	2.59	2,31 [0,61 ; 8,73]	2,4 [0,6 ; 9,51];	3,4 [-1,78 ; 8,57]; 0,333	0,333	0,8664
	0	155	13	8.39	157	5	3.18	2,63 [0,96 ; 7,21]	2,78 [0,97 ; 8];	5,2 [0,05 ; 10,36]; 0,055	0,055	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	8	7.41	92	1	1.09	6,81 [0,87 ; 53,48]	7,28 [0,89 ; 59,34];	6,32 [0,95 ; 11,69]; 0,04	0,04	0,3197
	>=3	42	5	11.90	58	2	3.45	3,45 [0,7 ; 16,95]	3,78 [0,7 ; 20,54];	8,46 [-2,41 ; 19,32]; 0,127	0,127	
	2	123	7	5.69	125	5	4.00	1,42 [0,46 ; 4,36]	1,45 [0,45 ; 4,69];	1,69 [-3,65 ; 7,04]; 0,569	0,569	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9999
	White	266	20	7.52	267	8	3.00	2,51 [1,13 ; 5,6]	2,63 [1,14 ; 6,09];	4,52 [0,75 ; 8,29]; 0,02	0,02	
	No	181	7	3.87	193	6	3.11	1,24 [0,43 ; 3,63]	1,25 [0,41 ; 3,8];	0,76 [-2,97 ; 4,48]; 0,781	0,781	0,0674

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	13	14.13	82	2	2.44	5,79 [1,35 ; 24,91]	6,58 [1,44 ; 30,12];	11,69 [3,83 ; 19,55]; 0,006	0,006	
Region	Eastern Europe	247	20	8.10	244	8	3.28	2,47 [1,11 ; 5,5]	2,6 [1,12 ; 6,02];	4,82 [0,75 ; 8,89]; 0,031	0,031	0,9999
	USA and Western Europe	26	0	0.00	31	0	0.00	1,19 [0,02 ; 57,76]	1,19 [0,02 ; 61,97];	0,29 [-6,37 ; 6,95]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Respiratory tract infection viral

4.2.50 General disorders and administration site conditions - Hyperthermia

Tabelle 107: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	7	4.67	146	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>= 38 years	123	6	4.88	129	2	1.55	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	201	8	3.98	208	1	0.48	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>3.5	72	5	6.94	67	1	1.49	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Gender	Female	167	9	5.39	180	2	1.11	4,85 [1,06 ; 22,12]	5,07 [1,08 ; 23,82];	4,28 [0,53 ; 8,03]; 0,03	0,03	0,2833
	Male	106	4	3.77	95	0	0.00	8,07 [0,44 ; 148,04]	8,39 [0,45 ; 157,83];	3,68 [-0,38 ; 7,75]; 0,123	0,123	
Number of baseline Gd-enhancing lesions	>=1	117	6	5.13	116	1	0.86	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	155	7	4.52	157	1	0.64	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	5	4.63	92	2	2.17	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	6	14.29	58	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	2	1.63	125	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9995
	White	266	13	4.89	267	2	0.75	6,52 [1,49 ; 28,63]	6,81 [1,52 ; 30,47];	4,14 [1,35 ; 6,93]; 0,004	0,004	
	No	181	6	3.31	193	2	1.04	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	7	7.61	82	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Region	Eastern Europe	247	13	5.26	244	2	0.82	6,42 [1,46 ; 28,16]	6,72 [1,5 ; 30,11];	4,44 [1,44 ; 7,45]; 0,007	0,007	0,9999
	USA and Western Europe	26	0	0.00	31	0	0.00	1,19 [0,02 ; 57,76]	1,19 [0,02 ; 61,97];	0,29 [-6,37 ; 6,95]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - General disorders and administration site conditions | Hyperthermia

4.2.51 General disorders and administration site conditions - Influenza like illness

Tabelle 108: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	8	5.33	146	1	0.68	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>= 38 years	123	3	2.44	129	3	2.33	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	201	9	4.48	208	2	0.96	4,66 [1,02 ; 21,29]	4,83 [1,03 ; 22,63];	3,52 [0,36 ; 6,67]; 0,033	0,033	0,1972
	>3.5	72	2	2.78	67	2	2.99	0,93 [0,13 ; 6,42]	0,93 [0,13 ; 6,79];	-0,21 [-5,78 ; 5,36]; 1	1	
Gender	Female	167	7	4.19	180	4	2.22	1,89 [0,56 ; 6,33]	1,92 [0,55 ; 6,7];	1,97 [-1,76 ; 5,69]; 0,366	0,366	0,1064
	Male	106	4	3.77	95	0	0.00	8,07 [0,44 ; 148,04]	8,39 [0,45 ; 157,83];	3,68 [-0,38 ; 7,75]; 0,123	0,123	
Number of baseline Gd-enhancing lesions	>=1	117	3	2.56	116	2	1.72	1,49 [0,25 ; 8,74]	1,5 [0,25 ; 9,15];	0,84 [-2,88 ; 4,56]; 1	1	0,3972
	0	155	8	5.16	157	2	1.27	4,05 [0,87 ; 18,78]	4,22 [0,88 ; 20,19];	3,89 [-0,01 ; 7,79]; 0,06	0,06	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	5	4.63	92	2	2.17	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	2	4.76	58	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	4	3.25	125	2	1.60	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9999
	White	266	11	4.14	267	4	1.50	2,76 [0,89 ; 8,56]	2,84 [0,89 ; 9,02];	2,64 [-0,16 ; 5,44]; 0,072	0,072	
	No	181	5	2.76	193	2	1.04	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	6	6.52	82	2	2.44	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Region	Eastern Europe	247	11	4.45	244	4	1.64	2,72 [0,88 ; 8,41]	2,8 [0,88 ; 8,91];	2,81 [-0,21 ; 5,84]; 0,113	0,113	0,9999
	USA and Western Europe	26	0	0.00	31	0	0.00	1,19 [0,02 ; 57,76]	1,19 [0,02 ; 61,97];	0,29 [-6,37 ; 6,95]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - General disorders and administration site conditions | Influenza like illness

4.2.52 Investigations - Alanine aminotransferase increased

Tabelle 109: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	6	4.00	146	10	6.85	0,58 [0,22 ; 1,57]	0,57 [0,2 ; 1,6];	-2,85 [-8,01 ; 2,31]; 0,313	0,313	0,327
	>= 38 years	123	4	3.25	129	3	2.33	1,4 [0,32 ; 6,12]	1,41 [0,31 ; 6,44];	0,93 [-3,15 ; 5]; 0,717	0,717	
Disease Severity at baseline (EDSS)	<=3.5	201	8	3.98	208	9	4.33	0,92 [0,36 ; 2,34]	0,92 [0,35 ; 2,42];	-0,35 [-4,21 ; 3,52]; 1	1	0,4753
	>3.5	72	2	2.78	67	4	5.97	0,47 [0,09 ; 2,46]	0,45 [0,08 ; 2,54];	-3,19 [-10,02 ; 3,63]; 0,429	0,429	
Gender	Female	167	4	2.40	180	5	2.78	0,86 [0,24 ; 3,16]	0,86 [0,23 ; 3,25];	-0,38 [-3,72 ; 2,96]; 1	1	0,7552
	Female	167	4	2.40	180	2	1.11	0,86 [0,24 ; 3,16]	0,86 [0,23 ; 3,25];	-0,38 [-3,72 ; 2,96]; 1	1	
	Female	167	7	4.19	180	5	2.78	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Female	167	7	4.19	180	2	1.11	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Male	106	6	5.66	95	8	8.42	0,67 [0,24 ; 1,87]	0,65 [0,22 ; 1,95];	-2,76 [-9,87 ; 4,35]; 0,581	0,581	
	Male	106	6	5.66	95	1	1.05	0,67 [0,24 ; 1,87]	0,65 [0,22 ; 1,95];	-2,76 [-9,87 ; 4,35]; 0,581	0,581	
	Male	106	5	4.72	95	8	8.42	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Male	106	5	4.72	95	1	1.05	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of baseline Gd-enhancing lesions	>=1	117	4	3.42	116	6	5.17	0,66 [0,19 ; 2,28]	0,65 [0,18 ; 2,36];	-1,75 [-6,96 ; 3,45]; 0,539	0,539	0,7429
	0	155	6	3.87	157	7	4.46	0,87 [0,3 ; 2,53]	0,86 [0,28 ; 2,63];	-0,59 [-5,02 ; 3,84]; 1	1	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Number of relapses experienced in the 2 years prior to study start	<=1	108	4	3.70	92	2	2.17	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	2	4.76	58	6	10.34	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	4	3.25	125	5	4.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	1
	White	266	10	3.76	267	13	4.87	0,77 [0,34 ; 1,73]	0,76 [0,33 ; 1,77];	-1,11 [-4,56 ; 2,34]; 0,671	0,671	
Received approved disease modifying MS drug prior to enrollment	No	181	7	3.87	193	8	4.15	0,93 [0,35 ; 2,52]	0,93 [0,33 ; 2,62];	-0,28 [-4,25 ; 3,7]; 1	1	0,5206
	Yes	92	3	3.26	82	5	6.10	0,53 [0,13 ; 2,17]	0,52 [0,12 ; 2,24];	-2,84 [-9,16 ; 3,49]; 0,478	0,478	
Region	Eastern Europe	247	10	4.05	244	13	5.33	0,76 [0,34 ; 1,7]	0,75 [0,32 ; 1,74];	-1,28 [-5,02 ; 2,46]; 0,529	0,529	1
	USA and Western Europe	26	0	0.00	31	0	0.00	1,19 [0,02 ; 57,76]	1,19 [0,02 ; 61,97];	0,29 [-6,37 ; 6,95]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Investigations | Alanine aminotransferase increased

4.2.53 Investigations - Body temperature increased

Tabelle 110: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	8	5.33	146	2	1.37	3,89 [0,84 ; 18,03]	4,06 [0,85 ; 19,43];	3,96 [-0,1 ; 8,02]; 0,104	0,104	0,9659
	>= 38 years	123	4	3.25	129	1	0.78	4,2 [0,48 ; 37,01]	4,3 [0,47 ; 39,04];	2,48 [-1 ; 5,96]; 0,204	0,204	
Disease Severity at baseline (EDSS)	<=3.5	201	10	4.98	208	3	1.44	3,45 [0,96 ; 12,35]	3,58 [0,97 ; 13,2];	3,53 [0,12 ; 6,95]; 0,05	0,05	0,35
	>3.5	72	2	2.78	67	0	0.00	4,66 [0,23 ; 95,28]	4,79 [0,23 ; 101,56];	2,69 [-1,95 ; 7,33]; 0,497	0,497	
Number of baseline Gd-enhancing lesions	>=1	117	3	2.56	116	3	2.59	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	155	9	5.81	157	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	6	5.56	92	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	2	4.76	58	1	1.72	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	4	3.25	125	2	1.60	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9998
	White	266	12	4.51	267	3	1.12	4,02 [1,15 ; 14,07]	4,16 [1,16 ; 14,91];	3,39 [0,59 ; 6,18]; 0,019	0,019	
Received approved disease modifying MS drug prior to enrollment	No	181	6	3.31	193	2	1.04	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	Yes	92	6	6.52	82	1	1.22	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	247	12	4.86	244	3	1.23	3,95 [1,13 ; 13,83]	4,1 [1,14 ; 14,72];	3,63 [0,61 ; 6,65]; 0,033	0,033	0,9999
	USA and Western Europe	26	0	0.00	31	0	0.00	1,19 [0,02 ; 57,76]	1,19 [0,02 ; 61,97];	0,29 [-6,37 ; 6,95]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Investigations | Body temperature increased

4.2.54 Investigations - Aspartate aminotransferase increased

Tabelle 111: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	9	6.00	146	3	2.05	2,92 [0,81 ; 10,57]	3,04 [0,81 ; 11,47];	3,95 [-0,5 ; 8,39]; 0,138	0,138	0,2094
	>= 38 years	123	3	2.44	129	0	0.00	7,34 [0,38 ; 140,63]	7,52 [0,38 ; 147,16];	2,44 [-0,67 ; 5,54]; 0,055	0,055	
Disease Severity at baseline (EDSS)	<=3.5	201	9	4.48	208	3	1.44	3,1 [0,85 ; 11,3]	3,2 [0,85 ; 12,01];	3,04 [-0,25 ; 6,32]; 0,083	0,083	0,2379
	>3.5	72	3	4.17	67	0	0.00	6,52 [0,34 ; 123,92]	6,8 [0,34 ; 134,12];	4,06 [-1,25 ; 9,36]; 0,121	0,121	
Gender	Female	167	8	4.79	180	2	1.11	4,31 [0,93 ; 20,01]	4,48 [0,94 ; 21,4];	3,68 [0,1 ; 7,26]; 0,054	0,054	0,8887
	Male	106	4	3.77	95	1	1.05	3,58 [0,41 ; 31,52]	3,69 [0,4 ; 33,57];	2,72 [-1,45 ; 6,89]; 0,373	0,373	
Number of baseline Gd-enhancing lesions	>=1	117	5	4.27	116	2	1.72	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	155	7	4.52	157	1	0.64	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	3	2.78	92	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	4	9.52	58	1	1.72	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	5	4.07	125	2	1.60	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9998
	White	266	12	4.51	267	3	1.12	4,02 [1,15 ; 14,07]	4,16 [1,16 ; 14,91];	3,39 [0,59 ; 6,18]; 0,019	0,019	
	No	181	8	4.42	193	1	0.52	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	4	4.35	82	2	2.44	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Region	Eastern Europe	247	12	4.86	244	3	1.23	3,95 [1,13 ; 13,83]	4,1 [1,14 ; 14,72];	3,63 [0,61 ; 6,65]; 0,033	0,033	0,9999
	USA and Western Europe	26	0	0.00	31	0	0.00	1,19 [0,02 ; 57,76]	1,19 [0,02 ; 61,97];	0,29 [-6,37 ; 6,95]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Investigations | Aspartate aminotransferase increased

4.2.55 Infections and infestations - Rhinitis

Tabelle 112: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	14	9.33	146	3	2.05	4,54 [1,33 ; 15,48]	4,91 [1,38 ; 17,45];	7,28 [2,09 ; 12,47]; 0,01	0,01	0,0281
	>= 38 years	123	3	2.44	129	5	3.88	0,63 [0,15 ; 2,58]	0,62 [0,14 ; 2,65];	-1,44 [-5,74 ; 2,87]; 0,723	0,723	
Disease Severity at baseline (EDSS)	<=3.5	201	12	5.97	208	7	3.37	1,77 [0,71 ; 4,41]	1,82 [0,7 ; 4,73];	2,6 [-1,49 ; 6,7]; 0,245	0,245	0,3815
	>3.5	72	5	6.94	67	1	1.49	4,65 [0,56 ; 38,81]	4,93 [0,56 ; 43,3];	5,45 [-1,1 ; 12]; 0,21	0,21	
Gender	Female	167	6	3.59	180	6	3.33	1,08 [0,35 ; 3,28]	1,08 [0,34 ; 3,42];	0,26 [-3,59 ; 4,11]; 1	1	0,0832
	Male	106	11	10.38	95	2	2.11	4,93 [1,12 ; 21,67]	5,38 [1,16 ; 24,95];	8,27 [1,79 ; 14,76]; 0,021	0,021	
Number of baseline Gd-enhancing lesions	>=1	117	8	6.84	116	5	4.31	1,59 [0,53 ; 4,71]	1,63 [0,52 ; 5,14];	2,53 [-3,35 ; 8,41]; 0,57	0,57	0,4538
	0	155	9	5.81	157	3	1.91	3,04 [0,84 ; 11,01]	3,16 [0,84 ; 11,92];	3,9 [-0,36 ; 8,15]; 0,085	0,085	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	1	0.93	92	4	4.35	0,21 [0,02 ; 1,87]	0,21 [0,02 ; 1,87];	-3,42 [-7,96 ; 1,12]; 0,182	0,182	0,0038
	>=3	42	1	2.38	58	2	3.45	0,69 [0,06 ; 7,37]	0,68 [0,06 ; 7,79];	-1,07 [-7,65 ; 5,51]; 1	1	
	2	123	15	12.20	125	2	1.60	7,62 [1,78 ; 32,63]	8,54 [1,91 ; 38,2];	10,6 [4,41 ; 16,78]; 0,001	0,001	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9999
	White	266	17	6.39	267	8	3.00	2,13 [0,94 ; 4,86]	2,21 [0,94 ; 5,21];	3,39 [-0,19 ; 6,98]; 0,068	0,068	
	No	181	11	6.08	193	7	3.63	1,68 [0,66 ; 4,23]	1,72 [0,65 ; 4,54];	2,45 [-1,92 ; 6,82]; 0,336	0,336	0,2818

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	6	6.52	82	1	1.22	5,35 [0,66 ; 43,5]	5,65 [0,67 ; 47,97];	5,3 [-0,27 ; 10,88]; 0,122	0,122	
Region	Eastern Europe	247	17	6.88	244	8	3.28	2,1 [0,92 ; 4,77]	2,18 [0,92 ; 5,15];	3,6 [-0,26 ; 7,47]; 0,099	0,099	0,9999
	USA and Western Europe	26	0	0.00	31	0	0.00	1,19 [0,02 ; 57,76]	1,19 [0,02 ; 61,97];	0,29 [-6,37 ; 6,95]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Rhinitis

4.3 Severe TEAE

4.3.1 Infections and infestations - any

Tabelle 113: Severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	10	6.67	146	1	0.68	9,73 [1,26 ; 75,08]	10,36 [1,31 ; 81,97];	5,98 [1,77 ; 10,19]; 0,01	0,01	0,0647
	>= 38 years	123	3	2.44	129	3	2.33	1,05 [0,22 ; 5,1]	1,05 [0,21 ; 5,3];	0,11 [-3,65 ; 3,88]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	201	10	4.98	208	1	0.48	10,35 [1,34 ; 80,1]	10,84 [1,37 ; 85,46];	4,49 [1,34 ; 7,64]; 0,005	0,005	0,0475
	>3.5	72	3	4.17	67	3	4.48	0,93 [0,19 ; 4,45]	0,93 [0,18 ; 4,76];	-0,31 [-7,08 ; 6,46]; 1	1	
Gender	Female	167	11	6.59	180	4	2.22	2,96 [0,96 ; 9,13]	3,1 [0,97 ; 9,94];	4,36 [0,03 ; 8,7]; 0,063	0,063	0,3266
	Male	106	2	1.89	95	0	0.00	4,49 [0,22 ; 92,28]	4,57 [0,22 ; 96,39];	1,82 [-1,39 ; 5,02]; 0,499	0,499	
Number of baseline Gd-enhancing lesions	>=1	117	9	7.69	116	1	0.86	8,92 [1,15 ; 69,31]	9,58 [1,19 ; 76,91];	6,83 [1,72 ; 11,94]; 0,019	0,019	0,1105
	0	155	4	2.58	157	3	1.91	1,35 [0,31 ; 5,94]	1,36 [0,3 ; 6,18];	0,67 [-2,62 ; 3,96]; 0,722	0,722	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	3	2.78	92	1	1.09	2,56 [0,27 ; 24,15]	2,6 [0,27 ; 25,43];	1,69 [-2,06 ; 5,45]; 0,626	0,626	0,7236
	>=3	42	1	2.38	58	1	1.72	1,38 [0,09 ; 21,46]	1,39 [0,08 ; 22,88];	0,66 [-5,04 ; 6,36]; 1	1	
	2	123	9	7.32	125	2	1.60	4,57 [1,01 ; 20,74]	4,86 [1,03 ; 22,95];	5,72 [0,62 ; 10,82]; 0,033	0,033	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9999
	White	266	13	4.89	267	4	1.50	3,26 [1,08 ; 9,88]	3,38 [1,09 ; 10,5];	3,39 [0,42 ; 6,36]; 0,028	0,028	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	No	181	9	4.97	193	2	1.04	4,8 [1,05 ; 21,91]	5 [1,06 ; 23,45];	3,94 [0,46 ; 7,41]; 0,031	0,031	0,3942
	Yes	92	4	4.35	82	2	2.44	1,78 [0,34 ; 9,48]	1,82 [0,32 ; 10,2];	1,91 [-3,43 ; 7,25]; 0,685	0,685	
Region	Eastern Europe	247	12	4.86	244	4	1.64	2,96 [0,97 ; 9,06]	3,06 [0,97 ; 9,64];	3,22 [0,1 ; 6,34]; 0,072	0,072	0,421
	USA and Western Europe	26	1	3.85	31	0	0.00	3,56 [0,15 ; 83,75]	3,71 [0,14 ; 94,9];	3,99 [-5,66 ; 13,64]; 0,214	0,214	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Severe TEAE - Infections and infestations | any

4.3.2 Investigations - any

Tabelle 114: Severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	17	11.33	146	9	6.16	1,84 [0,85 ; 3,99]	1,95 [0,84 ; 4,52];	5,17 [-1,23 ; 11,57]; 0,151	0,151	0,6466
	>= 38 years	123	16	13.01	129	7	5.43	2,4 [1,02 ; 5,63]	2,61 [1,03 ; 6,57];	7,58 [0,47 ; 14,7]; 0,048	0,048	
Disease Severity at baseline (EDSS)	<=3.5	201	26	12.94	208	11	5.29	2,45 [1,24 ; 4,82]	2,66 [1,28 ; 5,54];	7,65 [2,1 ; 13,19]; 0,009	0,009	0,3408
	>3.5	72	7	9.72	67	5	7.46	1,3 [0,43 ; 3,91]	1,34 [0,4 ; 4,43];	2,26 [-7,04 ; 11,56]; 0,766	0,766	
Gender	Female	167	19	11.38	180	11	6.11	1,86 [0,91 ; 3,79]	1,97 [0,91 ; 4,28];	5,27 [-0,69 ; 11,22]; 0,088	0,088	0,6218
	Male	106	14	13.21	95	5	5.26	2,51 [0,94 ; 6,71]	2,74 [0,95 ; 7,92];	7,94 [0,09 ; 15,8]; 0,089	0,089	
Number of baseline Gd-enhancing lesions	>=1	117	17	14.53	116	8	6.90	2,11 [0,95 ; 4,69]	2,3 [0,95 ; 5,55];	7,63 [-0,24 ; 15,51]; 0,089	0,089	0,9147
	0	155	16	10.32	157	8	5.10	2,03 [0,89 ; 4,6]	2,14 [0,89 ; 5,17];	5,23 [-0,67 ; 11,12]; 0,093	0,093	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	10	9.26	92	3	3.26	2,84 [0,81 ; 10,01]	3,03 [0,81 ; 11,35];	6 [-0,56 ; 12,56]; 0,148	0,148	0,7808
	>=3	42	9	21.43	58	5	8.62	2,49 [0,9 ; 6,88]	2,89 [0,89 ; 9,37];	12,81 [-1,55 ; 27,17]; 0,084	0,084	
	2	123	14	11.38	125	8	6.40	1,78 [0,77 ; 4,09]	1,88 [0,76 ; 4,65];	4,98 [-2,08 ; 12,05]; 0,187	0,187	
Race	Other	7	0	0.00	8	1	12.50	0,38 [0,02 ; 7,96]	0,33 [0,01 ; 9,57];	-10,42 [-39,98 ; 19,15]; 0,477	0,477	0,133
	White	266	33	12.41	267	15	5.62	2,21 [1,23 ; 3,97]	2,38 [1,26 ; 4,49];	6,79 [1,96 ; 11,62]; 0,006	0,006	
	No	181	23	12.71	193	10	5.18	2,45 [1,2 ; 5,01]	2,66 [1,23 ; 5,77];	7,53 [1,75 ; 13,3]; 0,011	0,011	0,4181

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	10	10.87	82	6	7.32	1,49 [0,56 ; 3,91]	1,54 [0,54 ; 4,45];	3,55 [-4,95 ; 12,05]; 0,446	0,446	
Region	Eastern Europe	247	32	12.96	244	14	5.74	2,26 [1,24 ; 4,13]	2,45 [1,27 ; 4,71];	7,22 [2,11 ; 12,32]; 0,008	0,008	0,2512
	USA and Western Europe	26	1	3.85	31	2	6.45	0,6 [0,06 ; 6,21]	0,58 [0,05 ; 6,78];	-2,61 [-13,98 ; 8,77]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Severe TEAE - Investigations | any

4.3.3 Blood and lymphatic system disorders - any

Tabelle 115: Severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	15	10.00	146	4	2.74	3,65 [1,24 ; 10,74]	3,94 [1,28 ; 12,18];	7,26 [1,78 ; 12,74]; 0,016	0,016	0,6278
	>= 38 years	123	7	5.69	129	3	2.33	2,45 [0,65 ; 9,25]	2,53 [0,64 ; 10,03];	3,37 [-1,48 ; 8,22]; 0,208	0,208	
Disease Severity at baseline (EDSS)	<=3.5	201	19	9.45	208	5	2.40	3,93 [1,5 ; 10,33]	4,24 [1,55 ; 11,58];	7,05 [2,5 ; 11,6]; 0,003	0,003	0,3132
	>3.5	72	3	4.17	67	2	2.99	1,4 [0,24 ; 8,1]	1,41 [0,23 ; 8,73];	1,18 [-4,98 ; 7,34]; 1	1	
Gender	Female	167	15	8.98	180	7	3.89	2,31 [0,97 ; 5,52]	2,44 [0,97 ; 6,14];	5,09 [-0,08 ; 10,27]; 0,076	0,076	0,048
	Male	106	7	6.60	95	0	0.00	13,46 [0,78 ; 232,52]	14,4 [0,81 ; 255,56];	6,49 [1,44 ; 11,54]; 0,007	0,007	
Number of baseline Gd-enhancing lesions	>=1	117	11	9.40	116	2	1.72	5,45 [1,24 ; 24,06]	5,92 [1,28 ; 27,31];	7,68 [1,88 ; 13,47]; 0,019	0,019	0,3127
	0	155	11	7.10	157	5	3.18	2,23 [0,79 ; 6,26]	2,32 [0,79 ; 6,85];	3,91 [-0,98 ; 8,8]; 0,131	0,131	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	7	6.48	92	3	3.26	1,99 [0,53 ; 7,47]	2,06 [0,52 ; 8,19];	3,22 [-2,67 ; 9,11]; 0,347	0,347	0,5737
	>=3	42	5	11.90	58	1	1.72	6,9 [0,84 ; 56,95]	7,7 [0,87 ; 68,59];	10,18 [-0,17 ; 20,53]; 0,08	0,08	
	2	123	10	8.13	125	3	2.40	3,39 [0,96 ; 12,01]	3,6 [0,97 ; 13,41];	5,73 [0,21 ; 11,26]; 0,05	0,05	
Race	Other	7	0	0.00	8	1	12.50	0,38 [0,02 ; 7,96]	0,33 [0,01 ; 9,57];	-10,42 [-39,98 ; 19,15]; 0,477	0,477	0,0888
	White	266	22	8.27	267	6	2.25	3,68 [1,52 ; 8,93]	3,92 [1,56 ; 9,84];	6,02 [2,27 ; 9,78]; 0,002	0,002	
	No	181	12	6.63	193	5	2.59	2,56 [0,92 ; 7,12]	2,67 [0,92 ; 7,74];	4,04 [-0,22 ; 8,3]; 0,081	0,081	0,5207

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	10	10.87	82	2	2.44	4,46 [1,01 ; 19,75]	4,88 [1,04 ; 22,96];	8,43 [1,25 ; 15,61]; 0,036	0,036	
Region	Eastern Europe	247	21	8.50	244	6	2.46	3,46 [1,42 ; 8,42]	3,69 [1,46 ; 9,3];	6,04 [2,06 ; 10,03]; 0,005	0,005	0,4662
	USA and Western Europe	26	1	3.85	31	1	3.23	1,19 [0,08 ; 18,14]	1,2 [0,07 ; 20,18];	0,62 [-9,04 ; 10,28]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Severe TEAE - Blood and lymphatic system disorders | any

4.3.4 Investigations - Lymphocyte count decreased

Tabelle 116: Severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	11	7.33	146	0	0	22,39 [1,33 ; 376,51]	24,15 [1,41 ; 413,79];	7,28 [2,94 ; 11,61]; 0	0	1
	>= 38 years	123	7	5.69	129	0	0	15,73 [0,91 ; 272,44]	16,67 [0,94 ; 295,15];	5,66 [1,34 ; 9,99]; 0,003	0,003	
Disease Severity at baseline (EDSS)	<=3.5	201	13	6.47	208	0	0	27,94 [1,67 ; 466,82]	29,86 [1,76 ; 505,84];	6,44 [2,94 ; 9,95]; 0	0	1
	>3.5	72	5	6.94	67	0	0	10,25 [0,58 ; 181,83]	11 [0,6 ; 202,87];	6,8 [0,41 ; 13,19]; 0,029	0,029	
Gender	Female	167	13	7.78	180	0	0	29,09 [1,74 ; 485,52]	31,54 [1,86 ; 534,97];	7,76 [3,58 ; 11,94]; 0	0	0,9999
	Male	106	5	4.72	95	0	0	9,87 [0,55 ; 176,15]	10,35 [0,56 ; 189,71];	4,62 [0,19 ; 9,04]; 0,031	0,031	
Number of baseline Gd-enhancing lesions	>=1	117	6	5.13	116	0	0	12,89 [0,73 ; 226,22]	13,58 [0,76 ; 243,95];	5,08 [0,8 ; 9,36]; 0,029	0,029	1
	0	155	12	7.74	157	0	0	25,32 [1,51 ; 423,96]	27,44 [1,61 ; 467,64];	7,7 [3,35 ; 12,05]; 0	0	
	NA	1	0	0.00	2	0	0	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	6	5.56	92	0	0	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	6	14.29	58	0	0	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	123	6	4.88	125	0	0	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	7	0	0.00	8	0	0	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9999
	White	266	18	6.77	267	0	0	37,14 [2,25 ; 613,12]	39,83 [2,39 ; 664,42];	6,74 [3,65 ; 9,83]; 0	0	
	No	181	14	7.73	193	0	0	30,91 [1,86 ; 514,44]	33,5 [1,98 ; 565,87];	7,71 [3,71 ; 11,71]; 0	0	0,9999

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	92	4	4.35	82	0	0	8,03 [0,44 ; 146,96]	8,39 [0,44 ; 158,24];	4,24 [-0,43 ; 8,9]; 0,123	0,123	
Region	Eastern Europe	247	18	7.29	244	0	0	36,55 [2,22 ; 603,18]	39,42 [2,36 ; 657,88];	7,26 [3,94 ; 10,57]; 0	0	0,9995
	USA and Western Europe	26	0	0.00	31	0	0	1,19 [0,02 ; 57,76]	1,19 [0,02 ; 61,97];	0,29 [-6,37 ; 6,95]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Severe TEAE - Investigations | Lymphocyte count decreased

4.3.5 Blood and lymphatic system disorders - Lymphopenia

Tabelle 117: Severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	9	6.00	146	1	0.68	8,76 [1,12 ; 68,28]	9,26 [1,16 ; 74,01];	5,32 [1,29 ; 9,34]; 0,02	0,02	0,4241
	>= 38 years	123	6	4.88	129	2	1.55	3,15 [0,65 ; 15,29]	3,26 [0,64 ; 16,45];	3,33 [-1,04 ; 7,69]; 0,164	0,164	
Disease Severity at baseline (EDSS)	<=3.5	201	13	6.47	208	1	0.48	13,45 [1,78 ; 101,89]	14,31 [1,85 ; 110,47];	5,99 [2,46 ; 9,51]; 0,001	0,001	0,0495
	>3.5	72	2	2.78	67	2	2.99	0,93 [0,13 ; 6,42]	0,93 [0,13 ; 6,79];	-0,21 [-5,78 ; 5,36]; 1	1	
Gender	Female	167	9	5.39	180	3	1.67	3,23 [0,89 ; 11,74]	3,36 [0,89 ; 12,63];	3,72 [-0,18 ; 7,62]; 0,078	0,078	0,1227
	Female	167	9	5.39	180	1	0.56	3,23 [0,89 ; 11,74]	3,36 [0,89 ; 12,63];	3,72 [-0,18 ; 7,62]; 0,078	0,078	
	Female	167	6	3.59	180	3	1.67	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Female	167	6	3.59	180	1	0.56	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Male	106	6	5.66	95	0	0.00	11,66 [0,67 ; 204,32]	12,35 [0,69 ; 222,29];	5,55 [0,8 ; 10,3]; 0,03	0,03	
	Male	106	6	5.66	95	1	1.05	11,66 [0,67 ; 204,32]	12,35 [0,69 ; 222,29];	5,55 [0,8 ; 10,3]; 0,03	0,03	
	Male	106	7	6.60	95	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Male	106	7	6.60	95	1	1.05	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of baseline Gd-enhancing lesions	>=1	117	8	6.84	116	1	0.86	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	155	7	4.52	157	2	1.27	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Number of relapses experienced in the 2 years prior to study start	<=1	108	3	2.78	92	0	0.00	5,97 [0,31 ; 114,14]	6,14 [0,31 ; 120,39];	2,67 [-0,95 ; 6,3]; 0,127	0,127	0,6244
	>=3	42	3	7.14	58	1	1.72	4,14 [0,45 ; 38,45]	4,38 [0,44 ; 43,71];	5,42 [-3,06 ; 13,9]; 0,307	0,307	
	2	123	9	7.32	125	2	1.60	4,57 [1,01 ; 20,74]	4,86 [1,03 ; 22,95];	5,72 [0,62 ; 10,82]; 0,033	0,033	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9998
	White	266	15	5.64	267	3	1.12	5,02 [1,47 ; 17,13]	5,26 [1,5 ; 18,38];	4,52 [1,47 ; 7,56]; 0,004	0,004	
Received approved disease modifying MS drug prior to enrollment	No	181	9	4.97	193	2	1.04	4,8 [1,05 ; 21,91]	5 [1,06 ; 23,45];	3,94 [0,46 ; 7,41]; 0,031	0,031	0,9269
	Yes	92	6	6.52	82	1	1.22	5,35 [0,66 ; 43,5]	5,65 [0,67 ; 47,97];	5,3 [-0,27 ; 10,88]; 0,122	0,122	
Region	Eastern Europe	247	15	6.07	244	3	1.23	4,94 [1,45 ; 16,85]	5,19 [1,48 ; 18,18];	4,84 [1,56 ; 8,13]; 0,007	0,007	0,9999
	USA and Western Europe	26	0	0.00	31	0	0.00	1,19 [0,02 ; 57,76]	1,19 [0,02 ; 61,97];	0,29 [-6,37 ; 6,95]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Severe TEAE - Blood and lymphatic system disorders | Lymphopenia

4.4 Serious TEAE

4.4.1 Infections and infestations - any

Tabelle 118: Serious TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	150	12	8.00	146	3	2.05	3,89 [1,12 ; 13,51]	4,14 [1,14 ; 15,01];	5,95 [1,03 ; 10,86]; 0,031	0,031	0,1903
	>= 38 years	123	3	2.44	129	3	2.33	1,05 [0,22 ; 5,1]	1,05 [0,21 ; 5,3];	0,11 [-3,65 ; 3,88]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	201	10	4.98	208	2	0.96	5,17 [1,15 ; 23,32]	5,39 [1,17 ; 24,93];	4,01 [0,73 ; 7,3]; 0,019	0,019	0,1325
	>3.5	72	5	6.94	67	4	5.97	1,16 [0,33 ; 4,15]	1,18 [0,3 ; 4,58];	0,97 [-7,19 ; 9,14]; 1	1	
Gender	Female	167	11	6.59	180	5	2.78	2,37 [0,84 ; 6,68]	2,47 [0,84 ; 7,26];	3,81 [-0,65 ; 8,27]; 0,124	0,124	0,7434
	Male	106	4	3.77	95	1	1.05	3,58 [0,41 ; 31,52]	3,69 [0,4 ; 33,57];	2,72 [-1,45 ; 6,89]; 0,373	0,373	
Number of baseline Gd-enhancing lesions	>=1	117	9	7.69	116	2	1.72	4,46 [0,99 ; 20,21]	4,75 [1 ; 22,48];	5,97 [0,59 ; 11,35]; 0,059	0,059	0,262
	0	155	6	3.87	157	4	2.55	1,52 [0,44 ; 5,28]	1,54 [0,43 ; 5,57];	1,32 [-2,59 ; 5,23]; 0,54	0,54	
	NA	1	0	0.00	2	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	108	4	3.70	92	3	3.26	1,14 [0,26 ; 4,94]	1,14 [0,25 ; 5,24];	0,44 [-4,64 ; 5,53]; 1	1	0,4143
	>=3	42	2	4.76	58	1	1.72	2,76 [0,26 ; 29,47]	2,85 [0,25 ; 32,51];	3,04 [-4,22 ; 10,3]; 0,571	0,571	
	2	123	9	7.32	125	2	1.60	4,57 [1,01 ; 20,74]	4,86 [1,03 ; 22,95];	5,72 [0,62 ; 10,82]; 0,033	0,033	
Race	Other	7	0	0.00	8	0	0.00	1,12 [0,03 ; 50,41]	1,13 [0,02 ; 64,47];	0,69 [-21,78 ; 23,17]; 1	1	0,9999
	White	266	15	5.64	267	6	2.25	2,51 [0,99 ; 6,37]	2,6 [0,99 ; 6,81];	3,39 [0,1 ; 6,69]; 0,048	0,048	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	No	181	10	5.52	193	4	2.07	2,67 [0,85 ; 8,35]	2,76 [0,85 ; 8,97];	3,45 [-0,44 ; 7,34]; 0,103	0,103	0,8604
	Yes	92	5	5.43	82	2	2.44	2,23 [0,44 ; 11,18]	2,3 [0,43 ; 12,18];	3 [-2,71 ; 8,71]; 0,449	0,449	
Region	Eastern Europe	247	14	5.67	244	6	2.46	2,3 [0,9 ; 5,9]	2,38 [0,9 ; 6,31];	3,21 [-0,27 ; 6,69]; 0,108	0,108	0,3703
	USA and Western Europe	26	1	3.85	31	0	0.00	3,56 [0,15 ; 83,75]	3,71 [0,14 ; 94,9];	3,99 [-5,66 ; 13,64]; 0,214	0,214	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Serious TEAE - Infections and infestations | any

5 Ultimate 2: Treatment Emergent Adverse events by SOC/PT

5.1 Any TEAE

5.1.1 General disorders and administration site conditions - any

Tabelle 119: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	92	52.27	156	34	21.79	2.4 [1.73 ; 3.33]	3.93 [2.43 ; 6.36];	30.48 [20.66 ; 40.3]; 0	0	0.0376
	>= 38 years	96	34	35.42	117	28	23.93	1.48 [0.97 ; 2.25]	1.74 [0.96 ; 3.16];	11.49 [-0.82 ; 23.79]; 0.071	0.071	
Disease Severity at baseline (EDSS)	<=3.5	218	107	49.08	207	44	21.26	2.31 [1.72 ; 3.1]	3.57 [2.33 ; 5.47];	27.83 [19.16 ; 36.49]; 0	0	0.0468
	>3.5	54	19	35.19	66	18	27.27	1.29 [0.76 ; 2.2]	1.45 [0.66 ; 3.15];	7.91 [-8.75 ; 24.58]; 0.428	0.428	
Gender	Female	178	89	50.00	176	44	25.00	2 [1.49 ; 2.69]	3 [1.91 ; 4.71];	25 [15.26 ; 34.74]; 0	0	0.899
	Male	94	37	39.36	97	18	18.56	2.12 [1.3 ; 3.45]	2.85 [1.48 ; 5.5];	20.81 [8.26 ; 33.35]; 0.002	0.002	
Number of baseline Gd-enhancing lesions	>=1	141	70	49.65	135	31	22.96	2.16 [1.52 ; 3.07]	3.31 [1.97 ; 5.56];	26.68 [15.8 ; 37.57]; 0	0	0.4782
	0	131	56	42.75	136	31	22.79	1.88 [1.3 ; 2.71]	2.53 [1.49 ; 4.29];	19.95 [8.93 ; 30.98]; 0.001	0.001	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	51	43.59	110	25	22.73	1.92 [1.28 ; 2.87]	2.63 [1.48 ; 4.68];	20.86 [8.94 ; 32.78]; 0.001	0.001	0.7541
	>=3	42	24	57.14	40	10	25.00	2.29 [1.26 ; 4.15]	4 [1.56 ; 10.25];	32.14 [12.04 ; 52.24]; 0.004	0.004	
	2	113	51	45.13	123	27	21.95	2.06 [1.39 ; 3.04]	2.92 [1.66 ; 5.15];	23.18 [11.45 ; 34.92]; 0	0	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	No	166	76	45.78	186	39	20.97	2.18 [1.58 ; 3.02]	3.18 [2 ; 5.08];	24.82 [15.24 ; 34.39]; 0	0	0.5282
	Yes	106	50	47.17	87	23	26.44	1.78 [1.19 ; 2.67]	2.48 [1.35 ; 4.57];	20.73 [7.46 ; 34.01]; 0.004	0.004	
Region	Eastern Europe	245	113	46.12	251	49	19.52	2.36 [1.78 ; 3.14]	3.53 [2.36 ; 5.27];	26.6 [18.66 ; 34.54]; 0	0	0.0054
	USA and Western Europe	27	13	48.15	22	13	59.09	0.81 [0.48 ; 1.38]	0.64 [0.21 ; 2];	-10.94 [-38.82 ; 16.94]; 0.567	0.567	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - General disorders and administration site conditions | any

5.1.2 Injury, poisoning and procedural complications - any

Tabelle 120: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	36	20.45	156	18	11.54	1.77 [1.05 ; 2.99]	1.97 [1.07 ; 3.64];	8.92 [1.13 ; 16.7]; 0.036	0.036	0.0841
	>= 38 years	96	10	10.42	117	15	12.82	0.81 [0.38 ; 1.73]	0.79 [0.34 ; 1.85];	-2.4 [-11.01 ; 6.2]; 0.671	0.671	
Disease Severity at baseline (EDSS)	<=3.5	218	40	18.35	207	23	11.11	1.65 [1.03 ; 2.66]	1.8 [1.03 ; 3.12];	7.24 [0.55 ; 13.93]; 0.041	0.041	0.1231
	>3.5	54	6	11.11	66	10	15.15	0.73 [0.28 ; 1.89]	0.7 [0.24 ; 2.07];	-4.04 [-16.09 ; 8]; 0.596	0.596	
Gender	Female	178	33	18.54	176	20	11.36	1.63 [0.97 ; 2.73]	1.78 [0.97 ; 3.23];	7.18 [-0.21 ; 14.56]; 0.073	0.073	0.3021
	Male	94	13	13.83	97	13	13.40	1.03 [0.51 ; 2.11]	1.04 [0.45 ; 2.37];	0.43 [-9.3 ; 10.16]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	22	15.60	135	17	12.59	1.24 [0.69 ; 2.23]	1.28 [0.65 ; 2.54];	3.01 [-5.19 ; 11.21]; 0.494	0.494	0.5827
	0	131	24	18.32	136	16	11.76	1.56 [0.87 ; 2.8]	1.68 [0.85 ; 3.33];	6.56 [-2 ; 15.11]; 0.17	0.17	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	25	21.37	110	18	16.36	1.31 [0.76 ; 2.26]	1.39 [0.71 ; 2.72];	5 [-5.14 ; 15.15]; 0.398	0.398	0.2573
	>=3	42	6	14.29	40	1	2.50	5.71 [0.72 ; 45.39]	6.5 [0.75 ; 56.64];	11.79 [0.15 ; 23.42]; 0.11	0.11	
	2	113	15	13.27	123	14	11.38	1.17 [0.59 ; 2.31]	1.19 [0.55 ; 2.59];	1.89 [-6.51 ; 10.3]; 0.695	0.695	
Received approved disease modifying MS drug prior to enrollment	No	166	30	18.07	186	26	13.98	1.29 [0.8 ; 2.09]	1.36 [0.77 ; 2.41];	4.09 [-3.59 ; 11.78]; 0.31	0.31	0.4676
	Yes	106	16	15.09	87	7	8.05	1.88 [0.81 ; 4.35]	2.03 [0.8 ; 5.19];	7.05 [-1.85 ; 15.94]; 0.18	0.18	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	38	15.51	251	24	9.56	1.62 [1 ; 2.62]	1.74 [1.01 ; 2.99];	5.95 [0.14 ; 11.76]; 0.057	0.057	0.1141
	USA and Western Europe	27	8	29.63	22	9	40.91	0.72 [0.34 ; 1.56]	0.61 [0.19 ; 1.99];	-11.28 [-38.09 ; 15.53]; 0.548	0.548	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Injury, poisoning and procedural complications | any

5.1.3 Musculoskeletal and connective tissue disorders - any

Tabelle 121: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	46	26.14	156	28	17.95	1.46 [0.96 ; 2.21]	1.62 [0.95 ; 2.75];	8.19 [-0.67 ; 17.04]; 0.086	0.086	0.5298
	>= 38 years	96	28	29.17	117	29	24.79	1.18 [0.76 ; 1.83]	1.25 [0.68 ; 2.3];	4.38 [-7.61 ; 16.38]; 0.535	0.535	
Disease Severity at baseline (EDSS)	<=3.5	218	67	30.73	207	44	21.26	1.45 [1.04 ; 2.01]	1.64 [1.06 ; 2.55];	9.48 [1.2 ; 17.76]; 0.028	0.028	0.0687
	>3.5	54	7	12.96	66	13	19.70	0.66 [0.28 ; 1.53]	0.61 [0.22 ; 1.65];	-6.73 [-19.86 ; 6.39]; 0.461	0.461	
Gender	Female	178	55	30.90	176	43	24.43	1.26 [0.9 ; 1.78]	1.38 [0.87 ; 2.21];	6.47 [-2.83 ; 15.76]; 0.192	0.192	0.856
	Male	94	19	20.21	97	14	14.43	1.4 [0.75 ; 2.63]	1.5 [0.7 ; 3.2];	5.78 [-4.94 ; 16.49]; 0.341	0.341	
Number of baseline Gd-enhancing lesions	>=1	141	41	29.08	135	28	20.74	1.4 [0.92 ; 2.13]	1.57 [0.9 ; 2.72];	8.34 [-1.81 ; 18.48]; 0.127	0.127	0.5664
	0	131	33	25.19	136	29	21.32	1.18 [0.76 ; 1.83]	1.24 [0.7 ; 2.2];	3.87 [-6.26 ; 14]; 0.472	0.472	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	32	27.35	110	28	25.45	1.07 [0.7 ; 1.66]	1.1 [0.61 ; 1.99];	1.9 [-9.57 ; 13.36]; 0.765	0.765	0.5238
	>=3	42	9	21.43	40	6	15.00	1.43 [0.56 ; 3.65]	1.55 [0.49 ; 4.83];	6.43 [-10.2 ; 23.06]; 0.571	0.571	
	2	113	33	29.20	123	23	18.70	1.56 [0.98 ; 2.49]	1.79 [0.98 ; 3.29];	10.5 [-0.35 ; 21.36]; 0.067	0.067	
Received approved disease modifying MS drug prior to enrollment	No	166	47	28.31	186	37	19.89	1.42 [0.98 ; 2.07]	1.59 [0.97 ; 2.61];	8.42 [-0.52 ; 17.36]; 0.079	0.079	0.4367
	Yes	106	27	25.47	87	20	22.99	1.11 [0.67 ; 1.83]	1.14 [0.59 ; 2.22];	2.48 [-9.64 ; 14.61]; 0.738	0.738	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	58	23.67	251	48	19.12	1.24 [0.88 ; 1.74]	1.31 [0.85 ; 2.02];	4.55 [-2.66 ; 11.76]; 0.23	0.23	0.4484
	USA and Western Europe	27	16	59.26	22	9	40.91	1.45 [0.8 ; 2.62]	2.1 [0.67 ; 6.6];	18.35 [-9.32 ; 46.02]; 0.256	0.256	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Musculoskeletal and connective tissue disorders | any

5.1.4 Respiratory, thoracic and mediastinal disorders - any

Tabelle 122: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	46	26.14	156	20	12.82	2.04 [1.26 ; 3.29]	2.41 [1.35 ; 4.29];	13.32 [4.97 ; 21.66]; 0.002	0.002	0.6251
	>= 38 years	96	17	17.71	117	12	10.26	1.73 [0.87 ; 3.44]	1.88 [0.85 ; 4.17];	7.45 [-1.96 ; 16.86]; 0.159	0.159	
Disease Severity at baseline (EDSS)	<=3.5	218	58	26.61	207	24	11.59	2.29 [1.48 ; 3.55]	2.76 [1.64 ; 4.65];	15.01 [7.7 ; 22.32]; 0	0	0.0421
	>3.5	54	5	9.26	66	8	12.12	0.76 [0.27 ; 2.2]	0.74 [0.23 ; 2.41];	-2.86 [-13.9 ; 8.17]; 0.77	0.77	
Gender	Female	178	45	25.28	176	22	12.50	2.02 [1.27 ; 3.22]	2.37 [1.35 ; 4.15];	12.78 [4.74 ; 20.82]; 0.003	0.003	0.7859
	Male	94	18	19.15	97	10	10.31	1.86 [0.9 ; 3.81]	2.06 [0.9 ; 4.74];	8.84 [-1.15 ; 18.83]; 0.103	0.103	
Number of baseline Gd-enhancing lesions	>=1	141	37	26.24	135	18	13.33	1.97 [1.18 ; 3.28]	2.31 [1.24 ; 4.31];	12.91 [3.66 ; 22.16]; 0.01	0.01	0.8848
	0	131	26	19.85	136	14	10.29	1.93 [1.05 ; 3.53]	2.16 [1.07 ; 4.35];	9.55 [1.02 ; 18.08]; 0.039	0.039	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	31	26.50	110	15	13.64	1.94 [1.11 ; 3.4]	2.28 [1.15 ; 4.52];	12.86 [2.61 ; 23.11]; 0.02	0.02	0.9765
	>=3	42	11	26.19	40	6	15.00	1.75 [0.71 ; 4.28]	2.01 [0.66 ; 6.09];	11.19 [-6.11 ; 28.49]; 0.279	0.279	
	2	113	21	18.58	123	11	8.94	2.08 [1.05 ; 4.12]	2.32 [1.07 ; 5.07];	9.64 [0.87 ; 18.41]; 0.037	0.037	
Received approved disease modifying MS drug prior to enrollment	No	166	35	21.08	186	23	12.37	1.71 [1.05 ; 2.76]	1.89 [1.07 ; 3.36];	8.72 [0.92 ; 16.52]; 0.031	0.031	0.3232
	Yes	106	28	26.42	87	9	10.34	2.55 [1.27 ; 5.12]	3.11 [1.38 ; 7.02];	16.07 [5.52 ; 26.62]; 0.006	0.006	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	55	22.45	251	29	11.55	1.94 [1.28 ; 2.94]	2.22 [1.36 ; 3.62];	10.9 [4.34 ; 17.45]; 0.002	0.002	0.8137
	USA and Western Europe	27	8	29.63	22	3	13.64	2.17 [0.65 ; 7.23]	2.67 [0.61 ; 11.61];	15.99 [-6.42 ; 38.41]; 0.303	0.303	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Respiratory, thoracic and mediastinal disorders | any

5.1.5 Gastrointestinal disorders - any

Tabelle 123: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	78	44.32	156	72	46.15	0.96 [0.76 ; 1.22]	0.93 [0.6 ; 1.43];	-1.84 [-12.56 ; 8.89]; 0.742	0.742	0.6097
	>= 38 years	96	32	33.33	117	46	39.32	0.85 [0.59 ; 1.22]	0.77 [0.44 ; 1.36];	-5.98 [-18.92 ; 6.95]; 0.394	0.394	
Disease Severity at baseline (EDSS)	<=3.5	218	93	42.66	207	96	46.38	0.92 [0.74 ; 1.14]	0.86 [0.59 ; 1.26];	-3.72 [-13.16 ; 5.73]; 0.494	0.494	0.8804
	>3.5	54	17	31.48	66	22	33.33	0.94 [0.56 ; 1.59]	0.92 [0.43 ; 1.98];	-1.85 [-18.67 ; 14.96]; 0.847	0.847	
Gender	Female	178	78	43.82	176	77	43.75	1 [0.79 ; 1.27]	1 [0.66 ; 1.53];	0.07 [-10.27 ; 10.41]; 1	1	0.3378
	Male	94	32	34.04	97	41	42.27	0.81 [0.56 ; 1.16]	0.7 [0.39 ; 1.27];	-8.23 [-21.95 ; 5.5]; 0.297	0.297	
Number of baseline Gd-enhancing lesions	>=1	141	62	43.97	135	59	43.70	1.01 [0.77 ; 1.31]	1.01 [0.63 ; 1.63];	0.27 [-11.44 ; 11.98]; 1	1	0.4523
	0	131	48	36.64	136	58	42.65	0.86 [0.64 ; 1.16]	0.78 [0.48 ; 1.27];	-6.01 [-17.72 ; 5.71]; 0.321	0.321	
	NA	0	0	0.00	2	1	50.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	45	38.46	110	48	43.64	0.88 [0.64 ; 1.2]	0.81 [0.48 ; 1.37];	-5.17 [-17.97 ; 7.62]; 0.5	0.5	0.8252
	>=3	42	20	47.62	40	18	45.00	1.06 [0.66 ; 1.69]	1.11 [0.47 ; 2.65];	2.62 [-18.96 ; 24.2]; 0.828	0.828	
	2	113	45	39.82	123	52	42.28	0.94 [0.69 ; 1.28]	0.9 [0.54 ; 1.52];	-2.45 [-15.01 ; 10.1]; 0.791	0.791	
Received approved disease modifying MS drug prior to enrollment	No	166	63	37.95	186	80	43.01	0.88 [0.68 ; 1.14]	0.81 [0.53 ; 1.24];	-5.06 [-15.31 ; 5.19]; 0.385	0.385	0.5147
	Yes	106	47	44.34	87	38	43.68	1.02 [0.74 ; 1.4]	1.03 [0.58 ; 1.82];	0.66 [-13.41 ; 14.73]; 1	1	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	96	39.18	251	104	41.43	0.95 [0.76 ; 1.17]	0.91 [0.64 ; 1.3];	-2.25 [-10.88 ; 6.38]; 0.647	0.647	0.5224
	USA and Western Europe	27	14	51.85	22	14	63.64	0.81 [0.5 ; 1.32]	0.62 [0.19 ; 1.95];	-11.78 [-39.34 ; 15.77]; 0.563	0.563	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Gastrointestinal disorders | any

5.1.6 Infections and infestations - any

Tabelle 124: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	117	66.48	156	103	66.03	1.01 [0.86 ; 1.17]	1.02 [0.65 ; 1.61];	0.45 [-9.74 ; 10.64]; 1	1	0.9403
	>= 38 years	96	52	54.17	117	62	52.99	1.02 [0.8 ; 1.31]	1.05 [0.61 ; 1.8];	1.18 [-12.28 ; 14.63]; 0.891	0.891	
Disease Severity at baseline (EDSS)	<=3.5	218	140	64.22	207	126	60.87	1.06 [0.91 ; 1.22]	1.15 [0.78 ; 1.71];	3.35 [-5.85 ; 12.55]; 0.484	0.484	0.3894
	>3.5	54	29	53.70	66	39	59.09	0.91 [0.66 ; 1.25]	0.8 [0.39 ; 1.66];	-5.39 [-23.21 ; 12.43]; 0.583	0.583	
Gender	Female	178	128	71.91	176	109	61.93	1.16 [1 ; 1.35]	1.57 [1.01 ; 2.46];	9.98 [0.23 ; 19.73]; 0.055	0.055	0.0056
	Male	94	41	43.62	97	56	57.73	0.76 [0.57 ; 1.01]	0.57 [0.32 ; 1];	-14.11 [-28.16 ; -0.07]; 0.06	0.06	
Number of baseline Gd-enhancing lesions	>=1	141	91	64.54	135	80	59.26	1.09 [0.9 ; 1.31]	1.25 [0.77 ; 2.04];	5.28 [-6.17 ; 16.73]; 0.387	0.387	0.3235
	0	131	78	59.54	136	85	62.50	0.95 [0.79 ; 1.15]	0.88 [0.54 ; 1.44];	-2.96 [-14.66 ; 8.74]; 0.707	0.707	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	74	63.25	110	65	59.09	1.07 [0.87 ; 1.32]	1.19 [0.7 ; 2.03];	4.16 [-8.52 ; 16.84]; 0.586	0.586	0.1081
	>=3	42	29	69.05	40	20	50.00	1.38 [0.95 ; 2]	2.23 [0.91 ; 5.49];	19.05 [-1.82 ; 39.92]; 0.115	0.115	
	2	113	66	58.41	123	80	65.04	0.9 [0.73 ; 1.1]	0.75 [0.45 ; 1.28];	-6.63 [-19.03 ; 5.76]; 0.348	0.348	
Received approved disease modifying MS drug prior to enrollment	No	166	99	59.64	186	112	60.22	0.99 [0.83 ; 1.18]	0.98 [0.64 ; 1.5];	-0.58 [-10.83 ; 9.68]; 0.914	0.914	0.5092
	Yes	106	70	66.04	87	53	60.92	1.08 [0.87 ; 1.35]	1.25 [0.69 ; 2.25];	5.12 [-8.53 ; 18.77]; 0.547	0.547	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	148	60.41	251	152	60.56	1 [0.87 ; 1.15]	0.99 [0.69 ; 1.42];	-0.15 [-8.76 ; 8.46]; 1	1	0.1726
	USA and Western Europe	27	21	77.78	22	13	59.09	1.32 [0.88 ; 1.97]	2.42 [0.7 ; 8.4];	18.69 [-7.16 ; 44.53]; 0.217	0.217	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | any

5.1.7 Investigations - any

Tabelle 125: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	49	27.84	156	32	20.51	1.36 [0.92 ; 2]	1.5 [0.9 ; 2.49];	7.33 [-1.84 ; 16.49]; 0.127	0.127	0.382
	>= 38 years	96	26	27.08	117	17	14.53	1.86 [1.08 ; 3.23]	2.18 [1.1 ; 4.33];	12.55 [1.61 ; 23.5]; 0.026	0.026	
Disease Severity at baseline (EDSS)	<=3.5	218	60	27.52	207	39	18.84	1.46 [1.02 ; 2.08]	1.64 [1.03 ; 2.59];	8.68 [0.71 ; 16.65]; 0.039	0.039	0.5917
	>3.5	54	15	27.78	66	10	15.15	1.83 [0.9 ; 3.75]	2.15 [0.88 ; 5.29];	12.63 [-2.12 ; 27.38]; 0.115	0.115	
Gender	Female	178	47	26.40	176	29	16.48	1.6 [1.06 ; 2.42]	1.82 [1.08 ; 3.06];	9.93 [1.44 ; 18.41]; 0.028	0.028	0.8023
	Male	94	28	29.79	97	20	20.62	1.44 [0.88 ; 2.38]	1.63 [0.84 ; 3.16];	9.17 [-3.09 ; 21.43]; 0.182	0.182	
Number of baseline Gd-enhancing lesions	>=1	141	42	29.79	135	27	20.00	1.49 [0.98 ; 2.27]	1.7 [0.97 ; 2.96];	9.79 [-0.34 ; 19.91]; 0.071	0.071	0.9469
	0	131	33	25.19	136	22	16.18	1.56 [0.96 ; 2.52]	1.74 [0.95 ; 3.19];	9.01 [-0.66 ; 18.69]; 0.072	0.072	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	28	23.93	110	21	19.09	1.25 [0.76 ; 2.07]	1.33 [0.7 ; 2.52];	4.84 [-5.82 ; 15.5]; 0.422	0.422	0.5522
	>=3	42	17	40.48	40	9	22.50	1.8 [0.91 ; 3.56]	2.34 [0.89 ; 6.15];	17.98 [-1.72 ; 37.67]; 0.099	0.099	
	2	113	30	26.55	123	19	15.45	1.72 [1.03 ; 2.88]	1.98 [1.04 ; 3.76];	11.1 [0.75 ; 21.45]; 0.038	0.038	
Received approved disease modifying MS drug prior to enrollment	No	166	47	28.31	186	29	15.59	1.82 [1.2 ; 2.74]	2.14 [1.27 ; 3.6];	12.72 [4.11 ; 21.33]; 0.004	0.004	0.1806
	Yes	106	28	26.42	87	20	22.99	1.15 [0.7 ; 1.89]	1.2 [0.62 ; 2.33];	3.43 [-8.76 ; 15.62]; 0.619	0.619	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	64	26.12	251	45	17.93	1.46 [1.04 ; 2.04]	1.62 [1.05 ; 2.49];	8.19 [0.93 ; 15.46]; 0.03	0.03	0.3533
	USA and Western Europe	27	11	40.74	22	4	18.18	2.24 [0.83 ; 6.07]	3.09 [0.82 ; 11.67];	22.56 [-2 ; 47.12]; 0.123	0.123	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Investigations | any

5.1.8 Metabolism and nutrition disorders - any

Tabelle 126: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	8	4.55	156	8	5.13	0.89 [0.34 ; 2.31]	0.88 [0.32 ; 2.41];	-0.58 [-5.21 ; 4.05]; 0.804	0.804	0.294
	>= 38 years	96	4	4.17	117	2	1.71	2.44 [0.46 ; 13.02]	2.5 [0.45 ; 13.95];	2.46 [-2.18 ; 7.09]; 0.413	0.413	
Disease Severity at baseline (EDSS)	<=3.5	218	12	5.50	207	5	2.42	2.28 [0.82 ; 6.36]	2.35 [0.81 ; 6.8];	3.09 [-0.59 ; 6.77]; 0.138	0.138	0.0032
	>3.5	54	0	0.00	66	5	7.58	0.11 [0.01 ; 1.96]	0.1 [0.01 ; 1.9];	-7.3 [-14.34 ; -0.26]; 0.033	0.033	
Gender	Female	178	7	3.93	176	5	2.84	1.38 [0.45 ; 4.28]	1.4 [0.44 ; 4.5];	1.09 [-2.67 ; 4.86]; 0.771	0.771	0.7304
	Male	94	5	5.32	97	5	5.15	1.03 [0.31 ; 3.45]	1.03 [0.29 ; 3.69];	0.16 [-6.16 ; 6.48]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	9	6.38	135	3	2.22	2.87 [0.79 ; 10.38]	3 [0.79 ; 11.33];	4.16 [-0.58 ; 8.9]; 0.138	0.138	0.0362
	0	131	3	2.29	136	7	5.15	0.44 [0.12 ; 1.68]	0.43 [0.11 ; 1.71];	-2.86 [-7.37 ; 1.65]; 0.335	0.335	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	6	5.13	110	3	2.73	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	2	4.76	40	2	5.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	4	3.54	123	5	4.07	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	5	3.01	186	6	3.23	0.93 [0.29 ; 3]	0.93 [0.28 ; 3.11];	-0.21 [-3.85 ; 3.42]; 1	1	0.6082
	Yes	106	7	6.60	87	4	4.60	1.44 [0.43 ; 4.75]	1.47 [0.42 ; 5.19];	2.01 [-4.45 ; 8.47]; 0.757	0.757	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	9	3.67	251	8	3.19	1.15 [0.45 ; 2.94]	1.16 [0.44 ; 3.05];	0.49 [-2.72 ; 3.69]; 0.809	0.809	0.9438
	USA and Western Europe	27	3	11.11	22	2	9.09	1.22 [0.22 ; 6.68]	1.25 [0.19 ; 8.23];	2.02 [-14.86 ; 18.9]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Metabolism and nutrition disorders | any

5.1.9 Nervous system disorders - any

Tabelle 127: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	92	52.27	156	70	44.87	1.16 [0.93 ; 1.46]	1.35 [0.87 ; 2.07];	7.4 [-3.34 ; 18.14]; 0.188	0.188	0.3266
	>= 38 years	96	34	35.42	117	43	36.75	0.96 [0.67 ; 1.38]	0.94 [0.54 ; 1.66];	-1.34 [-14.29 ; 11.62]; 0.887	0.887	
Disease Severity at baseline (EDSS)	<=3.5	218	110	50.46	207	86	41.55	1.21 [0.99 ; 1.5]	1.43 [0.98 ; 2.1];	8.91 [-0.53 ; 18.35]; 0.08	0.08	0.0474
	>3.5	54	16	29.63	66	27	40.91	0.72 [0.44 ; 1.2]	0.61 [0.28 ; 1.3];	-11.28 [-28.28 ; 5.72]; 0.252	0.252	
Gender	Female	178	93	52.25	176	76	43.18	1.21 [0.97 ; 1.51]	1.44 [0.95 ; 2.19];	9.07 [-1.3 ; 19.43]; 0.09	0.09	0.179
	Male	94	33	35.11	97	37	38.14	0.92 [0.63 ; 1.34]	0.88 [0.49 ; 1.58];	-3.04 [-16.7 ; 10.62]; 0.764	0.764	
Number of baseline Gd-enhancing lesions	>=1	141	67	47.52	135	55	40.74	1.17 [0.89 ; 1.52]	1.32 [0.82 ; 2.12];	6.78 [-4.91 ; 18.47]; 0.277	0.277	0.607
	0	131	59	45.04	136	58	42.65	1.06 [0.8 ; 1.39]	1.1 [0.68 ; 1.79];	2.39 [-9.51 ; 14.29]; 0.713	0.713	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	53	45.30	110	49	44.55	1.02 [0.76 ; 1.36]	1.03 [0.61 ; 1.74];	0.75 [-12.19 ; 13.7]; 1	1	0.6794
	>=3	42	19	45.24	40	14	35.00	1.29 [0.75 ; 2.21]	1.53 [0.63 ; 3.73];	10.24 [-10.86 ; 31.33]; 0.376	0.376	
	2	113	54	47.79	123	50	40.65	1.18 [0.88 ; 1.57]	1.34 [0.8 ; 2.24];	7.14 [-5.52 ; 19.79]; 0.295	0.295	
Received approved disease modifying MS	No	166	77	46.39	186	80	43.01	1.08 [0.85 ; 1.36]	1.15 [0.75 ; 1.75];	3.37 [-7.03 ; 13.78]; 0.591	0.591	0.5743
	Yes	106	49	46.23	87	33	37.93	1.22 [0.87 ; 1.71]	1.41 [0.79 ; 2.51];	8.3 [-5.63 ; 22.23]; 0.306	0.306	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
drug prior to enrollment												
Region	Eastern Europe	245	106	43.27	251	101	40.24	1.08 [0.87 ; 1.32]	1.13 [0.79 ; 1.62];	3.03 [-5.65 ; 11.7]; 0.524	0.524	0.2416
	USA and Western Europe	27	20	74.07	22	12	54.55	1.36 [0.87 ; 2.11]	2.38 [0.72 ; 7.92];	19.53 [-7.04 ; 46.1]; 0.228	0.228	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Nervous system disorders | any

5.1.10 Cardiac disorders - any

Tabelle 128: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	28	15.91	156	20	12.82	1.24 [0.73 ; 2.11]	1.29 [0.69 ; 2.39];	3.09 [-4.44 ; 10.62]; 0.439	0.439	0.4942
	>= 38 years	96	13	13.54	117	9	7.69	1.76 [0.79 ; 3.94]	1.88 [0.77 ; 4.61];	5.85 [-2.53 ; 14.23]; 0.181	0.181	
Disease Severity at baseline (EDSS)	<=3.5	218	34	15.60	207	20	9.66	1.61 [0.96 ; 2.71]	1.73 [0.96 ; 3.11];	5.93 [-0.34 ; 12.21]; 0.08	0.08	0.326
	>3.5	54	7	12.96	66	9	13.64	0.95 [0.38 ; 2.39]	0.94 [0.33 ; 2.72];	-0.67 [-12.87 ; 11.53]; 1	1	
Gender	Female	178	23	12.92	176	19	10.80	1.2 [0.68 ; 2.12]	1.23 [0.64 ; 2.34];	2.13 [-4.6 ; 8.86]; 0.623	0.623	0.3319
	Male	94	18	19.15	97	10	10.31	1.86 [0.9 ; 3.81]	2.06 [0.9 ; 4.74];	8.84 [-1.15 ; 18.83]; 0.103	0.103	
Number of baseline Gd-enhancing lesions	>=1	141	31	21.99	135	13	9.63	2.28 [1.25 ; 4.17]	2.64 [1.32 ; 5.31];	12.36 [3.9 ; 20.81]; 0.005	0.005	0.0074
	0	131	10	7.63	136	16	11.76	0.65 [0.31 ; 1.38]	0.62 [0.27 ; 1.42];	-4.13 [-11.2 ; 2.94]; 0.304	0.304	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	24	20.51	110	13	11.82	1.74 [0.93 ; 3.24]	1.93 [0.93 ; 4.01];	8.69 [-0.79 ; 18.18]; 0.105	0.105	0.525
	>=3	42	7	16.67	40	5	12.50	1.33 [0.46 ; 3.86]	1.4 [0.41 ; 4.84];	4.17 [-11.07 ; 19.4]; 0.757	0.757	
	2	113	10	8.85	123	11	8.94	0.99 [0.44 ; 2.24]	0.99 [0.4 ; 2.42];	-0.09 [-7.36 ; 7.18]; 1	1	
Received approved disease modifying MS drug prior to enrollment	No	166	22	13.25	186	21	11.29	1.17 [0.67 ; 2.06]	1.2 [0.63 ; 2.27];	1.96 [-4.91 ; 8.84]; 0.626	0.626	0.2855
	Yes	106	19	17.92	87	8	9.20	1.95 [0.9 ; 4.23]	2.16 [0.89 ; 5.2];	8.73 [-0.77 ; 18.23]; 0.097	0.097	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	38	15.51	251	26	10.36	1.5 [0.94 ; 2.39]	1.59 [0.93 ; 2.71];	5.15 [-0.74 ; 11.05]; 0.108	0.108	0.4481
	USA and Western Europe	27	3	11.11	22	3	13.64	0.81 [0.18 ; 3.64]	0.79 [0.14 ; 4.38];	-2.53 [-21.13 ; 16.08]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Cardiac disorders | any

5.1.11 Immune system disorders - any

Tabelle 129: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	10	5.68	156	4	2.56	2.22 [0.71 ; 6.92]	2.29 [0.7 ; 7.45];	3.12 [-1.11 ; 7.34]; 0.182	0.182	0.2438
	>= 38 years	96	5	5.21	117	7	5.98	0.87 [0.29 ; 2.66]	0.86 [0.27 ; 2.81];	-0.77 [-6.96 ; 5.41]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	218	13	5.96	207	7	3.38	1.76 [0.72 ; 4.33]	1.81 [0.71 ; 4.63];	2.58 [-1.41 ; 6.57]; 0.255	0.255	0.2573
	>3.5	54	2	3.70	66	4	6.06	0.61 [0.12 ; 3.21]	0.6 [0.1 ; 3.39];	-2.36 [-10.01 ; 5.29]; 0.689	0.689	
Gender	Female	178	12	6.74	176	9	5.11	1.32 [0.57 ; 3.05]	1.34 [0.55 ; 3.27];	1.63 [-3.29 ; 6.54]; 0.654	0.654	0.8802
	Male	94	3	3.19	97	2	2.06	1.55 [0.26 ; 9.06]	1.57 [0.26 ; 9.59];	1.13 [-3.41 ; 5.67]; 0.679	0.679	
Number of baseline Gd-enhancing lesions	>=1	141	3	2.13	135	4	2.96	0.72 [0.16 ; 3.15]	0.71 [0.16 ; 3.24];	-0.84 [-4.56 ; 2.89]; 0.718	0.718	0.2918
	0	131	12	9.16	136	7	5.15	1.78 [0.72 ; 4.38]	1.86 [0.71 ; 4.88];	4.01 [-2.17 ; 10.19]; 0.239	0.239	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	6	5.13	110	5	4.55	1.13 [0.35 ; 3.59]	1.14 [0.34 ; 3.83];	0.58 [-5 ; 6.16]; 1	1	0.8911
	>=3	42	0	0.00	40	0	0.00	0.95 [0.02 ; 46.94]	0.95 [0.02 ; 49.17];	-0.06 [-4.7 ; 4.59]; 1	1	
	2	113	9	7.96	123	6	4.88	1.63 [0.6 ; 4.44]	1.69 [0.58 ; 4.9];	3.09 [-3.19 ; 9.36]; 0.426	0.426	
Received approved disease modifying MS drug prior to enrollment	No	166	6	3.61	186	5	2.69	1.34 [0.42 ; 4.32]	1.36 [0.41 ; 4.53];	0.93 [-2.74 ; 4.6]; 0.762	0.762	0.9222
	Yes	106	9	8.49	87	6	6.90	1.23 [0.46 ; 3.32]	1.25 [0.43 ; 3.67];	1.59 [-5.92 ; 9.11]; 0.79	0.79	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	12	4.90	251	8	3.19	1.54 [0.64 ; 3.69]	1.56 [0.63 ; 3.9];	1.71 [-1.76 ; 5.18]; 0.369	0.369	0.4918
	USA and Western Europe	27	3	11.11	22	3	13.64	0.81 [0.18 ; 3.64]	0.79 [0.14 ; 4.38];	-2.53 [-21.13 ; 16.08]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Immune system disorders | any

5.1.12 Eye disorders - any

Tabelle 130: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	9	5.11	156	12	7.69	0.66 [0.29 ; 1.54]	0.65 [0.26 ; 1.58];	-2.58 [-7.88 ; 2.72]; 0.372	0.372	0.1721
	>= 38 years	96	5	5.21	117	3	2.56	2.03 [0.5 ; 8.28]	2.09 [0.49 ; 8.97];	2.64 [-2.64 ; 7.93]; 0.472	0.472	
Disease Severity at baseline (EDSS)	<=3.5	218	13	5.96	207	13	6.28	0.95 [0.45 ; 2]	0.95 [0.43 ; 2.09];	-0.32 [-4.88 ; 4.24]; 1	1	0.7258
	>3.5	54	1	1.85	66	2	3.03	0.61 [0.06 ; 6.56]	0.6 [0.05 ; 6.84];	-1.18 [-6.66 ; 4.3]; 1	1	
Gender	Female	178	14	7.87	176	9	5.11	1.54 [0.68 ; 3.46]	1.58 [0.67 ; 3.76];	2.75 [-2.37 ; 7.87]; 0.389	0.389	0.0022
	Male	94	0	0.00	97	6	6.19	0.08 [0 ; 1.39]	0.07 [0 ; 1.34];	-6.11 [-11.24 ; -0.97]; 0.029	0.029	
Number of baseline Gd-enhancing lesions	>=1	141	8	5.67	135	10	7.41	0.77 [0.31 ; 1.88]	0.75 [0.29 ; 1.97];	-1.73 [-7.57 ; 4.11]; 0.63	0.63	0.5135
	0	131	6	4.58	136	5	3.68	1.25 [0.39 ; 3.98]	1.26 [0.37 ; 4.23];	0.9 [-3.87 ; 5.68]; 0.766	0.766	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	4	3.42	110	9	8.18	0.42 [0.13 ; 1.32]	0.4 [0.12 ; 1.33];	-4.76 [-10.85 ; 1.33]; 0.157	0.157	0.1219
	>=3	42	2	4.76	40	2	5.00	0.95 [0.14 ; 6.44]	0.95 [0.13 ; 7.09];	-0.24 [-9.57 ; 9.09]; 1	1	
	2	113	8	7.08	123	4	3.25	2.18 [0.67 ; 7.03]	2.27 [0.66 ; 7.74];	3.83 [-1.85 ; 9.5]; 0.239	0.239	
Received approved disease modifying MS drug prior to enrollment	No	166	10	6.02	186	8	4.30	1.4 [0.57 ; 3.47]	1.43 [0.55 ; 3.7];	1.72 [-2.92 ; 6.37]; 0.479	0.479	0.1458
	Yes	106	4	3.77	87	7	8.05	0.47 [0.14 ; 1.55]	0.45 [0.13 ; 1.58];	-4.27 [-11.04 ; 2.5]; 0.227	0.227	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	12	4.90	251	13	5.18	0.95 [0.44 ; 2.03]	0.94 [0.42 ; 2.11];	-0.28 [-4.13 ; 3.57]; 1	1	0.8836
	USA and Western Europe	27	2	7.41	22	2	9.09	0.81 [0.12 ; 5.33]	0.8 [0.1 ; 6.19];	-1.68 [-17.24 ; 13.87]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Eye disorders | any

5.1.13 Psychiatric disorders - any

Tabelle 131: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	32	18.18	156	27	17.31	1.05 [0.66 ; 1.67]	1.06 [0.6 ; 1.87];	0.87 [-7.35 ; 9.1]; 0.886	0.886	0.1285
	>= 38 years	96	17	17.71	117	10	8.55	2.07 [1 ; 4.31]	2.3 [1 ; 5.3];	9.16 [0 ; 18.33]; 0.062	0.062	
Disease Severity at baseline (EDSS)	<=3.5	218	46	21.10	207	26	12.56	1.68 [1.08 ; 2.61]	1.86 [1.1 ; 3.14];	8.54 [1.49 ; 15.59]; 0.02	0.02	0.0061
	>3.5	54	3	5.56	66	11	16.67	0.33 [0.1 ; 1.13]	0.29 [0.08 ; 1.11];	-11.11 [-21.98 ; -0.24]; 0.086	0.086	
Gender	Female	178	37	20.79	176	24	13.64	1.52 [0.95 ; 2.44]	1.66 [0.95 ; 2.92];	7.15 [-0.68 ; 14.98]; 0.091	0.091	0.2743
	Male	94	12	12.77	97	13	13.40	0.95 [0.46 ; 1.98]	0.95 [0.41 ; 2.19];	-0.64 [-10.2 ; 8.93]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	30	21.28	135	22	16.30	1.31 [0.79 ; 2.15]	1.39 [0.75 ; 2.55];	4.98 [-4.21 ; 14.17]; 0.356	0.356	0.9763
	0	131	19	14.50	136	15	11.03	1.32 [0.7 ; 2.48]	1.37 [0.66 ; 2.82];	3.47 [-4.53 ; 11.48]; 0.464	0.464	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	21	17.95	110	16	14.55	1.23 [0.68 ; 2.24]	1.29 [0.63 ; 2.61];	3.4 [-6.18 ; 12.98]; 0.59	0.59	0.9046
	>=3	42	7	16.67	40	4	10.00	1.67 [0.53 ; 5.26]	1.8 [0.48 ; 6.7];	6.67 [-7.94 ; 21.28]; 0.52	0.52	
	2	113	21	18.58	123	17	13.82	1.34 [0.75 ; 2.42]	1.42 [0.71 ; 2.86];	4.76 [-4.65 ; 14.18]; 0.377	0.377	
Received approved disease modifying MS drug prior to enrollment	No	166	30	18.07	186	23	12.37	1.46 [0.89 ; 2.41]	1.56 [0.87 ; 2.82];	5.71 [-1.82 ; 13.23]; 0.139	0.139	0.5181
	Yes	106	19	17.92	87	14	16.09	1.11 [0.59 ; 2.09]	1.14 [0.53 ; 2.43];	1.83 [-8.79 ; 12.46]; 0.848	0.848	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	39	15.92	251	32	12.75	1.25 [0.81 ; 1.93]	1.3 [0.78 ; 2.15];	3.17 [-3 ; 9.33]; 0.37	0.37	0.5292
	USA and Western Europe	27	10	37.04	22	5	22.73	1.63 [0.65 ; 4.07]	2 [0.56 ; 7.1];	14.31 [-10.96 ; 39.58]; 0.358	0.358	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Psychiatric disorders | any

5.1.14 Vascular disorders - any

Tabelle 132: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	13	7.39	156	13	8.33	0.89 [0.42 ; 1.85]	0.88 [0.39 ; 1.95];	-0.95 [-6.76 ; 4.86]; 0.839	0.839	0.4864
	>= 38 years	96	8	8.33	117	16	13.68	0.61 [0.27 ; 1.36]	0.57 [0.23 ; 1.41];	-5.34 [-13.67 ; 2.98]; 0.278	0.278	
Disease Severity at baseline (EDSS)	<=3.5	218	19	8.72	207	23	11.11	0.78 [0.44 ; 1.4]	0.76 [0.4 ; 1.45];	-2.4 [-8.08 ; 3.29]; 0.421	0.421	0.43
	>3.5	54	2	3.70	66	6	9.09	0.41 [0.09 ; 1.94]	0.38 [0.07 ; 1.99];	-5.39 [-13.96 ; 3.18]; 0.293	0.293	
Gender	Female	178	14	7.87	176	21	11.93	0.66 [0.35 ; 1.25]	0.63 [0.31 ; 1.28];	-4.07 [-10.28 ; 2.14]; 0.217	0.217	0.5895
	Male	94	7	7.45	97	8	8.25	0.9 [0.34 ; 2.39]	0.9 [0.31 ; 2.57];	-0.8 [-8.43 ; 6.82]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	11	7.80	135	14	10.37	0.75 [0.35 ; 1.6]	0.73 [0.32 ; 1.67];	-2.57 [-9.35 ; 4.22]; 0.532	0.532	0.8776
	0	131	10	7.63	136	15	11.03	0.69 [0.32 ; 1.48]	0.67 [0.29 ; 1.54];	-3.4 [-10.35 ; 3.56]; 0.403	0.403	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	12	10.26	110	13	11.82	0.87 [0.41 ; 1.82]	0.85 [0.37 ; 1.96];	-1.56 [-9.72 ; 6.6]; 0.833	0.833	0.4502
	>=3	42	5	11.90	40	5	12.50	0.95 [0.3 ; 3.04]	0.95 [0.25 ; 3.55];	-0.6 [-14.77 ; 13.58]; 1	1	
	2	113	4	3.54	123	11	8.94	0.4 [0.13 ; 1.21]	0.37 [0.12 ; 1.21];	-5.4 [-11.49 ; 0.68]; 0.112	0.112	
Received approved disease modifying MS drug prior to enrollment	No	166	7	4.22	186	19	10.22	0.41 [0.18 ; 0.96]	0.39 [0.16 ; 0.95];	-6 [-11.32 ; -0.68]; 0.04	0.04	0.0748
	Yes	106	14	13.21	87	10	11.49	1.15 [0.54 ; 2.46]	1.17 [0.49 ; 2.79];	1.71 [-7.59 ; 11.01]; 0.828	0.828	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	19	7.76	251	25	9.96	0.78 [0.44 ; 1.38]	0.76 [0.41 ; 1.42];	-2.21 [-7.2 ; 2.79]; 0.432	0.432	0.4331
	USA and Western Europe	27	2	7.41	22	4	18.18	0.41 [0.08 ; 2.02]	0.36 [0.06 ; 2.18];	-10.77 [-29.68 ; 8.13]; 0.388	0.388	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Vascular disorders | any

5.1.15 Renal and urinary disorders - any

Tabelle 133: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	15	8.52	156	10	6.41	1.33 [0.62 ; 2.87]	1.36 [0.59 ; 3.12];	2.11 [-3.53 ; 7.75]; 0.535	0.535	0.5631
	>= 38 years	96	6	6.25	117	8	6.84	0.91 [0.33 ; 2.54]	0.91 [0.3 ; 2.71];	-0.59 [-7.25 ; 6.07]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	218	20	9.17	207	12	5.80	1.58 [0.79 ; 3.15]	1.64 [0.78 ; 3.45];	3.38 [-1.6 ; 8.36]; 0.203	0.203	0.0297
	>3.5	54	1	1.85	66	6	9.09	0.2 [0.03 ; 1.64]	0.19 [0.02 ; 1.62];	-7.24 [-15.05 ; 0.57]; 0.127	0.127	
Gender	Female	178	15	8.43	176	14	7.95	1.06 [0.53 ; 2.13]	1.06 [0.5 ; 2.28];	0.47 [-5.24 ; 6.19]; 1	1	0.6023
	Male	94	6	6.38	97	4	4.12	1.55 [0.45 ; 5.31]	1.59 [0.43 ; 5.81];	2.26 [-4.07 ; 8.59]; 0.532	0.532	
Number of baseline Gd-enhancing lesions	>=1	141	10	7.09	135	12	8.89	0.8 [0.36 ; 1.79]	0.78 [0.33 ; 1.88];	-1.8 [-8.2 ; 4.61]; 0.659	0.659	0.108
	0	131	11	8.40	136	5	3.68	2.28 [0.82 ; 6.39]	2.4 [0.81 ; 7.11];	4.72 [-0.99 ; 10.43]; 0.126	0.126	
	NA	0	0	0.00	2	1	50.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	8	6.84	110	9	8.18	0.84 [0.33 ; 2.09]	0.82 [0.31 ; 2.22];	-1.34 [-8.21 ; 5.52]; 0.803	0.803	0.1242
	>=3	42	3	7.14	40	0	0.00	6.67 [0.36 ; 125.26]	7.18 [0.36 ; 143.5];	6.92 [-1.92 ; 15.76]; 0.118	0.118	
	2	113	10	8.85	123	9	7.32	1.21 [0.51 ; 2.87]	1.23 [0.48 ; 3.15];	1.53 [-5.44 ; 8.5]; 0.812	0.812	
Received approved disease modifying MS drug prior to enrollment	No	166	10	6.02	186	8	4.30	1.4 [0.57 ; 3.47]	1.43 [0.55 ; 3.7];	1.72 [-2.92 ; 6.37]; 0.479	0.479	0.4841
	Yes	106	11	10.38	87	10	11.49	0.9 [0.4 ; 2.03]	0.89 [0.36 ; 2.21];	-1.12 [-9.98 ; 7.75]; 0.82	0.82	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	18	7.35	251	15	5.98	1.23 [0.63 ; 2.38]	1.25 [0.61 ; 2.54];	1.37 [-3.02 ; 5.76]; 0.592	0.592	0.6306
	USA and Western Europe	27	3	11.11	22	3	13.64	0.81 [0.18 ; 3.64]	0.79 [0.14 ; 4.38];	-2.53 [-21.13 ; 16.08]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Renal and urinary disorders | any

5.1.16 Skin and subcutaneous tissue disorders - any

Tabelle 134: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	35	19.89	156	44	28.21	0.71 [0.48 ; 1.04]	0.63 [0.38 ; 1.05];	-8.32 [-17.52 ; 0.88]; 0.093	0.093	0.7094
	>= 38 years	96	15	15.62	117	30	25.64	0.61 [0.35 ; 1.06]	0.54 [0.27 ; 1.07];	-10.02 [-20.76 ; 0.72]; 0.092	0.092	
Disease Severity at baseline (EDSS)	<=3.5	218	47	21.56	207	55	26.57	0.81 [0.58 ; 1.14]	0.76 [0.49 ; 1.19];	-5.01 [-13.13 ; 3.11]; 0.256	0.256	0.0077
	>3.5	54	3	5.56	66	19	28.79	0.19 [0.06 ; 0.62]	0.15 [0.04 ; 0.52];	-23.23 [-35.75 ; -10.72]; 0.002	0.002	
Gender	Female	178	32	17.98	176	61	34.66	0.52 [0.36 ; 0.75]	0.41 [0.25 ; 0.68];	-16.68 [-25.7 ; -7.67]; 0	0	0.005
	Male	94	18	19.15	97	13	13.40	1.43 [0.74 ; 2.75]	1.53 [0.7 ; 3.33];	5.75 [-4.7 ; 16.2]; 0.329	0.329	
Number of baseline Gd-enhancing lesions	>=1	141	28	19.86	135	36	26.67	0.74 [0.48 ; 1.15]	0.68 [0.39 ; 1.2];	-6.81 [-16.76 ; 3.14]; 0.201	0.201	0.5175
	0	131	22	16.79	136	38	27.94	0.6 [0.38 ; 0.96]	0.52 [0.29 ; 0.94];	-11.15 [-21.04 ; -1.26]; 0.04	0.04	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	22	18.80	110	30	27.27	0.69 [0.42 ; 1.12]	0.62 [0.33 ; 1.15];	-8.47 [-19.4 ; 2.46]; 0.155	0.155	0.8166
	>=3	42	6	14.29	40	11	27.50	0.52 [0.21 ; 1.27]	0.44 [0.15 ; 1.33];	-13.21 [-30.63 ; 4.21]; 0.177	0.177	
	2	113	22	19.47	123	33	26.83	0.73 [0.45 ; 1.17]	0.66 [0.36 ; 1.22];	-7.36 [-18.07 ; 3.35]; 0.218	0.218	
Received approved disease modifying MS	No	166	26	15.66	186	51	27.42	0.57 [0.37 ; 0.87]	0.49 [0.29 ; 0.83];	-11.76 [-20.22 ; -3.29]; 0.01	0.01	0.2403
	Yes	106	24	22.64	87	23	26.44	0.86 [0.52 ; 1.41]	0.81 [0.42 ; 1.57];	-3.8 [-16.02 ; 8.43]; 0.614	0.614	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
drug prior to enrollment												
Region	Eastern Europe	245	41	16.73	251	66	26.29	0.64 [0.45 ; 0.9]	0.56 [0.36 ; 0.87];	-9.56 [-16.74 ; -2.38]; 0.012	0.012	0.4933
	USA and Western Europe	27	9	33.33	22	8	36.36	0.92 [0.43 ; 1.98]	0.88 [0.27 ; 2.85];	-3.03 [-29.87 ; 23.81]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Skin and subcutaneous tissue disorders | any

5.1.17 Ear and labyrinth disorders - any

Tabelle 135: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	6	3.41	156	4	2.56	1.33 [0.38 ; 4.63]	1.34 [0.37 ; 4.84];	0.84 [-2.81 ; 4.5]; 0.755	0.755	0.5782
	>= 38 years	96	10	10.42	117	6	5.13	2.03 [0.77 ; 5.39]	2.15 [0.75 ; 6.15];	5.29 [-2.01 ; 12.59]; 0.192	0.192	
Disease Severity at baseline (EDSS)	<=3.5	218	13	5.96	207	6	2.90	2.06 [0.8 ; 5.31]	2.12 [0.79 ; 5.7];	3.06 [-0.82 ; 6.95]; 0.16	0.16	0.3612
	>3.5	54	3	5.56	66	4	6.06	0.92 [0.21 ; 3.92]	0.91 [0.2 ; 4.26];	-0.51 [-8.9 ; 7.89]; 1	1	
Gender	Female	178	11	6.18	176	4	2.27	2.72 [0.88 ; 8.38]	2.83 [0.88 ; 9.07];	3.91 [-0.26 ; 8.07]; 0.111	0.111	0.1558
	Male	94	5	5.32	97	6	6.19	0.86 [0.27 ; 2.72]	0.85 [0.25 ; 2.89];	-0.87 [-7.47 ; 5.73]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	5	3.55	135	6	4.44	0.8 [0.25 ; 2.55]	0.79 [0.24 ; 2.65];	-0.9 [-5.52 ; 3.73]; 0.766	0.766	0.1117
	0	131	11	8.40	136	4	2.94	2.85 [0.93 ; 8.74]	3.02 [0.94 ; 9.75];	5.46 [-0.08 ; 10.99]; 0.065	0.065	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	8	6.84	110	2	1.82	3.76 [0.82 ; 17.32]	3.96 [0.82 ; 19.09];	5.02 [-0.19 ; 10.23]; 0.103	0.103	0.1902
	>=3	42	3	7.14	40	1	2.50	2.86 [0.31 ; 26.34]	3 [0.3 ; 30.11];	4.64 [-4.53 ; 13.81]; 0.616	0.616	
	2	113	5	4.42	123	7	5.69	0.78 [0.25 ; 2.38]	0.77 [0.24 ; 2.49];	-1.27 [-6.85 ; 4.31]; 0.771	0.771	
Received approved disease modifying MS drug prior to enrollment	No	166	12	7.23	186	5	2.69	2.69 [0.97 ; 7.47]	2.82 [0.97 ; 8.18];	4.54 [-0.03 ; 9.11]; 0.079	0.079	0.0878
	Yes	106	4	3.77	87	5	5.75	0.66 [0.18 ; 2.37]	0.64 [0.17 ; 2.47];	-1.97 [-8.06 ; 4.12]; 0.734	0.734	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	11	4.49	251	7	2.79	1.61 [0.63 ; 4.08]	1.64 [0.62 ; 4.3];	1.7 [-1.6 ; 5]; 0.345	0.345	0.8899
	USA and Western Europe	27	5	18.52	22	3	13.64	1.36 [0.36 ; 5.06]	1.44 [0.3 ; 6.83];	4.88 [-15.62 ; 25.38]; 0.715	0.715	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Ear and labyrinth disorders | any

5.1.18 Reproductive system and breast disorders - any

Tabelle 136: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	23	13.07	156	20	12.82	1.02 [0.58 ; 1.78]	1.02 [0.54 ; 1.94];	0.25 [-6.99 ; 7.48]; 1	1	0.5035
	>= 38 years	96	7	7.29	117	12	10.26	0.71 [0.29 ; 1.74]	0.69 [0.26 ; 1.82];	-2.96 [-10.53 ; 4.6]; 0.481	0.481	
Disease Severity at baseline (EDSS)	<=3.5	218	29	13.30	207	24	11.59	1.15 [0.69 ; 1.9]	1.17 [0.66 ; 2.09];	1.71 [-4.56 ; 7.98]; 0.66	0.66	0.0202
	>3.5	54	1	1.85	66	8	12.12	0.15 [0.02 ; 1.18]	0.14 [0.02 ; 1.13];	-10.27 [-18.93 ; -1.61]; 0.04	0.04	
Gender	Female	178	28	15.73	176	29	16.48	0.95 [0.59 ; 1.54]	0.95 [0.54 ; 1.67];	-0.75 [-8.41 ; 6.91]; 0.886	0.886	0.7326
	Male	94	2	2.13	97	3	3.09	0.69 [0.12 ; 4.02]	0.68 [0.11 ; 4.17];	-0.97 [-5.48 ; 3.55]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	16	11.35	135	19	14.07	0.81 [0.43 ; 1.5]	0.78 [0.38 ; 1.59];	-2.73 [-10.59 ; 5.14]; 0.588	0.588	0.4959
	0	131	14	10.69	136	13	9.56	1.12 [0.55 ; 2.29]	1.13 [0.51 ; 2.51];	1.13 [-6.11 ; 8.37]; 0.84	0.84	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	12	10.26	110	12	10.91	0.94 [0.44 ; 2]	0.93 [0.4 ; 2.18];	-0.65 [-8.66 ; 7.36]; 1	1	0.9996
	>=3	42	6	14.29	40	6	15.00	0.95 [0.33 ; 2.71]	0.94 [0.28 ; 3.21];	-0.71 [-16.03 ; 14.6]; 1	1	
	2	113	12	10.62	123	14	11.38	0.93 [0.45 ; 1.93]	0.93 [0.41 ; 2.09];	-0.76 [-8.75 ; 7.22]; 1	1	
Received approved disease modifying MS drug prior to enrollment	No	166	19	11.45	186	21	11.29	1.01 [0.57 ; 1.82]	1.02 [0.53 ; 1.96];	0.16 [-6.49 ; 6.8]; 1	1	0.6727
	Yes	106	11	10.38	87	11	12.64	0.82 [0.37 ; 1.8]	0.8 [0.33 ; 1.95];	-2.27 [-11.35 ; 6.82]; 0.655	0.655	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	26	10.61	251	29	11.55	0.92 [0.56 ; 1.51]	0.91 [0.52 ; 1.59];	-0.94 [-6.47 ; 4.58]; 0.776	0.776	0.8253
	USA and Western Europe	27	4	14.81	22	3	13.64	1.09 [0.27 ; 4.35]	1.1 [0.22 ; 5.54];	1.18 [-18.45 ; 20.8]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Reproductive system and breast disorders | any

5.1.19 Blood and lymphatic system disorders - any

Tabelle 137: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	33	18.75	156	26	16.67	1.12 [0.71 ; 1.79]	1.15 [0.66 ; 2.03];	2.08 [-6.13 ; 10.3]; 0.667	0.667	0.5722
	>= 38 years	96	14	14.58	117	19	16.24	0.9 [0.48 ; 1.7]	0.88 [0.42 ; 1.86];	-1.66 [-11.38 ; 8.07]; 0.85	0.85	
Disease Severity at baseline (EDSS)	<=3.5	218	39	17.89	207	32	15.46	1.16 [0.76 ; 1.77]	1.19 [0.71 ; 1.99];	2.43 [-4.65 ; 9.51]; 0.518	0.518	0.3482
	>3.5	54	8	14.81	66	13	19.70	0.75 [0.34 ; 1.68]	0.71 [0.27 ; 1.86];	-4.88 [-18.37 ; 8.6]; 0.63	0.63	
Gender	Female	178	36	20.22	176	35	19.89	1.02 [0.67 ; 1.54]	1.02 [0.61 ; 1.72];	0.34 [-8 ; 8.68]; 1	1	0.8202
	Male	94	11	11.70	97	10	10.31	1.14 [0.51 ; 2.55]	1.15 [0.47 ; 2.86];	1.39 [-7.49 ; 10.27]; 0.82	0.82	
Number of baseline Gd-enhancing lesions	>=1	141	25	17.73	135	29	21.48	0.83 [0.51 ; 1.33]	0.79 [0.43 ; 1.43];	-3.75 [-13.12 ; 5.62]; 0.452	0.452	0.1602
	0	131	22	16.79	136	16	11.76	1.43 [0.79 ; 2.59]	1.51 [0.76 ; 3.03];	5.03 [-3.36 ; 13.41]; 0.294	0.294	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	22	18.80	110	21	19.09	0.98 [0.57 ; 1.69]	0.98 [0.51 ; 1.91];	-0.29 [-10.49 ; 9.91]; 1	1	0.937
	>=3	42	11	26.19	40	9	22.50	1.16 [0.54 ; 2.51]	1.22 [0.44 ; 3.36];	3.69 [-14.86 ; 22.25]; 0.799	0.799	
	2	113	14	12.39	123	15	12.20	1.02 [0.51 ; 2.01]	1.02 [0.47 ; 2.22];	0.19 [-8.19 ; 8.58]; 1	1	
Received approved disease modifying MS drug prior to enrollment	No	166	17	10.24	186	26	13.98	0.73 [0.41 ; 1.3]	0.7 [0.37 ; 1.35];	-3.74 [-10.53 ; 3.05]; 0.329	0.329	0.1369
	Yes	106	30	28.30	87	19	21.84	1.3 [0.79 ; 2.14]	1.41 [0.73 ; 2.74];	6.46 [-5.74 ; 18.67]; 0.324	0.324	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	43	17.55	251	45	17.93	0.98 [0.67 ; 1.43]	0.97 [0.61 ; 1.54];	-0.38 [-7.1 ; 6.35]; 1	1	0.0257
	USA and Western Europe	27	4	14.81	22	0	0.00	7.39 [0.42 ; 130.28]	8.62 [0.44 ; 169.38];	13.9 [-0.95 ; 28.75]; 0.121	0.121	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Blood and lymphatic system disorders | any

5.1.20 Musculoskeletal and connective tissue disorders - Pain in extremity

Tabelle 138: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	12	6.82	156	5	3.21	2.13 [0.77 ; 5.9]	2.21 [0.76 ; 6.42];	3.61 [-1.02 ; 8.25]; 0.211	0.211	0.1537
	>= 38 years	96	4	4.17	117	7	5.98	0.7 [0.21 ; 2.31]	0.68 [0.19 ; 2.41];	-1.82 [-7.69 ; 4.05]; 0.758	0.758	
Disease Severity at baseline (EDSS)	<=3.5	218	15	6.88	207	11	5.31	1.29 [0.61 ; 2.75]	1.32 [0.59 ; 2.94];	1.57 [-2.98 ; 6.11]; 0.548	0.548	0.9619
	>3.5	54	1	1.85	66	1	1.52	1.22 [0.08 ; 19.09]	1.23 [0.07 ; 20.08];	0.34 [-4.31 ; 4.99]; 1	1	
Gender	Female	178	15	8.43	176	10	5.68	1.48 [0.68 ; 3.21]	1.53 [0.67 ; 3.5];	2.75 [-2.58 ; 8.07]; 0.407	0.407	0.3858
	Male	94	1	1.06	97	2	2.06	0.52 [0.05 ; 5.6]	0.51 [0.05 ; 5.73];	-1 [-4.5 ; 2.51]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	8	5.67	135	4	2.96	1.91 [0.59 ; 6.21]	1.97 [0.58 ; 6.7];	2.71 [-2.06 ; 7.48]; 0.378	0.378	0.4264
	0	131	8	6.11	136	8	5.88	1.04 [0.4 ; 2.68]	1.04 [0.38 ; 2.86];	0.22 [-5.47 ; 5.92]; 1	1	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	8	6.84	110	5	4.55	1.5 [0.51 ; 4.46]	1.54 [0.49 ; 4.86];	2.29 [-3.71 ; 8.3]; 0.572	0.572	0.8747
	>=3	42	2	4.76	40	1	2.50	1.9 [0.18 ; 20.19]	1.95 [0.17 ; 22.39];	2.26 [-5.79 ; 10.32]; 1	1	
	2	113	6	5.31	123	6	4.88	1.09 [0.36 ; 3.28]	1.09 [0.34 ; 3.49];	0.43 [-5.19 ; 6.05]; 1	1	
Received approved disease modifying MS drug prior to enrollment	No	166	11	6.63	186	7	3.76	1.76 [0.7 ; 4.44]	1.81 [0.69 ; 4.8];	2.86 [-1.81 ; 7.53]; 0.237	0.237	0.325
	Yes	106	5	4.72	87	5	5.75	0.82 [0.25 ; 2.74]	0.81 [0.23 ; 2.9];	-1.03 [-7.37 ; 5.31]; 0.756	0.756	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	11	4.49	251	8	3.19	1.41 [0.58 ; 3.44]	1.43 [0.56 ; 3.61];	1.3 [-2.08 ; 4.69]; 0.491	0.491	0.7052
	USA and Western Europe	27	5	18.52	22	4	18.18	1.02 [0.31 ; 3.34]	1.02 [0.24 ; 4.38];	0.34 [-21.44 ; 22.12]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Musculoskeletal and connective tissue disorders | Pain in extremity

5.1.21 Gastrointestinal disorders - Diarrhoea

Tabelle 139: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	18	10.23	156	18	11.54	0.89 [0.48 ; 1.64]	0.87 [0.44 ; 1.74];	-1.31 [-8.03 ; 5.41]; 0.727	0.727	0.4894
	>= 38 years	96	7	7.29	117	14	11.97	0.61 [0.26 ; 1.45]	0.58 [0.22 ; 1.5];	-4.67 [-12.53 ; 3.18]; 0.356	0.356	
Disease Severity at baseline (EDSS)	<=3.5	218	22	10.09	207	25	12.08	0.84 [0.49 ; 1.43]	0.82 [0.45 ; 1.5];	-1.99 [-7.96 ; 3.99]; 0.539	0.539	0.5144
	>3.5	54	3	5.56	66	7	10.61	0.52 [0.14 ; 1.93]	0.5 [0.12 ; 2.02];	-5.05 [-14.67 ; 4.57]; 0.509	0.509	
Gender	Female	178	18	10.11	176	17	9.66	1.05 [0.56 ; 1.96]	1.05 [0.52 ; 2.12];	0.45 [-5.76 ; 6.67]; 1	1	0.1402
	Male	94	7	7.45	97	15	15.46	0.48 [0.21 ; 1.13]	0.44 [0.17 ; 1.13];	-8.02 [-16.96 ; 0.92]; 0.112	0.112	
Number of baseline Gd-enhancing lesions	>=1	141	20	14.18	135	16	11.85	1.2 [0.65 ; 2.21]	1.23 [0.61 ; 2.49];	2.33 [-5.6 ; 10.26]; 0.596	0.596	0.0294
	0	131	5	3.82	136	15	11.03	0.35 [0.13 ; 0.93]	0.32 [0.11 ; 0.91];	-7.21 [-13.42 ; -1.01]; 0.035	0.035	
	NA	0	0	0.00	2	1	50.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	12	10.26	110	13	11.82	0.87 [0.41 ; 1.82]	0.85 [0.37 ; 1.96];	-1.56 [-9.72 ; 6.6]; 0.833	0.833	0.5969
	>=3	42	5	11.90	40	4	10.00	1.19 [0.34 ; 4.12]	1.22 [0.3 ; 4.9];	1.9 [-11.6 ; 15.41]; 1	1	
	2	113	8	7.08	123	15	12.20	0.58 [0.26 ; 1.32]	0.55 [0.22 ; 1.35];	-5.12 [-12.59 ; 2.35]; 0.197	0.197	
Received approved disease modifying MS drug prior to enrollment	No	166	10	6.02	186	21	11.29	0.53 [0.26 ; 1.1]	0.5 [0.23 ; 1.1];	-5.27 [-11.08 ; 0.55]; 0.092	0.092	0.1583
	Yes	106	15	14.15	87	11	12.64	1.12 [0.54 ; 2.31]	1.14 [0.49 ; 2.63];	1.51 [-8.13 ; 11.14]; 0.834	0.834	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	22	8.98	251	29	11.55	0.78 [0.46 ; 1.31]	0.76 [0.42 ; 1.35];	-2.57 [-7.91 ; 2.76]; 0.377	0.377	0.9592
	USA and Western Europe	27	3	11.11	22	3	13.64	0.81 [0.18 ; 3.64]	0.79 [0.14 ; 4.38];	-2.53 [-21.13 ; 16.08]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Gastrointestinal disorders | Diarrhoea

5.1.22 Gastrointestinal disorders - Nausea

Tabelle 140: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	17	9.66	156	20	12.82	0.75 [0.41 ; 1.39]	0.73 [0.37 ; 1.44];	-3.16 [-9.99 ; 3.66]; 0.386	0.386	0.0942
	>= 38 years	96	12	12.50	117	8	6.84	1.83 [0.78 ; 4.29]	1.95 [0.76 ; 4.98];	5.66 [-2.38 ; 13.7]; 0.167	0.167	
Disease Severity at baseline (EDSS)	<=3.5	218	26	11.93	207	25	12.08	0.99 [0.59 ; 1.65]	0.99 [0.55 ; 1.77];	-0.15 [-6.33 ; 6.03]; 1	1	0.7999
	>3.5	54	3	5.56	66	3	4.55	1.22 [0.26 ; 5.81]	1.24 [0.24 ; 6.38];	1.01 [-6.9 ; 8.92]; 1	1	
Gender	Female	178	25	14.04	176	22	12.50	1.12 [0.66 ; 1.92]	1.14 [0.62 ; 2.12];	1.54 [-5.52 ; 8.61]; 0.755	0.755	0.4671
	Male	94	4	4.26	97	6	6.19	0.69 [0.2 ; 2.36]	0.67 [0.18 ; 2.47];	-1.93 [-8.23 ; 4.37]; 0.748	0.748	
Number of baseline Gd-enhancing lesions	>=1	141	16	11.35	135	18	13.33	0.85 [0.45 ; 1.6]	0.83 [0.41 ; 1.71];	-1.99 [-9.75 ; 5.78]; 0.715	0.715	0.3701
	0	131	13	9.92	136	10	7.35	1.35 [0.61 ; 2.97]	1.39 [0.59 ; 3.29];	2.57 [-4.17 ; 9.31]; 0.517	0.517	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	11	9.40	110	11	10.00	0.94 [0.42 ; 2.08]	0.93 [0.39 ; 2.25];	-0.6 [-8.31 ; 7.11]; 1	1	0.9074
	>=3	42	5	11.90	40	5	12.50	0.95 [0.3 ; 3.04]	0.95 [0.25 ; 3.55];	-0.6 [-14.77 ; 13.58]; 1	1	
	2	113	13	11.50	123	12	9.76	1.18 [0.56 ; 2.48]	1.2 [0.52 ; 2.76];	1.75 [-6.13 ; 9.63]; 0.678	0.678	
Received approved disease modifying MS drug prior to enrollment	No	166	19	11.45	186	19	10.22	1.12 [0.61 ; 2.04]	1.14 [0.58 ; 2.23];	1.23 [-5.28 ; 7.74]; 0.734	0.734	0.6989
	Yes	106	10	9.43	87	9	10.34	0.91 [0.39 ; 2.14]	0.9 [0.35 ; 2.33];	-0.91 [-9.39 ; 7.57]; 1	1	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	22	8.98	251	22	8.76	1.02 [0.58 ; 1.8]	1.03 [0.55 ; 1.91];	0.21 [-4.79 ; 5.22]; 1	1	0.8948
	USA and Western Europe	27	7	25.93	22	6	27.27	0.95 [0.37 ; 2.42]	0.93 [0.26 ; 3.33];	-1.35 [-26.24 ; 23.54]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Gastrointestinal disorders | Nausea

5.1.23 Nervous system disorders - Headache

Tabelle 141: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	77	43.75	156	57	36.54	1.2 [0.92 ; 1.56]	1.35 [0.87 ; 2.1];	7.21 [-3.32 ; 17.74]; 0.218	0.218	0.5563
	>= 38 years	96	26	27.08	117	30	25.64	1.06 [0.67 ; 1.66]	1.08 [0.58 ; 1.99];	1.44 [-10.46 ; 13.34]; 0.876	0.876	
Disease Severity at baseline (EDSS)	<=3.5	218	91	41.74	207	69	33.33	1.25 [0.98 ; 1.61]	1.43 [0.97 ; 2.13];	8.41 [-0.76 ; 17.58]; 0.089	0.089	0.1795
	>3.5	54	12	22.22	66	18	27.27	0.81 [0.43 ; 1.54]	0.76 [0.33 ; 1.76];	-5.05 [-20.49 ; 10.39]; 0.672	0.672	
Gender	Female	178	81	45.51	176	60	34.09	1.33 [1.03 ; 1.73]	1.61 [1.05 ; 2.48];	11.41 [1.29 ; 21.54]; 0.03	0.03	0.0731
	Male	94	22	23.40	97	27	27.84	0.84 [0.52 ; 1.37]	0.79 [0.41 ; 1.52];	-4.43 [-16.79 ; 7.93]; 0.511	0.511	
Number of baseline Gd-enhancing lesions	>=1	141	54	38.30	135	42	31.11	1.23 [0.89 ; 1.71]	1.37 [0.84 ; 2.26];	7.19 [-4.01 ; 18.38]; 0.255	0.255	0.7215
	0	131	49	37.40	136	45	33.09	1.13 [0.82 ; 1.57]	1.21 [0.73 ; 2];	4.32 [-7.14 ; 15.77]; 0.522	0.522	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	45	38.46	110	36	32.73	1.18 [0.83 ; 1.67]	1.28 [0.74 ; 2.22];	5.73 [-6.7 ; 18.17]; 0.407	0.407	0.8765
	>=3	42	16	38.10	40	11	27.50	1.39 [0.73 ; 2.61]	1.62 [0.64 ; 4.12];	10.6 [-9.58 ; 30.77]; 0.353	0.353	
	2	113	42	37.17	123	40	32.52	1.14 [0.81 ; 1.62]	1.23 [0.72 ; 2.1];	4.65 [-7.51 ; 16.81]; 0.495	0.495	
Received approved disease modifying MS drug prior to enrollment	No	166	63	37.95	186	61	32.80	1.16 [0.87 ; 1.54]	1.25 [0.81 ; 1.94];	5.16 [-4.84 ; 15.16]; 0.317	0.317	0.7402
	Yes	106	40	37.74	87	26	29.89	1.26 [0.84 ; 1.89]	1.42 [0.78 ; 2.6];	7.85 [-5.48 ; 21.18]; 0.287	0.287	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	91	37.14	251	78	31.08	1.2 [0.93 ; 1.53]	1.31 [0.9 ; 1.9];	6.07 [-2.26 ; 14.4]; 0.157	0.157	0.837
	USA and Western Europe	27	12	44.44	22	9	40.91	1.09 [0.56 ; 2.09]	1.16 [0.37 ; 3.61];	3.54 [-24.27 ; 31.35]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Nervous system disorders | Headache

5.1.24 General disorders and administration site conditions - Pyrexia

Tabelle 142: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	24	13.64	156	6	3.85	3.55 [1.49 ; 8.45]	3.95 [1.57 ; 9.93];	9.79 [3.89 ; 15.69]; 0.002	0.002	0.2301
	>= 38 years	96	11	11.46	117	8	6.84	1.68 [0.7 ; 4]	1.76 [0.68 ; 4.58];	4.62 [-3.22 ; 12.46]; 0.334	0.334	
Disease Severity at baseline (EDSS)	<=3.5	218	31	14.22	207	10	4.83	2.94 [1.48 ; 5.85]	3.27 [1.56 ; 6.85];	9.39 [3.91 ; 14.87]; 0.002	0.002	0.2423
	>3.5	54	4	7.41	66	4	6.06	1.22 [0.32 ; 4.66]	1.24 [0.3 ; 5.21];	1.35 [-7.7 ; 10.4]; 1	1	
Gender	Female	178	28	15.73	176	10	5.68	2.77 [1.39 ; 5.53]	3.1 [1.46 ; 6.59];	10.05 [3.7 ; 16.4]; 0.003	0.003	0.5061
	Male	94	7	7.45	97	4	4.12	1.81 [0.55 ; 5.97]	1.87 [0.53 ; 6.61];	3.32 [-3.3 ; 9.94]; 0.367	0.367	
Number of baseline Gd-enhancing lesions	>=1	141	17	12.06	135	5	3.70	3.26 [1.24 ; 8.58]	3.56 [1.28 ; 9.95];	8.35 [2.11 ; 14.6]; 0.013	0.013	0.492
	0	131	18	13.74	136	9	6.62	2.08 [0.97 ; 4.45]	2.25 [0.97 ; 5.2];	7.12 [-0.1 ; 14.35]; 0.067	0.067	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	17	14.53	110	6	5.45	2.66 [1.09 ; 6.51]	2.95 [1.12 ; 7.78];	9.08 [1.41 ; 16.74]; 0.028	0.028	0.9262
	>=3	42	6	14.29	40	2	5.00	2.86 [0.61 ; 13.34]	3.17 [0.6 ; 16.72];	9.29 [-3.27 ; 21.84]; 0.265	0.265	
	2	113	12	10.62	123	6	4.88	2.18 [0.85 ; 5.61]	2.32 [0.84 ; 6.4];	5.74 [-1.1 ; 12.58]; 0.14	0.14	
Received approved disease modifying MS drug prior to enrollment	No	166	19	11.45	186	7	3.76	3.04 [1.31 ; 7.05]	3.31 [1.35 ; 8.08];	7.68 [2.12 ; 13.24]; 0.007	0.007	0.462
	Yes	106	16	15.09	87	7	8.05	1.88 [0.81 ; 4.35]	2.03 [0.8 ; 5.19];	7.05 [-1.85 ; 15.94]; 0.18	0.18	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	29	11.84	251	13	5.18	2.29 [1.22 ; 4.29]	2.46 [1.25 ; 4.85];	6.66 [1.77 ; 11.54]; 0.009	0.009	0.416
	USA and Western Europe	27	6	22.22	22	1	4.55	4.89 [0.64 ; 37.63]	6 [0.66 ; 54.24];	17.68 [-0.26 ; 35.61]; 0.112	0.112	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - General disorders and administration site conditions | Pyrexia

5.1.25 Infections and infestations - Bronchitis

Tabelle 143: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	7	3.98	156	11	7.05	0.56 [0.22 ; 1.42]	0.55 [0.21 ; 1.44];	-3.07 [-8.02 ; 1.87]; 0.235	0.235	0.0613
	>= 38 years	96	5	5.21	117	2	1.71	3.05 [0.6 ; 15.36]	3.16 [0.6 ; 16.66];	3.5 [-1.53 ; 8.53]; 0.248	0.248	
Disease Severity at baseline (EDSS)	<=3.5	218	8	3.67	207	12	5.80	0.63 [0.26 ; 1.52]	0.62 [0.25 ; 1.55];	-2.13 [-6.17 ; 1.92]; 0.362	0.362	0.0538
	>3.5	54	4	7.41	66	1	1.52	4.89 [0.56 ; 42.46]	5.2 [0.56 ; 47.98];	5.89 [-1.69 ; 13.47]; 0.173	0.173	
Gender	Female	178	12	6.74	176	10	5.68	1.19 [0.53 ; 2.68]	1.2 [0.5 ; 2.85];	1.06 [-3.97 ; 6.09]; 0.826	0.826	0.0396
	Male	94	0	0.00	97	3	3.09	0.15 [0.01 ; 2.81]	0.14 [0.01 ; 2.8];	-3.05 [-7 ; 0.91]; 0.121	0.121	
Number of baseline Gd-enhancing lesions	>=1	141	4	2.84	135	5	3.70	0.77 [0.21 ; 2.79]	0.76 [0.2 ; 2.89];	-0.87 [-5.07 ; 3.34]; 0.745	0.745	0.7117
	0	131	8	6.11	136	8	5.88	1.04 [0.4 ; 2.68]	1.04 [0.38 ; 2.86];	0.22 [-5.47 ; 5.92]; 1	1	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	5	4.27	110	3	2.73	1.57 [0.38 ; 6.4]	1.59 [0.37 ; 6.83];	1.55 [-3.22 ; 6.31]; 0.723	0.723	0.1416
	>=3	42	1	2.38	40	5	12.50	0.19 [0.02 ; 1.56]	0.17 [0.02 ; 1.53];	-10.12 [-21.36 ; 1.12]; 0.105	0.105	
	2	113	6	5.31	123	5	4.07	1.31 [0.41 ; 4.16]	1.32 [0.39 ; 4.46];	1.24 [-4.17 ; 6.66]; 0.762	0.762	
Received approved disease modifying MS drug prior to enrollment	No	166	7	4.22	186	7	3.76	1.12 [0.4 ; 3.13]	1.13 [0.39 ; 3.28];	0.45 [-3.65 ; 4.56]; 1	1	0.5287
	Yes	106	5	4.72	87	6	6.90	0.68 [0.22 ; 2.17]	0.67 [0.2 ; 2.27];	-2.18 [-8.86 ; 4.5]; 0.548	0.548	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	11	4.49	251	12	4.78	0.94 [0.42 ; 2.09]	0.94 [0.41 ; 2.16];	-0.29 [-3.99 ; 3.41]; 1	1	0.9219
	USA and Western Europe	27	1	3.70	22	1	4.55	0.81 [0.05 ; 12.3]	0.81 [0.05 ; 13.7];	-0.84 [-12.09 ; 10.41]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Bronchitis

5.1.26 Nervous system disorders - Hypoaesthesia

Tabelle 144: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	4	2.27	156	5	3.21	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>= 38 years	96	0	0.00	117	5	4.27	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	218	4	1.83	207	8	3.86	0.47 [0.15 ; 1.55]	0.46 [0.14 ; 1.57];	-2.03 [-5.2 ; 1.14]; 0.25	0.25	0.2718
	>3.5	54	0	0.00	66	2	3.03	0.24 [0.01 ; 4.97]	0.24 [0.01 ; 5.04];	-2.82 [-8.01 ; 2.36]; 0.501	0.501	
Gender	Female	178	2	1.12	176	7	3.98	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	Male	94	2	2.13	97	3	3.09	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of baseline Gd-enhancing lesions	>=1	141	2	1.42	135	4	2.96	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	131	2	1.53	136	6	4.41	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	1	0.85	110	4	3.64	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	0	0.00	40	1	2.50	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	3	2.65	123	5	4.07	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	2	1.20	186	5	2.69	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	Yes	106	2	1.89	87	5	5.75	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	4	1.63	251	4	1.59	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	USA and Western Europe	27	0	0.00	22	6	27.27	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Nervous system disorders | Hypoaesthesia

5.1.27 Gastrointestinal disorders - Abdominal pain upper

Tabelle 145: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	10	5.68	156	6	3.85	1.48 [0.55 ; 3.97]	1.51 [0.53 ; 4.24];	1.84 [-2.73 ; 6.4]; 0.609	0.609	0.834
	>= 38 years	96	3	3.12	117	3	2.56	1.22 [0.25 ; 5.9]	1.23 [0.24 ; 6.22];	0.56 [-3.95 ; 5.07]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	218	12	5.50	207	7	3.38	1.63 [0.65 ; 4.05]	1.66 [0.64 ; 4.31];	2.12 [-1.78 ; 6.03]; 0.351	0.351	0.4328
	>3.5	54	1	1.85	66	2	3.03	0.61 [0.06 ; 6.56]	0.6 [0.05 ; 6.84];	-1.18 [-6.66 ; 4.3]; 1	1	
Gender	Female	178	12	6.74	176	8	4.55	1.48 [0.62 ; 3.54]	1.52 [0.61 ; 3.81];	2.2 [-2.6 ; 7]; 0.491	0.491	0.7971
	Male	94	1	1.06	97	1	1.03	1.03 [0.07 ; 16.26]	1.03 [0.06 ; 16.75];	0.03 [-2.86 ; 2.92]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	10	7.09	135	4	2.96	2.39 [0.77 ; 7.45]	2.5 [0.76 ; 8.17];	4.13 [-0.98 ; 9.24]; 0.17	0.17	0.1323
	0	131	3	2.29	136	5	3.68	0.62 [0.15 ; 2.55]	0.61 [0.14 ; 2.62];	-1.39 [-5.46 ; 2.68]; 0.723	0.723	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	5	4.27	110	4	3.64	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	5	11.90	40	2	5.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	3	2.65	123	3	2.44	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	7	4.22	186	7	3.76	1.12 [0.4 ; 3.13]	1.13 [0.39 ; 3.28];	0.45 [-3.65 ; 4.56]; 1	1	0.3978
	Yes	106	6	5.66	87	2	2.30	2.46 [0.51 ; 11.89]	2.55 [0.5 ; 12.97];	3.36 [-2.05 ; 8.77]; 0.298	0.298	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	10	4.08	251	6	2.39	1.71 [0.63 ; 4.63]	1.74 [0.62 ; 4.86];	1.69 [-1.42 ; 4.81]; 0.319	0.319	0.4406
	USA and Western Europe	27	3	11.11	22	3	13.64	0.81 [0.18 ; 3.64]	0.79 [0.14 ; 4.38];	-2.53 [-21.13 ; 16.08]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Gastrointestinal disorders | Abdominal pain upper

5.1.28 Infections and infestations - Nasopharyngitis

Tabelle 146: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	48	27.27	156	36	23.08	1.18 [0.81 ; 1.72]	1.25 [0.76 ; 2.06];	4.2 [-5.13 ; 13.52]; 0.448	0.448	0.9727
	>= 38 years	96	18	18.75	117	18	15.38	1.22 [0.67 ; 2.21]	1.27 [0.62 ; 2.6];	3.37 [-6.82 ; 13.55]; 0.583	0.583	
Disease Severity at baseline (EDSS)	<=3.5	218	59	27.06	207	40	19.32	1.4 [0.98 ; 1.99]	1.55 [0.98 ; 2.45];	7.74 [-0.24 ; 15.72]; 0.066	0.066	0.0586
	>3.5	54	7	12.96	66	14	21.21	0.61 [0.27 ; 1.41]	0.55 [0.21 ; 1.49];	-8.25 [-21.57 ; 5.08]; 0.335	0.335	
Gender	Female	178	53	29.78	176	36	20.45	1.46 [1.01 ; 2.1]	1.65 [1.01 ; 2.68];	9.32 [0.34 ; 18.3]; 0.05	0.05	0.0676
	Male	94	13	13.83	97	18	18.56	0.75 [0.39 ; 1.43]	0.7 [0.32 ; 1.53];	-4.73 [-15.15 ; 5.69]; 0.435	0.435	
Number of baseline Gd-enhancing lesions	>=1	141	35	24.82	135	31	22.96	1.08 [0.71 ; 1.65]	1.11 [0.64 ; 1.93];	1.86 [-8.2 ; 11.92]; 0.778	0.778	0.4455
	0	131	31	23.66	136	23	16.91	1.4 [0.86 ; 2.27]	1.52 [0.83 ; 2.78];	6.75 [-2.87 ; 16.38]; 0.175	0.175	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	30	25.64	110	25	22.73	1.13 [0.71 ; 1.79]	1.17 [0.64 ; 2.16];	2.91 [-8.22 ; 14.05]; 0.644	0.644	0.1075
	>=3	42	13	30.95	40	4	10.00	3.1 [1.1 ; 8.7]	4.03 [1.19 ; 13.7];	20.95 [4.16 ; 37.74]; 0.028	0.028	
	2	113	23	20.35	123	25	20.33	1 [0.6 ; 1.66]	1 [0.53 ; 1.89];	0.03 [-10.25 ; 10.31]; 1	1	
Received approved disease modifying MS drug prior to enrollment	No	166	48	28.92	186	38	20.43	1.42 [0.98 ; 2.05]	1.58 [0.97 ; 2.58];	8.49 [-0.52 ; 17.49]; 0.082	0.082	0.2207
	Yes	106	18	16.98	87	16	18.39	0.92 [0.5 ; 1.7]	0.91 [0.43 ; 1.91];	-1.41 [-12.24 ; 9.42]; 0.851	0.851	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	55	22.45	251	46	18.33	1.22 [0.86 ; 1.74]	1.29 [0.83 ; 2];	4.12 [-2.96 ; 11.21]; 0.267	0.267	0.9122
	USA and Western Europe	27	11	40.74	22	8	36.36	1.12 [0.55 ; 2.29]	1.2 [0.38 ; 3.84];	4.38 [-22.96 ; 31.72]; 0.777	0.777	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Nasopharyngitis

5.1.29 Infections and infestations - Sinusitis

Tabelle 147: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	11	6.25	156	6	3.85	1.62 [0.62 ; 4.29]	1.67 [0.6 ; 4.62];	2.4 [-2.28 ; 7.08]; 0.455	0.455	0.7024
	>= 38 years	96	6	6.25	117	6	5.13	1.22 [0.41 ; 3.66]	1.23 [0.38 ; 3.95];	1.12 [-5.16 ; 7.4]; 0.772	0.772	
Disease Severity at baseline (EDSS)	<=3.5	218	15	6.88	207	11	5.31	1.29 [0.61 ; 2.75]	1.32 [0.59 ; 2.94];	1.57 [-2.98 ; 6.11]; 0.548	0.548	0.6153
	>3.5	54	2	3.70	66	1	1.52	2.44 [0.23 ; 26.24]	2.5 [0.22 ; 28.34];	2.19 [-3.65 ; 8.02]; 0.588	0.588	
Gender	Female	178	14	7.87	176	7	3.98	1.98 [0.82 ; 4.78]	2.06 [0.81 ; 5.24];	3.89 [-1.01 ; 8.78]; 0.176	0.176	0.1586
	Male	94	3	3.19	97	5	5.15	0.62 [0.15 ; 2.52]	0.61 [0.14 ; 2.61];	-1.96 [-7.62 ; 3.69]; 0.721	0.721	
Number of baseline Gd-enhancing lesions	>=1	141	8	5.67	135	3	2.22	2.55 [0.69 ; 9.42]	2.65 [0.69 ; 10.19];	3.45 [-1.11 ; 8.01]; 0.218	0.218	0.2573
	0	131	9	6.87	136	9	6.62	1.04 [0.43 ; 2.53]	1.04 [0.4 ; 2.71];	0.25 [-5.77 ; 6.27]; 1	1	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	9	7.69	110	4	3.64	2.12 [0.67 ; 6.67]	2.21 [0.66 ; 7.39];	4.06 [-1.91 ; 10.02]; 0.256	0.256	0.1439
	>=3	42	2	4.76	40	5	12.50	0.38 [0.08 ; 1.85]	0.35 [0.06 ; 1.92];	-7.74 [-19.84 ; 4.37]; 0.259	0.259	
	2	113	6	5.31	123	3	2.44	2.18 [0.56 ; 8.5]	2.24 [0.55 ; 9.19];	2.87 [-2.08 ; 7.82]; 0.317	0.317	
Received approved disease modifying MS drug prior to enrollment	No	166	12	7.23	186	9	4.84	1.49 [0.65 ; 3.46]	1.53 [0.63 ; 3.73];	2.39 [-2.61 ; 7.39]; 0.375	0.375	0.9086
	Yes	106	5	4.72	87	3	3.45	1.37 [0.34 ; 5.56]	1.39 [0.32 ; 5.97];	1.27 [-4.3 ; 6.84]; 0.732	0.732	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	13	5.31	251	10	3.98	1.33 [0.6 ; 2.98]	1.35 [0.58 ; 3.14];	1.32 [-2.38 ; 5.03]; 0.527	0.527	0.8018
	USA and Western Europe	27	4	14.81	22	2	9.09	1.63 [0.33 ; 8.08]	1.74 [0.29 ; 10.52];	5.72 [-12.27 ; 23.72]; 0.678	0.678	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Sinusitis

5.1.30 Infections and infestations - Upper respiratory tract infection

Tabelle 148: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	15	8.52	156	11	7.05	1.21 [0.57 ; 2.55]	1.23 [0.55 ; 2.76];	1.47 [-4.29 ; 7.23]; 0.685	0.685	0.6225
	>= 38 years	96	9	9.38	117	12	10.26	0.91 [0.4 ; 2.08]	0.91 [0.36 ; 2.25];	-0.88 [-8.9 ; 7.13]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	218	18	8.26	207	17	8.21	1.01 [0.53 ; 1.9]	1.01 [0.5 ; 2.01];	0.04 [-5.18 ; 5.27]; 1	1	0.7576
	>3.5	54	6	11.11	66	6	9.09	1.22 [0.42 ; 3.57]	1.25 [0.38 ; 4.12];	2.02 [-8.86 ; 12.9]; 0.766	0.766	
Gender	Female	178	16	8.99	176	14	7.95	1.13 [0.57 ; 2.24]	1.14 [0.54 ; 2.42];	1.03 [-4.77 ; 6.83]; 0.849	0.849	0.7197
	Male	94	8	8.51	97	9	9.28	0.92 [0.37 ; 2.28]	0.91 [0.34 ; 2.47];	-0.77 [-8.84 ; 7.3]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	11	7.80	135	5	3.70	2.11 [0.75 ; 5.9]	2.2 [0.74 ; 6.51];	4.1 [-1.36 ; 9.55]; 0.198	0.198	0.091
	0	131	13	9.92	136	18	13.24	0.75 [0.38 ; 1.47]	0.72 [0.34 ; 1.54];	-3.31 [-10.97 ; 4.35]; 0.448	0.448	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	11	9.40	110	10	9.09	1.03 [0.46 ; 2.34]	1.04 [0.42 ; 2.55];	0.31 [-7.23 ; 7.85]; 1	1	0.3494
	>=3	42	4	9.52	40	1	2.50	3.81 [0.44 ; 32.64]	4.11 [0.44 ; 38.42];	7.02 [-3.09 ; 17.13]; 0.36	0.36	
	2	113	9	7.96	123	12	9.76	0.82 [0.36 ; 1.86]	0.8 [0.32 ; 1.98];	-1.79 [-9.03 ; 5.45]; 0.655	0.655	
Received approved disease modifying MS drug prior to enrollment	No	166	11	6.63	186	18	9.68	0.68 [0.33 ; 1.41]	0.66 [0.3 ; 1.45];	-3.05 [-8.74 ; 2.64]; 0.336	0.336	0.0586
	Yes	106	13	12.26	87	5	5.75	2.13 [0.79 ; 5.75]	2.29 [0.78 ; 6.71];	6.52 [-1.41 ; 14.45]; 0.141	0.141	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	21	8.57	251	18	7.17	1.2 [0.65 ; 2.19]	1.21 [0.63 ; 2.34];	1.4 [-3.34 ; 6.14]; 0.619	0.619	0.2175
	USA and Western Europe	27	3	11.11	22	5	22.73	0.49 [0.13 ; 1.82]	0.42 [0.09 ; 2.02];	-11.62 [-32.76 ; 9.53]; 0.44	0.44	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Upper respiratory tract infection

5.1.31 Musculoskeletal and connective tissue disorders - Arthralgia

Tabelle 149: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	9	5.11	156	6	3.85	1.33 [0.48 ; 3.65]	1.35 [0.47 ; 3.87];	1.27 [-3.17 ; 5.71]; 0.609	0.609	0.9387
	>= 38 years	96	8	8.33	117	7	5.98	1.39 [0.52 ; 3.7]	1.43 [0.5 ; 4.09];	2.35 [-4.65 ; 9.35]; 0.594	0.594	
Disease Severity at baseline (EDSS)	<=3.5	218	17	7.80	207	9	4.35	1.79 [0.82 ; 3.93]	1.86 [0.81 ; 4.27];	3.45 [-1.06 ; 7.97]; 0.159	0.159	0.01
	>3.5	54	0	0.00	66	4	6.06	0.14 [0.01 ; 2.46]	0.13 [0.01 ; 2.42];	-5.81 [-12.3 ; 0.69]; 0.126	0.126	
Gender	Female	178	9	5.06	176	9	5.11	0.99 [0.4 ; 2.43]	0.99 [0.38 ; 2.55];	-0.06 [-4.63 ; 4.52]; 1	1	0.3185
	Male	94	8	8.51	97	4	4.12	2.06 [0.64 ; 6.62]	2.16 [0.63 ; 7.44];	4.39 [-2.5 ; 11.28]; 0.245	0.245	
Number of baseline Gd-enhancing lesions	>=1	141	11	7.80	135	4	2.96	2.63 [0.86 ; 8.07]	2.77 [0.86 ; 8.93];	4.84 [-0.43 ; 10.11]; 0.11	0.11	0.0717
	0	131	6	4.58	136	9	6.62	0.69 [0.25 ; 1.89]	0.68 [0.23 ; 1.96];	-2.04 [-7.54 ; 3.46]; 0.598	0.598	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	10	8.55	110	7	6.36	1.34 [0.53 ; 3.4]	1.38 [0.5 ; 3.75];	2.18 [-4.63 ; 9]; 0.618	0.618	0.3995
	>=3	42	0	0.00	40	1	2.50	0.32 [0.01 ; 7.58]	0.31 [0.01 ; 7.83];	-2.5 [-9.08 ; 4.08]; 0.494	0.494	
	2	113	7	6.19	123	5	4.07	1.52 [0.5 ; 4.67]	1.56 [0.48 ; 5.06];	2.13 [-3.52 ; 7.78]; 0.558	0.558	
Received approved disease modifying MS drug prior to enrollment	No	166	9	5.42	186	5	2.69	2.02 [0.69 ; 5.9]	2.08 [0.68 ; 6.32];	2.73 [-1.42 ; 6.89]; 0.275	0.275	0.2169
	Yes	106	8	7.55	87	8	9.20	0.82 [0.32 ; 2.1]	0.81 [0.29 ; 2.24];	-1.65 [-9.53 ; 6.24]; 0.795	0.795	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	10	4.08	251	9	3.59	1.14 [0.47 ; 2.75]	1.14 [0.46 ; 2.87];	0.5 [-2.88 ; 3.88]; 0.819	0.819	0.7051
	USA and Western Europe	27	7	25.93	22	4	18.18	1.43 [0.48 ; 4.25]	1.57 [0.39 ; 6.28];	7.74 [-15.34 ; 30.83]; 0.732	0.732	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Musculoskeletal and connective tissue disorders | Arthralgia

5.1.32 Musculoskeletal and connective tissue disorders - Back pain

Tabelle 150: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	20	11.36	156	13	8.33	1.36 [0.7 ; 2.65]	1.41 [0.68 ; 2.94];	3.03 [-3.36 ; 9.42]; 0.463	0.463	0.5528
	>= 38 years	96	15	15.62	117	10	8.55	1.83 [0.86 ; 3.88]	1.98 [0.85 ; 4.64];	7.08 [-1.78 ; 15.93]; 0.135	0.135	
Disease Severity at baseline (EDSS)	<=3.5	218	32	14.68	207	17	8.21	1.79 [1.02 ; 3.12]	1.92 [1.03 ; 3.58];	6.47 [0.46 ; 12.47]; 0.048	0.048	0.1268
	>3.5	54	3	5.56	66	6	9.09	0.61 [0.16 ; 2.33]	0.59 [0.14 ; 2.47];	-3.54 [-12.78 ; 5.71]; 0.512	0.512	
Gender	Female	178	28	15.73	176	16	9.09	1.73 [0.97 ; 3.08]	1.87 [0.97 ; 3.59];	6.64 [-0.19 ; 13.47]; 0.076	0.076	0.3626
	Male	94	7	7.45	97	7	7.22	1.03 [0.38 ; 2.83]	1.03 [0.35 ; 3.07];	0.23 [-7.16 ; 7.63]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	23	16.31	135	10	7.41	2.2 [1.09 ; 4.45]	2.44 [1.11 ; 5.34];	8.9 [1.37 ; 16.44]; 0.026	0.026	0.1031
	0	131	12	9.16	136	13	9.56	0.96 [0.45 ; 2.02]	0.95 [0.42 ; 2.18];	-0.4 [-7.39 ; 6.59]; 1	1	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	11	9.40	110	10	9.09	1.03 [0.46 ; 2.34]	1.04 [0.42 ; 2.55];	0.31 [-7.23 ; 7.85]; 1	1	0.4529
	>=3	42	5	11.90	40	2	5.00	2.38 [0.49 ; 11.58]	2.57 [0.47 ; 14.07];	6.9 [-4.99 ; 18.8]; 0.433	0.433	
	2	113	19	16.81	123	11	8.94	1.88 [0.94 ; 3.78]	2.06 [0.93 ; 4.54];	7.87 [-0.67 ; 16.41]; 0.08	0.08	
Received approved disease modifying MS drug prior to enrollment	No	166	24	14.46	186	18	9.68	1.49 [0.84 ; 2.65]	1.58 [0.82 ; 3.02];	4.78 [-2.05 ; 11.61]; 0.189	0.189	0.7746
	Yes	106	11	10.38	87	5	5.75	1.81 [0.65 ; 5]	1.9 [0.63 ; 5.69];	4.63 [-2.96 ; 12.22]; 0.3	0.3	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	29	11.84	251	19	7.57	1.56 [0.9 ; 2.71]	1.64 [0.89 ; 3.01];	4.27 [-0.94 ; 9.47]; 0.129	0.129	0.7577
	USA and Western Europe	27	6	22.22	22	4	18.18	1.22 [0.39 ; 3.79]	1.29 [0.31 ; 5.28];	4.04 [-18.45 ; 26.53]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Musculoskeletal and connective tissue disorders | Back pain

5.1.33 General disorders and administration site conditions - Fatigue

Tabelle 151: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	11	6.25	156	5	3.21	1.95 [0.69 ; 5.49]	2.01 [0.68 ; 5.93];	3.04 [-1.47 ; 7.56]; 0.213	0.213	0.4068
	>= 38 years	96	5	5.21	117	6	5.13	1.02 [0.32 ; 3.23]	1.02 [0.3 ; 3.44];	0.08 [-5.9 ; 6.06]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	218	15	6.88	207	8	3.86	1.78 [0.77 ; 4.11]	1.84 [0.76 ; 4.43];	3.02 [-1.25 ; 7.28]; 0.201	0.201	0.1898
	>3.5	54	1	1.85	66	3	4.55	0.41 [0.04 ; 3.81]	0.4 [0.04 ; 3.92];	-2.69 [-8.87 ; 3.49]; 0.626	0.626	
Gender	Female	178	10	5.62	176	6	3.41	1.65 [0.61 ; 4.44]	1.69 [0.6 ; 4.74];	2.21 [-2.11 ; 6.53]; 0.444	0.444	0.7172
	Male	94	6	6.38	97	5	5.15	1.24 [0.39 ; 3.92]	1.25 [0.37 ; 4.26];	1.23 [-5.39 ; 7.85]; 0.765	0.765	
Number of baseline Gd-enhancing lesions	>=1	141	9	6.38	135	6	4.44	1.44 [0.53 ; 3.93]	1.47 [0.51 ; 4.24];	1.94 [-3.39 ; 7.26]; 0.598	0.598	0.9912
	0	131	7	5.34	136	5	3.68	1.45 [0.47 ; 4.46]	1.48 [0.46 ; 4.78];	1.67 [-3.32 ; 6.65]; 0.566	0.566	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	6	5.13	110	5	4.55	1.13 [0.35 ; 3.59]	1.14 [0.34 ; 3.83];	0.58 [-5 ; 6.16]; 1	1	0.7465
	>=3	42	3	7.14	40	1	2.50	2.86 [0.31 ; 26.34]	3 [0.3 ; 30.11];	4.64 [-4.53 ; 13.81]; 0.616	0.616	
	2	113	7	6.19	123	5	4.07	1.52 [0.5 ; 4.67]	1.56 [0.48 ; 5.06];	2.13 [-3.52 ; 7.78]; 0.558	0.558	
Received approved disease modifying MS drug prior to enrollment	No	166	10	6.02	186	7	3.76	1.6 [0.62 ; 4.11]	1.64 [0.61 ; 4.41];	2.26 [-2.28 ; 6.8]; 0.334	0.334	0.7419
	Yes	106	6	5.66	87	4	4.60	1.23 [0.36 ; 4.22]	1.24 [0.34 ; 4.56];	1.06 [-5.16 ; 7.29]; 1	1	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	11	4.49	251	4	1.59	2.82 [0.91 ; 8.73]	2.9 [0.91 ; 9.24];	2.9 [-0.12 ; 5.92]; 0.069	0.069	0.0413
	USA and Western Europe	27	5	18.52	22	7	31.82	0.58 [0.21 ; 1.58]	0.49 [0.13 ; 1.83];	-13.3 [-37.66 ; 11.06]; 0.331	0.331	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - General disorders and administration site conditions | Fatigue

5.1.34 Infections and infestations - Urinary tract infection

Tabelle 152: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	5	2.84	156	2	1.28	2.22 [0.44 ; 11.26]	2.25 [0.43 ; 11.77];	1.56 [-1.46 ; 4.58]; 0.454	0.454	0.2339
	>= 38 years	96	6	6.25	117	10	8.55	0.73 [0.28 ; 1.94]	0.71 [0.25 ; 2.04];	-2.3 [-9.3 ; 4.71]; 0.608	0.608	
Disease Severity at baseline (EDSS)	<=3.5	218	9	4.13	207	5	2.42	1.71 [0.58 ; 5.02]	1.74 [0.57 ; 5.28];	1.71 [-1.66 ; 5.08]; 0.418	0.418	0.0752
	>3.5	54	2	3.70	66	7	10.61	0.35 [0.08 ; 1.61]	0.32 [0.06 ; 1.63];	-6.9 [-15.88 ; 2.07]; 0.183	0.183	
Gender	Female	178	10	5.62	176	9	5.11	1.1 [0.46 ; 2.64]	1.1 [0.44 ; 2.79];	0.5 [-4.19 ; 5.2]; 1	1	0.3175
	Male	94	1	1.06	97	3	3.09	0.34 [0.04 ; 3.25]	0.34 [0.03 ; 3.3];	-2.03 [-6.05 ; 1.99]; 0.621	0.621	
Number of baseline Gd-enhancing lesions	>=1	141	4	2.84	135	6	4.44	0.64 [0.18 ; 2.21]	0.63 [0.17 ; 2.28];	-1.61 [-6.03 ; 2.82]; 0.534	0.534	0.4405
	0	131	7	5.34	136	6	4.41	1.21 [0.42 ; 3.51]	1.22 [0.4 ; 3.74];	0.93 [-4.24 ; 6.1]; 0.782	0.782	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	6	5.13	110	7	6.36	0.81 [0.28 ; 2.32]	0.8 [0.26 ; 2.44];	-1.24 [-7.3 ; 4.83]; 0.779	0.779	0.4713
	>=3	42	1	2.38	40	0	0.00	2.86 [0.12 ; 68.23]	2.93 [0.12 ; 73.99];	2.27 [-4.16 ; 8.7]; 0.495	0.495	
	2	113	4	3.54	123	5	4.07	0.87 [0.24 ; 3.16]	0.87 [0.23 ; 3.31];	-0.53 [-5.4 ; 4.35]; 1	1	
Received approved disease modifying MS drug prior to enrollment	No	166	8	4.82	186	8	4.30	1.12 [0.43 ; 2.92]	1.13 [0.41 ; 3.07];	0.52 [-3.85 ; 4.89]; 1	1	0.5019
	Yes	106	3	2.83	87	4	4.60	0.62 [0.14 ; 2.68]	0.6 [0.13 ; 2.78];	-1.77 [-7.18 ; 3.65]; 0.703	0.703	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	8	3.27	251	11	4.38	0.75 [0.3 ; 1.82]	0.74 [0.29 ; 1.86];	-1.12 [-4.49 ; 2.25]; 0.642	0.642	0.2956
	USA and Western Europe	27	3	11.11	22	1	4.55	2.44 [0.27 ; 21.89]	2.62 [0.25 ; 27.19];	6.57 [-8.14 ; 21.27]; 0.617	0.617	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Urinary tract infection

5.1.35 Cardiac disorders - Sinus tachycardia

Tabelle 153: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	12	6.82	156	5	3.21	2.13 [0.77 ; 5.9]	2.21 [0.76 ; 6.42];	3.61 [-1.02 ; 8.25]; 0.211	0.211	0.0179
	>= 38 years	96	8	8.33	117	0	0.00	20.68 [1.21 ; 353.78]	22.57 [1.29 ; 396.28];	8.34 [2.59 ; 14.09]; 0.001	0.001	
Disease Severity at baseline (EDSS)	<=3.5	218	16	7.34	207	4	1.93	3.8 [1.29 ; 11.17]	4.02 [1.32 ; 12.23];	5.41 [1.47 ; 9.34]; 0.01	0.01	0.8369
	>3.5	54	4	7.41	66	1	1.52	4.89 [0.56 ; 42.46]	5.2 [0.56 ; 47.98];	5.89 [-1.69 ; 13.47]; 0.173	0.173	
Gender	Female	178	13	7.30	176	2	1.14	6.43 [1.47 ; 28.07]	6.85 [1.52 ; 30.84];	6.17 [2.04 ; 10.3]; 0.006	0.006	0.3314
	Male	94	7	7.45	97	3	3.09	2.41 [0.64 ; 9.04]	2.52 [0.63 ; 10.06];	4.35 [-1.97 ; 10.68]; 0.208	0.208	
Number of baseline Gd-enhancing lesions	>=1	141	12	8.51	135	3	2.22	3.83 [1.11 ; 13.27]	4.09 [1.13 ; 14.84];	6.29 [1.05 ; 11.52]; 0.031	0.031	0.9517
	0	131	8	6.11	136	2	1.47	4.15 [0.9 ; 19.19]	4.36 [0.91 ; 20.92];	4.64 [0.06 ; 9.21]; 0.057	0.057	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	10	8.55	110	2	1.82	4.7 [1.05 ; 20.98]	5.05 [1.08 ; 23.58];	6.73 [1.08 ; 12.38]; 0.035	0.035	0.8542
	>=3	42	5	11.90	40	1	2.50	4.76 [0.58 ; 39]	5.27 [0.59 ; 47.26];	9.4 [-1.52 ; 20.33]; 0.202	0.202	
	2	113	5	4.42	123	2	1.63	2.72 [0.54 ; 13.75]	2.8 [0.53 ; 14.73];	2.8 [-1.6 ; 7.2]; 0.264	0.264	
Received approved disease modifying MS drug prior to enrollment	No	166	11	6.63	186	3	1.61	4.11 [1.17 ; 14.47]	4.33 [1.19 ; 15.8];	5.01 [0.82 ; 9.21]; 0.026	0.026	0.9282
	Yes	106	9	8.49	87	2	2.30	3.69 [0.82 ; 16.65]	3.94 [0.83 ; 18.76];	6.19 [0.02 ; 12.36]; 0.115	0.115	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	19	7.76	251	5	1.99	3.89 [1.48 ; 10.26]	4.14 [1.52 ; 11.26];	5.76 [1.99 ; 9.53]; 0.003	0.003	0.547
	USA and Western Europe	27	1	3.70	22	0	0.00	2.46 [0.11 ; 57.66]	2.55 [0.1 ; 65.66];	3.18 [-7.07 ; 13.43]; 0.497	0.497	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Cardiac disorders | Sinus tachycardia

5.1.36 Infections and infestations - Oral herpes

Tabelle 154: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	7	3.98	156	14	8.97	0.44 [0.18 ; 1.07]	0.42 [0.17 ; 1.07];	-5 [-10.33 ; 0.34]; 0.072	0.072	0.0061
	>= 38 years	96	7	7.29	117	2	1.71	4.27 [0.91 ; 20.06]	4.52 [0.92 ; 22.3];	5.58 [-0.12 ; 11.29]; 0.082	0.082	
Disease Severity at baseline (EDSS)	<=3.5	218	13	5.96	207	11	5.31	1.12 [0.51 ; 2.45]	1.13 [0.49 ; 2.58];	0.65 [-3.73 ; 5.03]; 0.835	0.835	0.1371
	>3.5	54	1	1.85	66	5	7.58	0.24 [0.03 ; 2.03]	0.23 [0.03 ; 2.03];	-5.72 [-13.05 ; 1.6]; 0.221	0.221	
Gender	Female	178	13	7.30	176	13	7.39	0.99 [0.47 ; 2.07]	0.99 [0.44 ; 2.2];	-0.08 [-5.52 ; 5.35]; 1	1	0.3564
	Male	94	1	1.06	97	3	3.09	0.34 [0.04 ; 3.25]	0.34 [0.03 ; 3.3];	-2.03 [-6.05 ; 1.99]; 0.621	0.621	
Number of baseline Gd-enhancing lesions	>=1	141	10	7.09	135	9	6.67	1.06 [0.45 ; 2.54]	1.07 [0.42 ; 2.72];	0.43 [-5.55 ; 6.4]; 1	1	0.4396
	0	131	4	3.05	136	7	5.15	0.59 [0.18 ; 1.98]	0.58 [0.17 ; 2.03];	-2.09 [-6.83 ; 2.65]; 0.541	0.541	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	7	5.98	110	8	7.27	0.82 [0.31 ; 2.19]	0.81 [0.28 ; 2.32];	-1.29 [-7.77 ; 5.19]; 0.792	0.792	0.1984
	>=3	42	2	4.76	40	0	0.00	4.77 [0.24 ; 96.34]	5 [0.23 ; 107.43];	4.59 [-3.16 ; 12.35]; 0.494	0.494	
	2	113	5	4.42	123	8	6.50	0.68 [0.23 ; 2.02]	0.67 [0.21 ; 2.1];	-2.08 [-7.86 ; 3.7]; 0.575	0.575	
Received approved disease modifying MS drug prior to enrollment	No	166	11	6.63	186	12	6.45	1.03 [0.47 ; 2.27]	1.03 [0.44 ; 2.4];	0.17 [-5 ; 5.35]; 1	1	0.548
	Yes	106	3	2.83	87	4	4.60	0.62 [0.14 ; 2.68]	0.6 [0.13 ; 2.78];	-1.77 [-7.18 ; 3.65]; 0.703	0.703	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	12	4.90	251	16	6.37	0.77 [0.37 ; 1.59]	0.76 [0.35 ; 1.63];	-1.48 [-5.53 ; 2.58]; 0.561	0.561	0.092
	USA and Western Europe	27	2	7.41	22	0	0.00	4.11 [0.21 ; 81.33]	4.41 [0.2 ; 96.84];	6.75 [-5.37 ; 18.88]; 0.497	0.497	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Oral herpes

5.1.37 Respiratory, thoracic and mediastinal disorders - Oropharyngeal pain

Tabelle 155: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	12	6.82	156	7	4.49	1.52 [0.61 ; 3.76]	1.56 [0.6 ; 4.06];	2.33 [-2.61 ; 7.27]; 0.479	0.479	0.3347
	>= 38 years	96	6	6.25	117	2	1.71	3.66 [0.76 ; 17.7]	3.83 [0.76 ; 19.45];	4.54 [-0.84 ; 9.92]; 0.144	0.144	
Disease Severity at baseline (EDSS)	<=3.5	218	15	6.88	207	6	2.90	2.37 [0.94 ; 6]	2.48 [0.94 ; 6.51];	3.98 [-0.08 ; 8.05]; 0.073	0.073	0.475
	>3.5	54	3	5.56	66	3	4.55	1.22 [0.26 ; 5.81]	1.24 [0.24 ; 6.38];	1.01 [-6.9 ; 8.92]; 1	1	
Gender	Female	178	15	8.43	176	7	3.98	2.12 [0.89 ; 5.07]	2.22 [0.88 ; 5.59];	4.45 [-0.55 ; 9.45]; 0.122	0.122	0.7379
	Male	94	3	3.19	97	2	2.06	1.55 [0.26 ; 9.06]	1.57 [0.26 ; 9.59];	1.13 [-3.41 ; 5.67]; 0.679	0.679	
Number of baseline Gd-enhancing lesions	>=1	141	11	7.80	135	3	2.22	3.51 [1 ; 12.31]	3.72 [1.02 ; 13.65];	5.58 [0.5 ; 10.66]; 0.052	0.052	0.1928
	0	131	7	5.34	136	6	4.41	1.21 [0.42 ; 3.51]	1.22 [0.4 ; 3.74];	0.93 [-4.24 ; 6.1]; 0.782	0.782	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	10	8.55	110	3	2.73	3.13 [0.89 ; 11.09]	3.33 [0.89 ; 12.45];	5.82 [-0.09 ; 11.73]; 0.085	0.085	0.0956
	>=3	42	3	7.14	40	0	0.00	6.67 [0.36 ; 125.26]	7.18 [0.36 ; 143.5];	6.92 [-1.92 ; 15.76]; 0.118	0.118	
	2	113	5	4.42	123	6	4.88	0.91 [0.28 ; 2.89]	0.9 [0.27 ; 3.04];	-0.45 [-5.83 ; 4.92]; 1	1	
Received approved disease modifying MS drug prior to enrollment	No	166	10	6.02	186	6	3.23	1.87 [0.69 ; 5.03]	1.92 [0.68 ; 5.41];	2.8 [-1.62 ; 7.22]; 0.305	0.305	0.8423
	Yes	106	8	7.55	87	3	3.45	2.19 [0.6 ; 8]	2.29 [0.59 ; 8.89];	4.1 [-2.22 ; 10.42]; 0.351	0.351	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	14	5.71	251	8	3.19	1.79 [0.77 ; 4.2]	1.84 [0.76 ; 4.47];	2.53 [-1.1 ; 6.16]; 0.195	0.195	0.5663
	USA and Western Europe	27	4	14.81	22	1	4.55	3.26 [0.39 ; 27.09]	3.65 [0.38 ; 35.34];	10.27 [-5.71 ; 26.25]; 0.362	0.362	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Respiratory, thoracic and mediastinal disorders | Oropharyngeal pain

5.1.38 Psychiatric disorders - Anxiety

Tabelle 156: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	14	7.95	156	8	5.13	1.55 [0.67 ; 3.6]	1.6 [0.65 ; 3.92];	2.83 [-2.46 ; 8.11]; 0.379	0.379	0.3106
	>= 38 years	96	2	2.08	117	4	3.42	0.61 [0.11 ; 3.26]	0.6 [0.11 ; 3.35];	-1.34 [-5.69 ; 3.02]; 0.692	0.692	
Disease Severity at baseline (EDSS)	<=3.5	218	15	6.88	207	8	3.86	1.78 [0.77 ; 4.11]	1.84 [0.76 ; 4.43];	3.02 [-1.25 ; 7.28]; 0.201	0.201	0.0959
	>3.5	54	1	1.85	66	4	6.06	0.31 [0.04 ; 2.65]	0.29 [0.03 ; 2.7];	-4.21 [-11 ; 2.58]; 0.377	0.377	
Gender	Female	178	12	6.74	176	10	5.68	1.19 [0.53 ; 2.68]	1.2 [0.5 ; 2.85];	1.06 [-3.97 ; 6.09]; 0.826	0.826	0.5596
	Male	94	4	4.26	97	2	2.06	2.06 [0.39 ; 11]	2.11 [0.38 ; 11.81];	2.19 [-2.77 ; 7.16]; 0.44	0.44	
Number of baseline Gd-enhancing lesions	>=1	141	12	8.51	135	7	5.19	1.64 [0.67 ; 4.04]	1.7 [0.65 ; 4.46];	3.33 [-2.61 ; 9.26]; 0.344	0.344	0.3871
	0	131	4	3.05	136	5	3.68	0.83 [0.23 ; 3.03]	0.83 [0.22 ; 3.14];	-0.62 [-4.95 ; 3.7]; 1	1	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	10	8.55	110	5	4.55	1.88 [0.66 ; 5.33]	1.96 [0.65 ; 5.94];	4 [-2.39 ; 10.39]; 0.289	0.289	0.4738
	>=3	42	3	7.14	40	2	5.00	1.43 [0.25 ; 8.11]	1.46 [0.23 ; 9.24];	2.14 [-8.17 ; 12.45]; 1	1	
	2	113	3	2.65	123	5	4.07	0.65 [0.16 ; 2.67]	0.64 [0.15 ; 2.76];	-1.41 [-5.99 ; 3.17]; 0.724	0.724	
Received approved disease modifying MS drug prior to enrollment	No	166	9	5.42	186	7	3.76	1.44 [0.55 ; 3.78]	1.47 [0.53 ; 4.03];	1.66 [-2.74 ; 6.06]; 0.61	0.61	0.7683
	Yes	106	7	6.60	87	5	5.75	1.15 [0.38 ; 3.49]	1.16 [0.35 ; 3.79];	0.86 [-5.95 ; 7.66]; 1	1	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	14	5.71	251	11	4.38	1.3 [0.6 ; 2.82]	1.32 [0.59 ; 2.97];	1.33 [-2.52 ; 5.19]; 0.543	0.543	0.8555
	USA and Western Europe	27	2	7.41	22	1	4.55	1.63 [0.16 ; 16.81]	1.68 [0.14 ; 19.85];	2.86 [-10.3 ; 16.03]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Psychiatric disorders | Anxiety

5.1.39 Vascular disorders - Hypertension

Tabelle 157: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	6	3.41	156	5	3.21	1.06 [0.33 ; 3.42]	1.07 [0.32 ; 3.56];	0.2 [-3.65 ; 4.05]; 1	1	0.3321
	>= 38 years	96	4	4.17	117	10	8.55	0.49 [0.16 ; 1.51]	0.47 [0.14 ; 1.53];	-4.38 [-10.83 ; 2.07]; 0.269	0.269	
Disease Severity at baseline (EDSS)	<=3.5	218	9	4.13	207	12	5.80	0.71 [0.31 ; 1.65]	0.7 [0.29 ; 1.7];	-1.67 [-5.8 ; 2.47]; 0.505	0.505	0.6401
	>3.5	54	1	1.85	66	3	4.55	0.41 [0.04 ; 3.81]	0.4 [0.04 ; 3.92];	-2.69 [-8.87 ; 3.49]; 0.626	0.626	
Gender	Female	178	7	3.93	176	9	5.11	0.77 [0.29 ; 2.02]	0.76 [0.28 ; 2.09];	-1.18 [-5.51 ; 3.15]; 0.619	0.619	0.6351
	Male	94	3	3.19	97	6	6.19	0.52 [0.13 ; 2]	0.5 [0.12 ; 2.06];	-2.99 [-8.96 ; 2.97]; 0.498	0.498	
Number of baseline Gd-enhancing lesions	>=1	141	4	2.84	135	6	4.44	0.64 [0.18 ; 2.21]	0.63 [0.17 ; 2.28];	-1.61 [-6.03 ; 2.82]; 0.534	0.534	0.9288
	0	131	6	4.58	136	9	6.62	0.69 [0.25 ; 1.89]	0.68 [0.23 ; 1.96];	-2.04 [-7.54 ; 3.46]; 0.598	0.598	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	5	4.27	110	6	5.45	0.78 [0.25 ; 2.49]	0.77 [0.23 ; 2.61];	-1.18 [-6.79 ; 4.43]; 0.763	0.763	0.9227
	>=3	42	2	4.76	40	3	7.50	0.63 [0.11 ; 3.6]	0.62 [0.1 ; 3.9];	-2.74 [-13.14 ; 7.66]; 0.672	0.672	
	2	113	3	2.65	123	6	4.88	0.54 [0.14 ; 2.13]	0.53 [0.13 ; 2.18];	-2.22 [-7.05 ; 2.6]; 0.503	0.503	
Received approved disease modifying MS drug prior to enrollment	No	166	3	1.81	186	9	4.84	0.37 [0.1 ; 1.36]	0.36 [0.1 ; 1.36];	-3.03 [-6.72 ; 0.66]; 0.147	0.147	0.2638
	Yes	106	7	6.60	87	6	6.90	0.96 [0.33 ; 2.74]	0.95 [0.31 ; 2.95];	-0.29 [-7.41 ; 6.83]; 1	1	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	10	4.08	251	13	5.18	0.79 [0.35 ; 1.76]	0.78 [0.34 ; 1.81];	-1.1 [-4.79 ; 2.6]; 0.671	0.671	0.1054
	USA and Western Europe	27	0	0.00	22	2	9.09	0.16 [0.01 ; 3.25]	0.15 [0.01 ; 3.28];	-9.08 [-22.72 ; 4.55]; 0.189	0.189	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Vascular disorders | Hypertension

5.1.40 Gastrointestinal disorders - Constipation

Tabelle 158: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	10	5.68	156	9	5.77	0.98 [0.41 ; 2.36]	0.98 [0.39 ; 2.49];	-0.09 [-5.1 ; 4.92]; 1	1	0.913
	>= 38 years	96	6	6.25	117	8	6.84	0.91 [0.33 ; 2.54]	0.91 [0.3 ; 2.71];	-0.59 [-7.25 ; 6.07]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	218	15	6.88	207	13	6.28	1.1 [0.53 ; 2.25]	1.1 [0.51 ; 2.38];	0.6 [-4.11 ; 5.31]; 0.847	0.847	0.2295
	>3.5	54	1	1.85	66	4	6.06	0.31 [0.04 ; 2.65]	0.29 [0.03 ; 2.7];	-4.21 [-11 ; 2.58]; 0.377	0.377	
Gender	Female	178	10	5.62	176	10	5.68	0.99 [0.42 ; 2.32]	0.99 [0.4 ; 2.44];	-0.06 [-4.87 ; 4.75]; 1	1	0.871
	Male	94	6	6.38	97	7	7.22	0.88 [0.31 ; 2.53]	0.88 [0.28 ; 2.71];	-0.83 [-7.97 ; 6.3]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	10	7.09	135	9	6.67	1.06 [0.45 ; 2.54]	1.07 [0.42 ; 2.72];	0.43 [-5.55 ; 6.4]; 1	1	0.6505
	0	131	6	4.58	136	8	5.88	0.78 [0.28 ; 2.18]	0.77 [0.26 ; 2.28];	-1.3 [-6.64 ; 4.03]; 0.785	0.785	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	6	5.13	110	6	5.45	0.94 [0.31 ; 2.83]	0.94 [0.29 ; 3];	-0.33 [-6.16 ; 5.5]; 1	1	0.8037
	>=3	42	1	2.38	40	2	5.00	0.48 [0.04 ; 5.05]	0.46 [0.04 ; 5.32];	-2.62 [-10.8 ; 5.56]; 0.611	0.611	
	2	113	9	7.96	123	9	7.32	1.09 [0.45 ; 2.65]	1.1 [0.42 ; 2.87];	0.65 [-6.14 ; 7.44]; 1	1	
Received approved disease modifying MS drug prior to enrollment	No	166	10	6.02	186	11	5.91	1.02 [0.44 ; 2.34]	1.02 [0.42 ; 2.47];	0.11 [-4.85 ; 5.07]; 1	1	0.7581
	Yes	106	6	5.66	87	6	6.90	0.82 [0.27 ; 2.45]	0.81 [0.25 ; 2.61];	-1.24 [-8.14 ; 5.67]; 0.771	0.771	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	13	5.31	251	16	6.37	0.83 [0.41 ; 1.69]	0.82 [0.39 ; 1.75];	-1.07 [-5.19 ; 3.06]; 0.703	0.703	0.3279
	USA and Western Europe	27	3	11.11	22	1	4.55	2.44 [0.27 ; 21.89]	2.62 [0.25 ; 27.19];	6.57 [-8.14 ; 21.27]; 0.617	0.617	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Gastrointestinal disorders | Constipation

5.1.41 Gastrointestinal disorders - Toothache

Tabelle 159: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	14	7.95	156	9	5.77	1.38 [0.61 ; 3.1]	1.41 [0.59 ; 3.36];	2.19 [-3.23 ; 7.6]; 0.519	0.519	0.1529
	>= 38 years	96	2	2.08	117	6	5.13	0.41 [0.08 ; 1.97]	0.39 [0.08 ; 2];	-3.04 [-7.96 ; 1.87]; 0.299	0.299	
Disease Severity at baseline (EDSS)	<=3.5	218	15	6.88	207	14	6.76	1.02 [0.5 ; 2.06]	1.02 [0.48 ; 2.17];	0.12 [-4.68 ; 4.91]; 1	1	0.9001
	>3.5	54	1	1.85	66	1	1.52	1.22 [0.08 ; 19.09]	1.23 [0.07 ; 20.08];	0.34 [-4.31 ; 4.99]; 1	1	
Gender	Female	178	9	5.06	176	13	7.39	0.68 [0.3 ; 1.56]	0.67 [0.28 ; 1.6];	-2.33 [-7.36 ; 2.7]; 0.388	0.388	0.0444
	Male	94	7	7.45	97	2	2.06	3.61 [0.77 ; 16.94]	3.82 [0.77 ; 18.89];	5.38 [-0.63 ; 11.4]; 0.097	0.097	
Number of baseline Gd-enhancing lesions	>=1	141	7	4.96	135	8	5.93	0.84 [0.31 ; 2.25]	0.83 [0.29 ; 2.35];	-0.96 [-6.32 ; 4.4]; 0.795	0.795	0.5053
	0	131	9	6.87	136	7	5.15	1.33 [0.51 ; 3.48]	1.36 [0.49 ; 3.76];	1.72 [-3.98 ; 7.43]; 0.613	0.613	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	6	5.13	110	8	7.27	0.71 [0.25 ; 1.97]	0.69 [0.23 ; 2.05];	-2.14 [-8.43 ; 4.14]; 0.587	0.587	0.1023
	>=3	42	3	7.14	40	0	0.00	6.67 [0.36 ; 125.26]	7.18 [0.36 ; 143.5];	6.92 [-1.92 ; 15.76]; 0.118	0.118	
	2	113	7	6.19	123	7	5.69	1.09 [0.39 ; 3.01]	1.09 [0.37 ; 3.22];	0.5 [-5.54 ; 6.55]; 1	1	
Received approved disease modifying MS drug prior to enrollment	No	166	11	6.63	186	12	6.45	1.03 [0.47 ; 2.27]	1.03 [0.44 ; 2.4];	0.17 [-5 ; 5.35]; 1	1	0.7279
	Yes	106	5	4.72	87	3	3.45	1.37 [0.34 ; 5.56]	1.39 [0.32 ; 5.97];	1.27 [-4.3 ; 6.84]; 0.732	0.732	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	14	5.71	251	14	5.58	1.02 [0.5 ; 2.1]	1.03 [0.48 ; 2.2];	0.14 [-3.93 ; 4.2]; 1	1	0.7036
	USA and Western Europe	27	2	7.41	22	1	4.55	1.63 [0.16 ; 16.81]	1.68 [0.14 ; 19.85];	2.86 [-10.3 ; 16.03]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Gastrointestinal disorders | Toothache

5.1.42 Injury, poisoning and procedural complications - Infusion related reaction

Tabelle 160: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	15	8.52	156	1	0.64	13.3 [1.78 ; 99.5]	14.44 [1.88 ; 110.64];	7.88 [3.57 ; 12.19]; 0.001	0.001	0.4978
	>= 38 years	96	4	4.17	117	1	0.85	4.87 [0.55 ; 42.89]	5.04 [0.55 ; 45.9];	3.31 [-1.02 ; 7.64]; 0.177	0.177	
Disease Severity at baseline (EDSS)	<=3.5	218	17	7.80	207	1	0.48	16.14 [2.17 ; 120.21]	17.42 [2.3 ; 132.15];	7.32 [3.63 ; 11]; 0	0	0.2416
	>3.5	54	2	3.70	66	1	1.52	2.44 [0.23 ; 26.24]	2.5 [0.22 ; 28.34];	2.19 [-3.65 ; 8.02]; 0.588	0.588	
Gender	Female	178	15	8.43	176	2	1.14	7.42 [1.72 ; 31.95]	8.01 [1.8 ; 35.55];	7.29 [2.92 ; 11.66]; 0.002	0.002	0.3439
	Male	94	4	4.26	97	0	0.00	9.28 [0.51 ; 170.1]	9.7 [0.51 ; 182.63];	4.23 [-0.27 ; 8.73]; 0.056	0.056	
Number of baseline Gd-enhancing lesions	>=1	141	10	7.09	135	1	0.74	9.57 [1.24 ; 73.78]	10.23 [1.29 ; 81.04];	6.35 [1.87 ; 10.83]; 0.01	0.01	0.9857
	0	131	9	6.87	136	1	0.74	9.34 [1.2 ; 72.73]	9.96 [1.24 ; 79.75];	6.13 [1.57 ; 10.7]; 0.009	0.009	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	12	10.26	110	1	0.91	11.28 [1.49 ; 85.33]	12.46 [1.59 ; 97.5];	9.35 [3.57 ; 15.12]; 0.003	0.003	0.8423
	>=3	42	1	2.38	40	0	0.00	2.86 [0.12 ; 68.23]	2.93 [0.12 ; 73.99];	2.27 [-4.16 ; 8.7]; 0.495	0.495	
	2	113	6	5.31	123	1	0.81	6.53 [0.8 ; 53.42]	6.84 [0.81 ; 57.73];	4.5 [0.07 ; 8.93]; 0.057	0.057	
Received approved disease modifying MS drug prior to enrollment	No	166	12	7.23	186	1	0.54	13.45 [1.77 ; 102.3]	14.42 [1.85 ; 112.11];	6.69 [2.61 ; 10.77]; 0.001	0.001	0.5698
	Yes	106	7	6.60	87	1	1.15	5.75 [0.72 ; 45.81]	6.08 [0.73 ; 50.41];	5.45 [0.22 ; 10.69]; 0.075	0.075	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	17	6.94	251	2	0.80	8.71 [2.03 ; 37.29]	9.28 [2.12 ; 40.62];	6.14 [2.78 ; 9.51]; 0	0	0.5574
	USA and Western Europe	27	2	7.41	22	0	0.00	4.11 [0.21 ; 81.33]	4.41 [0.2 ; 96.84];	6.75 [-5.37 ; 18.88]; 0.497	0.497	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Injury, poisoning and procedural complications | Infusion related reaction

5.1.43 Skin and subcutaneous tissue disorders - Rash

Tabelle 161: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	1	0.57	156	7	4.49	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>= 38 years	96	2	2.08	117	3	2.56	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	218	3	1.38	207	7	3.38	0.41 [0.11 ; 1.55]	0.4 [0.1 ; 1.56];	-2.01 [-4.91 ; 0.9]; 0.211	0.211	0.2177
	>3.5	54	0	0.00	66	3	4.55	0.17 [0.01 ; 3.3]	0.17 [0.01 ; 3.29];	-4.31 [-10.2 ; 1.57]; 0.129	0.129	
Gender	Female	178	3	1.69	176	6	3.41	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	Male	94	0	0.00	97	4	4.12	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of baseline Gd-enhancing lesions	>=1	141	2	1.42	135	3	2.22	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	131	1	0.76	136	7	5.15	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	2	1.71	110	3	2.73	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	0	0.00	40	1	2.50	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	1	0.88	123	6	4.88	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	0	0.00	186	5	2.69	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	Yes	106	3	2.83	87	5	5.75	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	1	0.41	251	7	2.79	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	USA and Western Europe	27	2	7.41	22	3	13.64	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Skin and subcutaneous tissue disorders | Rash

5.1.44 Gastrointestinal disorders - Vomiting

Tabelle 162: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	5	2.84	156	8	5.13	0.55 [0.19 ; 1.66]	0.54 [0.17 ; 1.69];	-2.29 [-6.53 ; 1.96]; 0.397	0.397	0.1083
	>= 38 years	96	0	0.00	117	4	3.42	0.14 [0.01 ; 2.48]	0.13 [0.01 ; 2.46];	-3.3 [-7.04 ; 0.44]; 0.129	0.129	
Disease Severity at baseline (EDSS)	<=3.5	218	5	2.29	207	10	4.83	0.47 [0.17 ; 1.37]	0.46 [0.16 ; 1.38];	-2.54 [-6.07 ; 1]; 0.193	0.193	0.2692
	>3.5	54	0	0.00	66	2	3.03	0.24 [0.01 ; 4.97]	0.24 [0.01 ; 5.04];	-2.82 [-8.01 ; 2.36]; 0.501	0.501	
Gender	Female	178	5	2.81	176	9	5.11	0.55 [0.19 ; 1.61]	0.54 [0.18 ; 1.63];	-2.3 [-6.36 ; 1.76]; 0.29	0.29	0.1326
	Male	94	0	0.00	97	3	3.09	0.15 [0.01 ; 2.81]	0.14 [0.01 ; 2.8];	-3.05 [-7 ; 0.91]; 0.121	0.121	
Number of baseline Gd-enhancing lesions	>=1	141	4	2.84	135	7	5.19	0.55 [0.16 ; 1.83]	0.53 [0.15 ; 1.87];	-2.35 [-6.99 ; 2.29]; 0.369	0.369	0.4223
	0	131	1	0.76	136	5	3.68	0.21 [0.02 ; 1.75]	0.2 [0.02 ; 1.75];	-2.91 [-6.41 ; 0.58]; 0.214	0.214	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	2	1.71	110	5	4.55	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	1	2.38	40	2	5.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	2	1.77	123	5	4.07	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	5	3.01	186	8	4.30	0.7 [0.23 ; 2.1]	0.69 [0.22 ; 2.16];	-1.29 [-5.2 ; 2.62]; 0.582	0.582	0.0429
	Yes	106	0	0.00	87	4	4.60	0.09 [0 ; 1.67]	0.09 [0 ; 1.64];	-4.65 [-9.43 ; 0.13]; 0.041	0.041	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	4	1.63	251	8	3.19	0.51 [0.16 ; 1.68]	0.5 [0.15 ; 1.7];	-1.55 [-4.25 ; 1.14]; 0.382	0.382	0.3953
	USA and Western Europe	27	1	3.70	22	4	18.18	0.2 [0.02 ; 1.69]	0.17 [0.02 ; 1.68];	-14.48 [-32.1 ; 3.14]; 0.16	0.16	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Gastrointestinal disorders | Vomiting

5.1.45 General disorders and administration site conditions - Chills

Tabelle 163: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	19	10.80	156	0	0.00	34.59 [2.11 ; 568.24]	38.75 [2.32 ; 647.43];	10.7 [6 ; 15.39]; 0	0	0.0105
	>= 38 years	96	6	6.25	117	3	2.56	2.44 [0.63 ; 9.49]	2.53 [0.62 ; 10.41];	3.69 [-1.94 ; 9.31]; 0.305	0.305	
Disease Severity at baseline (EDSS)	<=3.5	218	23	10.55	207	1	0.48	21.84 [2.98 ; 160.26]	24.3 [3.25 ; 181.64];	10.07 [5.88 ; 14.25]; 0	0	0.0313
	>3.5	54	2	3.70	66	2	3.03	1.22 [0.18 ; 8.39]	1.23 [0.17 ; 9.04];	0.67 [-5.84 ; 7.19]; 1	1	
Gender	Female	178	11	6.18	176	3	1.70	3.63 [1.03 ; 12.77]	3.8 [1.04 ; 13.86];	4.48 [0.45 ; 8.5]; 0.053	0.053	0.0265
	Male	94	14	14.89	97	0	0.00	29.92 [1.81 ; 494.44]	35.12 [2.06 ; 597.94];	14.75 [7.38 ; 22.12]; 0	0	
Number of baseline Gd-enhancing lesions	>=1	141	17	12.06	135	3	2.22	5.43 [1.63 ; 18.09]	6.03 [1.73 ; 21.09];	9.83 [3.91 ; 15.76]; 0.002	0.002	0.1378
	0	131	8	6.11	136	0	0.00	17.64 [1.03 ; 302.63]	18.79 [1.07 ; 328.93];	6.07 [1.77 ; 10.38]; 0.003	0.003	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	7	5.98	110	2	1.82	3.29 [0.7 ; 15.5]	3.44 [0.7 ; 16.91];	4.16 [-0.81 ; 9.13]; 0.173	0.173	0.311
	>=3	42	2	4.76	40	0	0.00	4.77 [0.24 ; 96.34]	5 [0.23 ; 107.43];	4.59 [-3.16 ; 12.35]; 0.494	0.494	
	2	113	16	14.16	123	1	0.81	17.42 [2.35 ; 129.21]	20.12 [2.62 ; 154.42];	13.35 [6.73 ; 19.97]; 0	0	
Received approved disease modifying MS drug prior to enrollment	No	166	13	7.83	186	1	0.54	14.57 [1.93 ; 110.15]	15.72 [2.03 ; 121.52];	7.29 [3.07 ; 11.51]; 0	0	0.3992
	Yes	106	12	11.32	87	2	2.30	4.92 [1.13 ; 21.41]	5.43 [1.18 ; 24.94];	9.02 [2.22 ; 15.83]; 0.023	0.023	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	21	8.57	251	2	0.80	10.76 [2.55 ; 45.39]	11.67 [2.71 ; 50.34];	7.77 [4.1 ; 11.45]; 0	0	0.4225
	USA and Western Europe	27	4	14.81	22	1	4.55	3.26 [0.39 ; 27.09]	3.65 [0.38 ; 35.34];	10.27 [-5.71 ; 26.25]; 0.362	0.362	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - General disorders and administration site conditions | Chills

5.1.46 Cardiac disorders - Tachycardia

Tabelle 164: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	8	4.55	156	7	4.49	1.01 [0.38 ; 2.73]	1.01 [0.36 ; 2.86];	0.06 [-4.42 ; 4.53]; 1	1	0.8312
	>= 38 years	96	2	2.08	117	3	2.56	0.81 [0.14 ; 4.76]	0.81 [0.13 ; 4.94];	-0.48 [-4.53 ; 3.56]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	218	9	4.13	207	7	3.38	1.22 [0.46 ; 3.22]	1.23 [0.45 ; 3.37];	0.75 [-2.86 ; 4.36]; 0.801	0.801	0.3505
	>3.5	54	1	1.85	66	3	4.55	0.41 [0.04 ; 3.81]	0.4 [0.04 ; 3.92];	-2.69 [-8.87 ; 3.49]; 0.626	0.626	
Gender	Female	178	7	3.93	176	7	3.98	0.99 [0.35 ; 2.76]	0.99 [0.34 ; 2.88];	-0.04 [-4.11 ; 4.02]; 1	1	0.9645
	Male	94	3	3.19	97	3	3.09	1.03 [0.21 ; 4.98]	1.03 [0.2 ; 5.25];	0.1 [-4.85 ; 5.05]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	10	7.09	135	4	2.96	2.39 [0.77 ; 7.45]	2.5 [0.76 ; 8.17];	4.13 [-0.98 ; 9.24]; 0.17	0.17	0.001
	0	131	0	0.00	136	6	4.41	0.08 [0 ; 1.4]	0.08 [0 ; 1.37];	-4.37 [-8.08 ; -0.65]; 0.03	0.03	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	6	5.13	110	3	2.73	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	1	2.38	40	2	5.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	3	2.65	123	5	4.07	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	3	1.81	186	9	4.84	0.37 [0.1 ; 1.36]	0.36 [0.1 ; 1.36];	-3.03 [-6.72 ; 0.66]; 0.147	0.147	0.0097
	Yes	106	7	6.60	87	1	1.15	5.75 [0.72 ; 45.81]	6.08 [0.73 ; 50.41];	5.45 [0.22 ; 10.69]; 0.075	0.075	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	9	3.67	251	9	3.59	1.02 [0.41 ; 2.54]	1.03 [0.4 ; 2.63];	0.09 [-3.2 ; 3.38]; 1	1	0.8755
	USA and Western Europe	27	1	3.70	22	1	4.55	0.81 [0.05 ; 12.3]	0.81 [0.05 ; 13.7];	-0.84 [-12.09 ; 10.41]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Cardiac disorders | Tachycardia

5.1.47 Respiratory, thoracic and mediastinal disorders - Throat irritation

Tabelle 165: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	10	5.68	156	0	0.00	18.63 [1.1 ; 315.29]	19.74 [1.15 ; 339.68];	5.61 [2.02 ; 9.2]; 0.002	0.002	0.1616
	>= 38 years	96	4	4.17	117	1	0.85	4.87 [0.55 ; 42.89]	5.04 [0.55 ; 45.9];	3.31 [-1.02 ; 7.64]; 0.177	0.177	
Disease Severity at baseline (EDSS)	<=3.5	218	13	5.96	207	0	0.00	25.64 [1.53 ; 428.63]	27.26 [1.61 ; 461.64];	5.92 [2.67 ; 9.18]; 0	0	0.0402
	>3.5	54	1	1.85	66	1	1.52	1.22 [0.08 ; 19.09]	1.23 [0.07 ; 20.08];	0.34 [-4.31 ; 4.99]; 1	1	
Gender	Female	178	10	5.62	176	1	0.57	9.89 [1.28 ; 76.43]	10.42 [1.32 ; 82.26];	5.05 [1.49 ; 8.61]; 0.011	0.011	0.4159
	Male	94	4	4.26	97	0	0.00	9.28 [0.51 ; 170.1]	9.7 [0.51 ; 182.63];	4.23 [-0.27 ; 8.73]; 0.056	0.056	
Number of baseline Gd-enhancing lesions	>=1	141	9	6.38	135	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	131	5	3.82	136	1	0.74	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	7	5.98	110	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	5	11.90	40	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	2	1.77	123	1	0.81	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	7	4.22	186	1	0.54	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	Yes	106	7	6.60	87	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	11	4.49	251	1	0.40	11.27 [1.47 ; 86.63]	11.75 [1.51 ; 91.73];	4.09 [1.38 ; 6.8]; 0.003	0.003	0.5255
	USA and Western Europe	27	3	11.11	22	0	0.00	5.75 [0.31 ; 105.7]	6.43 [0.31 ; 131.46];	10.33 [-3.3 ; 23.95]; 0.121	0.121	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Respiratory, thoracic and mediastinal disorders | Throat irritation

5.1.48 Investigations - Body temperature increased

Tabelle 166: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	8	4.55	156	2	1.28	3.55 [0.76 ; 16.45]	3.67 [0.77 ; 17.53];	3.26 [-0.28 ; 6.81]; 0.11	0.11	0.8158
	>= 38 years	96	4	4.17	117	1	0.85	4.87 [0.55 ; 42.89]	5.04 [0.55 ; 45.9];	3.31 [-1.02 ; 7.64]; 0.177	0.177	
Disease Severity at baseline (EDSS)	<=3.5	218	8	3.67	207	1	0.48	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>3.5	54	4	7.41	66	2	3.03	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Gender	Female	178	9	5.06	176	1	0.57	8.9 [1.14 ; 69.5]	9.32 [1.17 ; 74.36];	4.49 [1.08 ; 7.89]; 0.02	0.02	0.1882
	Male	94	3	3.19	97	2	2.06	1.55 [0.26 ; 9.06]	1.57 [0.26 ; 9.59];	1.13 [-3.41 ; 5.67]; 0.679	0.679	
Number of baseline Gd-enhancing lesions	>=1	141	4	2.84	135	1	0.74	3.83 [0.43 ; 33.83]	3.91 [0.43 ; 35.46];	2.1 [-1 ; 5.19]; 0.371	0.371	0.938
	0	131	8	6.11	136	2	1.47	4.15 [0.9 ; 19.19]	4.36 [0.91 ; 20.92];	4.64 [0.06 ; 9.21]; 0.057	0.057	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	2	1.71	110	1	0.91	1.88 [0.17 ; 20.45]	1.9 [0.17 ; 21.21];	0.8 [-2.14 ; 3.74]; 1	1	0.5397
	>=3	42	2	4.76	40	0	0.00	4.77 [0.24 ; 96.34]	5 [0.23 ; 107.43];	4.59 [-3.16 ; 12.35]; 0.494	0.494	
	2	113	8	7.08	123	2	1.63	4.35 [0.94 ; 20.07]	4.61 [0.96 ; 22.19];	5.45 [0.22 ; 10.68]; 0.052	0.052	
Received approved disease modifying MS drug prior to enrollment	No	166	6	3.61	186	1	0.54	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	Yes	106	6	5.66	87	2	2.30	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	10	4.08	251	3	1.20	3.41 [0.95 ; 12.26]	3.52 [0.96 ; 12.94];	2.89 [0.07 ; 5.71]; 0.052	0.052	0.3655
	USA and Western Europe	27	2	7.41	22	0	0.00	4.11 [0.21 ; 81.33]	4.41 [0.2 ; 96.84];	6.75 [-5.37 ; 18.88]; 0.497	0.497	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Investigations | Body temperature increased

5.1.49 Psychiatric disorders - Insomnia

Tabelle 167: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	11	6.25	156	8	5.13	1.22 [0.5 ; 2.95]	1.23 [0.48 ; 3.15];	1.12 [-3.86 ; 6.1]; 0.814	0.814	0.0012
	>= 38 years	96	10	10.42	117	0	0.00	25.55 [1.52 ; 430.43]	28.53 [1.65 ; 493.44];	10.4 [4.11 ; 16.69]; 0	0	
Disease Severity at baseline (EDSS)	<=3.5	218	21	9.63	207	6	2.90	3.32 [1.37 ; 8.07]	3.57 [1.41 ; 9.04];	6.73 [2.2 ; 11.27]; 0.005	0.005	0.0246
	>3.5	54	0	0.00	66	2	3.03	0.24 [0.01 ; 4.97]	0.24 [0.01 ; 5.04];	-2.82 [-8.01 ; 2.36]; 0.501	0.501	
Gender	Female	178	13	7.30	176	3	1.70	4.28 [1.24 ; 14.78]	4.54 [1.27 ; 16.23];	5.6 [1.32 ; 9.87]; 0.019	0.019	0.2584
	Male	94	8	8.51	97	5	5.15	1.65 [0.56 ; 4.87]	1.71 [0.54 ; 5.43];	3.36 [-3.8 ; 10.51]; 0.401	0.401	
Number of baseline Gd-enhancing lesions	>=1	141	12	8.51	135	5	3.70	2.3 [0.83 ; 6.35]	2.42 [0.83 ; 7.06];	4.81 [-0.79 ; 10.41]; 0.133	0.133	0.7277
	0	131	9	6.87	136	3	2.21	3.11 [0.86 ; 11.25]	3.27 [0.87 ; 12.36];	4.66 [-0.32 ; 9.65]; 0.08	0.08	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	8	6.84	110	1	0.91	7.52 [0.96 ; 59.16]	8 [0.98 ; 65.05];	5.93 [1.02 ; 10.83]; 0.036	0.036	0.1999
	>=3	42	2	4.76	40	0	0.00	4.77 [0.24 ; 96.34]	5 [0.23 ; 107.43];	4.59 [-3.16 ; 12.35]; 0.494	0.494	
	2	113	11	9.73	123	7	5.69	1.71 [0.69 ; 4.26]	1.79 [0.67 ; 4.78];	4.04 [-2.79 ; 10.87]; 0.327	0.327	
Received approved disease modifying MS drug prior to enrollment	No	166	15	9.04	186	6	3.23	2.8 [1.11 ; 7.05]	2.98 [1.13 ; 7.87];	5.81 [0.76 ; 10.86]; 0.025	0.025	0.8726
	Yes	106	6	5.66	87	2	2.30	2.46 [0.51 ; 11.89]	2.55 [0.5 ; 12.97];	3.36 [-2.05 ; 8.77]; 0.298	0.298	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	14	5.71	251	8	3.19	1.79 [0.77 ; 4.2]	1.84 [0.76 ; 4.47];	2.53 [-1.1 ; 6.16]; 0.195	0.195	0.0235
	USA and Western Europe	27	7	25.93	22	0	0.00	12.32 [0.74 ; 204.47]	16.46 [0.88 ; 306.66];	24.61 [7.16 ; 42.06]; 0.006	0.006	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Psychiatric disorders | Insomnia

5.1.50 Nervous system disorders - Dizziness

Tabelle 168: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	12	6.82	156	4	2.56	2.66 [0.88 ; 8.08]	2.78 [0.88 ; 8.81];	4.25 [-0.22 ; 8.73]; 0.078	0.078	0.0619
	>= 38 years	96	4	4.17	117	8	6.84	0.61 [0.19 ; 1.96]	0.59 [0.17 ; 2.03];	-2.67 [-8.74 ; 3.4]; 0.553	0.553	
Disease Severity at baseline (EDSS)	<=3.5	218	16	7.34	207	7	3.38	2.17 [0.91 ; 5.17]	2.26 [0.91 ; 5.62];	3.96 [-0.29 ; 8.21]; 0.087	0.087	0.0028
	>3.5	54	0	0.00	66	5	7.58	0.11 [0.01 ; 1.96]	0.1 [0.01 ; 1.9];	-7.3 [-14.34 ; -0.26]; 0.033	0.033	
Gender	Female	178	11	6.18	176	6	3.41	1.81 [0.69 ; 4.79]	1.87 [0.67 ; 5.16];	2.77 [-1.67 ; 7.21]; 0.32	0.32	0.3307
	Male	94	5	5.32	97	6	6.19	0.86 [0.27 ; 2.72]	0.85 [0.25 ; 2.89];	-0.87 [-7.47 ; 5.73]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	10	7.09	135	8	5.93	1.2 [0.49 ; 2.94]	1.21 [0.46 ; 3.17];	1.17 [-4.65 ; 6.98]; 0.809	0.809	0.7434
	0	131	6	4.58	136	4	2.94	1.56 [0.45 ; 5.39]	1.58 [0.44 ; 5.75];	1.64 [-2.93 ; 6.21]; 0.534	0.534	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	7	5.98	110	7	6.36	0.94 [0.34 ; 2.59]	0.94 [0.32 ; 2.76];	-0.38 [-6.65 ; 5.89]; 1	1	0.2623
	>=3	42	2	4.76	40	0	0.00	4.77 [0.24 ; 96.34]	5 [0.23 ; 107.43];	4.59 [-3.16 ; 12.35]; 0.494	0.494	
	2	113	7	6.19	123	5	4.07	1.52 [0.5 ; 4.67]	1.56 [0.48 ; 5.06];	2.13 [-3.52 ; 7.78]; 0.558	0.558	
Received approved disease modifying MS drug prior to enrollment	No	166	11	6.63	186	9	4.84	1.37 [0.58 ; 3.22]	1.4 [0.56 ; 3.46];	1.79 [-3.09 ; 6.67]; 0.498	0.498	0.9937
	Yes	106	5	4.72	87	3	3.45	1.37 [0.34 ; 5.56]	1.39 [0.32 ; 5.97];	1.27 [-4.3 ; 6.84]; 0.732	0.732	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	13	5.31	251	8	3.19	1.66 [0.7 ; 3.95]	1.7 [0.69 ; 4.18];	2.12 [-1.43 ; 5.67]; 0.271	0.271	0.2378
	USA and Western Europe	27	3	11.11	22	4	18.18	0.61 [0.15 ; 2.45]	0.56 [0.11 ; 2.83];	-7.07 [-27.08 ; 12.94]; 0.685	0.685	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Nervous system disorders | Dizziness

5.1.51 General disorders and administration site conditions - Asthenia

Tabelle 169: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	8	4.55	156	14	8.97	0.51 [0.22 ; 1.17]	0.48 [0.2 ; 1.18];	-4.43 [-9.87 ; 1.01]; 0.124	0.124	0.081
	>= 38 years	96	8	8.33	117	6	5.13	1.62 [0.58 ; 4.52]	1.68 [0.56 ; 5.03];	3.21 [-3.62 ; 10.03]; 0.411	0.411	
Disease Severity at baseline (EDSS)	<=3.5	218	14	6.42	207	12	5.80	1.11 [0.52 ; 2.34]	1.12 [0.5 ; 2.47];	0.62 [-3.93 ; 5.18]; 0.842	0.842	0.1036
	>3.5	54	2	3.70	66	8	12.12	0.31 [0.07 ; 1.38]	0.28 [0.06 ; 1.37];	-8.42 [-17.76 ; 0.93]; 0.182	0.182	
Gender	Female	178	12	6.74	176	13	7.39	0.91 [0.43 ; 1.94]	0.91 [0.4 ; 2.05];	-0.64 [-5.98 ; 4.69]; 0.839	0.839	0.5441
	Male	94	4	4.26	97	7	7.22	0.59 [0.18 ; 1.95]	0.57 [0.16 ; 2.02];	-2.96 [-9.53 ; 3.61]; 0.537	0.537	
Number of baseline Gd-enhancing lesions	>=1	141	6	4.26	135	9	6.67	0.64 [0.23 ; 1.74]	0.62 [0.22 ; 1.8];	-2.41 [-7.78 ; 2.96]; 0.434	0.434	0.5594
	0	131	10	7.63	136	11	8.09	0.94 [0.41 ; 2.15]	0.94 [0.38 ; 2.29];	-0.45 [-6.91 ; 6]; 1	1	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	10	8.55	110	6	5.45	1.57 [0.59 ; 4.17]	1.62 [0.57 ; 4.62];	3.09 [-3.52 ; 9.7]; 0.441	0.441	0.1614
	>=3	42	2	4.76	40	3	7.50	0.63 [0.11 ; 3.6]	0.62 [0.1 ; 3.9];	-2.74 [-13.14 ; 7.66]; 0.672	0.672	
	2	113	4	3.54	123	11	8.94	0.4 [0.13 ; 1.21]	0.37 [0.12 ; 1.21];	-5.4 [-11.49 ; 0.68]; 0.112	0.112	
Received approved disease modifying MS drug prior to enrollment	No	166	8	4.82	186	13	6.99	0.69 [0.29 ; 1.62]	0.67 [0.27 ; 1.67];	-2.17 [-7.07 ; 2.73]; 0.5	0.5	0.646
	Yes	106	8	7.55	87	7	8.05	0.94 [0.35 ; 2.48]	0.93 [0.32 ; 2.68];	-0.5 [-8.11 ; 7.11]; 1	1	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	15	6.12	251	19	7.57	0.81 [0.42 ; 1.56]	0.8 [0.4 ; 1.61];	-1.45 [-5.89 ; 2.99]; 0.596	0.596	0.9924
	USA and Western Europe	27	1	3.70	22	1	4.55	0.81 [0.05 ; 12.3]	0.81 [0.05 ; 13.7];	-0.84 [-12.09 ; 10.41]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - General disorders and administration site conditions | Asthenia

5.1.52 Investigations - Alanine aminotransferase increased

Tabelle 170: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	6	3.41	156	6	3.85	0.89 [0.29 ; 2.69]	0.88 [0.28 ; 2.79];	-0.44 [-4.47 ; 3.6]; 1	1	0.913
	>= 38 years	96	4	4.17	117	5	4.27	0.98 [0.27 ; 3.53]	0.97 [0.25 ; 3.73];	-0.11 [-5.53 ; 5.32]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	218	8	3.67	207	10	4.83	0.76 [0.31 ; 1.89]	0.75 [0.29 ; 1.94];	-1.16 [-5 ; 2.68]; 0.634	0.634	0.3507
	>3.5	54	2	3.70	66	1	1.52	2.44 [0.23 ; 26.24]	2.5 [0.22 ; 28.34];	2.19 [-3.65 ; 8.02]; 0.588	0.588	
Gender	Female	178	6	3.37	176	6	3.41	0.99 [0.33 ; 3.01]	0.99 [0.31 ; 3.13];	-0.04 [-3.81 ; 3.73]; 1	1	0.8338
	Male	94	4	4.26	97	5	5.15	0.83 [0.23 ; 2.98]	0.82 [0.21 ; 3.14];	-0.9 [-6.9 ; 5.1]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	10	7.09	135	6	4.44	1.6 [0.6 ; 4.27]	1.64 [0.58 ; 4.65];	2.65 [-2.83 ; 8.13]; 0.443	0.443	
	0	131	0	0.00	136	5	3.68	0.09 [0.01 ; 1.69]	0.09 [0 ; 1.66];	-3.64 [-7.09 ; -0.19]; 0.03	0.03	0.0057
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	5	4.27	110	4	3.64	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	>=3	42	2	4.76	40	2	5.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	2	113	3	2.65	123	5	4.07	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	6	3.61	186	6	3.23	1.12 [0.37 ; 3.41]	1.12 [0.36 ; 3.56];	0.39 [-3.42 ; 4.2]; 1	1	0.5355
	Yes	106	4	3.77	87	5	5.75	0.66 [0.18 ; 2.37]	0.64 [0.17 ; 2.47];	-1.97 [-8.06 ; 4.12]; 0.734	0.734	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	8	3.27	251	10	3.98	0.82 [0.33 ; 2.04]	0.81 [0.32 ; 2.1];	-0.72 [-4.01 ; 2.57]; 0.811	0.811	0.5828
	USA and Western Europe	27	2	7.41	22	1	4.55	1.63 [0.16 ; 16.81]	1.68 [0.14 ; 19.85];	2.86 [-10.3 ; 16.03]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Investigations | Alanine aminotransferase increased

5.1.53 Investigations - Aspartate aminotransferase increased

Tabelle 171: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Disease Severity at baseline (EDSS)	<=3.5	218	6	2.75	207	6	2.90	0.95 [0.31 ; 2.9]	0.95 [0.3 ; 2.99];	-0.15 [-3.3 ; 3.01]; 1	1	0.0193
	>3.5	54	4	7.41	66	0	0.00	10.96 [0.6 ; 199.23]	11.85 [0.62 ; 225.2];	7.44 [-0.1 ; 14.97]; 0.038	0.038	
Number of baseline Gd-enhancing lesions	>=1	141	8	5.67	135	3	2.22	2.55 [0.69 ; 9.42]	2.65 [0.69 ; 10.19];	3.45 [-1.11 ; 8.01]; 0.218	0.218	0.2319
	0	131	2	1.53	136	3	2.21	0.69 [0.12 ; 4.08]	0.69 [0.11 ; 4.18];	-0.68 [-3.92 ; 2.56]; 1	1	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	4	3.42	110	1	0.91	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	4	9.52	40	2	5.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	2	1.77	123	3	2.44	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	5	3.01	186	5	2.69	1.12 [0.33 ; 3.8]	1.12 [0.32 ; 3.95];	0.32 [-3.16 ; 3.81]; 1	1	0.2654
	Yes	106	5	4.72	87	1	1.15	4.1 [0.49 ; 34.47]	4.26 [0.49 ; 37.15];	3.57 [-1.05 ; 8.18]; 0.225	0.225	
Region	Eastern Europe	245	9	3.67	251	5	1.99	1.84 [0.63 ; 5.42]	1.88 [0.62 ; 5.68];	1.68 [-1.24 ; 4.6]; 0.29	0.29	0.5897
	USA and Western Europe	27	1	3.70	22	1	4.55	0.81 [0.05 ; 12.3]	0.81 [0.05 ; 13.7];	-0.84 [-12.09 ; 10.41]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
	p-value: fisher test; interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG; mo and m1 are logit models											
Any TEAE - Investigations | Aspartate aminotransferase increased												

5.1.54 Skin and subcutaneous tissue disorders - Alopecia

Tabelle 172: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	10	5.68	156	28	17.95	0.32 [0.16 ; 0.63]	0.28 [0.13 ; 0.59];	-12.27 [-19.19 ; -5.34]; 0	0	0.4347
	>= 38 years	96	3	3.12	117	20	17.09	0.18 [0.06 ; 0.6]	0.16 [0.04 ; 0.54];	-13.97 [-21.63 ; -6.31]; 0.001	0.001	
Disease Severity at baseline (EDSS)	<=3.5	218	11	5.05	207	39	18.84	0.27 [0.14 ; 0.51]	0.23 [0.11 ; 0.46];	-13.79 [-19.86 ; -7.73]; 0	0	0.9439
	>3.5	54	2	3.70	66	9	13.64	0.27 [0.06 ; 1.2]	0.24 [0.05 ; 1.18];	-9.93 [-19.62 ; -0.24]; 0.109	0.109	
Gender	Female	178	9	5.06	176	42	23.86	0.21 [0.11 ; 0.42]	0.17 [0.08 ; 0.36];	-18.81 [-25.88 ; -11.74]; 0	0	0.0814
	Male	94	4	4.26	97	6	6.19	0.69 [0.2 ; 2.36]	0.67 [0.18 ; 2.47];	-1.93 [-8.23 ; 4.37]; 0.748	0.748	
Number of baseline Gd-enhancing lesions	>=1	141	7	4.96	135	22	16.30	0.3 [0.13 ; 0.69]	0.27 [0.11 ; 0.65];	-11.33 [-18.52 ; -4.14]; 0.003	0.003	0.6694
	0	131	6	4.58	136	26	19.12	0.24 [0.1 ; 0.56]	0.2 [0.08 ; 0.51];	-14.54 [-22.05 ; -7.02]; 0	0	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	5	4.27	110	17	15.45	0.28 [0.11 ; 0.72]	0.24 [0.09 ; 0.69];	-11.18 [-18.87 ; -3.5]; 0.006	0.006	0.9753
	>=3	42	2	4.76	40	8	20.00	0.24 [0.05 ; 1.05]	0.2 [0.04 ; 1.01];	-15.24 [-29.21 ; -1.27]; 0.046	0.046	
	2	113	6	5.31	123	23	18.70	0.28 [0.12 ; 0.67]	0.24 [0.1 ; 0.62];	-13.39 [-21.43 ; -5.35]; 0.002	0.002	
Received approved disease	No	166	9	5.42	186	32	17.20	0.32 [0.16 ; 0.64]	0.28 [0.13 ; 0.6];	-11.78 [-18.21 ; -5.36]; 0.001	0.001	0.5054

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
modifying MS drug prior to enrollment	Yes	106	4	3.77	87	16	18.39	0.21 [0.07 ; 0.59]	0.17 [0.06 ; 0.54];	-14.62 [-23.53 ; -5.7]; 0.001	0.001	
Region	Eastern Europe	245	13	5.31	251	44	17.53	0.3 [0.17 ; 0.55]	0.26 [0.14 ; 0.5];	-12.22 [-17.7 ; -6.75]; 0	0	0.1182
	USA and Western Europe	27	0	0.00	22	4	18.18	0.09 [0.01 ; 1.61]	0.07 [0 ; 1.47];	-17.78 [-34.72 ; -0.84]; 0.032	0.032	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Skin and subcutaneous tissue disorders | Alopecia

5.1.55 Gastrointestinal disorders - Abdominal pain

Tabelle 173: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	21	11.93	156	5	3.21	3.72 [1.44 ; 9.64]	4.09 [1.5 ; 11.13];	8.73 [3.2 ; 14.26]; 0.004	0.004	0.1063
	>= 38 years	96	7	7.29	117	7	5.98	1.22 [0.44 ; 3.35]	1.24 [0.42 ; 3.66];	1.31 [-5.44 ; 8.06]; 0.784	0.784	
Disease Severity at baseline (EDSS)	<=3.5	218	23	10.55	207	10	4.83	2.18 [1.07 ; 4.48]	2.32 [1.08 ; 5.01];	5.72 [0.7 ; 10.74]; 0.03	0.03	0.7147
	>3.5	54	5	9.26	66	2	3.03	3.06 [0.62 ; 15.13]	3.27 [0.61 ; 17.55];	6.23 [-2.54 ; 15]; 0.241	0.241	
Gender	Female	178	22	12.36	176	9	5.11	2.42 [1.15 ; 5.1]	2.62 [1.17 ; 5.86];	7.25 [1.42 ; 13.07]; 0.023	0.023	0.8082
	Male	94	6	6.38	97	3	3.09	2.06 [0.53 ; 8.01]	2.14 [0.52 ; 8.8];	3.29 [-2.73 ; 9.31]; 0.326	0.326	
Number of baseline Gd-enhancing lesions	>=1	141	18	12.77	135	3	2.22	5.74 [1.73 ; 19.06]	6.44 [1.85 ; 22.4];	10.54 [4.5 ; 16.59]; 0.001	0.001	0.023
	0	131	10	7.63	136	9	6.62	1.15 [0.48 ; 2.75]	1.17 [0.46 ; 2.97];	1.02 [-5.16 ; 7.19]; 0.815	0.815	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	9	7.69	110	5	4.55	1.69 [0.59 ; 4.89]	1.75 [0.57 ; 5.39];	3.15 [-3.06 ; 9.35]; 0.412	0.412	0.7415
	>=3	42	6	14.29	40	2	5.00	2.86 [0.61 ; 13.34]	3.17 [0.6 ; 16.72];	9.29 [-3.27 ; 21.84]; 0.265	0.265	
	2	113	13	11.50	123	5	4.07	2.83 [1.04 ; 7.69]	3.07 [1.06 ; 8.9];	7.44 [0.6 ; 14.28]; 0.047	0.047	
Received approved disease modifying MS drug prior to enrollment	No	166	18	10.84	186	8	4.30	2.52 [1.13 ; 5.65]	2.71 [1.14 ; 6.4];	6.54 [0.99 ; 12.1]; 0.024	0.024	0.7662
	Yes	106	10	9.43	87	4	4.60	2.05 [0.67 ; 6.32]	2.16 [0.65 ; 7.15];	4.84 [-2.26 ; 11.93]; 0.268	0.268	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	25	10.20	251	11	4.38	2.33 [1.17 ; 4.63]	2.48 [1.19 ; 5.16];	5.82 [1.26 ; 10.38]; 0.015	0.015	0.9634
	USA and Western Europe	27	3	11.11	22	1	4.55	2.44 [0.27 ; 21.89]	2.62 [0.25 ; 27.19];	6.57 [-8.14 ; 21.27]; 0.617	0.617	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Gastrointestinal disorders | Abdominal pain

5.1.56 Blood and lymphatic system disorders - Anaemia

Tabelle 174: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	5	2.84	156	7	4.49	0.63 [0.21 ; 1.95]	0.62 [0.19 ; 2];	-1.65 [-5.72 ; 2.43]; 0.559	0.559	0.9153
	>= 38 years	96	4	4.17	117	7	5.98	0.7 [0.21 ; 2.31]	0.68 [0.19 ; 2.41];	-1.82 [-7.69 ; 4.05]; 0.758	0.758	
Disease Severity at baseline (EDSS)	<=3.5	218	6	2.75	207	9	4.35	0.63 [0.23 ; 1.75]	0.62 [0.22 ; 1.78];	-1.6 [-5.12 ; 1.93]; 0.437	0.437	0.8783
	>3.5	54	3	5.56	66	5	7.58	0.73 [0.18 ; 2.93]	0.72 [0.16 ; 3.15];	-2.02 [-10.86 ; 6.82]; 0.729	0.729	
Gender	Female	178	9	5.06	176	14	7.95	0.64 [0.28 ; 1.43]	0.62 [0.26 ; 1.46];	-2.9 [-8.03 ; 2.23]; 0.289	0.289	1
	Male	94	0	0.00	97	0	0.00	1.03 [0.02 ; 51.46]	1.03 [0.02 ; 52.53];	0.02 [-2.01 ; 2.04]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	7	4.96	135	6	4.44	1.12 [0.39 ; 3.24]	1.12 [0.37 ; 3.43];	0.52 [-4.47 ; 5.51]; 1	1	0.1057
	0	131	2	1.53	136	8	5.88	0.26 [0.06 ; 1.2]	0.25 [0.05 ; 1.19];	-4.36 [-8.83 ; 0.12]; 0.103	0.103	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	3	2.56	110	7	6.36	0.4 [0.11 ; 1.52]	0.39 [0.1 ; 1.54];	-3.8 [-9.19 ; 1.59]; 0.204	0.204	0.6569
	>=3	42	3	7.14	40	3	7.50	0.95 [0.2 ; 4.45]	0.95 [0.18 ; 5];	-0.36 [-11.64 ; 10.93]; 1	1	
	2	113	3	2.65	123	4	3.25	0.82 [0.19 ; 3.57]	0.81 [0.18 ; 3.71];	-0.6 [-4.91 ; 3.72]; 1	1	
Received approved disease modifying MS drug prior to enrollment	No	166	4	2.41	186	9	4.84	0.5 [0.16 ; 1.59]	0.49 [0.15 ; 1.61];	-2.43 [-6.3 ; 1.44]; 0.268	0.268	0.5622
	Yes	106	5	4.72	87	5	5.75	0.82 [0.25 ; 2.74]	0.81 [0.23 ; 2.9];	-1.03 [-7.37 ; 5.31]; 0.756	0.756	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	9	3.67	251	14	5.58	0.66 [0.29 ; 1.49]	0.65 [0.27 ; 1.52];	-1.9 [-5.59 ; 1.78]; 0.394	0.394	0.9999
	USA and Western Europe	27	0	0.00	22	0	0.00	0.82 [0.02 ; 39.81]	0.82 [0.02 ; 42.89];	-0.39 [-8.11 ; 7.33]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Blood and lymphatic system disorders | Anaemia

5.1.57 Blood and lymphatic system disorders - Lymphopenia

Tabelle 175: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	18	10.23	156	2	1.28	7.98 [1.88 ; 33.83]	8.77 [2 ; 38.44];	8.95 [4.13 ; 13.76]; 0.001	0.001	0.1817
	>= 38 years	96	8	8.33	117	0	0.00	20.68 [1.21 ; 353.78]	22.57 [1.29 ; 396.28];	8.34 [2.59 ; 14.09]; 0.001	0.001	
Disease Severity at baseline (EDSS)	<=3.5	218	22	10.09	207	2	0.97	10.44 [2.49 ; 43.86]	11.51 [2.67 ; 49.58];	9.13 [4.91 ; 13.34]; 0	0	0.3764
	>3.5	54	4	7.41	66	0	0.00	10.96 [0.6 ; 199.23]	11.85 [0.62 ; 225.2];	7.44 [-0.1 ; 14.97]; 0.038	0.038	
Gender	Female	178	18	10.11	176	1	0.57	17.8 [2.4 ; 131.89]	19.69 [2.6 ; 149.16];	9.54 [4.98 ; 14.11]; 0	0	0.5986
	Male	94	8	8.51	97	1	1.03	8.26 [1.05 ; 64.73]	8.93 [1.09 ; 72.86];	7.48 [1.49 ; 13.47]; 0.017	0.017	
Number of baseline Gd-enhancing lesions	>=1	141	13	9.22	135	2	1.48	6.22 [1.43 ; 27.06]	6.75 [1.49 ; 30.52];	7.74 [2.55 ; 12.93]; 0.006	0.006	0.0944
	0	131	13	9.92	136	0	0.00	28.02 [1.68 ; 466.63]	31.1 [1.83 ; 528.81];	9.86 [4.6 ; 15.13]; 0	0	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	14	11.97	110	1	0.91	13.16 [1.76 ; 98.43]	14.82 [1.91 ; 114.69];	11.06 [4.91 ; 17.2]; 0.001	0.001	0.7008
	>=3	42	4	9.52	40	0	0.00	8.58 [0.48 ; 154.45]	9.47 [0.49 ; 181.77];	9.25 [-0.5 ; 18.99]; 0.116	0.116	
	2	113	8	7.08	123	1	0.81	8.71 [1.11 ; 68.54]	9.3 [1.14 ; 75.54];	6.27 [1.28 ; 11.25]; 0.015	0.015	
Received approved disease modifying MS drug prior to enrollment	No	166	8	4.82	186	0	0.00	19.04 [1.11 ; 327.29]	20 [1.15 ; 349.29];	4.82 [1.41 ; 8.24]; 0.002	0.002	0.2012
	Yes	106	18	16.98	87	2	2.30	7.39 [1.76 ; 30.96]	8.69 [1.96 ; 38.61];	14.68 [6.87 ; 22.49]; 0.001	0.001	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	25	10.20	251	2	0.80	12.81 [3.07 ; 53.48]	14.15 [3.31 ; 60.41];	9.41 [5.46 ; 13.35]; 0	0	0.7354
	USA and Western Europe	27	1	3.70	22	0	0.00	2.46 [0.11 ; 57.66]	2.55 [0.1 ; 65.66];	3.18 [-7.07 ; 13.43]; 0.497	0.497	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Blood and lymphatic system disorders | Lymphopenia

5.1.58 Infections and infestations - Respiratory tract infection viral

Tabelle 176: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	16	9.09	156	15	9.62	0.95 [0.48 ; 1.85]	0.94 [0.45 ; 1.97];	-0.52 [-6.8 ; 5.76]; 1	1	0.9594
	>= 38 years	96	6	6.25	117	8	6.84	0.91 [0.33 ; 2.54]	0.91 [0.3 ; 2.71];	-0.59 [-7.25 ; 6.07]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	218	19	8.72	207	17	8.21	1.06 [0.57 ; 1.98]	1.07 [0.54 ; 2.11];	0.5 [-4.79 ; 5.8]; 0.864	0.864	0.4556
	>3.5	54	3	5.56	66	6	9.09	0.61 [0.16 ; 2.33]	0.59 [0.14 ; 2.47];	-3.54 [-12.78 ; 5.71]; 0.512	0.512	
Gender	Female	178	16	8.99	176	18	10.23	0.88 [0.46 ; 1.67]	0.87 [0.43 ; 1.76];	-1.24 [-7.38 ; 4.9]; 0.722	0.722	0.6074
	Male	94	6	6.38	97	5	5.15	1.24 [0.39 ; 3.92]	1.25 [0.37 ; 4.26];	1.23 [-5.39 ; 7.85]; 0.765	0.765	
Number of baseline Gd-enhancing lesions	>=1	141	10	7.09	135	13	9.63	0.74 [0.33 ; 1.62]	0.72 [0.3 ; 1.69];	-2.54 [-9.07 ; 4]; 0.517	0.517	0.3588
	0	131	12	9.16	136	10	7.35	1.25 [0.56 ; 2.78]	1.27 [0.53 ; 3.05];	1.81 [-4.8 ; 8.41]; 0.66	0.66	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	9	7.69	110	8	7.27	1.06 [0.42 ; 2.64]	1.06 [0.39 ; 2.86];	0.42 [-6.43 ; 7.27]; 1	1	0.8321
	>=3	42	3	7.14	40	2	5.00	1.43 [0.25 ; 8.11]	1.46 [0.23 ; 9.24];	2.14 [-8.17 ; 12.45]; 1	1	
	2	113	10	8.85	123	13	10.57	0.84 [0.38 ; 1.83]	0.82 [0.35 ; 1.96];	-1.72 [-9.27 ; 5.83]; 0.827	0.827	
Received approved disease modifying MS drug prior to enrollment	No	166	6	3.61	186	7	3.76	0.96 [0.33 ; 2.8]	0.96 [0.32 ; 2.91];	-0.15 [-4.09 ; 3.79]; 1	1	0.7765
	Yes	106	16	15.09	87	16	18.39	0.82 [0.44 ; 1.54]	0.79 [0.37 ; 1.69];	-3.3 [-13.91 ; 7.32]; 0.565	0.565	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	22	8.98	251	23	9.16	0.98 [0.56 ; 1.71]	0.98 [0.53 ; 1.81];	-0.18 [-5.24 ; 4.87]; 1	1	1
	USA and Western Europe	27	0	0.00	22	0	0.00	0.82 [0.02 ; 39.81]	0.82 [0.02 ; 42.89];	-0.39 [-8.11 ; 7.33]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Respiratory tract infection viral

5.1.59 Gastrointestinal disorders - Dyspepsia

Tabelle 177: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	13	7.39	156	8	5.13	1.44 [0.61 ; 3.38]	1.48 [0.59 ; 3.66];	2.26 [-2.93 ; 7.45]; 0.5	0.5	0.1924
	>= 38 years	96	3	3.12	117	7	5.98	0.52 [0.14 ; 1.97]	0.51 [0.13 ; 2.02];	-2.86 [-8.39 ; 2.67]; 0.517	0.517	
Disease Severity at baseline (EDSS)	<=3.5	218	14	6.42	207	12	5.80	1.11 [0.52 ; 2.34]	1.12 [0.5 ; 2.47];	0.62 [-3.93 ; 5.18]; 0.842	0.842	0.7495
	>3.5	54	2	3.70	66	3	4.55	0.81 [0.14 ; 4.7]	0.81 [0.13 ; 5.02];	-0.84 [-7.96 ; 6.27]; 1	1	
Gender	Female	178	6	3.37	176	9	5.11	0.66 [0.24 ; 1.81]	0.65 [0.23 ; 1.86];	-1.74 [-5.94 ; 2.45]; 0.443	0.443	0.1722
	Male	94	10	10.64	97	6	6.19	1.72 [0.65 ; 4.54]	1.81 [0.63 ; 5.18];	4.45 [-3.41 ; 12.32]; 0.305	0.305	
Number of baseline Gd-enhancing lesions	>=1	141	12	8.51	135	6	4.44	1.91 [0.74 ; 4.96]	2 [0.73 ; 5.49];	4.07 [-1.7 ; 9.84]; 0.224	0.224	0.0524
	0	131	4	3.05	136	9	6.62	0.46 [0.15 ; 1.46]	0.44 [0.13 ; 1.48];	-3.56 [-8.68 ; 1.55]; 0.256	0.256	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	9	7.69	110	7	6.36	1.21 [0.47 ; 3.13]	1.23 [0.44 ; 3.41];	1.33 [-5.31 ; 7.97]; 0.798	0.798	0.7564
	>=3	42	3	7.14	40	2	5.00	1.43 [0.25 ; 8.11]	1.46 [0.23 ; 9.24];	2.14 [-8.17 ; 12.45]; 1	1	
	2	113	4	3.54	123	6	4.88	0.73 [0.21 ; 2.51]	0.72 [0.2 ; 2.6];	-1.34 [-6.45 ; 3.77]; 0.751	0.751	
Received approved disease modifying MS drug prior to enrollment	No	166	9	5.42	186	8	4.30	1.26 [0.5 ; 3.19]	1.28 [0.48 ; 3.39];	1.12 [-3.39 ; 5.63]; 0.63	0.63	0.5407
	Yes	106	7	6.60	87	7	8.05	0.82 [0.3 ; 2.25]	0.81 [0.27 ; 2.4];	-1.44 [-8.86 ; 5.98]; 0.784	0.784	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	16	6.53	251	14	5.58	1.17 [0.58 ; 2.35]	1.18 [0.56 ; 2.48];	0.95 [-3.25 ; 5.15]; 0.709	0.709	0.1833
	USA and Western Europe	27	0	0.00	22	1	4.55	0.27 [0.01 ; 6.41]	0.26 [0.01 ; 6.72];	-4.74 [-15.96 ; 6.48]; 0.208	0.208	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Gastrointestinal disorders | Dyspepsia

5.1.60 Infections and infestations - Cystitis

Tabelle 178: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	13	7.39	156	8	5.13	1.44 [0.61 ; 3.38]	1.48 [0.59 ; 3.66];	2.26 [-2.93 ; 7.45]; 0.5	0.5	0.9004
	>= 38 years	96	4	4.17	117	3	2.56	1.62 [0.37 ; 7.08]	1.65 [0.36 ; 7.57];	1.6 [-3.31 ; 6.52]; 0.703	0.703	
Disease Severity at baseline (EDSS)	<=3.5	218	13	5.96	207	8	3.86	1.54 [0.65 ; 3.65]	1.58 [0.64 ; 3.89];	2.1 [-2 ; 6.19]; 0.375	0.375	0.9449
	>3.5	54	4	7.41	66	3	4.55	1.63 [0.38 ; 6.97]	1.68 [0.36 ; 7.85];	2.86 [-5.74 ; 11.47]; 0.699	0.699	
Gender	Female	178	16	8.99	176	11	6.25	1.44 [0.69 ; 3.01]	1.48 [0.67 ; 3.29];	2.74 [-2.78 ; 8.26]; 0.424	0.424	0.3089
	Male	94	1	1.06	97	0	0.00	3.09 [0.13 ; 75.03]	3.13 [0.13 ; 77.76];	1.07 [-1.81 ; 3.95]; 0.244	0.244	
Number of baseline Gd-enhancing lesions	>=1	141	10	7.09	135	6	4.44	1.6 [0.6 ; 4.27]	1.64 [0.58 ; 4.65];	2.65 [-2.83 ; 8.13]; 0.443	0.443	0.8966
	0	131	7	5.34	136	5	3.68	1.45 [0.47 ; 4.46]	1.48 [0.46 ; 4.78];	1.67 [-3.32 ; 6.65]; 0.566	0.566	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	4	3.42	110	6	5.45	0.63 [0.18 ; 2.16]	0.61 [0.17 ; 2.24];	-2.04 [-7.41 ; 3.34]; 0.529	0.529	0.0643
	>=3	42	3	7.14	40	0	0.00	6.67 [0.36 ; 125.26]	7.18 [0.36 ; 143.5];	6.92 [-1.92 ; 15.76]; 0.118	0.118	
	2	113	10	8.85	123	5	4.07	2.18 [0.77 ; 6.18]	2.29 [0.76 ; 6.92];	4.78 [-1.51 ; 11.08]; 0.182	0.182	
Received approved disease modifying MS drug prior to enrollment	No	166	6	3.61	186	7	3.76	0.96 [0.33 ; 2.8]	0.96 [0.32 ; 2.91];	-0.15 [-4.09 ; 3.79]; 1	1	0.2593
	Yes	106	11	10.38	87	4	4.60	2.26 [0.74 ; 6.84]	2.4 [0.74 ; 7.83];	5.78 [-1.51 ; 13.06]; 0.179	0.179	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	17	6.94	251	11	4.38	1.58 [0.76 ; 3.31]	1.63 [0.75 ; 3.55];	2.56 [-1.51 ; 6.62]; 0.246	0.246	0.9999
	USA and Western Europe	27	0	0.00	22	0	0.00	0.82 [0.02 ; 39.81]	0.82 [0.02 ; 42.89];	-0.39 [-8.11 ; 7.33]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Cystitis

5.1.61 Blood and lymphatic system disorders - Neutropenia

Tabelle 179: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	5	2.84	156	7	4.49	0.63 [0.21 ; 1.95]	0.62 [0.19 ; 2];	-1.65 [-5.72 ; 2.43]; 0.559	0.559	0.9738
	>= 38 years	96	2	2.08	117	4	3.42	0.61 [0.11 ; 3.26]	0.6 [0.11 ; 3.35];	-1.34 [-5.69 ; 3.02]; 0.692	0.692	
Disease Severity at baseline (EDSS)	<=3.5	218	6	2.75	207	8	3.86	0.71 [0.25 ; 2.02]	0.7 [0.24 ; 2.06];	-1.11 [-4.52 ; 2.3]; 0.593	0.593	0.6476
	>3.5	54	1	1.85	66	3	4.55	0.41 [0.04 ; 3.81]	0.4 [0.04 ; 3.92];	-2.69 [-8.87 ; 3.49]; 0.626	0.626	
Gender	Female	178	4	2.25	176	8	4.55	0.49 [0.15 ; 1.61]	0.48 [0.14 ; 1.63];	-2.3 [-6.07 ; 1.47]; 0.257	0.257	0.4625
	Male	94	3	3.19	97	3	3.09	1.03 [0.21 ; 4.98]	1.03 [0.2 ; 5.25];	0.1 [-4.85 ; 5.05]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	3	2.13	135	7	5.19	0.41 [0.11 ; 1.55]	0.4 [0.1 ; 1.57];	-3.06 [-7.49 ; 1.38]; 0.209	0.209	0.3335
	0	131	4	3.05	136	4	2.94	1.04 [0.27 ; 4.07]	1.04 [0.25 ; 4.25];	0.11 [-3.98 ; 4.2]; 1	1	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	5	4.27	110	5	4.55	0.94 [0.28 ; 3.16]	0.94 [0.26 ; 3.33];	-0.27 [-5.62 ; 5.07]; 1	1	0.4983
	>=3	42	1	2.38	40	4	10.00	0.24 [0.03 ; 2.04]	0.22 [0.02 ; 2.05];	-7.62 [-18 ; 2.76]; 0.196	0.196	
	2	113	1	0.88	123	2	1.63	0.54 [0.05 ; 5.92]	0.54 [0.05 ; 6.04];	-0.74 [-3.57 ; 2.08]; 1	1	
Received approved disease modifying MS drug prior to enrollment	No	166	4	2.41	186	9	4.84	0.5 [0.16 ; 1.59]	0.49 [0.15 ; 1.61];	-2.43 [-6.3 ; 1.44]; 0.268	0.268	0.392
	Yes	106	3	2.83	87	2	2.30	1.23 [0.21 ; 7.2]	1.24 [0.2 ; 7.58];	0.53 [-3.93 ; 4.99]; 1	1	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	6	2.45	251	11	4.38	0.56 [0.21 ; 1.49]	0.55 [0.2 ; 1.5];	-1.93 [-5.12 ; 1.25]; 0.324	0.324	0.1858
	USA and Western Europe	27	1	3.70	22	0	0.00	2.46 [0.11 ; 57.66]	2.55 [0.1 ; 65.66];	3.18 [-7.07 ; 13.43]; 0.497	0.497	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Blood and lymphatic system disorders | Neutropenia

5.1.62 Infections and infestations - Respiratory tract infection

Tabelle 180: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	20	11.36	156	17	10.90	1.04 [0.57 ; 1.92]	1.05 [0.53 ; 2.08];	0.47 [-6.31 ; 7.24]; 1	1	0.9083
	>= 38 years	96	10	10.42	117	11	9.40	1.11 [0.49 ; 2.5]	1.12 [0.45 ; 2.76];	1.01 [-7.07 ; 9.1]; 0.821	0.821	
Disease Severity at baseline (EDSS)	<=3.5	218	26	11.93	207	20	9.66	1.23 [0.71 ; 2.14]	1.27 [0.68 ; 2.35];	2.26 [-3.63 ; 8.16]; 0.533	0.533	0.2658
	>3.5	54	4	7.41	66	8	12.12	0.61 [0.19 ; 1.92]	0.58 [0.16 ; 2.04];	-4.71 [-15.24 ; 5.81]; 0.544	0.544	
Gender	Female	178	23	12.92	176	18	10.23	1.26 [0.71 ; 2.26]	1.3 [0.68 ; 2.51];	2.69 [-3.96 ; 9.35]; 0.507	0.507	0.3093
	Male	94	7	7.45	97	10	10.31	0.72 [0.29 ; 1.82]	0.7 [0.25 ; 1.92];	-2.86 [-10.91 ; 5.19]; 0.613	0.613	
Number of baseline Gd-enhancing lesions	>=1	141	26	18.44	135	12	8.89	2.07 [1.09 ; 3.94]	2.32 [1.12 ; 4.81];	9.55 [1.55 ; 17.55]; 0.024	0.024	0.0003
	0	131	4	3.05	136	16	11.76	0.26 [0.09 ; 0.76]	0.24 [0.08 ; 0.73];	-8.71 [-14.88 ; -2.55]; 0.009	0.009	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	16	13.68	110	12	10.91	1.25 [0.62 ; 2.53]	1.29 [0.58 ; 2.87];	2.77 [-5.76 ; 11.29]; 0.552	0.552	0.7275
	>=3	42	4	9.52	40	3	7.50	1.27 [0.3 ; 5.32]	1.3 [0.27 ; 6.2];	2.02 [-10.04 ; 14.08]; 1	1	
	2	113	10	8.85	123	13	10.57	0.84 [0.38 ; 1.83]	0.82 [0.35 ; 1.96];	-1.72 [-9.27 ; 5.83]; 0.827	0.827	
Received approved disease modifying MS drug prior to enrollment	No	166	19	11.45	186	19	10.22	1.12 [0.61 ; 2.04]	1.14 [0.58 ; 2.23];	1.23 [-5.28 ; 7.74]; 0.734	0.734	0.8325
	Yes	106	11	10.38	87	9	10.34	1 [0.44 ; 2.31]	1 [0.4 ; 2.54];	0.03 [-8.61 ; 8.67]; 1	1	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	29	11.84	251	27	10.76	1.1 [0.67 ; 1.8]	1.11 [0.64 ; 1.94];	1.08 [-4.49 ; 6.65]; 0.777	0.777	0.8274
	USA and Western Europe	27	1	3.70	22	1	4.55	0.81 [0.05 ; 12.3]	0.81 [0.05 ; 13.7];	-0.84 [-12.09 ; 10.41]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Respiratory tract infection

5.1.63 Infections and infestations - Pharyngitis

Tabelle 181: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	17	9.66	156	6	3.85	2.51 [1.02 ; 6.21]	2.67 [1.03 ; 6.96];	5.81 [0.51 ; 11.12]; 0.05	0.05	0.0328
	>= 38 years	96	7	7.29	117	0	0.00	18.25 [1.06 ; 315.48]	19.69 [1.11 ; 349.37];	7.31 [1.87 ; 12.75]; 0.002	0.002	
Disease Severity at baseline (EDSS)	<=3.5	218	20	9.17	207	6	2.90	3.17 [1.3 ; 7.72]	3.38 [1.33 ; 8.6];	6.28 [1.81 ; 10.74]; 0.008	0.008	0.125
	>3.5	54	4	7.41	66	0	0.00	10.96 [0.6 ; 199.23]	11.85 [0.62 ; 225.2];	7.44 [-0.1 ; 14.97]; 0.038	0.038	
Gender	Female	178	19	10.67	176	6	3.41	3.13 [1.28 ; 7.65]	3.39 [1.32 ; 8.69];	7.27 [2 ; 12.53]; 0.011	0.011	0.1157
	Male	94	5	5.32	97	0	0.00	11.35 [0.64 ; 202.4]	11.98 [0.65 ; 219.81];	5.28 [0.38 ; 10.18]; 0.014	0.014	
Number of baseline Gd-enhancing lesions	>=1	141	11	7.80	135	3	2.22	3.51 [1 ; 12.31]	3.72 [1.02 ; 13.65];	5.58 [0.5 ; 10.66]; 0.052	0.052	0.7706
	0	131	13	9.92	136	3	2.21	4.5 [1.31 ; 15.43]	4.88 [1.36 ; 17.56];	7.72 [2.03 ; 13.4]; 0.009	0.009	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	12	10.26	110	2	1.82	5.64 [1.29 ; 24.64]	6.17 [1.35 ; 28.24];	8.44 [2.4 ; 14.48]; 0.011	0.011	0.8036
	>=3	42	6	14.29	40	2	5.00	2.86 [0.61 ; 13.34]	3.17 [0.6 ; 16.72];	9.29 [-3.27 ; 21.84]; 0.265	0.265	
	2	113	6	5.31	123	2	1.63	3.27 [0.67 ; 15.85]	3.39 [0.67 ; 17.17];	3.68 [-1.02 ; 8.38]; 0.157	0.157	
Received approved disease modifying MS drug prior to enrollment	No	166	12	7.23	186	4	2.15	3.36 [1.11 ; 10.22]	3.55 [1.12 ; 11.22];	5.08 [0.62 ; 9.54]; 0.037	0.037	0.6585
	Yes	106	12	11.32	87	2	2.30	4.92 [1.13 ; 21.41]	5.43 [1.18 ; 24.94];	9.02 [2.22 ; 15.83]; 0.023	0.023	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	23	9.39	251	6	2.39	3.93 [1.63 ; 9.48]	4.23 [1.69 ; 10.58];	7 [2.89 ; 11.11]; 0.001	0.001	0.5504
	USA and Western Europe	27	1	3.70	22	0	0.00	2.46 [0.11 ; 57.66]	2.55 [0.1 ; 65.66];	3.18 [-7.07 ; 13.43]; 0.497	0.497	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Pharyngitis

5.1.64 General disorders and administration site conditions - Influenza like illness

Tabelle 182: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	20	11.36	156	4	2.56	4.43 [1.55 ; 12.69]	4.87 [1.63 ; 14.58];	8.8 [3.5 ; 14.1]; 0.002	0.002	0.7004
	>= 38 years	96	8	8.33	117	3	2.56	3.25 [0.89 ; 11.92]	3.45 [0.89 ; 13.4];	5.77 [-0.46 ; 12]; 0.069	0.069	
Disease Severity at baseline (EDSS)	<=3.5	218	23	10.55	207	4	1.93	5.46 [1.92 ; 15.52]	5.99 [2.03 ; 17.62];	8.62 [4.13 ; 13.11]; 0	0	0.2768
	>3.5	54	5	9.26	66	3	4.55	2.04 [0.51 ; 8.14]	2.14 [0.49 ; 9.41];	4.71 [-4.51 ; 13.93]; 0.465	0.465	
Gender	Female	178	20	11.24	176	7	3.98	2.83 [1.23 ; 6.51]	3.06 [1.26 ; 7.42];	7.26 [1.79 ; 12.72]; 0.015	0.015	0.0402
	Male	94	8	8.51	97	0	0.00	17.54 [1.03 ; 299.61]	19.16 [1.09 ; 336.89];	8.44 [2.53 ; 14.35]; 0.003	0.003	
Number of baseline Gd-enhancing lesions	>=1	141	15	10.64	135	3	2.22	4.79 [1.42 ; 16.17]	5.24 [1.48 ; 18.53];	8.42 [2.75 ; 14.08]; 0.006	0.006	0.6737
	0	131	13	9.92	136	4	2.94	3.37 [1.13 ; 10.08]	3.64 [1.15 ; 11.46];	6.98 [1.13 ; 12.84]; 0.024	0.024	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	9	7.69	110	2	1.82	4.23 [0.93 ; 19.15]	4.5 [0.95 ; 21.31];	5.87 [0.44 ; 11.31]; 0.06	0.06	0.9
	>=3	42	6	14.29	40	2	5.00	2.86 [0.61 ; 13.34]	3.17 [0.6 ; 16.72];	9.29 [-3.27 ; 21.84]; 0.265	0.265	
	2	113	13	11.50	123	3	2.44	4.72 [1.38 ; 16.12]	5.2 [1.44 ; 18.76];	9.07 [2.58 ; 15.55]; 0.008	0.008	
Received approved disease modifying MS drug prior to enrollment	No	166	21	12.65	186	5	2.69	4.71 [1.82 ; 12.2]	5.24 [1.93 ; 14.24];	9.96 [4.4 ; 15.53]; 0	0	0.5719
	Yes	106	7	6.60	87	2	2.30	2.87 [0.61 ; 13.48]	3.01 [0.61 ; 14.85];	4.3 [-1.38 ; 9.99]; 0.189	0.189	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	28	11.43	251	7	2.79	4.1 [1.82 ; 9.21]	4.5 [1.93 ; 10.5];	8.64 [4.17 ; 13.11]; 0	0	0.9998
	USA and Western Europe	27	0	0.00	22	0	0.00	0.82 [0.02 ; 39.81]	0.82 [0.02 ; 42.89];	-0.39 [-8.11 ; 7.33]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - General disorders and administration site conditions | Influenza like illness

5.1.65 Respiratory, thoracic and mediastinal disorders - Cough

Tabelle 183: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	7	3.98	156	3	1.92	2.07 [0.54 ; 7.86]	2.11 [0.54 ; 8.31];	2.05 [-1.55 ; 5.66]; 0.345	0.345	0.0607
	>= 38 years	96	5	5.21	117	0	0.00	13.38 [0.75 ; 238.99]	14.13 [0.77 ; 258.77];	5.25 [0.5 ; 10]; 0.008	0.008	
Disease Severity at baseline (EDSS)	<=3.5	218	11	5.05	207	3	1.45	3.48 [0.99 ; 12.3]	3.61 [0.99 ; 13.14];	3.6 [0.27 ; 6.93]; 0.055	0.055	0.4529
	>3.5	54	1	1.85	66	0	0.00	3.65 [0.15 ; 87.94]	3.73 [0.15 ; 93.4];	1.98 [-2.79 ; 6.75]; 0.209	0.209	
Gender	Female	178	10	5.62	176	2	1.14	4.94 [1.1 ; 22.24]	5.18 [1.12 ; 23.99];	4.48 [0.75 ; 8.21]; 0.035	0.035	0.5439
	Male	94	2	2.13	97	1	1.03	2.06 [0.19 ; 22.38]	2.09 [0.19 ; 23.41];	1.1 [-2.45 ; 4.64]; 0.617	0.617	
Number of baseline Gd-enhancing lesions	>=1	141	5	3.55	135	2	1.48	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	131	7	5.34	136	1	0.74	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	8	6.84	110	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	2	4.76	40	1	2.50	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	2	1.77	123	2	1.63	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	8	4.82	186	2	1.08	4.48 [0.97 ; 20.81]	4.66 [0.97 ; 22.26];	3.74 [0.16 ; 7.32]; 0.051	0.051	0.8172
	Yes	106	4	3.77	87	1	1.15	3.28 [0.37 ; 28.84]	3.37 [0.37 ; 30.74];	2.62 [-1.64 ; 6.89]; 0.381	0.381	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	12	4.90	251	3	1.20	4.1 [1.17 ; 14.34]	4.26 [1.19 ; 15.28];	3.7 [0.68 ; 6.72]; 0.018	0.018	0.9999
	USA and Western Europe	27	0	0.00	22	0	0.00	0.82 [0.02 ; 39.81]	0.82 [0.02 ; 42.89];	-0.39 [-8.11 ; 7.33]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Respiratory, thoracic and mediastinal disorders | Cough

5.1.66 Reproductive system and breast disorders - Dysmenorrhoea

Tabelle 184: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	12	6.82	156	12	7.69	0.89 [0.41 ; 1.92]	0.88 [0.38 ; 2.02];	-0.87 [-6.47 ; 4.73]; 0.833	0.833	0.0813
	>= 38 years	96	0	0.00	117	3	2.56	0.17 [0.01 ; 3.32]	0.17 [0.01 ; 3.32];	-2.45 [-5.83 ; 0.93]; 0.129	0.129	
Disease Severity at baseline (EDSS)	<=3.5	218	12	5.50	207	14	6.76	0.81 [0.39 ; 1.72]	0.8 [0.36 ; 1.78];	-1.26 [-5.83 ; 3.31]; 0.687	0.687	0.3193
	>3.5	54	0	0.00	66	1	1.52	0.41 [0.02 ; 9.77]	0.4 [0.02 ; 10.03];	-1.33 [-5.67 ; 3.01]; 0.503	0.503	
Gender	Female	178	12	6.74	176	15	8.52	0.79 [0.38 ; 1.64]	0.78 [0.35 ; 1.71];	-1.78 [-7.31 ; 3.75]; 0.554	0.554	1
	Male	94	0	0.00	97	0	0.00	1.03 [0.02 ; 51.46]	1.03 [0.02 ; 52.53];	0.02 [-2.01 ; 2.04]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	6	4.26	135	7	5.19	0.82 [0.28 ; 2.38]	0.81 [0.27 ; 2.48];	-0.93 [-5.94 ; 4.08]; 0.782	0.782	0.9433
	0	131	6	4.58	136	8	5.88	0.78 [0.28 ; 2.18]	0.77 [0.26 ; 2.28];	-1.3 [-6.64 ; 4.03]; 0.785	0.785	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	6	5.13	110	6	5.45	0.94 [0.31 ; 2.83]	0.94 [0.29 ; 3];	-0.33 [-6.16 ; 5.5]; 1	1	0.2035
	>=3	42	1	2.38	40	5	12.50	0.19 [0.02 ; 1.56]	0.17 [0.02 ; 1.53];	-10.12 [-21.36 ; 1.12]; 0.105	0.105	
	2	113	5	4.42	123	4	3.25	1.36 [0.37 ; 4.94]	1.38 [0.36 ; 5.26];	1.17 [-3.75 ; 6.09]; 0.741	0.741	
Received approved disease modifying MS drug prior to enrollment	No	166	7	4.22	186	13	6.99	0.6 [0.25 ; 1.48]	0.59 [0.23 ; 1.51];	-2.77 [-7.54 ; 2]; 0.357	0.357	0.1728
	Yes	106	5	4.72	87	2	2.30	2.05 [0.41 ; 10.32]	2.1 [0.4 ; 11.12];	2.42 [-2.7 ; 7.54]; 0.461	0.461	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	12	4.90	251	15	5.98	0.82 [0.39 ; 1.72]	0.81 [0.37 ; 1.77];	-1.08 [-5.07 ; 2.91]; 0.694	0.694	1
	USA and Western Europe	27	0	0.00	22	0	0.00	0.82 [0.02 ; 39.81]	0.82 [0.02 ; 42.89];	-0.39 [-8.11 ; 7.33]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Reproductive system and breast disorders | Dysmenorrhoea

5.1.67 Infections and infestations - Rhinitis

Tabelle 185: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	6	3.41	156	11	7.05	0.48 [0.18 ; 1.28]	0.47 [0.17 ; 1.29];	-3.64 [-8.47 ; 1.19]; 0.144	0.144	0.8457
	>= 38 years	96	1	1.04	117	2	1.71	0.61 [0.06 ; 6.62]	0.61 [0.05 ; 6.78];	-0.67 [-3.77 ; 2.44]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	218	7	3.21	207	11	5.31	0.6 [0.24 ; 1.53]	0.59 [0.22 ; 1.56];	-2.1 [-5.95 ; 1.75]; 0.339	0.339	0.2195
	>3.5	54	0	0.00	66	2	3.03	0.24 [0.01 ; 4.97]	0.24 [0.01 ; 5.04];	-2.82 [-8.01 ; 2.36]; 0.501	0.501	
Gender	Female	178	4	2.25	176	10	5.68	0.4 [0.13 ; 1.24]	0.38 [0.12 ; 1.24];	-3.43 [-7.49 ; 0.62]; 0.11	0.11	0.3305
	Male	94	3	3.19	97	3	3.09	1.03 [0.21 ; 4.98]	1.03 [0.2 ; 5.25];	0.1 [-4.85 ; 5.05]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	4	2.84	135	6	4.44	0.64 [0.18 ; 2.21]	0.63 [0.17 ; 2.28];	-1.61 [-6.03 ; 2.82]; 0.534	0.534	0.6963
	0	131	3	2.29	136	7	5.15	0.44 [0.12 ; 1.68]	0.43 [0.11 ; 1.71];	-2.86 [-7.37 ; 1.65]; 0.335	0.335	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	2	1.71	110	8	7.27	0.24 [0.05 ; 1.08]	0.22 [0.05 ; 1.07];	-5.56 [-10.95 ; -0.17]; 0.053	0.053	0.2417
	>=3	42	2	4.76	40	1	2.50	1.9 [0.18 ; 20.19]	1.95 [0.17 ; 22.39];	2.26 [-5.79 ; 10.32]; 1	1	
	2	113	3	2.65	123	4	3.25	0.82 [0.19 ; 3.57]	0.81 [0.18 ; 3.71];	-0.6 [-4.91 ; 3.72]; 1	1	
Received approved disease modifying MS drug prior to enrollment	No	166	6	3.61	186	9	4.84	0.75 [0.27 ; 2.05]	0.74 [0.26 ; 2.12];	-1.22 [-5.42 ; 2.97]; 0.608	0.608	0.2597
	Yes	106	1	0.94	87	4	4.60	0.21 [0.02 ; 1.8]	0.2 [0.02 ; 1.8];	-3.65 [-8.42 ; 1.12]; 0.177	0.177	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	7	2.86	251	13	5.18	0.55 [0.22 ; 1.36]	0.54 [0.21 ; 1.37];	-2.32 [-5.77 ; 1.12]; 0.254	0.254	0.9999
	USA and Western Europe	27	0	0.00	22	0	0.00	0.82 [0.02 ; 39.81]	0.82 [0.02 ; 42.89];	-0.39 [-8.11 ; 7.33]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Rhinitis

5.1.68 General disorders and administration site conditions - Hyperthermia

Tabelle 186: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	18	10.23	156	2	1.28	7.98 [1.88 ; 33.83]	8.77 [2 ; 38.44];	8.95 [4.13 ; 13.76]; 0.001	0.001	0.0076
	>= 38 years	96	0	0.00	117	2	1.71	0.24 [0.01 ; 5.01]	0.24 [0.01 ; 5.05];	-1.6 [-4.57 ; 1.36]; 0.503	0.503	
Disease Severity at baseline (EDSS)	<=3.5	218	14	6.42	207	2	0.97	6.65 [1.53 ; 28.89]	7.03 [1.58 ; 31.34];	5.46 [1.94 ; 8.97]; 0.004	0.004	0.3891
	>3.5	54	4	7.41	66	2	3.03	2.44 [0.47 ; 12.84]	2.56 [0.45 ; 14.54];	4.38 [-3.74 ; 12.49]; 0.407	0.407	
Gender	Female	178	13	7.30	176	3	1.70	4.28 [1.24 ; 14.78]	4.54 [1.27 ; 16.23];	5.6 [1.32 ; 9.87]; 0.019	0.019	0.8927
	Male	94	5	5.32	97	1	1.03	5.16 [0.61 ; 43.34]	5.39 [0.62 ; 47.06];	4.29 [-0.67 ; 9.25]; 0.114	0.114	
Number of baseline Gd-enhancing lesions	>=1	141	11	7.80	135	3	2.22	3.51 [1 ; 12.31]	3.72 [1.02 ; 13.65];	5.58 [0.5 ; 10.66]; 0.052	0.052	0.557
	0	131	7	5.34	136	1	0.74	7.27 [0.91 ; 58.26]	7.62 [0.92 ; 62.82];	4.61 [0.5 ; 8.72]; 0.033	0.033	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	3	2.56	110	0	0.00	6.58 [0.34 ; 126.04]	6.76 [0.34 ; 132.3];	2.52 [-0.79 ; 5.82]; 0.123	0.123	0.4243
	>=3	42	7	16.67	40	1	2.50	6.67 [0.86 ; 51.79]	7.8 [0.91 ; 66.59];	14.17 [1.9 ; 26.43]; 0.058	0.058	
	2	113	8	7.08	123	3	2.44	2.9 [0.79 ; 10.67]	3.05 [0.79 ; 11.79];	4.64 [-0.82 ; 10.1]; 0.124	0.124	
Received approved disease modifying MS drug prior to enrollment	No	166	11	6.63	186	2	1.08	6.16 [1.39 ; 27.4]	6.53 [1.43 ; 29.9];	5.55 [1.49 ; 9.62]; 0.008	0.008	0.493
	Yes	106	7	6.60	87	2	2.30	2.87 [0.61 ; 13.48]	3.01 [0.61 ; 14.85];	4.3 [-1.38 ; 9.99]; 0.189	0.189	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	18	7.35	251	4	1.59	4.61 [1.58 ; 13.43]	4.9 [1.63 ; 14.68];	5.75 [2.14 ; 9.37]; 0.002	0.002	0.9998
	USA and Western Europe	27	0	0.00	22	0	0.00	0.82 [0.02 ; 39.81]	0.82 [0.02 ; 42.89];	-0.39 [-8.11 ; 7.33]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - General disorders and administration site conditions | Hyperthermia

5.1.69 Infections and infestations - Acute sinusitis

Tabelle 187: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	10	5.68	156	1	0.64	8.86 [1.15 ; 68.46]	9.34 [1.18 ; 73.79];	5.04 [1.4 ; 8.68]; 0.012	0.012	0.0554
	>= 38 years	96	0	0.00	117	1	0.85	0.41 [0.02 ; 9.84]	0.4 [0.02 ; 9.99];	-0.76 [-3.23 ; 1.72]; 0.503	0.503	
Disease Severity at baseline (EDSS)	<=3.5	218	9	4.13	207	2	0.97	4.27 [0.93 ; 19.54]	4.41 [0.94 ; 20.68];	3.16 [0.2 ; 6.12]; 0.063	0.063	0.494
	>3.5	54	1	1.85	66	0	0.00	3.65 [0.15 ; 87.94]	3.73 [0.15 ; 93.4];	1.98 [-2.79 ; 6.75]; 0.209	0.209	
Gender	Female	178	9	5.06	176	2	1.14	4.45 [0.98 ; 20.3]	4.63 [0.99 ; 21.76];	3.92 [0.34 ; 7.5]; 0.061	0.061	0.5345
	Male	94	1	1.06	97	0	0.00	3.09 [0.13 ; 75.03]	3.13 [0.13 ; 77.76];	1.07 [-1.81 ; 3.95]; 0.244	0.244	
Number of baseline Gd-enhancing lesions	>=1	141	4	2.84	135	1	0.74	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	131	6	4.58	136	1	0.74	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	4	3.42	110	1	0.91	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	2	4.76	40	1	2.50	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	4	3.54	123	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	6	3.61	186	1	0.54	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	Yes	106	4	3.77	87	1	1.15	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	10	4.08	251	2	0.80	5.12 [1.13 ; 23.14]	5.3 [1.15 ; 24.43];	3.28 [0.57 ; 6]; 0.02	0.02	0.9999
	USA and Western Europe	27	0	0.00	22	0	0.00	0.82 [0.02 ; 39.81]	0.82 [0.02 ; 42.89];	-0.39 [-8.11 ; 7.33]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Acute sinusitis

5.1.70 Infections and infestations - Gastroenteritis

Tabelle 188: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	3	1.70	156	8	5.13	0.33 [0.09 ; 1.23]	0.32 [0.08 ; 1.23];	-3.42 [-7.38 ; 0.53]; 0.123	0.123	0.3504
	>= 38 years	96	0	0.00	117	2	1.71	0.24 [0.01 ; 5.01]	0.24 [0.01 ; 5.05];	-1.6 [-4.57 ; 1.36]; 0.503	0.503	
Disease Severity at baseline (EDSS)	<=3.5	218	3	1.38	207	9	4.35	0.32 [0.09 ; 1.15]	0.31 [0.08 ; 1.15];	-2.97 [-6.15 ; 0.21]; 0.081	0.081	0.5094
	>3.5	54	0	0.00	66	1	1.52	0.41 [0.02 ; 9.77]	0.4 [0.02 ; 10.03];	-1.33 [-5.67 ; 3.01]; 0.503	0.503	
Gender	Female	178	2	1.12	176	8	4.55	0.25 [0.05 ; 1.15]	0.24 [0.05 ; 1.14];	-3.42 [-6.87 ; 0.02]; 0.061	0.061	0.6114
	Male	94	1	1.06	97	2	2.06	0.52 [0.05 ; 5.6]	0.51 [0.05 ; 5.73];	-1 [-4.5 ; 2.51]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	1	0.71	135	4	2.96	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	131	2	1.53	136	6	4.41	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	2	1.71	110	4	3.64	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	0	0.00	40	1	2.50	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	1	0.88	123	5	4.07	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	2	1.20	186	6	3.23	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	Yes	106	1	0.94	87	4	4.60	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	3	1.22	251	9	3.59	0.34 [0.09 ; 1.25]	0.33 [0.09 ; 1.25];	-2.36 [-5.04 ; 0.32]; 0.141	0.141	0.4134
	USA and Western Europe	27	0	0.00	22	1	4.55	0.27 [0.01 ; 6.41]	0.26 [0.01 ; 6.72];	-4.74 [-15.96 ; 6.48]; 0.208	0.208	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Gastroenteritis

5.1.71 Blood and lymphatic system disorders - Leukocytosis

Tabelle 189: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	4	2.27	156	9	5.77	0.39 [0.12 ; 1.25]	0.38 [0.11 ; 1.26];	-3.5 [-7.77 ; 0.77]; 0.155	0.155	0.9687
	>= 38 years	96	1	1.04	117	3	2.56	0.41 [0.04 ; 3.84]	0.4 [0.04 ; 3.91];	-1.52 [-5.03 ; 1.99]; 0.629	0.629	
Disease Severity at baseline (EDSS)	<=3.5	218	3	1.38	207	9	4.35	0.32 [0.09 ; 1.15]	0.31 [0.08 ; 1.15];	-2.97 [-6.15 ; 0.21]; 0.081	0.081	0.4052
	>3.5	54	2	3.70	66	3	4.55	0.81 [0.14 ; 4.7]	0.81 [0.13 ; 5.02];	-0.84 [-7.96 ; 6.27]; 1	1	
Gender	Female	178	4	2.25	176	9	5.11	0.44 [0.14 ; 1.4]	0.43 [0.13 ; 1.41];	-2.87 [-6.78 ; 1.05]; 0.17	0.17	0.8561
	Male	94	1	1.06	97	3	3.09	0.34 [0.04 ; 3.25]	0.34 [0.03 ; 3.3];	-2.03 [-6.05 ; 1.99]; 0.621	0.621	
Number of baseline Gd-enhancing lesions	>=1	141	3	2.13	135	9	6.67	0.32 [0.09 ; 1.15]	0.3 [0.08 ; 1.15];	-4.54 [-9.37 ; 0.3]; 0.08	0.08	0.4799
	0	131	2	1.53	136	3	2.21	0.69 [0.12 ; 4.08]	0.69 [0.11 ; 4.18];	-0.68 [-3.92 ; 2.56]; 1	1	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	0	0.00	110	8	7.27	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	2	4.76	40	1	2.50	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	3	2.65	123	3	2.44	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	0	0.00	186	6	3.23	0.09 [0 ; 1.52]	0.08 [0 ; 1.49];	-3.18 [-5.93 ; -0.42]; 0.031	0.031	0.0366
	Yes	106	5	4.72	87	6	6.90	0.68 [0.22 ; 2.17]	0.67 [0.2 ; 2.27];	-2.18 [-8.86 ; 4.5]; 0.548	0.548	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	5	2.04	251	12	4.78	0.43 [0.15 ; 1.19]	0.41 [0.14 ; 1.2];	-2.74 [-5.92 ; 0.44]; 0.137	0.137	0.9999
	USA and Western Europe	27	0	0.00	22	0	0.00	0.82 [0.02 ; 39.81]	0.82 [0.02 ; 42.89];	-0.39 [-8.11 ; 7.33]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Blood and lymphatic system disorders | Leukocytosis

5.1.72 Blood and lymphatic system disorders - Neutrophilia

Tabelle 190: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	5	2.84	156	8	5.13	0.55 [0.19 ; 1.66]	0.54 [0.17 ; 1.69];	-2.29 [-6.53 ; 1.96]; 0.397	0.397	0.4853
	>= 38 years	96	1	1.04	117	5	4.27	0.24 [0.03 ; 2.05]	0.24 [0.03 ; 2.05];	-3.23 [-7.42 ; 0.96]; 0.226	0.226	
Disease Severity at baseline (EDSS)	<=3.5	218	4	1.83	207	8	3.86	0.47 [0.15 ; 1.55]	0.46 [0.14 ; 1.57];	-2.03 [-5.2 ; 1.14]; 0.25	0.25	0.9931
	>3.5	54	2	3.70	66	5	7.58	0.49 [0.1 ; 2.42]	0.47 [0.09 ; 2.52];	-3.87 [-12 ; 4.26]; 0.456	0.456	
Gender	Female	178	5	2.81	176	9	5.11	0.55 [0.19 ; 1.61]	0.54 [0.18 ; 1.63];	-2.3 [-6.36 ; 1.76]; 0.29	0.29	0.5292
	Male	94	1	1.06	97	4	4.12	0.26 [0.03 ; 2.27]	0.25 [0.03 ; 2.28];	-3.06 [-7.53 ; 1.41]; 0.369	0.369	
Number of baseline Gd-enhancing lesions	>=1	141	3	2.13	135	9	6.67	0.32 [0.09 ; 1.15]	0.3 [0.08 ; 1.15];	-4.54 [-9.37 ; 0.3]; 0.08	0.08	0.364
	0	131	3	2.29	136	4	2.94	0.78 [0.18 ; 3.41]	0.77 [0.17 ; 3.52];	-0.65 [-4.48 ; 3.17]; 1	1	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	0	0.00	110	9	8.18	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	3	7.14	40	2	5.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	3	2.65	123	2	1.63	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	1	0.60	186	6	3.23	0.19 [0.02 ; 1.54]	0.18 [0.02 ; 1.53];	-2.62 [-5.42 ; 0.18]; 0.126	0.126	0.3295
	Yes	106	5	4.72	87	7	8.05	0.59 [0.19 ; 1.78]	0.57 [0.17 ; 1.85];	-3.33 [-10.33 ; 3.67]; 0.381	0.381	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	6	2.45	251	13	5.18	0.47 [0.18 ; 1.22]	0.46 [0.17 ; 1.23];	-2.73 [-6.09 ; 0.63]; 0.159	0.159	0.9999
	USA and Western Europe	27	0	0.00	22	0	0.00	0.82 [0.02 ; 39.81]	0.82 [0.02 ; 42.89];	-0.39 [-8.11 ; 7.33]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Blood and lymphatic system disorders | Neutrophilia

5.1.73 Investigations - Lymphocyte count decreased

Tabelle 191: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	9	5.11	156	2	1.28	3.99 [0.88 ; 18.18]	4.15 [0.88 ; 19.51];	3.83 [0.13 ; 7.53]; 0.066	0.066	0.1217
	< 38 years	176	9	5.11	156	0	0.00	3.99 [0.88 ; 18.18]	4.15 [0.88 ; 19.51];	3.83 [0.13 ; 7.53]; 0.066	0.066	
	< 38 years	176	6	3.41	156	2	1.28	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	< 38 years	176	6	3.41	156	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	>= 38 years	96	6	6.25	117	0	0.00	15.81 [0.9 ; 277.22]	16.88 [0.94 ; 303.54];	6.28 [1.17 ; 11.39]; 0.007	0.007	
	>= 38 years	96	6	6.25	117	0	0.00	15.81 [0.9 ; 277.22]	16.88 [0.94 ; 303.54];	6.28 [1.17 ; 11.39]; 0.007	0.007	
	>= 38 years	96	6	6.25	117	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	>= 38 years	96	6	6.25	117	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	218	12	5.50	207	2	0.97	5.7 [1.29 ; 25.15]	5.97 [1.32 ; 27.01];	4.54 [1.23 ; 7.85]; 0.012	0.012	0.3107
	>3.5	54	3	5.56	66	0	0.00	8.53 [0.45 ; 161.57]	9.04 [0.46 ; 178.93];	5.62 [-1.16 ; 12.39]; 0.042	0.042	
Gender	Female	178	8	4.49	176	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	Male	94	4	4.26	97	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of baseline Gd-enhancing lesions	>=1	141	8	5.67	135	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	131	7	5.34	136	2	1.47	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Number of relapses experienced in the 2 years prior to study start	<=1	117	3	2.56	110	1	0.91	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	5	11.90	40	1	2.50	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	7	6.19	123	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	12	7.23	186	2	1.08	6.72 [1.53 ; 29.6]	7.17 [1.58 ; 32.52];	6.15 [1.94 ; 10.36]; 0.005	0.005	0.4334
	Yes	106	3	2.83	87	0	0.00	5.76 [0.3 ; 109.96]	5.92 [0.3 ; 116.14];	2.7 [-1.02 ; 6.42]; 0.129	0.129	
Region	Eastern Europe	245	15	6.12	251	2	0.80	7.68 [1.78 ; 33.25]	8.12 [1.84 ; 35.89];	5.33 [2.13 ; 8.52]; 0.001	0.001	0.9999
	USA and Western Europe	27	0	0.00	22	0	0.00	0.82 [0.02 ; 39.81]	0.82 [0.02 ; 42.89];	-0.39 [-8.11 ; 7.33]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Investigations | Lymphocyte count decreased

5.2 Non-severe TEAE

5.2.1 General disorders and administration site conditions - any

Tabelle 192: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	92	52.27	156	34	21.79	2.4 [1.73 ; 3.33]	3.93 [2.43 ; 6.36];	30.48 [20.66 ; 40.3]; 0	0	0.0376
	>= 38 years	96	34	35.42	117	28	23.93	1.48 [0.97 ; 2.25]	1.74 [0.96 ; 3.16];	11.49 [-0.82 ; 23.79]; 0.071	0.071	
Disease Severity at baseline (EDSS)	<=3.5	218	107	49.08	207	44	21.26	2.31 [1.72 ; 3.1]	3.57 [2.33 ; 5.47];	27.83 [19.16 ; 36.49]; 0	0	0.0468
	>3.5	54	19	35.19	66	18	27.27	1.29 [0.76 ; 2.2]	1.45 [0.66 ; 3.15];	7.91 [-8.75 ; 24.58]; 0.428	0.428	
Gender	Female	178	89	50.00	176	44	25.00	2 [1.49 ; 2.69]	3 [1.91 ; 4.71];	25 [15.26 ; 34.74]; 0	0	0.899
	Male	94	37	39.36	97	18	18.56	2.12 [1.3 ; 3.45]	2.85 [1.48 ; 5.5];	20.81 [8.26 ; 33.35]; 0.002	0.002	
Number of baseline Gd-enhancing lesions	>=1	141	70	49.65	135	31	22.96	2.16 [1.52 ; 3.07]	3.31 [1.97 ; 5.56];	26.68 [15.8 ; 37.57]; 0	0	0.4782
	0	131	56	42.75	136	31	22.79	1.88 [1.3 ; 2.71]	2.53 [1.49 ; 4.29];	19.95 [8.93 ; 30.98]; 0.001	0.001	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	51	43.59	110	25	22.73	1.92 [1.28 ; 2.87]	2.63 [1.48 ; 4.68];	20.86 [8.94 ; 32.78]; 0.001	0.001	0.7541
	>=3	42	24	57.14	40	10	25.00	2.29 [1.26 ; 4.15]	4 [1.56 ; 10.25];	32.14 [12.04 ; 52.24]; 0.004	0.004	
	2	113	51	45.13	123	27	21.95	2.06 [1.39 ; 3.04]	2.92 [1.66 ; 5.15];	23.18 [11.45 ; 34.92]; 0	0	
Received approved disease modifying MS	No	166	76	45.78	186	39	20.97	2.18 [1.58 ; 3.02]	3.18 [2 ; 5.08];	24.82 [15.24 ; 34.39]; 0	0	0.5282
	Yes	106	50	47.17	87	23	26.44	1.78 [1.19 ; 2.67]	2.48 [1.35 ; 4.57];	20.73 [7.46 ; 34.01]; 0.004	0.004	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
drug prior to enrollment												
Region	Eastern Europe	245	113	46.12	251	49	19.52	2.36 [1.78 ; 3.14]	3.53 [2.36 ; 5.27];	26.6 [18.66 ; 34.54]; 0	0	0.0054
	USA and Western Europe	27	13	48.15	22	13	59.09	0.81 [0.48 ; 1.38]	0.64 [0.21 ; 2];	-10.94 [-38.82 ; 16.94]; 0.567	0.567	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - General disorders and administration site conditions | any

5.2.2 Injury, poisoning and procedural complications - any

Tabelle 193: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	36	20.45	156	18	11.54	1.77 [1.05 ; 2.99]	1.97 [1.07 ; 3.64];	8.92 [1.13 ; 16.7]; 0.036	0.036	0.0841
	>= 38 years	96	10	10.42	117	15	12.82	0.81 [0.38 ; 1.73]	0.79 [0.34 ; 1.85];	-2.4 [-11.01 ; 6.2]; 0.671	0.671	
Disease Severity at baseline (EDSS)	<=3.5	218	40	18.35	207	23	11.11	1.65 [1.03 ; 2.66]	1.8 [1.03 ; 3.12];	7.24 [0.55 ; 13.93]; 0.041	0.041	0.1231
	>3.5	54	6	11.11	66	10	15.15	0.73 [0.28 ; 1.89]	0.7 [0.24 ; 2.07];	-4.04 [-16.09 ; 8]; 0.596	0.596	
Gender	Female	178	33	18.54	176	20	11.36	1.63 [0.97 ; 2.73]	1.78 [0.97 ; 3.23];	7.18 [-0.21 ; 14.56]; 0.073	0.073	0.3021
	Male	94	13	13.83	97	13	13.40	1.03 [0.51 ; 2.11]	1.04 [0.45 ; 2.37];	0.43 [-9.3 ; 10.16]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	22	15.60	135	17	12.59	1.24 [0.69 ; 2.23]	1.28 [0.65 ; 2.54];	3.01 [-5.19 ; 11.21]; 0.494	0.494	0.5827
	0	131	24	18.32	136	16	11.76	1.56 [0.87 ; 2.8]	1.68 [0.85 ; 3.33];	6.56 [-2 ; 15.11]; 0.17	0.17	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	25	21.37	110	18	16.36	1.31 [0.76 ; 2.26]	1.39 [0.71 ; 2.72];	5 [-5.14 ; 15.15]; 0.398	0.398	0.2573
	>=3	42	6	14.29	40	1	2.50	5.71 [0.72 ; 45.39]	6.5 [0.75 ; 56.64];	11.79 [0.15 ; 23.42]; 0.11	0.11	
	2	113	15	13.27	123	14	11.38	1.17 [0.59 ; 2.31]	1.19 [0.55 ; 2.59];	1.89 [-6.51 ; 10.3]; 0.695	0.695	
Received approved disease modifying MS drug prior to enrollment	No	166	30	18.07	186	26	13.98	1.29 [0.8 ; 2.09]	1.36 [0.77 ; 2.41];	4.09 [-3.59 ; 11.78]; 0.31	0.31	0.4676
	Yes	106	16	15.09	87	7	8.05	1.88 [0.81 ; 4.35]	2.03 [0.8 ; 5.19];	7.05 [-1.85 ; 15.94]; 0.18	0.18	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	38	15.51	251	24	9.56	1.62 [1 ; 2.62]	1.74 [1.01 ; 2.99];	5.95 [0.14 ; 11.76]; 0.057	0.057	0.1141
	USA and Western Europe	27	8	29.63	22	9	40.91	0.72 [0.34 ; 1.56]	0.61 [0.19 ; 1.99];	-11.28 [-38.09 ; 15.53]; 0.548	0.548	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Injury, poisoning and procedural complications | any

5.2.3 Musculoskeletal and connective tissue disorders - any

Tabelle 194: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	46	26.14	156	28	17.95	1.46 [0.96 ; 2.21]	1.62 [0.95 ; 2.75];	8.19 [-0.67 ; 17.04]; 0.086	0.086	0.5298
	>= 38 years	96	28	29.17	117	29	24.79	1.18 [0.76 ; 1.83]	1.25 [0.68 ; 2.3];	4.38 [-7.61 ; 16.38]; 0.535	0.535	
Disease Severity at baseline (EDSS)	<=3.5	218	67	30.73	207	44	21.26	1.45 [1.04 ; 2.01]	1.64 [1.06 ; 2.55];	9.48 [1.2 ; 17.76]; 0.028	0.028	0.0687
	>3.5	54	7	12.96	66	13	19.70	0.66 [0.28 ; 1.53]	0.61 [0.22 ; 1.65];	-6.73 [-19.86 ; 6.39]; 0.461	0.461	
Gender	Female	178	55	30.90	176	43	24.43	1.26 [0.9 ; 1.78]	1.38 [0.87 ; 2.21];	6.47 [-2.83 ; 15.76]; 0.192	0.192	0.856
	Male	94	19	20.21	97	14	14.43	1.4 [0.75 ; 2.63]	1.5 [0.7 ; 3.2];	5.78 [-4.94 ; 16.49]; 0.341	0.341	
Number of baseline Gd-enhancing lesions	>=1	141	41	29.08	135	28	20.74	1.4 [0.92 ; 2.13]	1.57 [0.9 ; 2.72];	8.34 [-1.81 ; 18.48]; 0.127	0.127	0.5664
	0	131	33	25.19	136	29	21.32	1.18 [0.76 ; 1.83]	1.24 [0.7 ; 2.2];	3.87 [-6.26 ; 14]; 0.472	0.472	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	32	27.35	110	28	25.45	1.07 [0.7 ; 1.66]	1.1 [0.61 ; 1.99];	1.9 [-9.57 ; 13.36]; 0.765	0.765	0.5238
	>=3	42	9	21.43	40	6	15.00	1.43 [0.56 ; 3.65]	1.55 [0.49 ; 4.83];	6.43 [-10.2 ; 23.06]; 0.571	0.571	
	2	113	33	29.20	123	23	18.70	1.56 [0.98 ; 2.49]	1.79 [0.98 ; 3.29];	10.5 [-0.35 ; 21.36]; 0.067	0.067	
Received approved disease modifying MS drug prior to enrollment	No	166	47	28.31	186	37	19.89	1.42 [0.98 ; 2.07]	1.59 [0.97 ; 2.61];	8.42 [-0.52 ; 17.36]; 0.079	0.079	0.4367
	Yes	106	27	25.47	87	20	22.99	1.11 [0.67 ; 1.83]	1.14 [0.59 ; 2.22];	2.48 [-9.64 ; 14.61]; 0.738	0.738	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	58	23.67	251	48	19.12	1.24 [0.88 ; 1.74]	1.31 [0.85 ; 2.02];	4.55 [-2.66 ; 11.76]; 0.23	0.23	0.4484
	USA and Western Europe	27	16	59.26	22	9	40.91	1.45 [0.8 ; 2.62]	2.1 [0.67 ; 6.6];	18.35 [-9.32 ; 46.02]; 0.256	0.256	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Musculoskeletal and connective tissue disorders | any

5.2.4 Respiratory, thoracic and mediastinal disorders - any

Tabelle 195: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	46	26.14	156	20	12.82	2.04 [1.26 ; 3.29]	2.41 [1.35 ; 4.29];	13.32 [4.97 ; 21.66]; 0.002	0.002	0.6251
	>= 38 years	96	17	17.71	117	12	10.26	1.73 [0.87 ; 3.44]	1.88 [0.85 ; 4.17];	7.45 [-1.96 ; 16.86]; 0.159	0.159	
Disease Severity at baseline (EDSS)	<=3.5	218	58	26.61	207	24	11.59	2.29 [1.48 ; 3.55]	2.76 [1.64 ; 4.65];	15.01 [7.7 ; 22.32]; 0	0	0.0421
	>3.5	54	5	9.26	66	8	12.12	0.76 [0.27 ; 2.2]	0.74 [0.23 ; 2.41];	-2.86 [-13.9 ; 8.17]; 0.77	0.77	
Gender	Female	178	45	25.28	176	22	12.50	2.02 [1.27 ; 3.22]	2.37 [1.35 ; 4.15];	12.78 [4.74 ; 20.82]; 0.003	0.003	0.7859
	Male	94	18	19.15	97	10	10.31	1.86 [0.9 ; 3.81]	2.06 [0.9 ; 4.74];	8.84 [-1.15 ; 18.83]; 0.103	0.103	
Number of baseline Gd-enhancing lesions	>=1	141	37	26.24	135	18	13.33	1.97 [1.18 ; 3.28]	2.31 [1.24 ; 4.31];	12.91 [3.66 ; 22.16]; 0.01	0.01	0.8848
	0	131	26	19.85	136	14	10.29	1.93 [1.05 ; 3.53]	2.16 [1.07 ; 4.35];	9.55 [1.02 ; 18.08]; 0.039	0.039	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	31	26.50	110	15	13.64	1.94 [1.11 ; 3.4]	2.28 [1.15 ; 4.52];	12.86 [2.61 ; 23.11]; 0.02	0.02	0.9765
	>=3	42	11	26.19	40	6	15.00	1.75 [0.71 ; 4.28]	2.01 [0.66 ; 6.09];	11.19 [-6.11 ; 28.49]; 0.279	0.279	
	2	113	21	18.58	123	11	8.94	2.08 [1.05 ; 4.12]	2.32 [1.07 ; 5.07];	9.64 [0.87 ; 18.41]; 0.037	0.037	
Received approved disease modifying MS drug prior to enrollment	No	166	35	21.08	186	23	12.37	1.71 [1.05 ; 2.76]	1.89 [1.07 ; 3.36];	8.72 [0.92 ; 16.52]; 0.031	0.031	0.3232
	Yes	106	28	26.42	87	9	10.34	2.55 [1.27 ; 5.12]	3.11 [1.38 ; 7.02];	16.07 [5.52 ; 26.62]; 0.006	0.006	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	55	22.45	251	29	11.55	1.94 [1.28 ; 2.94]	2.22 [1.36 ; 3.62];	10.9 [4.34 ; 17.45]; 0.002	0.002	0.8137
	USA and Western Europe	27	8	29.63	22	3	13.64	2.17 [0.65 ; 7.23]	2.67 [0.61 ; 11.61];	15.99 [-6.42 ; 38.41]; 0.303	0.303	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Respiratory, thoracic and mediastinal disorders | any

5.2.5 Gastrointestinal disorders - any

Tabelle 196: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	77	43.75	156	71	45.51	0.96 [0.76 ; 1.22]	0.93 [0.6 ; 1.44];	-1.76 [-12.48 ; 8.95]; 0.825	0.825	0.6045
	>= 38 years	96	32	33.33	117	46	39.32	0.85 [0.59 ; 1.22]	0.77 [0.44 ; 1.36];	-5.98 [-18.92 ; 6.95]; 0.394	0.394	
Disease Severity at baseline (EDSS)	<=3.5	218	92	42.20	207	95	45.89	0.92 [0.74 ; 1.14]	0.86 [0.59 ; 1.26];	-3.69 [-13.13 ; 5.75]; 0.494	0.494	0.8816
	>3.5	54	17	31.48	66	22	33.33	0.94 [0.56 ; 1.59]	0.92 [0.43 ; 1.98];	-1.85 [-18.67 ; 14.96]; 0.847	0.847	
Gender	Female	178	77	43.26	176	76	43.18	1 [0.79 ; 1.27]	1 [0.66 ; 1.53];	0.08 [-10.24 ; 10.4]; 1	1	0.3377
	Male	94	32	34.04	97	41	42.27	0.81 [0.56 ; 1.16]	0.7 [0.39 ; 1.27];	-8.23 [-21.95 ; 5.5]; 0.297	0.297	
Number of baseline Gd-enhancing lesions	>=1	141	61	43.26	135	59	43.70	0.99 [0.76 ; 1.3]	0.98 [0.61 ; 1.58];	-0.44 [-12.14 ; 11.26]; 1	1	0.5606
	0	131	48	36.64	136	57	41.91	0.87 [0.65 ; 1.18]	0.8 [0.49 ; 1.31];	-5.27 [-16.97 ; 6.43]; 0.384	0.384	
	NA	0	0	0.00	2	1	50.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	44	37.61	110	48	43.64	0.86 [0.63 ; 1.18]	0.78 [0.46 ; 1.32];	-6.03 [-18.79 ; 6.73]; 0.417	0.417	0.7678
	>=3	42	20	47.62	40	18	45.00	1.06 [0.66 ; 1.69]	1.11 [0.47 ; 2.65];	2.62 [-18.96 ; 24.2]; 0.828	0.828	
	2	113	45	39.82	123	51	41.46	0.96 [0.71 ; 1.31]	0.93 [0.56 ; 1.57];	-1.64 [-14.18 ; 10.9]; 0.895	0.895	
Received approved disease modifying MS drug prior to enrollment	No	166	63	37.95	186	80	43.01	0.88 [0.68 ; 1.14]	0.81 [0.53 ; 1.24];	-5.06 [-15.31 ; 5.19]; 0.385	0.385	0.5004
	Yes	106	46	43.40	87	37	42.53	1.02 [0.74 ; 1.42]	1.04 [0.58 ; 1.84];	0.87 [-13.17 ; 14.9]; 1	1	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	95	38.78	251	103	41.04	0.94 [0.76 ; 1.17]	0.91 [0.64 ; 1.3];	-2.26 [-10.88 ; 6.36]; 0.647	0.647	0.5232
	USA and Western Europe	27	14	51.85	22	14	63.64	0.81 [0.5 ; 1.32]	0.62 [0.19 ; 1.95];	-11.78 [-39.34 ; 15.77]; 0.563	0.563	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Gastrointestinal disorders | any

5.2.6 Infections and infestations - any

Tabelle 197: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	116	65.91	156	102	65.38	1.01 [0.86 ; 1.18]	1.02 [0.65 ; 1.61];	0.52 [-9.71 ; 10.76]; 1	1	0.9637
	>= 38 years	96	51	53.12	117	61	52.14	1.02 [0.79 ; 1.32]	1.04 [0.61 ; 1.79];	0.99 [-12.49 ; 14.46]; 0.891	0.891	
Disease Severity at baseline (EDSS)	<=3.5	218	139	63.76	207	125	60.39	1.06 [0.91 ; 1.23]	1.15 [0.78 ; 1.71];	3.37 [-5.85 ; 12.6]; 0.485	0.485	0.3719
	>3.5	54	28	51.85	66	38	57.58	0.9 [0.65 ; 1.25]	0.79 [0.38 ; 1.64];	-5.72 [-23.61 ; 12.16]; 0.583	0.583	
Gender	Female	178	127	71.35	176	109	61.93	1.15 [0.99 ; 1.34]	1.53 [0.98 ; 2.39];	9.42 [-0.36 ; 19.19]; 0.071	0.071	0.0096
	Male	94	40	42.55	97	54	55.67	0.76 [0.57 ; 1.03]	0.59 [0.33 ; 1.05];	-13.12 [-27.18 ; 0.94]; 0.083	0.083	
Number of baseline Gd-enhancing lesions	>=1	141	90	63.83	135	79	58.52	1.09 [0.9 ; 1.32]	1.25 [0.77 ; 2.03];	5.31 [-6.18 ; 16.8]; 0.389	0.389	0.3217
	0	131	77	58.78	136	84	61.76	0.95 [0.78 ; 1.16]	0.88 [0.54 ; 1.44];	-2.99 [-14.72 ; 8.75]; 0.708	0.708	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	73	62.39	110	65	59.09	1.06 [0.86 ; 1.3]	1.15 [0.67 ; 1.96];	3.3 [-9.4 ; 16.01]; 0.684	0.684	0.1338
	>=3	42	28	66.67	40	19	47.50	1.4 [0.95 ; 2.07]	2.21 [0.91 ; 5.4];	19.17 [-1.87 ; 40.21]; 0.118	0.118	
	2	113	66	58.41	123	79	64.23	0.91 [0.74 ; 1.12]	0.78 [0.46 ; 1.32];	-5.82 [-18.24 ; 6.6]; 0.422	0.422	
Received approved disease modifying MS	No	166	99	59.64	186	110	59.14	1.01 [0.85 ; 1.2]	1.02 [0.67 ; 1.56];	0.5 [-9.78 ; 10.78]; 1	1	0.7509
	Yes	106	68	64.15	87	53	60.92	1.05 [0.84 ; 1.31]	1.15 [0.64 ; 2.06];	3.23 [-10.5 ; 16.96]; 0.657	0.657	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
drug prior to enrollment												
Region	Eastern Europe	245	146	59.59	251	150	59.76	1 [0.86 ; 1.15]	0.99 [0.69 ; 1.42];	-0.17 [-8.8 ; 8.47]; 1	1	0.1721
	USA and Western Europe	27	21	77.78	22	13	59.09	1.32 [0.88 ; 1.97]	2.42 [0.7 ; 8.4];	18.69 [-7.16 ; 44.53]; 0.217	0.217	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | any

5.2.7 Investigations - any

Tabelle 198: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	43	24.43	156	30	19.23	1.27 [0.84 ; 1.92]	1.36 [0.8 ; 2.3];	5.2 [-3.66 ; 14.06]; 0.289	0.289	0.6673
	>= 38 years	96	21	21.88	117	17	14.53	1.51 [0.84 ; 2.69]	1.65 [0.81 ; 3.34];	7.35 [-3.1 ; 17.79]; 0.208	0.208	
Disease Severity at baseline (EDSS)	<=3.5	218	51	23.39	207	37	17.87	1.31 [0.9 ; 1.91]	1.4 [0.87 ; 2.25];	5.52 [-2.15 ; 13.19]; 0.188	0.188	0.6545
	>3.5	54	13	24.07	66	10	15.15	1.59 [0.76 ; 3.34]	1.78 [0.71 ; 4.44];	8.92 [-5.39 ; 23.24]; 0.249	0.249	
Gender	Female	178	40	22.47	176	28	15.91	1.41 [0.91 ; 2.18]	1.53 [0.9 ; 2.62];	6.56 [-1.61 ; 14.74]; 0.138	0.138	0.8482
	Male	94	24	25.53	97	19	19.59	1.3 [0.77 ; 2.22]	1.41 [0.71 ; 2.79];	5.94 [-5.89 ; 17.78]; 0.387	0.387	
Number of baseline Gd-enhancing lesions	>=1	141	36	25.53	135	25	18.52	1.38 [0.88 ; 2.17]	1.51 [0.85 ; 2.68];	7.01 [-2.72 ; 16.75]; 0.192	0.192	0.8738
	0	131	28	21.37	136	22	16.18	1.32 [0.8 ; 2.19]	1.41 [0.76 ; 2.62];	5.2 [-4.16 ; 14.56]; 0.347	0.347	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	25	21.37	110	21	19.09	1.12 [0.67 ; 1.88]	1.15 [0.6 ; 2.2];	2.28 [-8.17 ; 12.72]; 0.742	0.742	0.6144
	>=3	42	15	35.71	40	9	22.50	1.59 [0.79 ; 3.21]	1.91 [0.72 ; 5.07];	13.21 [-6.21 ; 32.64]; 0.229	0.229	
	2	113	24	21.24	123	17	13.82	1.54 [0.87 ; 2.71]	1.68 [0.85 ; 3.33];	7.42 [-2.28 ; 17.12]; 0.169	0.169	
Received approved disease modifying MS drug prior to enrollment	No	166	42	25.30	186	27	14.52	1.74 [1.13 ; 2.7]	1.99 [1.17 ; 3.41];	10.79 [2.46 ; 19.11]; 0.015	0.015	0.0647
	Yes	106	22	20.75	87	20	22.99	0.9 [0.53 ; 1.54]	0.88 [0.44 ; 1.74];	-2.23 [-13.97 ; 9.5]; 0.729	0.729	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	53	21.63	251	43	17.13	1.26 [0.88 ; 1.81]	1.34 [0.85 ; 2.09];	4.5 [-2.45 ; 11.45]; 0.213	0.213	0.2282
	USA and Western Europe	27	11	40.74	22	4	18.18	2.24 [0.83 ; 6.07]	3.09 [0.82 ; 11.67];	22.56 [-2 ; 47.12]; 0.123	0.123	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Investigations | any

5.2.8 Metabolism and nutrition disorders - any

Tabelle 199: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	8	4.55	156	6	3.85	1.18 [0.42 ; 3.33]	1.19 [0.4 ; 3.51];	0.7 [-3.61 ; 5.01]; 0.792	0.792	0.4675
	>= 38 years	96	4	4.17	117	2	1.71	2.44 [0.46 ; 13.02]	2.5 [0.45 ; 13.95];	2.46 [-2.18 ; 7.09]; 0.413	0.413	
Disease Severity at baseline (EDSS)	<=3.5	218	12	5.50	207	3	1.45	3.8 [1.09 ; 13.27]	3.96 [1.1 ; 14.25];	4.06 [0.62 ; 7.49]; 0.033	0.033	0.001
	>3.5	54	0	0.00	66	5	7.58	0.11 [0.01 ; 1.96]	0.1 [0.01 ; 1.9];	-7.3 [-14.34 ; -0.26]; 0.033	0.033	
Gender	Female	178	7	3.93	176	4	2.27	1.73 [0.52 ; 5.81]	1.76 [0.51 ; 6.12];	1.66 [-1.95 ; 5.27]; 0.542	0.542	0.7498
	Male	94	5	5.32	97	4	4.12	1.29 [0.36 ; 4.66]	1.31 [0.34 ; 5.02];	1.2 [-4.82 ; 7.22]; 0.745	0.745	
Number of baseline Gd-enhancing lesions	>=1	141	9	6.38	135	3	2.22	2.87 [0.79 ; 10.38]	3 [0.79 ; 11.33];	4.16 [-0.58 ; 8.9]; 0.138	0.138	0.1027
	0	131	3	2.29	136	5	3.68	0.62 [0.15 ; 2.55]	0.61 [0.14 ; 2.62];	-1.39 [-5.46 ; 2.68]; 0.723	0.723	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	6	5.13	110	3	2.73	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	2	4.76	40	1	2.50	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	4	3.54	123	4	3.25	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	5	3.01	186	4	2.15	1.4 [0.38 ; 5.13]	1.41 [0.37 ; 5.35];	0.86 [-2.47 ; 4.19]; 0.74	0.74	0.968
	Yes	106	7	6.60	87	4	4.60	1.44 [0.43 ; 4.75]	1.47 [0.42 ; 5.19];	2.01 [-4.45 ; 8.47]; 0.757	0.757	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	9	3.67	251	6	2.39	1.54 [0.56 ; 4.25]	1.56 [0.55 ; 4.44];	1.28 [-1.74 ; 4.3]; 0.443	0.443	0.8423
	USA and Western Europe	27	3	11.11	22	2	9.09	1.22 [0.22 ; 6.68]	1.25 [0.19 ; 8.23];	2.02 [-14.86 ; 18.9]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Metabolism and nutrition disorders | any

5.2.9 Nervous system disorders - any

Tabelle 200: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	92	52.27	156	70	44.87	1.16 [0.93 ; 1.46]	1.35 [0.87 ; 2.07];	7.4 [-3.34 ; 18.14]; 0.188	0.188	0.3803
	>= 38 years	96	34	35.42	117	42	35.90	0.99 [0.69 ; 1.42]	0.98 [0.56 ; 1.72];	-0.48 [-13.41 ; 12.45]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	218	110	50.46	207	86	41.55	1.21 [0.99 ; 1.5]	1.43 [0.98 ; 2.1];	8.91 [-0.53 ; 18.35]; 0.08	0.08	0.0671
	>3.5	54	16	29.63	66	26	39.39	0.75 [0.45 ; 1.25]	0.65 [0.3 ; 1.39];	-9.76 [-26.71 ; 7.19]; 0.337	0.337	
Gender	Female	178	93	52.25	176	75	42.61	1.23 [0.98 ; 1.53]	1.47 [0.97 ; 2.24];	9.63 [-0.72 ; 19.99]; 0.072	0.072	0.1596
	Male	94	33	35.11	97	37	38.14	0.92 [0.63 ; 1.34]	0.88 [0.49 ; 1.58];	-3.04 [-16.7 ; 10.62]; 0.764	0.764	
Number of baseline Gd-enhancing lesions	>=1	141	67	47.52	135	55	40.74	1.17 [0.89 ; 1.52]	1.32 [0.82 ; 2.12];	6.78 [-4.91 ; 18.47]; 0.277	0.277	0.6693
	0	131	59	45.04	136	57	41.91	1.07 [0.82 ; 1.41]	1.14 [0.7 ; 1.84];	3.13 [-8.76 ; 15.02]; 0.623	0.623	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	53	45.30	110	48	43.64	1.04 [0.78 ; 1.39]	1.07 [0.63 ; 1.81];	1.66 [-11.27 ; 14.6]; 0.894	0.894	0.7382
	>=3	42	19	45.24	40	14	35.00	1.29 [0.75 ; 2.21]	1.53 [0.63 ; 3.73];	10.24 [-10.86 ; 31.33]; 0.376	0.376	
	2	113	54	47.79	123	50	40.65	1.18 [0.88 ; 1.57]	1.34 [0.8 ; 2.24];	7.14 [-5.52 ; 19.79]; 0.295	0.295	
Received approved disease modifying MS drug prior to enrollment	No	166	77	46.39	186	79	42.47	1.09 [0.86 ; 1.38]	1.17 [0.77 ; 1.79];	3.91 [-6.48 ; 14.31]; 0.519	0.519	0.6162
	Yes	106	49	46.23	87	33	37.93	1.22 [0.87 ; 1.71]	1.41 [0.79 ; 2.51];	8.3 [-5.63 ; 22.23]; 0.306	0.306	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	106	43.27	251	100	39.84	1.09 [0.88 ; 1.34]	1.15 [0.81 ; 1.65];	3.42 [-5.25 ; 12.09]; 0.467	0.467	0.2524
	USA and Western Europe	27	20	74.07	22	12	54.55	1.36 [0.87 ; 2.11]	2.38 [0.72 ; 7.92];	19.53 [-7.04 ; 46.1]; 0.228	0.228	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Nervous system disorders | any

5.2.10 Cardiac disorders - any

Tabelle 201: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	28	15.91	156	20	12.82	1.24 [0.73 ; 2.11]	1.29 [0.69 ; 2.39];	3.09 [-4.44 ; 10.62]; 0.439	0.439	0.4942
	>= 38 years	96	13	13.54	117	9	7.69	1.76 [0.79 ; 3.94]	1.88 [0.77 ; 4.61];	5.85 [-2.53 ; 14.23]; 0.181	0.181	
Disease Severity at baseline (EDSS)	<=3.5	218	34	15.60	207	20	9.66	1.61 [0.96 ; 2.71]	1.73 [0.96 ; 3.11];	5.93 [-0.34 ; 12.21]; 0.08	0.08	0.326
	>3.5	54	7	12.96	66	9	13.64	0.95 [0.38 ; 2.39]	0.94 [0.33 ; 2.72];	-0.67 [-12.87 ; 11.53]; 1	1	
Gender	Female	178	23	12.92	176	19	10.80	1.2 [0.68 ; 2.12]	1.23 [0.64 ; 2.34];	2.13 [-4.6 ; 8.86]; 0.623	0.623	0.3319
	Male	94	18	19.15	97	10	10.31	1.86 [0.9 ; 3.81]	2.06 [0.9 ; 4.74];	8.84 [-1.15 ; 18.83]; 0.103	0.103	
Number of baseline Gd-enhancing lesions	>=1	141	31	21.99	135	13	9.63	2.28 [1.25 ; 4.17]	2.64 [1.32 ; 5.31];	12.36 [3.9 ; 20.81]; 0.005	0.005	0.0074
	0	131	10	7.63	136	16	11.76	0.65 [0.31 ; 1.38]	0.62 [0.27 ; 1.42];	-4.13 [-11.2 ; 2.94]; 0.304	0.304	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	24	20.51	110	13	11.82	1.74 [0.93 ; 3.24]	1.93 [0.93 ; 4.01];	8.69 [-0.79 ; 18.18]; 0.105	0.105	0.525
	>=3	42	7	16.67	40	5	12.50	1.33 [0.46 ; 3.86]	1.4 [0.41 ; 4.84];	4.17 [-11.07 ; 19.4]; 0.757	0.757	
	2	113	10	8.85	123	11	8.94	0.99 [0.44 ; 2.24]	0.99 [0.4 ; 2.42];	-0.09 [-7.36 ; 7.18]; 1	1	
Received approved disease modifying MS drug prior to enrollment	No	166	22	13.25	186	21	11.29	1.17 [0.67 ; 2.06]	1.2 [0.63 ; 2.27];	1.96 [-4.91 ; 8.84]; 0.626	0.626	0.2855
	Yes	106	19	17.92	87	8	9.20	1.95 [0.9 ; 4.23]	2.16 [0.89 ; 5.2];	8.73 [-0.77 ; 18.23]; 0.097	0.097	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	38	15.51	251	26	10.36	1.5 [0.94 ; 2.39]	1.59 [0.93 ; 2.71];	5.15 [-0.74 ; 11.05]; 0.108	0.108	0.4481
	USA and Western Europe	27	3	11.11	22	3	13.64	0.81 [0.18 ; 3.64]	0.79 [0.14 ; 4.38];	-2.53 [-21.13 ; 16.08]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Cardiac disorders | any

5.2.11 Immune system disorders - any

Tabelle 202: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	10	5.68	156	4	2.56	2.22 [0.71 ; 6.92]	2.29 [0.7 ; 7.45];	3.12 [-1.11 ; 7.34]; 0.182	0.182	0.2438
	>= 38 years	96	5	5.21	117	7	5.98	0.87 [0.29 ; 2.66]	0.86 [0.27 ; 2.81];	-0.77 [-6.96 ; 5.41]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	218	13	5.96	207	7	3.38	1.76 [0.72 ; 4.33]	1.81 [0.71 ; 4.63];	2.58 [-1.41 ; 6.57]; 0.255	0.255	0.2573
	>3.5	54	2	3.70	66	4	6.06	0.61 [0.12 ; 3.21]	0.6 [0.1 ; 3.39];	-2.36 [-10.01 ; 5.29]; 0.689	0.689	
Gender	Female	178	12	6.74	176	9	5.11	1.32 [0.57 ; 3.05]	1.34 [0.55 ; 3.27];	1.63 [-3.29 ; 6.54]; 0.654	0.654	0.8802
	Male	94	3	3.19	97	2	2.06	1.55 [0.26 ; 9.06]	1.57 [0.26 ; 9.59];	1.13 [-3.41 ; 5.67]; 0.679	0.679	
Number of baseline Gd-enhancing lesions	>=1	141	3	2.13	135	4	2.96	0.72 [0.16 ; 3.15]	0.71 [0.16 ; 3.24];	-0.84 [-4.56 ; 2.89]; 0.718	0.718	0.2918
	0	131	12	9.16	136	7	5.15	1.78 [0.72 ; 4.38]	1.86 [0.71 ; 4.88];	4.01 [-2.17 ; 10.19]; 0.239	0.239	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	6	5.13	110	5	4.55	1.13 [0.35 ; 3.59]	1.14 [0.34 ; 3.83];	0.58 [-5 ; 6.16]; 1	1	0.8911
	>=3	42	0	0.00	40	0	0.00	0.95 [0.02 ; 46.94]	0.95 [0.02 ; 49.17];	-0.06 [-4.7 ; 4.59]; 1	1	
	2	113	9	7.96	123	6	4.88	1.63 [0.6 ; 4.44]	1.69 [0.58 ; 4.9];	3.09 [-3.19 ; 9.36]; 0.426	0.426	
Received approved disease modifying MS drug prior to enrollment	No	166	6	3.61	186	5	2.69	1.34 [0.42 ; 4.32]	1.36 [0.41 ; 4.53];	0.93 [-2.74 ; 4.6]; 0.762	0.762	0.9222
	Yes	106	9	8.49	87	6	6.90	1.23 [0.46 ; 3.32]	1.25 [0.43 ; 3.67];	1.59 [-5.92 ; 9.11]; 0.79	0.79	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	12	4.90	251	8	3.19	1.54 [0.64 ; 3.69]	1.56 [0.63 ; 3.9];	1.71 [-1.76 ; 5.18]; 0.369	0.369	0.4918
	USA and Western Europe	27	3	11.11	22	3	13.64	0.81 [0.18 ; 3.64]	0.79 [0.14 ; 4.38];	-2.53 [-21.13 ; 16.08]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Immune system disorders | any

5.2.12 Eye disorders - any

Tabelle 203: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	9	5.11	156	12	7.69	0.66 [0.29 ; 1.54]	0.65 [0.26 ; 1.58];	-2.58 [-7.88 ; 2.72]; 0.372	0.372	0.1721
	>= 38 years	96	5	5.21	117	3	2.56	2.03 [0.5 ; 8.28]	2.09 [0.49 ; 8.97];	2.64 [-2.64 ; 7.93]; 0.472	0.472	
Disease Severity at baseline (EDSS)	<=3.5	218	13	5.96	207	13	6.28	0.95 [0.45 ; 2]	0.95 [0.43 ; 2.09];	-0.32 [-4.88 ; 4.24]; 1	1	0.7258
	>3.5	54	1	1.85	66	2	3.03	0.61 [0.06 ; 6.56]	0.6 [0.05 ; 6.84];	-1.18 [-6.66 ; 4.3]; 1	1	
Gender	Female	178	14	7.87	176	9	5.11	1.54 [0.68 ; 3.46]	1.58 [0.67 ; 3.76];	2.75 [-2.37 ; 7.87]; 0.389	0.389	0.0022
	Male	94	0	0.00	97	6	6.19	0.08 [0 ; 1.39]	0.07 [0 ; 1.34];	-6.11 [-11.24 ; -0.97]; 0.029	0.029	
Number of baseline Gd-enhancing lesions	>=1	141	8	5.67	135	10	7.41	0.77 [0.31 ; 1.88]	0.75 [0.29 ; 1.97];	-1.73 [-7.57 ; 4.11]; 0.63	0.63	0.5135
	0	131	6	4.58	136	5	3.68	1.25 [0.39 ; 3.98]	1.26 [0.37 ; 4.23];	0.9 [-3.87 ; 5.68]; 0.766	0.766	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	4	3.42	110	9	8.18	0.42 [0.13 ; 1.32]	0.4 [0.12 ; 1.33];	-4.76 [-10.85 ; 1.33]; 0.157	0.157	0.1219
	>=3	42	2	4.76	40	2	5.00	0.95 [0.14 ; 6.44]	0.95 [0.13 ; 7.09];	-0.24 [-9.57 ; 9.09]; 1	1	
	2	113	8	7.08	123	4	3.25	2.18 [0.67 ; 7.03]	2.27 [0.66 ; 7.74];	3.83 [-1.85 ; 9.5]; 0.239	0.239	
Received approved disease modifying MS drug prior to enrollment	No	166	10	6.02	186	8	4.30	1.4 [0.57 ; 3.47]	1.43 [0.55 ; 3.7];	1.72 [-2.92 ; 6.37]; 0.479	0.479	0.1458
	Yes	106	4	3.77	87	7	8.05	0.47 [0.14 ; 1.55]	0.45 [0.13 ; 1.58];	-4.27 [-11.04 ; 2.5]; 0.227	0.227	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	12	4.90	251	13	5.18	0.95 [0.44 ; 2.03]	0.94 [0.42 ; 2.11];	-0.28 [-4.13 ; 3.57]; 1	1	0.8836
	USA and Western Europe	27	2	7.41	22	2	9.09	0.81 [0.12 ; 5.33]	0.8 [0.1 ; 6.19];	-1.68 [-17.24 ; 13.87]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Eye disorders | any

5.2.13 Psychiatric disorders - any

Tabelle 204: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	32	18.18	156	27	17.31	1.05 [0.66 ; 1.67]	1.06 [0.6 ; 1.87];	0.87 [-7.35 ; 9.1]; 0.886	0.886	0.1285
	>= 38 years	96	17	17.71	117	10	8.55	2.07 [1 ; 4.31]	2.3 [1 ; 5.3];	9.16 [0 ; 18.33]; 0.062	0.062	
Disease Severity at baseline (EDSS)	<=3.5	218	46	21.10	207	26	12.56	1.68 [1.08 ; 2.61]	1.86 [1.1 ; 3.14];	8.54 [1.49 ; 15.59]; 0.02	0.02	0.0061
	>3.5	54	3	5.56	66	11	16.67	0.33 [0.1 ; 1.13]	0.29 [0.08 ; 1.11];	-11.11 [-21.98 ; -0.24]; 0.086	0.086	
Gender	Female	178	37	20.79	176	24	13.64	1.52 [0.95 ; 2.44]	1.66 [0.95 ; 2.92];	7.15 [-0.68 ; 14.98]; 0.091	0.091	0.2743
	Male	94	12	12.77	97	13	13.40	0.95 [0.46 ; 1.98]	0.95 [0.41 ; 2.19];	-0.64 [-10.2 ; 8.93]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	30	21.28	135	22	16.30	1.31 [0.79 ; 2.15]	1.39 [0.75 ; 2.55];	4.98 [-4.21 ; 14.17]; 0.356	0.356	0.9763
	0	131	19	14.50	136	15	11.03	1.32 [0.7 ; 2.48]	1.37 [0.66 ; 2.82];	3.47 [-4.53 ; 11.48]; 0.464	0.464	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	21	17.95	110	16	14.55	1.23 [0.68 ; 2.24]	1.29 [0.63 ; 2.61];	3.4 [-6.18 ; 12.98]; 0.59	0.59	0.9046
	>=3	42	7	16.67	40	4	10.00	1.67 [0.53 ; 5.26]	1.8 [0.48 ; 6.7];	6.67 [-7.94 ; 21.28]; 0.52	0.52	
	2	113	21	18.58	123	17	13.82	1.34 [0.75 ; 2.42]	1.42 [0.71 ; 2.86];	4.76 [-4.65 ; 14.18]; 0.377	0.377	
Received approved disease modifying MS drug prior to enrollment	No	166	30	18.07	186	23	12.37	1.46 [0.89 ; 2.41]	1.56 [0.87 ; 2.82];	5.71 [-1.82 ; 13.23]; 0.139	0.139	0.5181
	Yes	106	19	17.92	87	14	16.09	1.11 [0.59 ; 2.09]	1.14 [0.53 ; 2.43];	1.83 [-8.79 ; 12.46]; 0.848	0.848	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	39	15.92	251	32	12.75	1.25 [0.81 ; 1.93]	1.3 [0.78 ; 2.15];	3.17 [-3 ; 9.33]; 0.37	0.37	0.5292
	USA and Western Europe	27	10	37.04	22	5	22.73	1.63 [0.65 ; 4.07]	2 [0.56 ; 7.1];	14.31 [-10.96 ; 39.58]; 0.358	0.358	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Psychiatric disorders | any

5.2.14 Vascular disorders - any

Tabelle 205: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	13	7.39	156	13	8.33	0.89 [0.42 ; 1.85]	0.88 [0.39 ; 1.95];	-0.95 [-6.76 ; 4.86]; 0.839	0.839	0.5685
	>= 38 years	96	8	8.33	117	15	12.82	0.65 [0.29 ; 1.47]	0.62 [0.25 ; 1.53];	-4.49 [-12.69 ; 3.71]; 0.376	0.376	
Disease Severity at baseline (EDSS)	<=3.5	218	19	8.72	207	22	10.63	0.82 [0.46 ; 1.47]	0.8 [0.42 ; 1.53];	-1.91 [-7.54 ; 3.71]; 0.516	0.516	0.3969
	>3.5	54	2	3.70	66	6	9.09	0.41 [0.09 ; 1.94]	0.38 [0.07 ; 1.99];	-5.39 [-13.96 ; 3.18]; 0.293	0.293	
Gender	Female	178	14	7.87	176	21	11.93	0.66 [0.35 ; 1.25]	0.63 [0.31 ; 1.28];	-4.07 [-10.28 ; 2.14]; 0.217	0.217	0.4549
	Male	94	7	7.45	97	7	7.22	1.03 [0.38 ; 2.83]	1.03 [0.35 ; 3.07];	0.23 [-7.16 ; 7.63]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	11	7.80	135	14	10.37	0.75 [0.35 ; 1.6]	0.73 [0.32 ; 1.67];	-2.57 [-9.35 ; 4.22]; 0.532	0.532	0.9798
	0	131	10	7.63	136	14	10.29	0.74 [0.34 ; 1.61]	0.72 [0.31 ; 1.68];	-2.66 [-9.5 ; 4.18]; 0.524	0.524	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	12	10.26	110	13	11.82	0.87 [0.41 ; 1.82]	0.85 [0.37 ; 1.96];	-1.56 [-9.72 ; 6.6]; 0.833	0.833	0.3669
	>=3	42	5	11.90	40	4	10.00	1.19 [0.34 ; 4.12]	1.22 [0.3 ; 4.9];	1.9 [-11.6 ; 15.41]; 1	1	
	2	113	4	3.54	123	11	8.94	0.4 [0.13 ; 1.21]	0.37 [0.12 ; 1.21];	-5.4 [-11.49 ; 0.68]; 0.112	0.112	
Received approved disease modifying MS drug prior to enrollment	No	166	7	4.22	186	19	10.22	0.41 [0.18 ; 0.96]	0.39 [0.16 ; 0.95];	-6 [-11.32 ; -0.68]; 0.04	0.04	0.051
	Yes	106	14	13.21	87	9	10.34	1.28 [0.58 ; 2.81]	1.32 [0.54 ; 3.21];	2.86 [-6.22 ; 11.95]; 0.657	0.657	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	19	7.76	251	24	9.56	0.81 [0.46 ; 1.44]	0.8 [0.42 ; 1.49];	-1.81 [-6.75 ; 3.14]; 0.525	0.525	0.4058
	USA and Western Europe	27	2	7.41	22	4	18.18	0.41 [0.08 ; 2.02]	0.36 [0.06 ; 2.18];	-10.77 [-29.68 ; 8.13]; 0.388	0.388	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Vascular disorders | any

5.2.15 Renal and urinary disorders - any

Tabelle 206: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	15	8.52	156	10	6.41	1.33 [0.62 ; 2.87]	1.36 [0.59 ; 3.12];	2.11 [-3.53 ; 7.75]; 0.535	0.535	0.5631
	>= 38 years	96	6	6.25	117	8	6.84	0.91 [0.33 ; 2.54]	0.91 [0.3 ; 2.71];	-0.59 [-7.25 ; 6.07]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	218	20	9.17	207	12	5.80	1.58 [0.79 ; 3.15]	1.64 [0.78 ; 3.45];	3.38 [-1.6 ; 8.36]; 0.203	0.203	0.0297
	>3.5	54	1	1.85	66	6	9.09	0.2 [0.03 ; 1.64]	0.19 [0.02 ; 1.62];	-7.24 [-15.05 ; 0.57]; 0.127	0.127	
Gender	Female	178	15	8.43	176	14	7.95	1.06 [0.53 ; 2.13]	1.06 [0.5 ; 2.28];	0.47 [-5.24 ; 6.19]; 1	1	0.6023
	Male	94	6	6.38	97	4	4.12	1.55 [0.45 ; 5.31]	1.59 [0.43 ; 5.81];	2.26 [-4.07 ; 8.59]; 0.532	0.532	
Number of baseline Gd-enhancing lesions	>=1	141	10	7.09	135	12	8.89	0.8 [0.36 ; 1.79]	0.78 [0.33 ; 1.88];	-1.8 [-8.2 ; 4.61]; 0.659	0.659	0.108
	0	131	11	8.40	136	5	3.68	2.28 [0.82 ; 6.39]	2.4 [0.81 ; 7.11];	4.72 [-0.99 ; 10.43]; 0.126	0.126	
	NA	0	0	0.00	2	1	50.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	8	6.84	110	9	8.18	0.84 [0.33 ; 2.09]	0.82 [0.31 ; 2.22];	-1.34 [-8.21 ; 5.52]; 0.803	0.803	0.1242
	>=3	42	3	7.14	40	0	0.00	6.67 [0.36 ; 125.26]	7.18 [0.36 ; 143.5];	6.92 [-1.92 ; 15.76]; 0.118	0.118	
	2	113	10	8.85	123	9	7.32	1.21 [0.51 ; 2.87]	1.23 [0.48 ; 3.15];	1.53 [-5.44 ; 8.5]; 0.812	0.812	
Received approved disease modifying MS drug prior to enrollment	No	166	10	6.02	186	8	4.30	1.4 [0.57 ; 3.47]	1.43 [0.55 ; 3.7];	1.72 [-2.92 ; 6.37]; 0.479	0.479	0.4841
	Yes	106	11	10.38	87	10	11.49	0.9 [0.4 ; 2.03]	0.89 [0.36 ; 2.21];	-1.12 [-9.98 ; 7.75]; 0.82	0.82	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	18	7.35	251	15	5.98	1.23 [0.63 ; 2.38]	1.25 [0.61 ; 2.54];	1.37 [-3.02 ; 5.76]; 0.592	0.592	0.6306
	USA and Western Europe	27	3	11.11	22	3	13.64	0.81 [0.18 ; 3.64]	0.79 [0.14 ; 4.38];	-2.53 [-21.13 ; 16.08]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Renal and urinary disorders | any

5.2.16 Skin and subcutaneous tissue disorders - any

Tabelle 207: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	35	19.89	156	44	28.21	0.71 [0.48 ; 1.04]	0.63 [0.38 ; 1.05];	-8.32 [-17.52 ; 0.88]; 0.093	0.093	0.7094
	>= 38 years	96	15	15.62	117	30	25.64	0.61 [0.35 ; 1.06]	0.54 [0.27 ; 1.07];	-10.02 [-20.76 ; 0.72]; 0.092	0.092	
Disease Severity at baseline (EDSS)	<=3.5	218	47	21.56	207	55	26.57	0.81 [0.58 ; 1.14]	0.76 [0.49 ; 1.19];	-5.01 [-13.13 ; 3.11]; 0.256	0.256	0.0077
	>3.5	54	3	5.56	66	19	28.79	0.19 [0.06 ; 0.62]	0.15 [0.04 ; 0.52];	-23.23 [-35.75 ; -10.72]; 0.002	0.002	
Gender	Female	178	32	17.98	176	61	34.66	0.52 [0.36 ; 0.75]	0.41 [0.25 ; 0.68];	-16.68 [-25.7 ; -7.67]; 0	0	0.005
	Male	94	18	19.15	97	13	13.40	1.43 [0.74 ; 2.75]	1.53 [0.7 ; 3.33];	5.75 [-4.7 ; 16.2]; 0.329	0.329	
Number of baseline Gd-enhancing lesions	>=1	141	28	19.86	135	36	26.67	0.74 [0.48 ; 1.15]	0.68 [0.39 ; 1.2];	-6.81 [-16.76 ; 3.14]; 0.201	0.201	0.5175
	0	131	22	16.79	136	38	27.94	0.6 [0.38 ; 0.96]	0.52 [0.29 ; 0.94];	-11.15 [-21.04 ; -1.26]; 0.04	0.04	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	22	18.80	110	30	27.27	0.69 [0.42 ; 1.12]	0.62 [0.33 ; 1.15];	-8.47 [-19.4 ; 2.46]; 0.155	0.155	0.8166
	>=3	42	6	14.29	40	11	27.50	0.52 [0.21 ; 1.27]	0.44 [0.15 ; 1.33];	-13.21 [-30.63 ; 4.21]; 0.177	0.177	
	2	113	22	19.47	123	33	26.83	0.73 [0.45 ; 1.17]	0.66 [0.36 ; 1.22];	-7.36 [-18.07 ; 3.35]; 0.218	0.218	
Received approved disease modifying MS	No	166	26	15.66	186	51	27.42	0.57 [0.37 ; 0.87]	0.49 [0.29 ; 0.83];	-11.76 [-20.22 ; -3.29]; 0.01	0.01	0.2403
	Yes	106	24	22.64	87	23	26.44	0.86 [0.52 ; 1.41]	0.81 [0.42 ; 1.57];	-3.8 [-16.02 ; 8.43]; 0.614	0.614	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
drug prior to enrollment												
Region	Eastern Europe	245	41	16.73	251	66	26.29	0.64 [0.45 ; 0.9]	0.56 [0.36 ; 0.87];	-9.56 [-16.74 ; -2.38]; 0.012	0.012	0.4933
	USA and Western Europe	27	9	33.33	22	8	36.36	0.92 [0.43 ; 1.98]	0.88 [0.27 ; 2.85];	-3.03 [-29.87 ; 23.81]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Skin and subcutaneous tissue disorders | any

5.2.17 Ear and labyrinth disorders - any

Tabelle 208: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	6	3.41	156	4	2.56	1.33 [0.38 ; 4.63]	1.34 [0.37 ; 4.84];	0.84 [-2.81 ; 4.5]; 0.755	0.755	0.4449
	>= 38 years	96	10	10.42	117	5	4.27	2.44 [0.86 ; 6.89]	2.6 [0.86 ; 7.9];	6.14 [-0.98 ; 13.27]; 0.107	0.107	
Disease Severity at baseline (EDSS)	<=3.5	218	13	5.96	207	6	2.90	2.06 [0.8 ; 5.31]	2.12 [0.79 ; 5.7];	3.06 [-0.82 ; 6.95]; 0.16	0.16	0.5792
	>3.5	54	3	5.56	66	3	4.55	1.22 [0.26 ; 5.81]	1.24 [0.24 ; 6.38];	1.01 [-6.9 ; 8.92]; 1	1	
Gender	Female	178	11	6.18	176	4	2.27	2.72 [0.88 ; 8.38]	2.83 [0.88 ; 9.07];	3.91 [-0.26 ; 8.07]; 0.111	0.111	0.2475
	Male	94	5	5.32	97	5	5.15	1.03 [0.31 ; 3.45]	1.03 [0.29 ; 3.69];	0.16 [-6.16 ; 6.48]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	5	3.55	135	5	3.70	0.96 [0.28 ; 3.23]	0.96 [0.27 ; 3.38];	-0.16 [-4.57 ; 4.25]; 1	1	0.1852
	0	131	11	8.40	136	4	2.94	2.85 [0.93 ; 8.74]	3.02 [0.94 ; 9.75];	5.46 [-0.08 ; 10.99]; 0.065	0.065	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	8	6.84	110	2	1.82	3.76 [0.82 ; 17.32]	3.96 [0.82 ; 19.09];	5.02 [-0.19 ; 10.23]; 0.103	0.103	0.2795
	>=3	42	3	7.14	40	1	2.50	2.86 [0.31 ; 26.34]	3 [0.3 ; 30.11];	4.64 [-4.53 ; 13.81]; 0.616	0.616	
	2	113	5	4.42	123	6	4.88	0.91 [0.28 ; 2.89]	0.9 [0.27 ; 3.04];	-0.45 [-5.83 ; 4.92]; 1	1	
Received approved disease modifying MS drug prior to enrollment	No	166	12	7.23	186	4	2.15	3.36 [1.11 ; 10.22]	3.55 [1.12 ; 11.22];	5.08 [0.62 ; 9.54]; 0.037	0.037	0.0546
	Yes	106	4	3.77	87	5	5.75	0.66 [0.18 ; 2.37]	0.64 [0.17 ; 2.47];	-1.97 [-8.06 ; 4.12]; 0.734	0.734	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	11	4.49	251	6	2.39	1.88 [0.71 ; 5]	1.92 [0.7 ; 5.27];	2.1 [-1.11 ; 5.31]; 0.225	0.225	0.762
	USA and Western Europe	27	5	18.52	22	3	13.64	1.36 [0.36 ; 5.06]	1.44 [0.3 ; 6.83];	4.88 [-15.62 ; 25.38]; 0.715	0.715	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Ear and labyrinth disorders | any

5.2.18 Reproductive system and breast disorders - any

Tabelle 209: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	23	13.07	156	20	12.82	1.02 [0.58 ; 1.78]	1.02 [0.54 ; 1.94];	0.25 [-6.99 ; 7.48]; 1	1	0.6174
	>= 38 years	96	7	7.29	117	11	9.40	0.78 [0.31 ; 1.92]	0.76 [0.28 ; 2.04];	-2.11 [-9.53 ; 5.31]; 0.629	0.629	
Disease Severity at baseline (EDSS)	<=3.5	218	29	13.30	207	24	11.59	1.15 [0.69 ; 1.9]	1.17 [0.66 ; 2.09];	1.71 [-4.56 ; 7.98]; 0.66	0.66	0.0355
	>3.5	54	1	1.85	66	7	10.61	0.17 [0.02 ; 1.38]	0.16 [0.02 ; 1.34];	-8.75 [-17.01 ; -0.5]; 0.072	0.072	
Gender	Female	178	28	15.73	176	28	15.91	0.99 [0.61 ; 1.6]	0.99 [0.56 ; 1.75];	-0.18 [-7.78 ; 7.42]; 1	1	0.7001
	Male	94	2	2.13	97	3	3.09	0.69 [0.12 ; 4.02]	0.68 [0.11 ; 4.17];	-0.97 [-5.48 ; 3.55]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	16	11.35	135	18	13.33	0.85 [0.45 ; 1.6]	0.83 [0.41 ; 1.71];	-1.99 [-9.75 ; 5.78]; 0.715	0.715	0.5734
	0	131	14	10.69	136	13	9.56	1.12 [0.55 ; 2.29]	1.13 [0.51 ; 2.51];	1.13 [-6.11 ; 8.37]; 0.84	0.84	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	12	10.26	110	12	10.91	0.94 [0.44 ; 2]	0.93 [0.4 ; 2.18];	-0.65 [-8.66 ; 7.36]; 1	1	0.9918
	>=3	42	6	14.29	40	6	15.00	0.95 [0.33 ; 2.71]	0.94 [0.28 ; 3.21];	-0.71 [-16.03 ; 14.6]; 1	1	
	2	113	12	10.62	123	13	10.57	1 [0.48 ; 2.11]	1.01 [0.44 ; 2.31];	0.05 [-7.81 ; 7.91]; 1	1	
Received approved disease modifying MS drug prior to enrollment	No	166	19	11.45	186	20	10.75	1.06 [0.59 ; 1.92]	1.07 [0.55 ; 2.09];	0.69 [-5.89 ; 7.27]; 0.866	0.866	0.6047
	Yes	106	11	10.38	87	11	12.64	0.82 [0.37 ; 1.8]	0.8 [0.33 ; 1.95];	-2.27 [-11.35 ; 6.82]; 0.655	0.655	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	26	10.61	251	28	11.16	0.95 [0.57 ; 1.57]	0.95 [0.54 ; 1.66];	-0.54 [-6.02 ; 4.94]; 0.886	0.886	0.861
	USA and Western Europe	27	4	14.81	22	3	13.64	1.09 [0.27 ; 4.35]	1.1 [0.22 ; 5.54];	1.18 [-18.45 ; 20.8]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Reproductive system and breast disorders | any

5.2.19 Blood and lymphatic system disorders - any

Tabelle 210: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	28	15.91	156	26	16.67	0.95 [0.59 ; 1.56]	0.95 [0.53 ; 1.7];	-0.76 [-8.72 ; 7.2]; 0.882	0.882	0.8136
	>= 38 years	96	12	12.50	117	17	14.53	0.86 [0.43 ; 1.71]	0.84 [0.38 ; 1.86];	-2.03 [-11.22 ; 7.16]; 0.694	0.694	
Disease Severity at baseline (EDSS)	<=3.5	218	32	14.68	207	30	14.49	1.01 [0.64 ; 1.6]	1.02 [0.59 ; 1.74];	0.19 [-6.53 ; 6.9]; 1	1	0.5226
	>3.5	54	8	14.81	66	13	19.70	0.75 [0.34 ; 1.68]	0.71 [0.27 ; 1.86];	-4.88 [-18.37 ; 8.6]; 0.63	0.63	
Gender	Female	178	33	18.54	176	33	18.75	0.99 [0.64 ; 1.53]	0.99 [0.58 ; 1.68];	-0.21 [-8.33 ; 7.9]; 1	1	0.5551
	Male	94	7	7.45	97	10	10.31	0.72 [0.29 ; 1.82]	0.7 [0.25 ; 1.92];	-2.86 [-10.91 ; 5.19]; 0.613	0.613	
Number of baseline Gd-enhancing lesions	>=1	141	21	14.89	135	29	21.48	0.69 [0.42 ; 1.15]	0.64 [0.34 ; 1.19];	-6.59 [-15.67 ; 2.5]; 0.163	0.163	0.0862
	0	131	19	14.50	136	14	10.29	1.41 [0.74 ; 2.69]	1.48 [0.71 ; 3.09];	4.21 [-3.69 ; 12.11]; 0.354	0.354	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	16	13.68	110	20	18.18	0.75 [0.41 ; 1.38]	0.71 [0.35 ; 1.46];	-4.51 [-14.03 ; 5.02]; 0.37	0.37	0.6437
	>=3	42	10	23.81	40	8	20.00	1.19 [0.52 ; 2.71]	1.25 [0.44 ; 3.58];	3.81 [-14.07 ; 21.69]; 0.792	0.792	
	2	113	14	12.39	123	15	12.20	1.02 [0.51 ; 2.01]	1.02 [0.47 ; 2.22];	0.19 [-8.19 ; 8.58]; 1	1	
Received approved disease modifying MS drug prior to enrollment	No	166	15	9.04	186	25	13.44	0.67 [0.37 ; 1.23]	0.64 [0.32 ; 1.26];	-4.4 [-10.97 ; 2.16]; 0.239	0.239	0.2084
	Yes	106	25	23.58	87	18	20.69	1.14 [0.67 ; 1.95]	1.18 [0.6 ; 2.35];	2.9 [-8.84 ; 14.63]; 0.729	0.729	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	38	15.51	251	43	17.13	0.91 [0.61 ; 1.35]	0.89 [0.55 ; 1.43];	-1.62 [-8.12 ; 4.88]; 0.63	0.63	0.1055
	USA and Western Europe	27	2	7.41	22	0	0.00	4.11 [0.21 ; 81.33]	4.41 [0.2 ; 96.84];	6.75 [-5.37 ; 18.88]; 0.497	0.497	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Blood and lymphatic system disorders | any

5.2.20 Musculoskeletal and connective tissue disorders - Pain in extremity

Tabelle 211: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	12	6.82	156	5	3.21	2.13 [0.77 ; 5.9]	2.21 [0.76 ; 6.42];	3.61 [-1.02 ; 8.25]; 0.211	0.211	0.1537
	>= 38 years	96	4	4.17	117	7	5.98	0.7 [0.21 ; 2.31]	0.68 [0.19 ; 2.41];	-1.82 [-7.69 ; 4.05]; 0.758	0.758	
Disease Severity at baseline (EDSS)	<=3.5	218	15	6.88	207	11	5.31	1.29 [0.61 ; 2.75]	1.32 [0.59 ; 2.94];	1.57 [-2.98 ; 6.11]; 0.548	0.548	0.9619
	>3.5	54	1	1.85	66	1	1.52	1.22 [0.08 ; 19.09]	1.23 [0.07 ; 20.08];	0.34 [-4.31 ; 4.99]; 1	1	
Gender	Female	178	15	8.43	176	10	5.68	1.48 [0.68 ; 3.21]	1.53 [0.67 ; 3.5];	2.75 [-2.58 ; 8.07]; 0.407	0.407	0.3858
	Male	94	1	1.06	97	2	2.06	0.52 [0.05 ; 5.6]	0.51 [0.05 ; 5.73];	-1 [-4.5 ; 2.51]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	8	5.67	135	4	2.96	1.91 [0.59 ; 6.21]	1.97 [0.58 ; 6.7];	2.71 [-2.06 ; 7.48]; 0.378	0.378	0.4264
	0	131	8	6.11	136	8	5.88	1.04 [0.4 ; 2.68]	1.04 [0.38 ; 2.86];	0.22 [-5.47 ; 5.92]; 1	1	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	8	6.84	110	5	4.55	1.5 [0.51 ; 4.46]	1.54 [0.49 ; 4.86];	2.29 [-3.71 ; 8.3]; 0.572	0.572	0.8747
	>=3	42	2	4.76	40	1	2.50	1.9 [0.18 ; 20.19]	1.95 [0.17 ; 22.39];	2.26 [-5.79 ; 10.32]; 1	1	
	2	113	6	5.31	123	6	4.88	1.09 [0.36 ; 3.28]	1.09 [0.34 ; 3.49];	0.43 [-5.19 ; 6.05]; 1	1	
Received approved disease modifying MS drug prior to enrollment	No	166	11	6.63	186	7	3.76	1.76 [0.7 ; 4.44]	1.81 [0.69 ; 4.8];	2.86 [-1.81 ; 7.53]; 0.237	0.237	0.325
	Yes	106	5	4.72	87	5	5.75	0.82 [0.25 ; 2.74]	0.81 [0.23 ; 2.9];	-1.03 [-7.37 ; 5.31]; 0.756	0.756	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	11	4.49	251	8	3.19	1.41 [0.58 ; 3.44]	1.43 [0.56 ; 3.61];	1.3 [-2.08 ; 4.69]; 0.491	0.491	0.7052
	USA and Western Europe	27	5	18.52	22	4	18.18	1.02 [0.31 ; 3.34]	1.02 [0.24 ; 4.38];	0.34 [-21.44 ; 22.12]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Musculoskeletal and connective tissue disorders | Pain in extremity

5.2.21 Gastrointestinal disorders - Diarrhoea

Tabelle 212: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	18	10.23	156	18	11.54	0.89 [0.48 ; 1.64]	0.87 [0.44 ; 1.74];	-1.31 [-8.03 ; 5.41]; 0.727	0.727	0.4894
	>= 38 years	96	7	7.29	117	14	11.97	0.61 [0.26 ; 1.45]	0.58 [0.22 ; 1.5];	-4.67 [-12.53 ; 3.18]; 0.356	0.356	
Disease Severity at baseline (EDSS)	<=3.5	218	22	10.09	207	25	12.08	0.84 [0.49 ; 1.43]	0.82 [0.45 ; 1.5];	-1.99 [-7.96 ; 3.99]; 0.539	0.539	0.5144
	>3.5	54	3	5.56	66	7	10.61	0.52 [0.14 ; 1.93]	0.5 [0.12 ; 2.02];	-5.05 [-14.67 ; 4.57]; 0.509	0.509	
Gender	Female	178	18	10.11	176	17	9.66	1.05 [0.56 ; 1.96]	1.05 [0.52 ; 2.12];	0.45 [-5.76 ; 6.67]; 1	1	0.1402
	Male	94	7	7.45	97	15	15.46	0.48 [0.21 ; 1.13]	0.44 [0.17 ; 1.13];	-8.02 [-16.96 ; 0.92]; 0.112	0.112	
Number of baseline Gd-enhancing lesions	>=1	141	20	14.18	135	16	11.85	1.2 [0.65 ; 2.21]	1.23 [0.61 ; 2.49];	2.33 [-5.6 ; 10.26]; 0.596	0.596	0.0294
	0	131	5	3.82	136	15	11.03	0.35 [0.13 ; 0.93]	0.32 [0.11 ; 0.91];	-7.21 [-13.42 ; -1.01]; 0.035	0.035	
	NA	0	0	0.00	2	1	50.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	12	10.26	110	13	11.82	0.87 [0.41 ; 1.82]	0.85 [0.37 ; 1.96];	-1.56 [-9.72 ; 6.6]; 0.833	0.833	0.5969
	>=3	42	5	11.90	40	4	10.00	1.19 [0.34 ; 4.12]	1.22 [0.3 ; 4.9];	1.9 [-11.6 ; 15.41]; 1	1	
	2	113	8	7.08	123	15	12.20	0.58 [0.26 ; 1.32]	0.55 [0.22 ; 1.35];	-5.12 [-12.59 ; 2.35]; 0.197	0.197	
Received approved disease modifying MS drug prior to enrollment	No	166	10	6.02	186	21	11.29	0.53 [0.26 ; 1.1]	0.5 [0.23 ; 1.1];	-5.27 [-11.08 ; 0.55]; 0.092	0.092	0.1583
	Yes	106	15	14.15	87	11	12.64	1.12 [0.54 ; 2.31]	1.14 [0.49 ; 2.63];	1.51 [-8.13 ; 11.14]; 0.834	0.834	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	22	8.98	251	29	11.55	0.78 [0.46 ; 1.31]	0.76 [0.42 ; 1.35];	-2.57 [-7.91 ; 2.76]; 0.377	0.377	0.9592
	USA and Western Europe	27	3	11.11	22	3	13.64	0.81 [0.18 ; 3.64]	0.79 [0.14 ; 4.38];	-2.53 [-21.13 ; 16.08]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Gastrointestinal disorders | Diarrhoea

5.2.22 Gastrointestinal disorders - Nausea

Tabelle 213: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	17	9.66	156	20	12.82	0.75 [0.41 ; 1.39]	0.73 [0.37 ; 1.44];	-3.16 [-9.99 ; 3.66]; 0.386	0.386	0.0942
	>= 38 years	96	12	12.50	117	8	6.84	1.83 [0.78 ; 4.29]	1.95 [0.76 ; 4.98];	5.66 [-2.38 ; 13.7]; 0.167	0.167	
Disease Severity at baseline (EDSS)	<=3.5	218	26	11.93	207	25	12.08	0.99 [0.59 ; 1.65]	0.99 [0.55 ; 1.77];	-0.15 [-6.33 ; 6.03]; 1	1	0.7999
	>3.5	54	3	5.56	66	3	4.55	1.22 [0.26 ; 5.81]	1.24 [0.24 ; 6.38];	1.01 [-6.9 ; 8.92]; 1	1	
Gender	Female	178	25	14.04	176	22	12.50	1.12 [0.66 ; 1.92]	1.14 [0.62 ; 2.12];	1.54 [-5.52 ; 8.61]; 0.755	0.755	0.4671
	Male	94	4	4.26	97	6	6.19	0.69 [0.2 ; 2.36]	0.67 [0.18 ; 2.47];	-1.93 [-8.23 ; 4.37]; 0.748	0.748	
Number of baseline Gd-enhancing lesions	>=1	141	16	11.35	135	18	13.33	0.85 [0.45 ; 1.6]	0.83 [0.41 ; 1.71];	-1.99 [-9.75 ; 5.78]; 0.715	0.715	0.3701
	0	131	13	9.92	136	10	7.35	1.35 [0.61 ; 2.97]	1.39 [0.59 ; 3.29];	2.57 [-4.17 ; 9.31]; 0.517	0.517	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	11	9.40	110	11	10.00	0.94 [0.42 ; 2.08]	0.93 [0.39 ; 2.25];	-0.6 [-8.31 ; 7.11]; 1	1	0.9074
	>=3	42	5	11.90	40	5	12.50	0.95 [0.3 ; 3.04]	0.95 [0.25 ; 3.55];	-0.6 [-14.77 ; 13.58]; 1	1	
	2	113	13	11.50	123	12	9.76	1.18 [0.56 ; 2.48]	1.2 [0.52 ; 2.76];	1.75 [-6.13 ; 9.63]; 0.678	0.678	
Received approved disease modifying MS drug prior to enrollment	No	166	19	11.45	186	19	10.22	1.12 [0.61 ; 2.04]	1.14 [0.58 ; 2.23];	1.23 [-5.28 ; 7.74]; 0.734	0.734	0.6989
	Yes	106	10	9.43	87	9	10.34	0.91 [0.39 ; 2.14]	0.9 [0.35 ; 2.33];	-0.91 [-9.39 ; 7.57]; 1	1	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	22	8.98	251	22	8.76	1.02 [0.58 ; 1.8]	1.03 [0.55 ; 1.91];	0.21 [-4.79 ; 5.22]; 1	1	0.8948
	USA and Western Europe	27	7	25.93	22	6	27.27	0.95 [0.37 ; 2.42]	0.93 [0.26 ; 3.33];	-1.35 [-26.24 ; 23.54]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Gastrointestinal disorders | Nausea

5.2.23 Nervous system disorders - Headache

Tabelle 214: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	77	43.75	156	57	36.54	1.2 [0.92 ; 1.56]	1.35 [0.87 ; 2.1];	7.21 [-3.32 ; 17.74]; 0.218	0.218	0.5563
	>= 38 years	96	26	27.08	117	30	25.64	1.06 [0.67 ; 1.66]	1.08 [0.58 ; 1.99];	1.44 [-10.46 ; 13.34]; 0.876	0.876	
Disease Severity at baseline (EDSS)	<=3.5	218	91	41.74	207	69	33.33	1.25 [0.98 ; 1.61]	1.43 [0.97 ; 2.13];	8.41 [-0.76 ; 17.58]; 0.089	0.089	0.1795
	>3.5	54	12	22.22	66	18	27.27	0.81 [0.43 ; 1.54]	0.76 [0.33 ; 1.76];	-5.05 [-20.49 ; 10.39]; 0.672	0.672	
Gender	Female	178	81	45.51	176	60	34.09	1.33 [1.03 ; 1.73]	1.61 [1.05 ; 2.48];	11.41 [1.29 ; 21.54]; 0.03	0.03	0.0731
	Male	94	22	23.40	97	27	27.84	0.84 [0.52 ; 1.37]	0.79 [0.41 ; 1.52];	-4.43 [-16.79 ; 7.93]; 0.511	0.511	
Number of baseline Gd-enhancing lesions	>=1	141	54	38.30	135	42	31.11	1.23 [0.89 ; 1.71]	1.37 [0.84 ; 2.26];	7.19 [-4.01 ; 18.38]; 0.255	0.255	0.7215
	0	131	49	37.40	136	45	33.09	1.13 [0.82 ; 1.57]	1.21 [0.73 ; 2];	4.32 [-7.14 ; 15.77]; 0.522	0.522	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	45	38.46	110	36	32.73	1.18 [0.83 ; 1.67]	1.28 [0.74 ; 2.22];	5.73 [-6.7 ; 18.17]; 0.407	0.407	0.8765
	>=3	42	16	38.10	40	11	27.50	1.39 [0.73 ; 2.61]	1.62 [0.64 ; 4.12];	10.6 [-9.58 ; 30.77]; 0.353	0.353	
	2	113	42	37.17	123	40	32.52	1.14 [0.81 ; 1.62]	1.23 [0.72 ; 2.1];	4.65 [-7.51 ; 16.81]; 0.495	0.495	
Received approved disease modifying MS drug prior to enrollment	No	166	63	37.95	186	61	32.80	1.16 [0.87 ; 1.54]	1.25 [0.81 ; 1.94];	5.16 [-4.84 ; 15.16]; 0.317	0.317	0.7402
	Yes	106	40	37.74	87	26	29.89	1.26 [0.84 ; 1.89]	1.42 [0.78 ; 2.6];	7.85 [-5.48 ; 21.18]; 0.287	0.287	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	91	37.14	251	78	31.08	1.2 [0.93 ; 1.53]	1.31 [0.9 ; 1.9];	6.07 [-2.26 ; 14.4]; 0.157	0.157	0.837
	USA and Western Europe	27	12	44.44	22	9	40.91	1.09 [0.56 ; 2.09]	1.16 [0.37 ; 3.61];	3.54 [-24.27 ; 31.35]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Nervous system disorders | Headache

5.2.24 General disorders and administration site conditions - Pyrexia

Tabelle 215: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	24	13.64	156	6	3.85	3.55 [1.49 ; 8.45]	3.95 [1.57 ; 9.93];	9.79 [3.89 ; 15.69]; 0.002	0.002	0.2301
	>= 38 years	96	11	11.46	117	8	6.84	1.68 [0.7 ; 4]	1.76 [0.68 ; 4.58];	4.62 [-3.22 ; 12.46]; 0.334	0.334	
Disease Severity at baseline (EDSS)	<=3.5	218	31	14.22	207	10	4.83	2.94 [1.48 ; 5.85]	3.27 [1.56 ; 6.85];	9.39 [3.91 ; 14.87]; 0.002	0.002	0.2423
	>3.5	54	4	7.41	66	4	6.06	1.22 [0.32 ; 4.66]	1.24 [0.3 ; 5.21];	1.35 [-7.7 ; 10.4]; 1	1	
Gender	Female	178	28	15.73	176	10	5.68	2.77 [1.39 ; 5.53]	3.1 [1.46 ; 6.59];	10.05 [3.7 ; 16.4]; 0.003	0.003	0.5061
	Male	94	7	7.45	97	4	4.12	1.81 [0.55 ; 5.97]	1.87 [0.53 ; 6.61];	3.32 [-3.3 ; 9.94]; 0.367	0.367	
Number of baseline Gd-enhancing lesions	>=1	141	17	12.06	135	5	3.70	3.26 [1.24 ; 8.58]	3.56 [1.28 ; 9.95];	8.35 [2.11 ; 14.6]; 0.013	0.013	0.492
	0	131	18	13.74	136	9	6.62	2.08 [0.97 ; 4.45]	2.25 [0.97 ; 5.2];	7.12 [-0.1 ; 14.35]; 0.067	0.067	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	17	14.53	110	6	5.45	2.66 [1.09 ; 6.51]	2.95 [1.12 ; 7.78];	9.08 [1.41 ; 16.74]; 0.028	0.028	0.9262
	>=3	42	6	14.29	40	2	5.00	2.86 [0.61 ; 13.34]	3.17 [0.6 ; 16.72];	9.29 [-3.27 ; 21.84]; 0.265	0.265	
	2	113	12	10.62	123	6	4.88	2.18 [0.85 ; 5.61]	2.32 [0.84 ; 6.4];	5.74 [-1.1 ; 12.58]; 0.14	0.14	
Received approved disease modifying MS drug prior to enrollment	No	166	19	11.45	186	7	3.76	3.04 [1.31 ; 7.05]	3.31 [1.35 ; 8.08];	7.68 [2.12 ; 13.24]; 0.007	0.007	0.462
	Yes	106	16	15.09	87	7	8.05	1.88 [0.81 ; 4.35]	2.03 [0.8 ; 5.19];	7.05 [-1.85 ; 15.94]; 0.18	0.18	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	29	11.84	251	13	5.18	2.29 [1.22 ; 4.29]	2.46 [1.25 ; 4.85];	6.66 [1.77 ; 11.54]; 0.009	0.009	0.416
	USA and Western Europe	27	6	22.22	22	1	4.55	4.89 [0.64 ; 37.63]	6 [0.66 ; 54.24];	17.68 [-0.26 ; 35.61]; 0.112	0.112	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - General disorders and administration site conditions | Pyrexia

5.2.25 Infections and infestations - Bronchitis

Tabelle 216: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	7	3.98	156	10	6.41	0.62 [0.24 ; 1.59]	0.6 [0.22 ; 1.63];	-2.43 [-7.24 ; 2.37]; 0.332	0.332	0.0803
	< 38 years	176	7	3.98	156	5	3.21	0.62 [0.24 ; 1.59]	0.6 [0.22 ; 1.63];	-2.43 [-7.24 ; 2.37]; 0.332	0.332	
	< 38 years	176	4	2.27	156	10	6.41	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	< 38 years	176	4	2.27	156	5	3.21	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	>= 38 years	96	0	0.00	117	2	1.71	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	>= 38 years	96	0	0.00	117	5	4.27	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	>= 38 years	96	5	5.21	117	2	1.71	3.05 [0.6 ; 15.36]	3.16 [0.6 ; 16.66];	3.5 [-1.53 ; 8.53]; 0.248	0.248	
	>= 38 years	96	5	5.21	117	5	4.27	3.05 [0.6 ; 15.36]	3.16 [0.6 ; 16.66];	3.5 [-1.53 ; 8.53]; 0.248	0.248	
Disease Severity at baseline (EDSS)	<=3.5	218	8	3.67	207	11	5.31	0.69 [0.28 ; 1.68]	0.68 [0.27 ; 1.72];	-1.64 [-5.59 ; 2.3]; 0.485	0.485	0.0667
	>3.5	54	4	7.41	66	1	1.52	4.89 [0.56 ; 42.46]	5.2 [0.56 ; 47.98];	5.89 [-1.69 ; 13.47]; 0.173	0.173	
Gender	Female	178	12	6.74	176	10	5.68	1.19 [0.53 ; 2.68]	1.2 [0.5 ; 2.85];	1.06 [-3.97 ; 6.09]; 0.826	0.826	0.0885
	Female	178	12	6.74	176	7	3.98	1.19 [0.53 ; 2.68]	1.2 [0.5 ; 2.85];	1.06 [-3.97 ; 6.09]; 0.826	0.826	
	Female	178	2	1.12	176	10	5.68	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Female	178	2	1.12	176	7	3.98	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Male	94	0	0.00	97	2	2.06	0.21 [0.01 ; 4.24]	0.2 [0.01 ; 4.27];	-2.02 [-5.47 ; 1.42]; 0.498	0.498	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
	Male	94	0	0.00	97	3	3.09	0.21 [0.01 ; 4.24]	0.2 [0.01 ; 4.27];	-2.02 [-5.47 ; 1.42]; 0.498	0.498	
	Male	94	2	2.13	97	2	2.06	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Male	94	2	2.13	97	3	3.09	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of baseline Gd-enhancing lesions	>=1	141	4	2.84	135	5	3.70	0.77 [0.21 ; 2.79]	0.76 [0.2 ; 2.89];	-0.87 [-5.07 ; 3.34]; 0.745	0.745	0.5967
	0	131	8	6.11	136	7	5.15	1.19 [0.44 ; 3.18]	1.2 [0.42 ; 3.4];	0.96 [-4.57 ; 6.49]; 0.795	0.795	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	5	4.27	110	3	2.73	1.57 [0.38 ; 6.4]	1.59 [0.37 ; 6.83];	1.55 [-3.22 ; 6.31]; 0.723	0.723	0.2451
	>=3	42	1	2.38	40	4	10.00	0.24 [0.03 ; 2.04]	0.22 [0.02 ; 2.05];	-7.62 [-18 ; 2.76]; 0.196	0.196	
	2	113	6	5.31	123	5	4.07	1.31 [0.41 ; 4.16]	1.32 [0.39 ; 4.46];	1.24 [-4.17 ; 6.66]; 0.762	0.762	
Received approved disease modifying MS drug prior to enrollment	No	166	7	4.22	186	7	3.76	1.12 [0.4 ; 3.13]	1.13 [0.39 ; 3.28];	0.45 [-3.65 ; 4.56]; 1	1	0.7001
	Yes	106	5	4.72	87	5	5.75	0.82 [0.25 ; 2.74]	0.81 [0.23 ; 2.9];	-1.03 [-7.37 ; 5.31]; 0.756	0.756	
Region	Eastern Europe	245	11	4.49	251	11	4.38	1.02 [0.45 ; 2.32]	1.03 [0.44 ; 2.41];	0.11 [-3.52 ; 3.73]; 1	1	0.8743
	Eastern Europe	245	11	4.49	251	4	1.59	1.02 [0.45 ; 2.32]	1.03 [0.44 ; 2.41];	0.11 [-3.52 ; 3.73]; 1	1	
	Eastern Europe	245	4	1.63	251	11	4.38	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Eastern Europe	245	4	1.63	251	4	1.59	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	USA and Western Europe	27	1	3.70	22	1	4.55	0.81 [0.05 ; 12.3]	0.81 [0.05 ; 13.7];	-0.84 [-12.09 ; 10.41]; 1	1	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
	USA and Western Europe	27	1	3.70	22	6	27.27	0.81 [0.05 ; 12.3]	0.81 [0.05 ; 13.7];	-0.84 [-12.09 ; 10.41]; 1	1	
	USA and Western Europe	27	0	0.00	22	1	4.55	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	USA and Western Europe	27	0	0.00	22	6	27.27	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Bronchitis

5.2.26 Nervous system disorders - Hypoaesthesia

Tabelle 217: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Disease Severity at baseline (EDSS)	<=3.5	218	4	1.83	207	8	3.86	0.47 [0.15 ; 1.55]	0.46 [0.14 ; 1.57];	-2.03 [-5.2 ; 1.14]; 0.25	0.25	0.2718
	>3.5	54	0	0.00	66	2	3.03	0.24 [0.01 ; 4.97]	0.24 [0.01 ; 5.04];	-2.82 [-8.01 ; 2.36]; 0.501	0.501	
Number of baseline Gd-enhancing lesions	>=1	141	2	1.42	135	4	2.96	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	131	2	1.53	136	6	4.41	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	1	0.85	110	4	3.64	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	0	0.00	40	1	2.50	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	3	2.65	123	5	4.07	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	2	1.20	186	5	2.69	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	Yes	106	2	1.89	87	5	5.75	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Nervous system disorders | Hypoaesthesia

5.2.27 Gastrointestinal disorders - Abdominal pain upper

Tabelle 218: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	10	5.68	156	6	3.85	1.48 [0.55 ; 3.97]	1.51 [0.53 ; 4.24];	1.84 [-2.73 ; 6.4]; 0.609	0.609	0.834
	>= 38 years	96	3	3.12	117	3	2.56	1.22 [0.25 ; 5.9]	1.23 [0.24 ; 6.22];	0.56 [-3.95 ; 5.07]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	218	12	5.50	207	7	3.38	1.63 [0.65 ; 4.05]	1.66 [0.64 ; 4.31];	2.12 [-1.78 ; 6.03]; 0.351	0.351	0.4328
	>3.5	54	1	1.85	66	2	3.03	0.61 [0.06 ; 6.56]	0.6 [0.05 ; 6.84];	-1.18 [-6.66 ; 4.3]; 1	1	
Gender	Female	178	12	6.74	176	8	4.55	1.48 [0.62 ; 3.54]	1.52 [0.61 ; 3.81];	2.2 [-2.6 ; 7]; 0.491	0.491	0.7971
	Male	94	1	1.06	97	1	1.03	1.03 [0.07 ; 16.26]	1.03 [0.06 ; 16.75];	0.03 [-2.86 ; 2.92]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	10	7.09	135	4	2.96	2.39 [0.77 ; 7.45]	2.5 [0.76 ; 8.17];	4.13 [-0.98 ; 9.24]; 0.17	0.17	0.1323
	0	131	3	2.29	136	5	3.68	0.62 [0.15 ; 2.55]	0.61 [0.14 ; 2.62];	-1.39 [-5.46 ; 2.68]; 0.723	0.723	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	5	4.27	110	4	3.64	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	5	11.90	40	2	5.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	3	2.65	123	3	2.44	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	7	4.22	186	7	3.76	1.12 [0.4 ; 3.13]	1.13 [0.39 ; 3.28];	0.45 [-3.65 ; 4.56]; 1	1	0.3978
	Yes	106	6	5.66	87	2	2.30	2.46 [0.51 ; 11.89]	2.55 [0.5 ; 12.97];	3.36 [-2.05 ; 8.77]; 0.298	0.298	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	10	4.08	251	6	2.39	1.71 [0.63 ; 4.63]	1.74 [0.62 ; 4.86];	1.69 [-1.42 ; 4.81]; 0.319	0.319	0.4406
	USA and Western Europe	27	3	11.11	22	3	13.64	0.81 [0.18 ; 3.64]	0.79 [0.14 ; 4.38];	-2.53 [-21.13 ; 16.08]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Gastrointestinal disorders | Abdominal pain upper

5.2.28 Infections and infestations - Nasopharyngitis

Tabelle 219: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	48	27.27	156	36	23.08	1.18 [0.81 ; 1.72]	1.25 [0.76 ; 2.06];	4.2 [-5.13 ; 13.52]; 0.448	0.448	0.9727
	>= 38 years	96	18	18.75	117	18	15.38	1.22 [0.67 ; 2.21]	1.27 [0.62 ; 2.6];	3.37 [-6.82 ; 13.55]; 0.583	0.583	
Disease Severity at baseline (EDSS)	<=3.5	218	59	27.06	207	40	19.32	1.4 [0.98 ; 1.99]	1.55 [0.98 ; 2.45];	7.74 [-0.24 ; 15.72]; 0.066	0.066	0.0586
	>3.5	54	7	12.96	66	14	21.21	0.61 [0.27 ; 1.41]	0.55 [0.21 ; 1.49];	-8.25 [-21.57 ; 5.08]; 0.335	0.335	
Gender	Female	178	53	29.78	176	36	20.45	1.46 [1.01 ; 2.1]	1.65 [1.01 ; 2.68];	9.32 [0.34 ; 18.3]; 0.05	0.05	0.0676
	Male	94	13	13.83	97	18	18.56	0.75 [0.39 ; 1.43]	0.7 [0.32 ; 1.53];	-4.73 [-15.15 ; 5.69]; 0.435	0.435	
Number of baseline Gd-enhancing lesions	>=1	141	35	24.82	135	31	22.96	1.08 [0.71 ; 1.65]	1.11 [0.64 ; 1.93];	1.86 [-8.2 ; 11.92]; 0.778	0.778	0.4455
	0	131	31	23.66	136	23	16.91	1.4 [0.86 ; 2.27]	1.52 [0.83 ; 2.78];	6.75 [-2.87 ; 16.38]; 0.175	0.175	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	30	25.64	110	25	22.73	1.13 [0.71 ; 1.79]	1.17 [0.64 ; 2.16];	2.91 [-8.22 ; 14.05]; 0.644	0.644	0.1075
	>=3	42	13	30.95	40	4	10.00	3.1 [1.1 ; 8.7]	4.03 [1.19 ; 13.7];	20.95 [4.16 ; 37.74]; 0.028	0.028	
	2	113	23	20.35	123	25	20.33	1 [0.6 ; 1.66]	1 [0.53 ; 1.89];	0.03 [-10.25 ; 10.31]; 1	1	
Received approved disease modifying MS drug prior to enrollment	No	166	48	28.92	186	38	20.43	1.42 [0.98 ; 2.05]	1.58 [0.97 ; 2.58];	8.49 [-0.52 ; 17.49]; 0.082	0.082	0.2207
	Yes	106	18	16.98	87	16	18.39	0.92 [0.5 ; 1.7]	0.91 [0.43 ; 1.91];	-1.41 [-12.24 ; 9.42]; 0.851	0.851	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	55	22.45	251	46	18.33	1.22 [0.86 ; 1.74]	1.29 [0.83 ; 2];	4.12 [-2.96 ; 11.21]; 0.267	0.267	0.9122
	USA and Western Europe	27	11	40.74	22	8	36.36	1.12 [0.55 ; 2.29]	1.2 [0.38 ; 3.84];	4.38 [-22.96 ; 31.72]; 0.777	0.777	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Nasopharyngitis

5.2.29 Infections and infestations - Sinusitis

Tabelle 220: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	11	6.25	156	6	3.85	1.62 [0.62 ; 4.29]	1.67 [0.6 ; 4.62];	2.4 [-2.28 ; 7.08]; 0.455	0.455	0.7024
	>= 38 years	96	6	6.25	117	6	5.13	1.22 [0.41 ; 3.66]	1.23 [0.38 ; 3.95];	1.12 [-5.16 ; 7.4]; 0.772	0.772	
Disease Severity at baseline (EDSS)	<=3.5	218	15	6.88	207	11	5.31	1.29 [0.61 ; 2.75]	1.32 [0.59 ; 2.94];	1.57 [-2.98 ; 6.11]; 0.548	0.548	0.6153
	>3.5	54	2	3.70	66	1	1.52	2.44 [0.23 ; 26.24]	2.5 [0.22 ; 28.34];	2.19 [-3.65 ; 8.02]; 0.588	0.588	
Gender	Female	178	14	7.87	176	7	3.98	1.98 [0.82 ; 4.78]	2.06 [0.81 ; 5.24];	3.89 [-1.01 ; 8.78]; 0.176	0.176	0.1586
	Male	94	3	3.19	97	5	5.15	0.62 [0.15 ; 2.52]	0.61 [0.14 ; 2.61];	-1.96 [-7.62 ; 3.69]; 0.721	0.721	
Number of baseline Gd-enhancing lesions	>=1	141	8	5.67	135	3	2.22	2.55 [0.69 ; 9.42]	2.65 [0.69 ; 10.19];	3.45 [-1.11 ; 8.01]; 0.218	0.218	0.2573
	0	131	9	6.87	136	9	6.62	1.04 [0.43 ; 2.53]	1.04 [0.4 ; 2.71];	0.25 [-5.77 ; 6.27]; 1	1	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	9	7.69	110	4	3.64	2.12 [0.67 ; 6.67]	2.21 [0.66 ; 7.39];	4.06 [-1.91 ; 10.02]; 0.256	0.256	0.1439
	>=3	42	2	4.76	40	5	12.50	0.38 [0.08 ; 1.85]	0.35 [0.06 ; 1.92];	-7.74 [-19.84 ; 4.37]; 0.259	0.259	
	2	113	6	5.31	123	3	2.44	2.18 [0.56 ; 8.5]	2.24 [0.55 ; 9.19];	2.87 [-2.08 ; 7.82]; 0.317	0.317	
Received approved disease modifying MS drug prior to enrollment	No	166	12	7.23	186	9	4.84	1.49 [0.65 ; 3.46]	1.53 [0.63 ; 3.73];	2.39 [-2.61 ; 7.39]; 0.375	0.375	0.9086
	Yes	106	5	4.72	87	3	3.45	1.37 [0.34 ; 5.56]	1.39 [0.32 ; 5.97];	1.27 [-4.3 ; 6.84]; 0.732	0.732	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	13	5.31	251	10	3.98	1.33 [0.6 ; 2.98]	1.35 [0.58 ; 3.14];	1.32 [-2.38 ; 5.03]; 0.527	0.527	0.8018
	USA and Western Europe	27	4	14.81	22	2	9.09	1.63 [0.33 ; 8.08]	1.74 [0.29 ; 10.52];	5.72 [-12.27 ; 23.72]; 0.678	0.678	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Sinusitis

5.2.30 Infections and infestations - Upper respiratory tract infection

Tabelle 221: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	15	8.52	156	11	7.05	1.21 [0.57 ; 2.55]	1.23 [0.55 ; 2.76];	1.47 [-4.29 ; 7.23]; 0.685	0.685	0.6225
	>= 38 years	96	9	9.38	117	12	10.26	0.91 [0.4 ; 2.08]	0.91 [0.36 ; 2.25];	-0.88 [-8.9 ; 7.13]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	218	18	8.26	207	17	8.21	1.01 [0.53 ; 1.9]	1.01 [0.5 ; 2.01];	0.04 [-5.18 ; 5.27]; 1	1	0.7576
	>3.5	54	6	11.11	66	6	9.09	1.22 [0.42 ; 3.57]	1.25 [0.38 ; 4.12];	2.02 [-8.86 ; 12.9]; 0.766	0.766	
Gender	Female	178	16	8.99	176	14	7.95	1.13 [0.57 ; 2.24]	1.14 [0.54 ; 2.42];	1.03 [-4.77 ; 6.83]; 0.849	0.849	0.7197
	Male	94	8	8.51	97	9	9.28	0.92 [0.37 ; 2.28]	0.91 [0.34 ; 2.47];	-0.77 [-8.84 ; 7.3]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	11	7.80	135	5	3.70	2.11 [0.75 ; 5.9]	2.2 [0.74 ; 6.51];	4.1 [-1.36 ; 9.55]; 0.198	0.198	0.091
	0	131	13	9.92	136	18	13.24	0.75 [0.38 ; 1.47]	0.72 [0.34 ; 1.54];	-3.31 [-10.97 ; 4.35]; 0.448	0.448	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	11	9.40	110	10	9.09	1.03 [0.46 ; 2.34]	1.04 [0.42 ; 2.55];	0.31 [-7.23 ; 7.85]; 1	1	0.3494
	>=3	42	4	9.52	40	1	2.50	3.81 [0.44 ; 32.64]	4.11 [0.44 ; 38.42];	7.02 [-3.09 ; 17.13]; 0.36	0.36	
	2	113	9	7.96	123	12	9.76	0.82 [0.36 ; 1.86]	0.8 [0.32 ; 1.98];	-1.79 [-9.03 ; 5.45]; 0.655	0.655	
Received approved disease modifying MS drug prior to enrollment	No	166	11	6.63	186	18	9.68	0.68 [0.33 ; 1.41]	0.66 [0.3 ; 1.45];	-3.05 [-8.74 ; 2.64]; 0.336	0.336	0.0586
	Yes	106	13	12.26	87	5	5.75	2.13 [0.79 ; 5.75]	2.29 [0.78 ; 6.71];	6.52 [-1.41 ; 14.45]; 0.141	0.141	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	21	8.57	251	18	7.17	1.2 [0.65 ; 2.19]	1.21 [0.63 ; 2.34];	1.4 [-3.34 ; 6.14]; 0.619	0.619	0.2175
	USA and Western Europe	27	3	11.11	22	5	22.73	0.49 [0.13 ; 1.82]	0.42 [0.09 ; 2.02];	-11.62 [-32.76 ; 9.53]; 0.44	0.44	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Upper respiratory tract infection

5.2.31 Musculoskeletal and connective tissue disorders - Arthralgia

Tabelle 222: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	9	5.11	156	6	3.85	1.33 [0.48 ; 3.65]	1.35 [0.47 ; 3.87];	1.27 [-3.17 ; 5.71]; 0.609	0.609	0.9387
	>= 38 years	96	8	8.33	117	7	5.98	1.39 [0.52 ; 3.7]	1.43 [0.5 ; 4.09];	2.35 [-4.65 ; 9.35]; 0.594	0.594	
Disease Severity at baseline (EDSS)	<=3.5	218	17	7.80	207	9	4.35	1.79 [0.82 ; 3.93]	1.86 [0.81 ; 4.27];	3.45 [-1.06 ; 7.97]; 0.159	0.159	0.01
	>3.5	54	0	0.00	66	4	6.06	0.14 [0.01 ; 2.46]	0.13 [0.01 ; 2.42];	-5.81 [-12.3 ; 0.69]; 0.126	0.126	
Gender	Female	178	9	5.06	176	9	5.11	0.99 [0.4 ; 2.43]	0.99 [0.38 ; 2.55];	-0.06 [-4.63 ; 4.52]; 1	1	0.3185
	Male	94	8	8.51	97	4	4.12	2.06 [0.64 ; 6.62]	2.16 [0.63 ; 7.44];	4.39 [-2.5 ; 11.28]; 0.245	0.245	
Number of baseline Gd-enhancing lesions	>=1	141	11	7.80	135	4	2.96	2.63 [0.86 ; 8.07]	2.77 [0.86 ; 8.93];	4.84 [-0.43 ; 10.11]; 0.11	0.11	0.0717
	0	131	6	4.58	136	9	6.62	0.69 [0.25 ; 1.89]	0.68 [0.23 ; 1.96];	-2.04 [-7.54 ; 3.46]; 0.598	0.598	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	10	8.55	110	7	6.36	1.34 [0.53 ; 3.4]	1.38 [0.5 ; 3.75];	2.18 [-4.63 ; 9]; 0.618	0.618	0.3995
	>=3	42	0	0.00	40	1	2.50	0.32 [0.01 ; 7.58]	0.31 [0.01 ; 7.83];	-2.5 [-9.08 ; 4.08]; 0.494	0.494	
	2	113	7	6.19	123	5	4.07	1.52 [0.5 ; 4.67]	1.56 [0.48 ; 5.06];	2.13 [-3.52 ; 7.78]; 0.558	0.558	
Received approved disease modifying MS drug prior to enrollment	No	166	9	5.42	186	5	2.69	2.02 [0.69 ; 5.9]	2.08 [0.68 ; 6.32];	2.73 [-1.42 ; 6.89]; 0.275	0.275	0.2169
	Yes	106	8	7.55	87	8	9.20	0.82 [0.32 ; 2.1]	0.81 [0.29 ; 2.24];	-1.65 [-9.53 ; 6.24]; 0.795	0.795	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	10	4.08	251	9	3.59	1.14 [0.47 ; 2.75]	1.14 [0.46 ; 2.87];	0.5 [-2.88 ; 3.88]; 0.819	0.819	0.7051
	USA and Western Europe	27	7	25.93	22	4	18.18	1.43 [0.48 ; 4.25]	1.57 [0.39 ; 6.28];	7.74 [-15.34 ; 30.83]; 0.732	0.732	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Musculoskeletal and connective tissue disorders | Arthralgia

5.2.32 Musculoskeletal and connective tissue disorders - Back pain

Tabelle 223: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	20	11.36	156	13	8.33	1.36 [0.7 ; 2.65]	1.41 [0.68 ; 2.94];	3.03 [-3.36 ; 9.42]; 0.463	0.463	0.5528
	>= 38 years	96	15	15.62	117	10	8.55	1.83 [0.86 ; 3.88]	1.98 [0.85 ; 4.64];	7.08 [-1.78 ; 15.93]; 0.135	0.135	
Disease Severity at baseline (EDSS)	<=3.5	218	32	14.68	207	17	8.21	1.79 [1.02 ; 3.12]	1.92 [1.03 ; 3.58];	6.47 [0.46 ; 12.47]; 0.048	0.048	0.1268
	>3.5	54	3	5.56	66	6	9.09	0.61 [0.16 ; 2.33]	0.59 [0.14 ; 2.47];	-3.54 [-12.78 ; 5.71]; 0.512	0.512	
Gender	Female	178	28	15.73	176	16	9.09	1.73 [0.97 ; 3.08]	1.87 [0.97 ; 3.59];	6.64 [-0.19 ; 13.47]; 0.076	0.076	0.3626
	Male	94	7	7.45	97	7	7.22	1.03 [0.38 ; 2.83]	1.03 [0.35 ; 3.07];	0.23 [-7.16 ; 7.63]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	23	16.31	135	10	7.41	2.2 [1.09 ; 4.45]	2.44 [1.11 ; 5.34];	8.9 [1.37 ; 16.44]; 0.026	0.026	0.1031
	0	131	12	9.16	136	13	9.56	0.96 [0.45 ; 2.02]	0.95 [0.42 ; 2.18];	-0.4 [-7.39 ; 6.59]; 1	1	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	11	9.40	110	10	9.09	1.03 [0.46 ; 2.34]	1.04 [0.42 ; 2.55];	0.31 [-7.23 ; 7.85]; 1	1	0.4529
	>=3	42	5	11.90	40	2	5.00	2.38 [0.49 ; 11.58]	2.57 [0.47 ; 14.07];	6.9 [-4.99 ; 18.8]; 0.433	0.433	
	2	113	19	16.81	123	11	8.94	1.88 [0.94 ; 3.78]	2.06 [0.93 ; 4.54];	7.87 [-0.67 ; 16.41]; 0.08	0.08	
Received approved disease modifying MS drug prior to enrollment	No	166	24	14.46	186	18	9.68	1.49 [0.84 ; 2.65]	1.58 [0.82 ; 3.02];	4.78 [-2.05 ; 11.61]; 0.189	0.189	0.7746
	Yes	106	11	10.38	87	5	5.75	1.81 [0.65 ; 5]	1.9 [0.63 ; 5.69];	4.63 [-2.96 ; 12.22]; 0.3	0.3	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	29	11.84	251	19	7.57	1.56 [0.9 ; 2.71]	1.64 [0.89 ; 3.01];	4.27 [-0.94 ; 9.47]; 0.129	0.129	0.7577
	USA and Western Europe	27	6	22.22	22	4	18.18	1.22 [0.39 ; 3.79]	1.29 [0.31 ; 5.28];	4.04 [-18.45 ; 26.53]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Musculoskeletal and connective tissue disorders | Back pain

5.2.33 General disorders and administration site conditions - Fatigue

Tabelle 224: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	11	6.25	156	5	3.21	1.95 [0.69 ; 5.49]	2.01 [0.68 ; 5.93];	3.04 [-1.47 ; 7.56]; 0.213	0.213	0.4068
	>= 38 years	96	5	5.21	117	6	5.13	1.02 [0.32 ; 3.23]	1.02 [0.3 ; 3.44];	0.08 [-5.9 ; 6.06]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	218	15	6.88	207	8	3.86	1.78 [0.77 ; 4.11]	1.84 [0.76 ; 4.43];	3.02 [-1.25 ; 7.28]; 0.201	0.201	0.1898
	>3.5	54	1	1.85	66	3	4.55	0.41 [0.04 ; 3.81]	0.4 [0.04 ; 3.92];	-2.69 [-8.87 ; 3.49]; 0.626	0.626	
Gender	Female	178	10	5.62	176	6	3.41	1.65 [0.61 ; 4.44]	1.69 [0.6 ; 4.74];	2.21 [-2.11 ; 6.53]; 0.444	0.444	0.7172
	Male	94	6	6.38	97	5	5.15	1.24 [0.39 ; 3.92]	1.25 [0.37 ; 4.26];	1.23 [-5.39 ; 7.85]; 0.765	0.765	
Number of baseline Gd-enhancing lesions	>=1	141	9	6.38	135	6	4.44	1.44 [0.53 ; 3.93]	1.47 [0.51 ; 4.24];	1.94 [-3.39 ; 7.26]; 0.598	0.598	0.9912
	0	131	7	5.34	136	5	3.68	1.45 [0.47 ; 4.46]	1.48 [0.46 ; 4.78];	1.67 [-3.32 ; 6.65]; 0.566	0.566	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	6	5.13	110	5	4.55	1.13 [0.35 ; 3.59]	1.14 [0.34 ; 3.83];	0.58 [-5 ; 6.16]; 1	1	0.7465
	>=3	42	3	7.14	40	1	2.50	2.86 [0.31 ; 26.34]	3 [0.3 ; 30.11];	4.64 [-4.53 ; 13.81]; 0.616	0.616	
	2	113	7	6.19	123	5	4.07	1.52 [0.5 ; 4.67]	1.56 [0.48 ; 5.06];	2.13 [-3.52 ; 7.78]; 0.558	0.558	
Received approved disease modifying MS drug prior to enrollment	No	166	10	6.02	186	7	3.76	1.6 [0.62 ; 4.11]	1.64 [0.61 ; 4.41];	2.26 [-2.28 ; 6.8]; 0.334	0.334	0.7419
	Yes	106	6	5.66	87	4	4.60	1.23 [0.36 ; 4.22]	1.24 [0.34 ; 4.56];	1.06 [-5.16 ; 7.29]; 1	1	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	11	4.49	251	4	1.59	2.82 [0.91 ; 8.73]	2.9 [0.91 ; 9.24];	2.9 [-0.12 ; 5.92]; 0.069	0.069	0.0413
	USA and Western Europe	27	5	18.52	22	7	31.82	0.58 [0.21 ; 1.58]	0.49 [0.13 ; 1.83];	-13.3 [-37.66 ; 11.06]; 0.331	0.331	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - General disorders and administration site conditions | Fatigue

5.2.34 Infections and infestations - Urinary tract infection

Tabelle 225: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	5	2.84	156	2	1.28	2.22 [0.44 ; 11.26]	2.25 [0.43 ; 11.77];	1.56 [-1.46 ; 4.58]; 0.454	0.454	0.2339
	>= 38 years	96	6	6.25	117	10	8.55	0.73 [0.28 ; 1.94]	0.71 [0.25 ; 2.04];	-2.3 [-9.3 ; 4.71]; 0.608	0.608	
Disease Severity at baseline (EDSS)	<=3.5	218	9	4.13	207	5	2.42	1.71 [0.58 ; 5.02]	1.74 [0.57 ; 5.28];	1.71 [-1.66 ; 5.08]; 0.418	0.418	0.0752
	>3.5	54	2	3.70	66	7	10.61	0.35 [0.08 ; 1.61]	0.32 [0.06 ; 1.63];	-6.9 [-15.88 ; 2.07]; 0.183	0.183	
Gender	Female	178	10	5.62	176	9	5.11	1.1 [0.46 ; 2.64]	1.1 [0.44 ; 2.79];	0.5 [-4.19 ; 5.2]; 1	1	0.3175
	Male	94	1	1.06	97	3	3.09	0.34 [0.04 ; 3.25]	0.34 [0.03 ; 3.3];	-2.03 [-6.05 ; 1.99]; 0.621	0.621	
Number of baseline Gd-enhancing lesions	>=1	141	4	2.84	135	6	4.44	0.64 [0.18 ; 2.21]	0.63 [0.17 ; 2.28];	-1.61 [-6.03 ; 2.82]; 0.534	0.534	0.4405
	0	131	7	5.34	136	6	4.41	1.21 [0.42 ; 3.51]	1.22 [0.4 ; 3.74];	0.93 [-4.24 ; 6.1]; 0.782	0.782	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	6	5.13	110	7	6.36	0.81 [0.28 ; 2.32]	0.8 [0.26 ; 2.44];	-1.24 [-7.3 ; 4.83]; 0.779	0.779	0.4713
	>=3	42	1	2.38	40	0	0.00	2.86 [0.12 ; 68.23]	2.93 [0.12 ; 73.99];	2.27 [-4.16 ; 8.7]; 0.495	0.495	
	2	113	4	3.54	123	5	4.07	0.87 [0.24 ; 3.16]	0.87 [0.23 ; 3.31];	-0.53 [-5.4 ; 4.35]; 1	1	
Received approved disease modifying MS drug prior to enrollment	No	166	8	4.82	186	8	4.30	1.12 [0.43 ; 2.92]	1.13 [0.41 ; 3.07];	0.52 [-3.85 ; 4.89]; 1	1	0.5019
	Yes	106	3	2.83	87	4	4.60	0.62 [0.14 ; 2.68]	0.6 [0.13 ; 2.78];	-1.77 [-7.18 ; 3.65]; 0.703	0.703	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	8	3.27	251	11	4.38	0.75 [0.3 ; 1.82]	0.74 [0.29 ; 1.86];	-1.12 [-4.49 ; 2.25]; 0.642	0.642	0.2956
	USA and Western Europe	27	3	11.11	22	1	4.55	2.44 [0.27 ; 21.89]	2.62 [0.25 ; 27.19];	6.57 [-8.14 ; 21.27]; 0.617	0.617	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Urinary tract infection

5.2.35 Cardiac disorders - Sinus tachycardia

Tabelle 226: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	12	6.82	156	5	3.21	2.13 [0.77 ; 5.9]	2.21 [0.76 ; 6.42];	3.61 [-1.02 ; 8.25]; 0.211	0.211	0.0179
	>= 38 years	96	8	8.33	117	0	0.00	20.68 [1.21 ; 353.78]	22.57 [1.29 ; 396.28];	8.34 [2.59 ; 14.09]; 0.001	0.001	
Disease Severity at baseline (EDSS)	<=3.5	218	16	7.34	207	4	1.93	3.8 [1.29 ; 11.17]	4.02 [1.32 ; 12.23];	5.41 [1.47 ; 9.34]; 0.01	0.01	0.8369
	>3.5	54	4	7.41	66	1	1.52	4.89 [0.56 ; 42.46]	5.2 [0.56 ; 47.98];	5.89 [-1.69 ; 13.47]; 0.173	0.173	
Gender	Female	178	13	7.30	176	2	1.14	6.43 [1.47 ; 28.07]	6.85 [1.52 ; 30.84];	6.17 [2.04 ; 10.3]; 0.006	0.006	0.3314
	Male	94	7	7.45	97	3	3.09	2.41 [0.64 ; 9.04]	2.52 [0.63 ; 10.06];	4.35 [-1.97 ; 10.68]; 0.208	0.208	
Number of baseline Gd-enhancing lesions	>=1	141	12	8.51	135	3	2.22	3.83 [1.11 ; 13.27]	4.09 [1.13 ; 14.84];	6.29 [1.05 ; 11.52]; 0.031	0.031	0.9517
	0	131	8	6.11	136	2	1.47	4.15 [0.9 ; 19.19]	4.36 [0.91 ; 20.92];	4.64 [0.06 ; 9.21]; 0.057	0.057	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	10	8.55	110	2	1.82	4.7 [1.05 ; 20.98]	5.05 [1.08 ; 23.58];	6.73 [1.08 ; 12.38]; 0.035	0.035	0.8542
	>=3	42	5	11.90	40	1	2.50	4.76 [0.58 ; 39]	5.27 [0.59 ; 47.26];	9.4 [-1.52 ; 20.33]; 0.202	0.202	
	2	113	5	4.42	123	2	1.63	2.72 [0.54 ; 13.75]	2.8 [0.53 ; 14.73];	2.8 [-1.6 ; 7.2]; 0.264	0.264	
Received approved disease modifying MS drug prior to enrollment	No	166	11	6.63	186	3	1.61	4.11 [1.17 ; 14.47]	4.33 [1.19 ; 15.8];	5.01 [0.82 ; 9.21]; 0.026	0.026	0.9282
	Yes	106	9	8.49	87	2	2.30	3.69 [0.82 ; 16.65]	3.94 [0.83 ; 18.76];	6.19 [0.02 ; 12.36]; 0.115	0.115	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	19	7.76	251	5	1.99	3.89 [1.48 ; 10.26]	4.14 [1.52 ; 11.26];	5.76 [1.99 ; 9.53]; 0.003	0.003	0.547
	USA and Western Europe	27	1	3.70	22	0	0.00	2.46 [0.11 ; 57.66]	2.55 [0.1 ; 65.66];	3.18 [-7.07 ; 13.43]; 0.497	0.497	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Cardiac disorders | Sinus tachycardia

5.2.36 Infections and infestations - Oral herpes

Tabelle 227: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	7	3.98	156	14	8.97	0.44 [0.18 ; 1.07]	0.42 [0.17 ; 1.07];	-5 [-10.33 ; 0.34]; 0.072	0.072	0.0061
	>= 38 years	96	7	7.29	117	2	1.71	4.27 [0.91 ; 20.06]	4.52 [0.92 ; 22.3];	5.58 [-0.12 ; 11.29]; 0.082	0.082	
Disease Severity at baseline (EDSS)	<=3.5	218	13	5.96	207	11	5.31	1.12 [0.51 ; 2.45]	1.13 [0.49 ; 2.58];	0.65 [-3.73 ; 5.03]; 0.835	0.835	0.1371
	>3.5	54	1	1.85	66	5	7.58	0.24 [0.03 ; 2.03]	0.23 [0.03 ; 2.03];	-5.72 [-13.05 ; 1.6]; 0.221	0.221	
Gender	Female	178	13	7.30	176	13	7.39	0.99 [0.47 ; 2.07]	0.99 [0.44 ; 2.2];	-0.08 [-5.52 ; 5.35]; 1	1	0.3564
	Male	94	1	1.06	97	3	3.09	0.34 [0.04 ; 3.25]	0.34 [0.03 ; 3.3];	-2.03 [-6.05 ; 1.99]; 0.621	0.621	
Number of baseline Gd-enhancing lesions	>=1	141	10	7.09	135	9	6.67	1.06 [0.45 ; 2.54]	1.07 [0.42 ; 2.72];	0.43 [-5.55 ; 6.4]; 1	1	0.4396
	0	131	4	3.05	136	7	5.15	0.59 [0.18 ; 1.98]	0.58 [0.17 ; 2.03];	-2.09 [-6.83 ; 2.65]; 0.541	0.541	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	7	5.98	110	8	7.27	0.82 [0.31 ; 2.19]	0.81 [0.28 ; 2.32];	-1.29 [-7.77 ; 5.19]; 0.792	0.792	0.1984
	>=3	42	2	4.76	40	0	0.00	4.77 [0.24 ; 96.34]	5 [0.23 ; 107.43];	4.59 [-3.16 ; 12.35]; 0.494	0.494	
	2	113	5	4.42	123	8	6.50	0.68 [0.23 ; 2.02]	0.67 [0.21 ; 2.1];	-2.08 [-7.86 ; 3.7]; 0.575	0.575	
Received approved disease modifying MS drug prior to enrollment	No	166	11	6.63	186	12	6.45	1.03 [0.47 ; 2.27]	1.03 [0.44 ; 2.4];	0.17 [-5 ; 5.35]; 1	1	0.548
	Yes	106	3	2.83	87	4	4.60	0.62 [0.14 ; 2.68]	0.6 [0.13 ; 2.78];	-1.77 [-7.18 ; 3.65]; 0.703	0.703	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	12	4.90	251	16	6.37	0.77 [0.37 ; 1.59]	0.76 [0.35 ; 1.63];	-1.48 [-5.53 ; 2.58]; 0.561	0.561	0.092
	USA and Western Europe	27	2	7.41	22	0	0.00	4.11 [0.21 ; 81.33]	4.41 [0.2 ; 96.84];	6.75 [-5.37 ; 18.88]; 0.497	0.497	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Oral herpes

5.2.37 Respiratory, thoracic and mediastinal disorders - Oropharyngeal pain

Tabelle 228: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	12	6.82	156	7	4.49	1.52 [0.61 ; 3.76]	1.56 [0.6 ; 4.06];	2.33 [-2.61 ; 7.27]; 0.479	0.479	0.3347
	>= 38 years	96	6	6.25	117	2	1.71	3.66 [0.76 ; 17.7]	3.83 [0.76 ; 19.45];	4.54 [-0.84 ; 9.92]; 0.144	0.144	
Disease Severity at baseline (EDSS)	<=3.5	218	15	6.88	207	6	2.90	2.37 [0.94 ; 6]	2.48 [0.94 ; 6.51];	3.98 [-0.08 ; 8.05]; 0.073	0.073	0.475
	>3.5	54	3	5.56	66	3	4.55	1.22 [0.26 ; 5.81]	1.24 [0.24 ; 6.38];	1.01 [-6.9 ; 8.92]; 1	1	
Gender	Female	178	15	8.43	176	7	3.98	2.12 [0.89 ; 5.07]	2.22 [0.88 ; 5.59];	4.45 [-0.55 ; 9.45]; 0.122	0.122	0.7379
	Male	94	3	3.19	97	2	2.06	1.55 [0.26 ; 9.06]	1.57 [0.26 ; 9.59];	1.13 [-3.41 ; 5.67]; 0.679	0.679	
Number of baseline Gd-enhancing lesions	>=1	141	11	7.80	135	3	2.22	3.51 [1 ; 12.31]	3.72 [1.02 ; 13.65];	5.58 [0.5 ; 10.66]; 0.052	0.052	0.1928
	0	131	7	5.34	136	6	4.41	1.21 [0.42 ; 3.51]	1.22 [0.4 ; 3.74];	0.93 [-4.24 ; 6.1]; 0.782	0.782	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	10	8.55	110	3	2.73	3.13 [0.89 ; 11.09]	3.33 [0.89 ; 12.45];	5.82 [-0.09 ; 11.73]; 0.085	0.085	0.0956
	>=3	42	3	7.14	40	0	0.00	6.67 [0.36 ; 125.26]	7.18 [0.36 ; 143.5];	6.92 [-1.92 ; 15.76]; 0.118	0.118	
	2	113	5	4.42	123	6	4.88	0.91 [0.28 ; 2.89]	0.9 [0.27 ; 3.04];	-0.45 [-5.83 ; 4.92]; 1	1	
Received approved disease modifying MS drug prior to enrollment	No	166	10	6.02	186	6	3.23	1.87 [0.69 ; 5.03]	1.92 [0.68 ; 5.41];	2.8 [-1.62 ; 7.22]; 0.305	0.305	0.8423
	Yes	106	8	7.55	87	3	3.45	2.19 [0.6 ; 8]	2.29 [0.59 ; 8.89];	4.1 [-2.22 ; 10.42]; 0.351	0.351	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	14	5.71	251	8	3.19	1.79 [0.77 ; 4.2]	1.84 [0.76 ; 4.47];	2.53 [-1.1 ; 6.16]; 0.195	0.195	0.5663
	USA and Western Europe	27	4	14.81	22	1	4.55	3.26 [0.39 ; 27.09]	3.65 [0.38 ; 35.34];	10.27 [-5.71 ; 26.25]; 0.362	0.362	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Respiratory, thoracic and mediastinal disorders | Oropharyngeal pain

5.2.38 Psychiatric disorders - Anxiety

Tabelle 229: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	14	7.95	156	8	5.13	1.55 [0.67 ; 3.6]	1.6 [0.65 ; 3.92];	2.83 [-2.46 ; 8.11]; 0.379	0.379	0.3106
	>= 38 years	96	2	2.08	117	4	3.42	0.61 [0.11 ; 3.26]	0.6 [0.11 ; 3.35];	-1.34 [-5.69 ; 3.02]; 0.692	0.692	
Disease Severity at baseline (EDSS)	<=3.5	218	15	6.88	207	8	3.86	1.78 [0.77 ; 4.11]	1.84 [0.76 ; 4.43];	3.02 [-1.25 ; 7.28]; 0.201	0.201	0.0959
	>3.5	54	1	1.85	66	4	6.06	0.31 [0.04 ; 2.65]	0.29 [0.03 ; 2.7];	-4.21 [-11 ; 2.58]; 0.377	0.377	
Gender	Female	178	12	6.74	176	10	5.68	1.19 [0.53 ; 2.68]	1.2 [0.5 ; 2.85];	1.06 [-3.97 ; 6.09]; 0.826	0.826	0.5596
	Male	94	4	4.26	97	2	2.06	2.06 [0.39 ; 11]	2.11 [0.38 ; 11.81];	2.19 [-2.77 ; 7.16]; 0.44	0.44	
Number of baseline Gd-enhancing lesions	>=1	141	12	8.51	135	7	5.19	1.64 [0.67 ; 4.04]	1.7 [0.65 ; 4.46];	3.33 [-2.61 ; 9.26]; 0.344	0.344	0.3871
	0	131	4	3.05	136	5	3.68	0.83 [0.23 ; 3.03]	0.83 [0.22 ; 3.14];	-0.62 [-4.95 ; 3.7]; 1	1	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	10	8.55	110	5	4.55	1.88 [0.66 ; 5.33]	1.96 [0.65 ; 5.94];	4 [-2.39 ; 10.39]; 0.289	0.289	0.4738
	>=3	42	3	7.14	40	2	5.00	1.43 [0.25 ; 8.11]	1.46 [0.23 ; 9.24];	2.14 [-8.17 ; 12.45]; 1	1	
	2	113	3	2.65	123	5	4.07	0.65 [0.16 ; 2.67]	0.64 [0.15 ; 2.76];	-1.41 [-5.99 ; 3.17]; 0.724	0.724	
Received approved disease modifying MS drug prior to enrollment	No	166	9	5.42	186	7	3.76	1.44 [0.55 ; 3.78]	1.47 [0.53 ; 4.03];	1.66 [-2.74 ; 6.06]; 0.61	0.61	0.7683
	Yes	106	7	6.60	87	5	5.75	1.15 [0.38 ; 3.49]	1.16 [0.35 ; 3.79];	0.86 [-5.95 ; 7.66]; 1	1	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	14	5.71	251	11	4.38	1.3 [0.6 ; 2.82]	1.32 [0.59 ; 2.97];	1.33 [-2.52 ; 5.19]; 0.543	0.543	0.8555
	USA and Western Europe	27	2	7.41	22	1	4.55	1.63 [0.16 ; 16.81]	1.68 [0.14 ; 19.85];	2.86 [-10.3 ; 16.03]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Psychiatric disorders | Anxiety

5.2.39 Vascular disorders - Hypertension

Tabelle 230: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	6	3.41	156	5	3.21	1.06 [0.33 ; 3.42]	1.07 [0.32 ; 3.56];	0.2 [-3.65 ; 4.05]; 1	1	0.4077
	>= 38 years	96	4	4.17	117	9	7.69	0.54 [0.17 ; 1.7]	0.52 [0.16 ; 1.75];	-3.53 [-9.79 ; 2.74]; 0.391	0.391	
Disease Severity at baseline (EDSS)	<=3.5	218	9	4.13	207	11	5.31	0.78 [0.33 ; 1.84]	0.77 [0.31 ; 1.89];	-1.19 [-5.22 ; 2.85]; 0.65	0.65	0.5863
	>3.5	54	1	1.85	66	3	4.55	0.41 [0.04 ; 3.81]	0.4 [0.04 ; 3.92];	-2.69 [-8.87 ; 3.49]; 0.626	0.626	
Gender	Female	178	7	3.93	176	9	5.11	0.77 [0.29 ; 2.02]	0.76 [0.28 ; 2.09];	-1.18 [-5.51 ; 3.15]; 0.619	0.619	0.8034
	Male	94	3	3.19	97	5	5.15	0.62 [0.15 ; 2.52]	0.61 [0.14 ; 2.61];	-1.96 [-7.62 ; 3.69]; 0.721	0.721	
Number of baseline Gd-enhancing lesions	>=1	141	4	2.84	135	6	4.44	0.64 [0.18 ; 2.21]	0.63 [0.17 ; 2.28];	-1.61 [-6.03 ; 2.82]; 0.534	0.534	0.8143
	0	131	6	4.58	136	8	5.88	0.78 [0.28 ; 2.18]	0.77 [0.26 ; 2.28];	-1.3 [-6.64 ; 4.03]; 0.785	0.785	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	5	4.27	110	6	5.45	0.78 [0.25 ; 2.49]	0.77 [0.23 ; 2.61];	-1.18 [-6.79 ; 4.43]; 0.763	0.763	0.8763
	>=3	42	2	4.76	40	2	5.00	0.95 [0.14 ; 6.44]	0.95 [0.13 ; 7.09];	-0.24 [-9.57 ; 9.09]; 1	1	
	2	113	3	2.65	123	6	4.88	0.54 [0.14 ; 2.13]	0.53 [0.13 ; 2.18];	-2.22 [-7.05 ; 2.6]; 0.503	0.503	
Received approved disease modifying MS drug prior to enrollment	No	166	3	1.81	186	9	4.84	0.37 [0.1 ; 1.36]	0.36 [0.1 ; 1.36];	-3.03 [-6.72 ; 0.66]; 0.147	0.147	0.1866
	Yes	106	7	6.60	87	5	5.75	1.15 [0.38 ; 3.49]	1.16 [0.35 ; 3.79];	0.86 [-5.95 ; 7.66]; 1	1	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	10	4.08	251	12	4.78	0.85 [0.38 ; 1.94]	0.85 [0.36 ; 2];	-0.7 [-4.32 ; 2.92]; 0.828	0.828	0.096
	USA and Western Europe	27	0	0.00	22	2	9.09	0.16 [0.01 ; 3.25]	0.15 [0.01 ; 3.28];	-9.08 [-22.72 ; 4.55]; 0.189	0.189	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Vascular disorders | Hypertension

5.2.40 Gastrointestinal disorders - Constipation

Tabelle 231: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	10	5.68	156	9	5.77	0.98 [0.41 ; 2.36]	0.98 [0.39 ; 2.49];	-0.09 [-5.1 ; 4.92]; 1	1	0.913
	>= 38 years	96	6	6.25	117	8	6.84	0.91 [0.33 ; 2.54]	0.91 [0.3 ; 2.71];	-0.59 [-7.25 ; 6.07]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	218	15	6.88	207	13	6.28	1.1 [0.53 ; 2.25]	1.1 [0.51 ; 2.38];	0.6 [-4.11 ; 5.31]; 0.847	0.847	0.2295
	>3.5	54	1	1.85	66	4	6.06	0.31 [0.04 ; 2.65]	0.29 [0.03 ; 2.7];	-4.21 [-11 ; 2.58]; 0.377	0.377	
Gender	Female	178	10	5.62	176	10	5.68	0.99 [0.42 ; 2.32]	0.99 [0.4 ; 2.44];	-0.06 [-4.87 ; 4.75]; 1	1	0.871
	Male	94	6	6.38	97	7	7.22	0.88 [0.31 ; 2.53]	0.88 [0.28 ; 2.71];	-0.83 [-7.97 ; 6.3]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	10	7.09	135	9	6.67	1.06 [0.45 ; 2.54]	1.07 [0.42 ; 2.72];	0.43 [-5.55 ; 6.4]; 1	1	0.6505
	0	131	6	4.58	136	8	5.88	0.78 [0.28 ; 2.18]	0.77 [0.26 ; 2.28];	-1.3 [-6.64 ; 4.03]; 0.785	0.785	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	6	5.13	110	6	5.45	0.94 [0.31 ; 2.83]	0.94 [0.29 ; 3];	-0.33 [-6.16 ; 5.5]; 1	1	0.8037
	>=3	42	1	2.38	40	2	5.00	0.48 [0.04 ; 5.05]	0.46 [0.04 ; 5.32];	-2.62 [-10.8 ; 5.56]; 0.611	0.611	
	2	113	9	7.96	123	9	7.32	1.09 [0.45 ; 2.65]	1.1 [0.42 ; 2.87];	0.65 [-6.14 ; 7.44]; 1	1	
Received approved disease modifying MS drug prior to enrollment	No	166	10	6.02	186	11	5.91	1.02 [0.44 ; 2.34]	1.02 [0.42 ; 2.47];	0.11 [-4.85 ; 5.07]; 1	1	0.7581
	Yes	106	6	5.66	87	6	6.90	0.82 [0.27 ; 2.45]	0.81 [0.25 ; 2.61];	-1.24 [-8.14 ; 5.67]; 0.771	0.771	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	13	5.31	251	16	6.37	0.83 [0.41 ; 1.69]	0.82 [0.39 ; 1.75];	-1.07 [-5.19 ; 3.06]; 0.703	0.703	0.3279
	USA and Western Europe	27	3	11.11	22	1	4.55	2.44 [0.27 ; 21.89]	2.62 [0.25 ; 27.19];	6.57 [-8.14 ; 21.27]; 0.617	0.617	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Gastrointestinal disorders | Constipation

5.2.41 Gastrointestinal disorders - Toothache

Tabelle 232: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	14	7.95	156	9	5.77	1.38 [0.61 ; 3.1]	1.41 [0.59 ; 3.36];	2.19 [-3.23 ; 7.6]; 0.519	0.519	0.1529
	>= 38 years	96	2	2.08	117	6	5.13	0.41 [0.08 ; 1.97]	0.39 [0.08 ; 2];	-3.04 [-7.96 ; 1.87]; 0.299	0.299	
Disease Severity at baseline (EDSS)	<=3.5	218	15	6.88	207	14	6.76	1.02 [0.5 ; 2.06]	1.02 [0.48 ; 2.17];	0.12 [-4.68 ; 4.91]; 1	1	0.9001
	>3.5	54	1	1.85	66	1	1.52	1.22 [0.08 ; 19.09]	1.23 [0.07 ; 20.08];	0.34 [-4.31 ; 4.99]; 1	1	
Gender	Female	178	9	5.06	176	13	7.39	0.68 [0.3 ; 1.56]	0.67 [0.28 ; 1.6];	-2.33 [-7.36 ; 2.7]; 0.388	0.388	0.0444
	Male	94	7	7.45	97	2	2.06	3.61 [0.77 ; 16.94]	3.82 [0.77 ; 18.89];	5.38 [-0.63 ; 11.4]; 0.097	0.097	
Number of baseline Gd-enhancing lesions	>=1	141	7	4.96	135	8	5.93	0.84 [0.31 ; 2.25]	0.83 [0.29 ; 2.35];	-0.96 [-6.32 ; 4.4]; 0.795	0.795	0.5053
	0	131	9	6.87	136	7	5.15	1.33 [0.51 ; 3.48]	1.36 [0.49 ; 3.76];	1.72 [-3.98 ; 7.43]; 0.613	0.613	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	6	5.13	110	8	7.27	0.71 [0.25 ; 1.97]	0.69 [0.23 ; 2.05];	-2.14 [-8.43 ; 4.14]; 0.587	0.587	0.1023
	>=3	42	3	7.14	40	0	0.00	6.67 [0.36 ; 125.26]	7.18 [0.36 ; 143.5];	6.92 [-1.92 ; 15.76]; 0.118	0.118	
	2	113	7	6.19	123	7	5.69	1.09 [0.39 ; 3.01]	1.09 [0.37 ; 3.22];	0.5 [-5.54 ; 6.55]; 1	1	
Received approved disease modifying MS drug prior to enrollment	No	166	11	6.63	186	12	6.45	1.03 [0.47 ; 2.27]	1.03 [0.44 ; 2.4];	0.17 [-5 ; 5.35]; 1	1	0.7279
	Yes	106	5	4.72	87	3	3.45	1.37 [0.34 ; 5.56]	1.39 [0.32 ; 5.97];	1.27 [-4.3 ; 6.84]; 0.732	0.732	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	14	5.71	251	14	5.58	1.02 [0.5 ; 2.1]	1.03 [0.48 ; 2.2];	0.14 [-3.93 ; 4.2]; 1	1	0.7036
	USA and Western Europe	27	2	7.41	22	1	4.55	1.63 [0.16 ; 16.81]	1.68 [0.14 ; 19.85];	2.86 [-10.3 ; 16.03]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Gastrointestinal disorders | Toothache

5.2.42 Injury, poisoning and procedural complications - Infusion related reaction

Tabelle 233: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	15	8.52	156	1	0.64	13.3 [1.78 ; 99.5]	14.44 [1.88 ; 110.64];	7.88 [3.57 ; 12.19]; 0.001	0.001	0.4978
	< 38 years	176	15	8.52	156	7	4.49	13.3 [1.78 ; 99.5]	14.44 [1.88 ; 110.64];	7.88 [3.57 ; 12.19]; 0.001	0.001	
	< 38 years	176	1	0.57	156	1	0.64	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	< 38 years	176	1	0.57	156	7	4.49	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	>= 38 years	96	2	2.08	117	1	0.85	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	>= 38 years	96	2	2.08	117	3	2.56	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	>= 38 years	96	4	4.17	117	1	0.85	4.87 [0.55 ; 42.89]	5.04 [0.55 ; 45.9];	3.31 [-1.02 ; 7.64]; 0.177	0.177	
	>= 38 years	96	4	4.17	117	3	2.56	4.87 [0.55 ; 42.89]	5.04 [0.55 ; 45.9];	3.31 [-1.02 ; 7.64]; 0.177	0.177	
Disease Severity at baseline (EDSS)	<=3.5	218	17	7.80	207	1	0.48	16.14 [2.17 ; 120.21]	17.42 [2.3 ; 132.15];	7.32 [3.63 ; 11]; 0	0	0.2416
	>3.5	54	2	3.70	66	1	1.52	2.44 [0.23 ; 26.24]	2.5 [0.22 ; 28.34];	2.19 [-3.65 ; 8.02]; 0.588	0.588	
Gender	Female	178	15	8.43	176	2	1.14	7.42 [1.72 ; 31.95]	8.01 [1.8 ; 35.55];	7.29 [2.92 ; 11.66]; 0.002	0.002	0.3439
	Female	178	15	8.43	176	6	3.41	7.42 [1.72 ; 31.95]	8.01 [1.8 ; 35.55];	7.29 [2.92 ; 11.66]; 0.002	0.002	
	Female	178	3	1.69	176	2	1.14	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Female	178	3	1.69	176	6	3.41	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Male	94	4	4.26	97	0	0.00	9.28 [0.51 ; 170.1]	9.7 [0.51 ; 182.63];	4.23 [-0.27 ; 8.73]; 0.056	0.056	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
	Male	94	4	4.26	97	4	4.12	9.28 [0.51 ; 170.1]	9.7 [0.51 ; 182.63];	4.23 [-0.27 ; 8.73]; 0.056	0.056	
	Male	94	0	0.00	97	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Male	94	0	0.00	97	4	4.12	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of baseline Gd-enhancing lesions	>=1	141	10	7.09	135	1	0.74	9.57 [1.24 ; 73.78]	10.23 [1.29 ; 81.04];	6.35 [1.87 ; 10.83]; 0.01	0.01	
	0	131	9	6.87	136	1	0.74	9.34 [1.2 ; 72.73]	9.96 [1.24 ; 79.75];	6.13 [1.57 ; 10.7]; 0.009	0.009	0.9857
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	12	10.26	110	1	0.91	11.28 [1.49 ; 85.33]	12.46 [1.59 ; 97.5];	9.35 [3.57 ; 15.12]; 0.003	0.003	
	>=3	42	1	2.38	40	0	0.00	2.86 [0.12 ; 68.23]	2.93 [0.12 ; 73.99];	2.27 [-4.16 ; 8.7]; 0.495	0.495	0.8423
	2	113	6	5.31	123	1	0.81	6.53 [0.8 ; 53.42]	6.84 [0.81 ; 57.73];	4.5 [0.07 ; 8.93]; 0.057	0.057	
Received approved disease modifying MS drug prior to enrollment	No	166	12	7.23	186	1	0.54	13.45 [1.77 ; 102.3]	14.42 [1.85 ; 112.11];	6.69 [2.61 ; 10.77]; 0.001	0.001	
	Yes	106	7	6.60	87	1	1.15	5.75 [0.72 ; 45.81]	6.08 [0.73 ; 50.41];	5.45 [0.22 ; 10.69]; 0.075	0.075	0.5698
Region	Eastern Europe	245	17	6.94	251	2	0.80	8.71 [2.03 ; 37.29]	9.28 [2.12 ; 40.62];	6.14 [2.78 ; 9.51]; 0	0	
	Eastern Europe	245	17	6.94	251	7	2.79	8.71 [2.03 ; 37.29]	9.28 [2.12 ; 40.62];	6.14 [2.78 ; 9.51]; 0	0	
	Eastern Europe	245	1	0.41	251	2	0.80	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	0.5574
	Eastern Europe	245	1	0.41	251	7	2.79	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	USA and Western Europe	27	2	7.41	22	0	0.00	4.11 [0.21 ; 81.33]	4.41 [0.2 ; 96.84];	6.75 [-5.37 ; 18.88]; 0.497	0.497	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
	USA and Western Europe	27	2	7.41	22	3	13.64	4.11 [0.21 ; 81.33]	4.41 [0.2 ; 96.84];	6.75 [-5.37 ; 18.88]; 0.497	0.497	
	USA and Western Europe	27	2	7.41	22	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	USA and Western Europe	27	2	7.41	22	3	13.64	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Injury, poisoning and procedural complications | Infusion related reaction

5.2.43 Skin and subcutaneous tissue disorders - Rash

Tabelle 234: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Disease Severity at baseline (EDSS)	<=3.5	218	3	1.38	207	7	3.38	0.41 [0.11 ; 1.55]	0.4 [0.1 ; 1.56];	-2.01 [-4.91 ; 0.9]; 0.211	0.211	0.2177
	>3.5	54	0	0.00	66	3	4.55	0.17 [0.01 ; 3.3]	0.17 [0.01 ; 3.29];	-4.31 [-10.2 ; 1.57]; 0.129	0.129	
Number of baseline Gd-enhancing lesions	>=1	141	2	1.42	135	3	2.22	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	131	1	0.76	136	7	5.15	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	2	1.71	110	3	2.73	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	0	0.00	40	1	2.50	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	1	0.88	123	6	4.88	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	0	0.00	186	5	2.69	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	Yes	106	3	2.83	87	5	5.75	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Skin and subcutaneous tissue disorders | Rash

5.2.44 Gastrointestinal disorders - Vomiting

Tabelle 235: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	5	2.84	156	8	5.13	0.55 [0.19 ; 1.66]	0.54 [0.17 ; 1.69];	-2.29 [-6.53 ; 1.96]; 0.397	0.397	0.1083
	>= 38 years	96	0	0.00	117	4	3.42	0.14 [0.01 ; 2.48]	0.13 [0.01 ; 2.46];	-3.3 [-7.04 ; 0.44]; 0.129	0.129	
Disease Severity at baseline (EDSS)	<=3.5	218	5	2.29	207	10	4.83	0.47 [0.17 ; 1.37]	0.46 [0.16 ; 1.38];	-2.54 [-6.07 ; 1]; 0.193	0.193	0.2692
	>3.5	54	0	0.00	66	2	3.03	0.24 [0.01 ; 4.97]	0.24 [0.01 ; 5.04];	-2.82 [-8.01 ; 2.36]; 0.501	0.501	
Gender	Female	178	5	2.81	176	9	5.11	0.55 [0.19 ; 1.61]	0.54 [0.18 ; 1.63];	-2.3 [-6.36 ; 1.76]; 0.29	0.29	0.1326
	Male	94	0	0.00	97	3	3.09	0.15 [0.01 ; 2.81]	0.14 [0.01 ; 2.8];	-3.05 [-7 ; 0.91]; 0.121	0.121	
Number of baseline Gd-enhancing lesions	>=1	141	4	2.84	135	7	5.19	0.55 [0.16 ; 1.83]	0.53 [0.15 ; 1.87];	-2.35 [-6.99 ; 2.29]; 0.369	0.369	0.4223
	0	131	1	0.76	136	5	3.68	0.21 [0.02 ; 1.75]	0.2 [0.02 ; 1.75];	-2.91 [-6.41 ; 0.58]; 0.214	0.214	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	2	1.71	110	5	4.55	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	1	2.38	40	2	5.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	2	1.77	123	5	4.07	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	5	3.01	186	8	4.30	0.7 [0.23 ; 2.1]	0.69 [0.22 ; 2.16];	-1.29 [-5.2 ; 2.62]; 0.582	0.582	0.0429
	Yes	106	0	0.00	87	4	4.60	0.09 [0 ; 1.67]	0.09 [0 ; 1.64];	-4.65 [-9.43 ; 0.13]; 0.041	0.041	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	4	1.63	251	8	3.19	0.51 [0.16 ; 1.68]	0.5 [0.15 ; 1.7];	-1.55 [-4.25 ; 1.14]; 0.382	0.382	0.3953
	USA and Western Europe	27	1	3.70	22	4	18.18	0.2 [0.02 ; 1.69]	0.17 [0.02 ; 1.68];	-14.48 [-32.1 ; 3.14]; 0.16	0.16	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Gastrointestinal disorders | Vomiting

5.2.45 General disorders and administration site conditions - Chills

Tabelle 236: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	19	10.80	156	0	0.00	34.59 [2.11 ; 568.24]	38.75 [2.32 ; 647.43];	10.7 [6 ; 15.39]; 0	0	0.0074
	>= 38 years	96	5	5.21	117	3	2.56	2.03 [0.5 ; 8.28]	2.09 [0.49 ; 8.97];	2.64 [-2.64 ; 7.93]; 0.472	0.472	
Disease Severity at baseline (EDSS)	<=3.5	218	22	10.09	207	1	0.48	20.89 [2.84 ; 153.58]	23.12 [3.09 ; 173.18];	9.61 [5.5 ; 13.72]; 0	0	0.0342
	>3.5	54	2	3.70	66	2	3.03	1.22 [0.18 ; 8.39]	1.23 [0.17 ; 9.04];	0.67 [-5.84 ; 7.19]; 1	1	
Gender	Female	178	10	5.62	176	3	1.70	3.3 [0.92 ; 11.77]	3.43 [0.93 ; 12.69];	3.91 [0.03 ; 7.8]; 0.086	0.086	0.0223
	Male	94	14	14.89	97	0	0.00	29.92 [1.81 ; 494.44]	35.12 [2.06 ; 597.94];	14.75 [7.38 ; 22.12]; 0	0	
Number of baseline Gd-enhancing lesions	>=1	141	17	12.06	135	3	2.22	5.43 [1.63 ; 18.09]	6.03 [1.73 ; 21.09];	9.83 [3.91 ; 15.76]; 0.002	0.002	0.1619
	0	131	7	5.34	136	0	0.00	15.57 [0.9 ; 269.87]	16.45 [0.93 ; 290.93];	5.32 [1.24 ; 9.39]; 0.003	0.003	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	6	5.13	110	2	1.82	2.82 [0.58 ; 13.68]	2.92 [0.58 ; 14.78];	3.31 [-1.4 ; 8.02]; 0.282	0.282	0.2604
	>=3	42	2	4.76	40	0	0.00	4.77 [0.24 ; 96.34]	5 [0.23 ; 107.43];	4.59 [-3.16 ; 12.35]; 0.494	0.494	
	2	113	16	14.16	123	1	0.81	17.42 [2.35 ; 129.21]	20.12 [2.62 ; 154.42];	13.35 [6.73 ; 19.97]; 0	0	
Received approved disease modifying MS drug prior to enrollment	No	166	13	7.83	186	1	0.54	14.57 [1.93 ; 110.15]	15.72 [2.03 ; 121.52];	7.29 [3.07 ; 11.51]; 0	0	0.3579
	Yes	106	11	10.38	87	2	2.30	4.51 [1.03 ; 19.82]	4.92 [1.06 ; 22.84];	8.08 [1.47 ; 14.68]; 0.04	0.04	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	21	8.57	251	2	0.80	10.76 [2.55 ; 45.39]	11.67 [2.71 ; 50.34];	7.77 [4.1 ; 11.45]; 0	0	0.3186
	USA and Western Europe	27	3	11.11	22	1	4.55	2.44 [0.27 ; 21.89]	2.62 [0.25 ; 27.19];	6.57 [-8.14 ; 21.27]; 0.617	0.617	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - General disorders and administration site conditions | Chills

5.2.46 Cardiac disorders - Tachycardia

Tabelle 237: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	8	4.55	156	7	4.49	1.01 [0.38 ; 2.73]	1.01 [0.36 ; 2.86];	0.06 [-4.42 ; 4.53]; 1	1	0.8312
	>= 38 years	96	2	2.08	117	3	2.56	0.81 [0.14 ; 4.76]	0.81 [0.13 ; 4.94];	-0.48 [-4.53 ; 3.56]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	218	9	4.13	207	7	3.38	1.22 [0.46 ; 3.22]	1.23 [0.45 ; 3.37];	0.75 [-2.86 ; 4.36]; 0.801	0.801	0.3505
	>3.5	54	1	1.85	66	3	4.55	0.41 [0.04 ; 3.81]	0.4 [0.04 ; 3.92];	-2.69 [-8.87 ; 3.49]; 0.626	0.626	
Gender	Female	178	7	3.93	176	7	3.98	0.99 [0.35 ; 2.76]	0.99 [0.34 ; 2.88];	-0.04 [-4.11 ; 4.02]; 1	1	0.9645
	Male	94	3	3.19	97	3	3.09	1.03 [0.21 ; 4.98]	1.03 [0.2 ; 5.25];	0.1 [-4.85 ; 5.05]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	10	7.09	135	4	2.96	2.39 [0.77 ; 7.45]	2.5 [0.76 ; 8.17];	4.13 [-0.98 ; 9.24]; 0.17	0.17	0.001
	0	131	0	0.00	136	6	4.41	0.08 [0 ; 1.4]	0.08 [0 ; 1.37];	-4.37 [-8.08 ; -0.65]; 0.03	0.03	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	6	5.13	110	3	2.73	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	1	2.38	40	2	5.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	3	2.65	123	5	4.07	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	3	1.81	186	9	4.84	0.37 [0.1 ; 1.36]	0.36 [0.1 ; 1.36];	-3.03 [-6.72 ; 0.66]; 0.147	0.147	0.0097
	Yes	106	7	6.60	87	1	1.15	5.75 [0.72 ; 45.81]	6.08 [0.73 ; 50.41];	5.45 [0.22 ; 10.69]; 0.075	0.075	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	9	3.67	251	9	3.59	1.02 [0.41 ; 2.54]	1.03 [0.4 ; 2.63];	0.09 [-3.2 ; 3.38]; 1	1	0.8755
	USA and Western Europe	27	1	3.70	22	1	4.55	0.81 [0.05 ; 12.3]	0.81 [0.05 ; 13.7];	-0.84 [-12.09 ; 10.41]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Cardiac disorders | Tachycardia

5.2.47 Respiratory, thoracic and mediastinal disorders - Throat irritation

Tabelle 238: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	10	5.68	156	0	0.00	18.63 [1.1 ; 315.29]	19.74 [1.15 ; 339.68];	5.61 [2.02 ; 9.2]; 0.002	0.002	0.1616
	>= 38 years	96	4	4.17	117	1	0.85	4.87 [0.55 ; 42.89]	5.04 [0.55 ; 45.9];	3.31 [-1.02 ; 7.64]; 0.177	0.177	
Disease Severity at baseline (EDSS)	<=3.5	218	13	5.96	207	0	0.00	25.64 [1.53 ; 428.63]	27.26 [1.61 ; 461.64];	5.92 [2.67 ; 9.18]; 0	0	0.0402
	>3.5	54	1	1.85	66	1	1.52	1.22 [0.08 ; 19.09]	1.23 [0.07 ; 20.08];	0.34 [-4.31 ; 4.99]; 1	1	
Gender	Female	178	10	5.62	176	1	0.57	9.89 [1.28 ; 76.43]	10.42 [1.32 ; 82.26];	5.05 [1.49 ; 8.61]; 0.011	0.011	0.4159
	Male	94	4	4.26	97	0	0.00	9.28 [0.51 ; 170.1]	9.7 [0.51 ; 182.63];	4.23 [-0.27 ; 8.73]; 0.056	0.056	
Number of baseline Gd-enhancing lesions	>=1	141	9	6.38	135	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	131	5	3.82	136	1	0.74	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	7	5.98	110	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	5	11.90	40	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	2	1.77	123	1	0.81	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	7	4.22	186	1	0.54	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	Yes	106	7	6.60	87	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	11	4.49	251	1	0.40	11.27 [1.47 ; 86.63]	11.75 [1.51 ; 91.73];	4.09 [1.38 ; 6.8]; 0.003	0.003	0.5255
	USA and Western Europe	27	3	11.11	22	0	0.00	5.75 [0.31 ; 105.7]	6.43 [0.31 ; 131.46];	10.33 [-3.3 ; 23.95]; 0.121	0.121	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Respiratory, thoracic and mediastinal disorders | Throat irritation

5.2.48 Investigations - Body temperature increased

Tabelle 239: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	8	4.55	156	2	1.28	3.55 [0.76 ; 16.45]	3.67 [0.77 ; 17.53];	3.26 [-0.28 ; 6.81]; 0.11	0.11	0.8158
	>= 38 years	96	4	4.17	117	1	0.85	4.87 [0.55 ; 42.89]	5.04 [0.55 ; 45.9];	3.31 [-1.02 ; 7.64]; 0.177	0.177	
Disease Severity at baseline (EDSS)	<=3.5	218	8	3.67	207	1	0.48	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>3.5	54	4	7.41	66	2	3.03	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Gender	Female	178	9	5.06	176	1	0.57	8.9 [1.14 ; 69.5]	9.32 [1.17 ; 74.36];	4.49 [1.08 ; 7.89]; 0.02	0.02	0.1882
	Male	94	3	3.19	97	2	2.06	1.55 [0.26 ; 9.06]	1.57 [0.26 ; 9.59];	1.13 [-3.41 ; 5.67]; 0.679	0.679	
Number of baseline Gd-enhancing lesions	>=1	141	4	2.84	135	1	0.74	3.83 [0.43 ; 33.83]	3.91 [0.43 ; 35.46];	2.1 [-1 ; 5.19]; 0.371	0.371	0.938
	0	131	8	6.11	136	2	1.47	4.15 [0.9 ; 19.19]	4.36 [0.91 ; 20.92];	4.64 [0.06 ; 9.21]; 0.057	0.057	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	2	1.71	110	1	0.91	1.88 [0.17 ; 20.45]	1.9 [0.17 ; 21.21];	0.8 [-2.14 ; 3.74]; 1	1	0.5397
	>=3	42	2	4.76	40	0	0.00	4.77 [0.24 ; 96.34]	5 [0.23 ; 107.43];	4.59 [-3.16 ; 12.35]; 0.494	0.494	
	2	113	8	7.08	123	2	1.63	4.35 [0.94 ; 20.07]	4.61 [0.96 ; 22.19];	5.45 [0.22 ; 10.68]; 0.052	0.052	
Received approved disease modifying MS drug prior to enrollment	No	166	6	3.61	186	1	0.54	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	Yes	106	6	5.66	87	2	2.30	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	10	4.08	251	3	1.20	3.41 [0.95 ; 12.26]	3.52 [0.96 ; 12.94];	2.89 [0.07 ; 5.71]; 0.052	0.052	0.3655
	USA and Western Europe	27	2	7.41	22	0	0.00	4.11 [0.21 ; 81.33]	4.41 [0.2 ; 96.84];	6.75 [-5.37 ; 18.88]; 0.497	0.497	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Investigations | Body temperature increased

5.2.49 Psychiatric disorders - Insomnia

Tabelle 240: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	11	6.25	156	8	5.13	1.22 [0.5 ; 2.95]	1.23 [0.48 ; 3.15];	1.12 [-3.86 ; 6.1]; 0.814	0.814	0.0012
	>= 38 years	96	10	10.42	117	0	0.00	25.55 [1.52 ; 430.43]	28.53 [1.65 ; 493.44];	10.4 [4.11 ; 16.69]; 0	0	
Disease Severity at baseline (EDSS)	<=3.5	218	21	9.63	207	6	2.90	3.32 [1.37 ; 8.07]	3.57 [1.41 ; 9.04];	6.73 [2.2 ; 11.27]; 0.005	0.005	0.0246
	>3.5	54	0	0.00	66	2	3.03	0.24 [0.01 ; 4.97]	0.24 [0.01 ; 5.04];	-2.82 [-8.01 ; 2.36]; 0.501	0.501	
Gender	Female	178	13	7.30	176	3	1.70	4.28 [1.24 ; 14.78]	4.54 [1.27 ; 16.23];	5.6 [1.32 ; 9.87]; 0.019	0.019	0.2584
	Male	94	8	8.51	97	5	5.15	1.65 [0.56 ; 4.87]	1.71 [0.54 ; 5.43];	3.36 [-3.8 ; 10.51]; 0.401	0.401	
Number of baseline Gd-enhancing lesions	>=1	141	12	8.51	135	5	3.70	2.3 [0.83 ; 6.35]	2.42 [0.83 ; 7.06];	4.81 [-0.79 ; 10.41]; 0.133	0.133	0.7277
	0	131	9	6.87	136	3	2.21	3.11 [0.86 ; 11.25]	3.27 [0.87 ; 12.36];	4.66 [-0.32 ; 9.65]; 0.08	0.08	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	8	6.84	110	1	0.91	7.52 [0.96 ; 59.16]	8 [0.98 ; 65.05];	5.93 [1.02 ; 10.83]; 0.036	0.036	0.1999
	>=3	42	2	4.76	40	0	0.00	4.77 [0.24 ; 96.34]	5 [0.23 ; 107.43];	4.59 [-3.16 ; 12.35]; 0.494	0.494	
	2	113	11	9.73	123	7	5.69	1.71 [0.69 ; 4.26]	1.79 [0.67 ; 4.78];	4.04 [-2.79 ; 10.87]; 0.327	0.327	
Received approved disease modifying MS drug prior to enrollment	No	166	15	9.04	186	6	3.23	2.8 [1.11 ; 7.05]	2.98 [1.13 ; 7.87];	5.81 [0.76 ; 10.86]; 0.025	0.025	0.8726
	Yes	106	6	5.66	87	2	2.30	2.46 [0.51 ; 11.89]	2.55 [0.5 ; 12.97];	3.36 [-2.05 ; 8.77]; 0.298	0.298	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	14	5.71	251	8	3.19	1.79 [0.77 ; 4.2]	1.84 [0.76 ; 4.47];	2.53 [-1.1 ; 6.16]; 0.195	0.195	0.0235
	USA and Western Europe	27	7	25.93	22	0	0.00	12.32 [0.74 ; 204.47]	16.46 [0.88 ; 306.66];	24.61 [7.16 ; 42.06]; 0.006	0.006	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Psychiatric disorders | Insomnia

5.2.50 Nervous system disorders - Dizziness

Tabelle 241: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	12	6.82	156	4	2.56	2.66 [0.88 ; 8.08]	2.78 [0.88 ; 8.81];	4.25 [-0.22 ; 8.73]; 0.078	0.078	0.0619
	>= 38 years	96	4	4.17	117	8	6.84	0.61 [0.19 ; 1.96]	0.59 [0.17 ; 2.03];	-2.67 [-8.74 ; 3.4]; 0.553	0.553	
Disease Severity at baseline (EDSS)	<=3.5	218	16	7.34	207	7	3.38	2.17 [0.91 ; 5.17]	2.26 [0.91 ; 5.62];	3.96 [-0.29 ; 8.21]; 0.087	0.087	0.0028
	>3.5	54	0	0.00	66	5	7.58	0.11 [0.01 ; 1.96]	0.1 [0.01 ; 1.9];	-7.3 [-14.34 ; -0.26]; 0.033	0.033	
Gender	Female	178	11	6.18	176	6	3.41	1.81 [0.69 ; 4.79]	1.87 [0.67 ; 5.16];	2.77 [-1.67 ; 7.21]; 0.32	0.32	0.3307
	Male	94	5	5.32	97	6	6.19	0.86 [0.27 ; 2.72]	0.85 [0.25 ; 2.89];	-0.87 [-7.47 ; 5.73]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	10	7.09	135	8	5.93	1.2 [0.49 ; 2.94]	1.21 [0.46 ; 3.17];	1.17 [-4.65 ; 6.98]; 0.809	0.809	0.7434
	0	131	6	4.58	136	4	2.94	1.56 [0.45 ; 5.39]	1.58 [0.44 ; 5.75];	1.64 [-2.93 ; 6.21]; 0.534	0.534	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	7	5.98	110	7	6.36	0.94 [0.34 ; 2.59]	0.94 [0.32 ; 2.76];	-0.38 [-6.65 ; 5.89]; 1	1	0.2623
	>=3	42	2	4.76	40	0	0.00	4.77 [0.24 ; 96.34]	5 [0.23 ; 107.43];	4.59 [-3.16 ; 12.35]; 0.494	0.494	
	2	113	7	6.19	123	5	4.07	1.52 [0.5 ; 4.67]	1.56 [0.48 ; 5.06];	2.13 [-3.52 ; 7.78]; 0.558	0.558	
Received approved disease modifying MS drug prior to enrollment	No	166	11	6.63	186	9	4.84	1.37 [0.58 ; 3.22]	1.4 [0.56 ; 3.46];	1.79 [-3.09 ; 6.67]; 0.498	0.498	0.9937
	Yes	106	5	4.72	87	3	3.45	1.37 [0.34 ; 5.56]	1.39 [0.32 ; 5.97];	1.27 [-4.3 ; 6.84]; 0.732	0.732	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	13	5.31	251	8	3.19	1.66 [0.7 ; 3.95]	1.7 [0.69 ; 4.18];	2.12 [-1.43 ; 5.67]; 0.271	0.271	0.2378
	USA and Western Europe	27	3	11.11	22	4	18.18	0.61 [0.15 ; 2.45]	0.56 [0.11 ; 2.83];	-7.07 [-27.08 ; 12.94]; 0.685	0.685	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Nervous system disorders | Dizziness

5.2.51 General disorders and administration site conditions - Asthenia

Tabelle 242: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	8	4.55	156	14	8.97	0.51 [0.22 ; 1.17]	0.48 [0.2 ; 1.18];	-4.43 [-9.87 ; 1.01]; 0.124	0.124	0.081
	>= 38 years	96	8	8.33	117	6	5.13	1.62 [0.58 ; 4.52]	1.68 [0.56 ; 5.03];	3.21 [-3.62 ; 10.03]; 0.411	0.411	
Disease Severity at baseline (EDSS)	<=3.5	218	14	6.42	207	12	5.80	1.11 [0.52 ; 2.34]	1.12 [0.5 ; 2.47];	0.62 [-3.93 ; 5.18]; 0.842	0.842	0.1036
	>3.5	54	2	3.70	66	8	12.12	0.31 [0.07 ; 1.38]	0.28 [0.06 ; 1.37];	-8.42 [-17.76 ; 0.93]; 0.182	0.182	
Gender	Female	178	12	6.74	176	13	7.39	0.91 [0.43 ; 1.94]	0.91 [0.4 ; 2.05];	-0.64 [-5.98 ; 4.69]; 0.839	0.839	0.5441
	Male	94	4	4.26	97	7	7.22	0.59 [0.18 ; 1.95]	0.57 [0.16 ; 2.02];	-2.96 [-9.53 ; 3.61]; 0.537	0.537	
Number of baseline Gd-enhancing lesions	>=1	141	6	4.26	135	9	6.67	0.64 [0.23 ; 1.74]	0.62 [0.22 ; 1.8];	-2.41 [-7.78 ; 2.96]; 0.434	0.434	0.5594
	0	131	10	7.63	136	11	8.09	0.94 [0.41 ; 2.15]	0.94 [0.38 ; 2.29];	-0.45 [-6.91 ; 6]; 1	1	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	10	8.55	110	6	5.45	1.57 [0.59 ; 4.17]	1.62 [0.57 ; 4.62];	3.09 [-3.52 ; 9.7]; 0.441	0.441	0.1614
	>=3	42	2	4.76	40	3	7.50	0.63 [0.11 ; 3.6]	0.62 [0.1 ; 3.9];	-2.74 [-13.14 ; 7.66]; 0.672	0.672	
	2	113	4	3.54	123	11	8.94	0.4 [0.13 ; 1.21]	0.37 [0.12 ; 1.21];	-5.4 [-11.49 ; 0.68]; 0.112	0.112	
Received approved disease modifying MS drug prior to enrollment	No	166	8	4.82	186	13	6.99	0.69 [0.29 ; 1.62]	0.67 [0.27 ; 1.67];	-2.17 [-7.07 ; 2.73]; 0.5	0.5	0.646
	Yes	106	8	7.55	87	7	8.05	0.94 [0.35 ; 2.48]	0.93 [0.32 ; 2.68];	-0.5 [-8.11 ; 7.11]; 1	1	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	15	6.12	251	19	7.57	0.81 [0.42 ; 1.56]	0.8 [0.4 ; 1.61];	-1.45 [-5.89 ; 2.99]; 0.596	0.596	0.9924
	USA and Western Europe	27	1	3.70	22	1	4.55	0.81 [0.05 ; 12.3]	0.81 [0.05 ; 13.7];	-0.84 [-12.09 ; 10.41]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - General disorders and administration site conditions | Asthenia

5.2.52 Investigations - Alanine aminotransferase increased

Tabelle 243: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	6	3.41	156	6	3.85	0.89 [0.29 ; 2.69]	0.88 [0.28 ; 2.79];	-0.44 [-4.47 ; 3.6]; 1	1	0.9736
	< 38 years	176	6	3.41	156	4	2.56	0.89 [0.29 ; 2.69]	0.88 [0.28 ; 2.79];	-0.44 [-4.47 ; 3.6]; 1	1	
	< 38 years	176	4	2.27	156	6	3.85	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	< 38 years	176	4	2.27	156	4	2.56	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	>= 38 years	96	6	6.25	117	4	3.42	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	>= 38 years	96	6	6.25	117	2	1.71	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	>= 38 years	96	3	3.12	117	4	3.42	0.91 [0.21 ; 3.99]	0.91 [0.2 ; 4.17];	-0.29 [-5.08 ; 4.5]; 1	1	
	>= 38 years	96	3	3.12	117	2	1.71	0.91 [0.21 ; 3.99]	0.91 [0.2 ; 4.17];	-0.29 [-5.08 ; 4.5]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	218	8	3.67	207	9	4.35	0.84 [0.33 ; 2.15]	0.84 [0.32 ; 2.22];	-0.68 [-4.41 ; 3.06]; 0.807	0.807	0.8013
	>3.5	54	1	1.85	66	1	1.52	1.22 [0.08 ; 19.09]	1.23 [0.07 ; 20.08];	0.34 [-4.31 ; 4.99]; 1	1	
Gender	Female	178	5	2.81	176	6	3.41	0.82 [0.26 ; 2.65]	0.82 [0.25 ; 2.73];	-0.6 [-4.22 ; 3.02]; 0.77	0.77	0.8063
	Female	178	5	2.81	176	3	1.70	0.82 [0.26 ; 2.65]	0.82 [0.25 ; 2.73];	-0.6 [-4.22 ; 3.02]; 0.77	0.77	
	Female	178	6	3.37	176	6	3.41	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Female	178	6	3.37	176	3	1.70	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Male	94	4	4.26	97	4	4.12	1.03 [0.27 ; 4.01]	1.03 [0.25 ; 4.26];	0.13 [-5.55 ; 5.82]; 1	1	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
	Male	94	4	4.26	97	3	3.09	1.03 [0.27 ; 4.01]	1.03 [0.25 ; 4.26];	0.13 [-5.55 ; 5.82]; 1	1	
	Male	94	4	4.26	97	4	4.12	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Male	94	4	4.26	97	3	3.09	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of baseline Gd-enhancing lesions	>=1	141	9	6.38	135	6	4.44	1.44 [0.53 ; 3.93]	1.47 [0.51 ; 4.24];	1.94 [-3.39 ; 7.26]; 0.598	0.598	0.0153
	0	131	0	0.00	136	4	2.94	0.12 [0.01 ; 2.12]	0.11 [0.01 ; 2.1];	-2.91 [-6.07 ; 0.26]; 0.122	0.122	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	5	4.27	110	4	3.64	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	2	4.76	40	2	5.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	2	1.77	123	4	3.25	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	6	3.61	186	6	3.23	1.12 [0.37 ; 3.41]	1.12 [0.36 ; 3.56];	0.39 [-3.42 ; 4.2]; 1	1	0.5225
	Yes	106	3	2.83	87	4	4.60	0.62 [0.14 ; 2.68]	0.6 [0.13 ; 2.78];	-1.77 [-7.18 ; 3.65]; 0.703	0.703	
Region	Eastern Europe	245	7	2.86	251	9	3.59	0.8 [0.3 ; 2.11]	0.79 [0.29 ; 2.16];	-0.73 [-3.83 ; 2.38]; 0.801	0.801	0.5713
	USA and Western Europe	27	2	7.41	22	1	4.55	1.63 [0.16 ; 16.81]	1.68 [0.14 ; 19.85];	2.86 [-10.3 ; 16.03]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
	interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG; mo and m1 are logit models											
Non-severe TEAE - Investigations | Alanine aminotransferase increased												

5.2.53 Skin and subcutaneous tissue disorders - Alopecia

Tabelle 244: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	10	5.68	156	28	17.95	0.32 [0.16 ; 0.63]	0.28 [0.13 ; 0.59];	-12.27 [-19.19 ; -5.34]; 0	0	0.4347
	>= 38 years	96	3	3.12	117	20	17.09	0.18 [0.06 ; 0.6]	0.16 [0.04 ; 0.54];	-13.97 [-21.63 ; -6.31]; 0.001	0.001	
Disease Severity at baseline (EDSS)	<=3.5	218	11	5.05	207	39	18.84	0.27 [0.14 ; 0.51]	0.23 [0.11 ; 0.46];	-13.79 [-19.86 ; -7.73]; 0	0	0.9439
	>3.5	54	2	3.70	66	9	13.64	0.27 [0.06 ; 1.2]	0.24 [0.05 ; 1.18];	-9.93 [-19.62 ; -0.24]; 0.109	0.109	
Gender	Female	178	9	5.06	176	42	23.86	0.21 [0.11 ; 0.42]	0.17 [0.08 ; 0.36];	-18.81 [-25.88 ; -11.74]; 0	0	0.0814
	Male	94	4	4.26	97	6	6.19	0.69 [0.2 ; 2.36]	0.67 [0.18 ; 2.47];	-1.93 [-8.23 ; 4.37]; 0.748	0.748	
Number of baseline Gd-enhancing lesions	>=1	141	7	4.96	135	22	16.30	0.3 [0.13 ; 0.69]	0.27 [0.11 ; 0.65];	-11.33 [-18.52 ; -4.14]; 0.003	0.003	0.6694
	0	131	6	4.58	136	26	19.12	0.24 [0.1 ; 0.56]	0.2 [0.08 ; 0.51];	-14.54 [-22.05 ; -7.02]; 0	0	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	5	4.27	110	17	15.45	0.28 [0.11 ; 0.72]	0.24 [0.09 ; 0.69];	-11.18 [-18.87 ; -3.5]; 0.006	0.006	0.9753
	>=3	42	2	4.76	40	8	20.00	0.24 [0.05 ; 1.05]	0.2 [0.04 ; 1.01];	-15.24 [-29.21 ; -1.27]; 0.046	0.046	
	2	113	6	5.31	123	23	18.70	0.28 [0.12 ; 0.67]	0.24 [0.1 ; 0.62];	-13.39 [-21.43 ; -5.35]; 0.002	0.002	
Received approved disease	No	166	9	5.42	186	32	17.20	0.32 [0.16 ; 0.64]	0.28 [0.13 ; 0.6];	-11.78 [-18.21 ; -5.36]; 0.001	0.001	0.5054

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
modifying MS drug prior to enrollment	Yes	106	4	3.77	87	16	18.39	0.21 [0.07 ; 0.59]	0.17 [0.06 ; 0.54];	-14.62 [-23.53 ; -5.7]; 0.001	0.001	
Region	Eastern Europe	245	13	5.31	251	44	17.53	0.3 [0.17 ; 0.55]	0.26 [0.14 ; 0.5];	-12.22 [-17.7 ; -6.75]; 0	0	0.1182
	USA and Western Europe	27	0	0.00	22	4	18.18	0.09 [0.01 ; 1.61]	0.07 [0 ; 1.47];	-17.78 [-34.72 ; -0.84]; 0.032	0.032	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Skin and subcutaneous tissue disorders | Alopecia

5.2.54 Gastrointestinal disorders - Abdominal pain

Tabelle 245: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	21	11.93	156	5	3.21	3.72 [1.44 ; 9.64]	4.09 [1.5 ; 11.13];	8.73 [3.2 ; 14.26]; 0.004	0.004	0.1063
	>= 38 years	96	7	7.29	117	7	5.98	1.22 [0.44 ; 3.35]	1.24 [0.42 ; 3.66];	1.31 [-5.44 ; 8.06]; 0.784	0.784	
Disease Severity at baseline (EDSS)	<=3.5	218	23	10.55	207	10	4.83	2.18 [1.07 ; 4.48]	2.32 [1.08 ; 5.01];	5.72 [0.7 ; 10.74]; 0.03	0.03	0.7147
	>3.5	54	5	9.26	66	2	3.03	3.06 [0.62 ; 15.13]	3.27 [0.61 ; 17.55];	6.23 [-2.54 ; 15]; 0.241	0.241	
Gender	Female	178	22	12.36	176	9	5.11	2.42 [1.15 ; 5.1]	2.62 [1.17 ; 5.86];	7.25 [1.42 ; 13.07]; 0.023	0.023	0.8082
	Male	94	6	6.38	97	3	3.09	2.06 [0.53 ; 8.01]	2.14 [0.52 ; 8.8];	3.29 [-2.73 ; 9.31]; 0.326	0.326	
Number of baseline Gd-enhancing lesions	>=1	141	18	12.77	135	3	2.22	5.74 [1.73 ; 19.06]	6.44 [1.85 ; 22.4];	10.54 [4.5 ; 16.59]; 0.001	0.001	0.023
	0	131	10	7.63	136	9	6.62	1.15 [0.48 ; 2.75]	1.17 [0.46 ; 2.97];	1.02 [-5.16 ; 7.19]; 0.815	0.815	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	9	7.69	110	5	4.55	1.69 [0.59 ; 4.89]	1.75 [0.57 ; 5.39];	3.15 [-3.06 ; 9.35]; 0.412	0.412	0.7415
	>=3	42	6	14.29	40	2	5.00	2.86 [0.61 ; 13.34]	3.17 [0.6 ; 16.72];	9.29 [-3.27 ; 21.84]; 0.265	0.265	
	2	113	13	11.50	123	5	4.07	2.83 [1.04 ; 7.69]	3.07 [1.06 ; 8.9];	7.44 [0.6 ; 14.28]; 0.047	0.047	
Received approved disease modifying MS drug prior to enrollment	No	166	18	10.84	186	8	4.30	2.52 [1.13 ; 5.65]	2.71 [1.14 ; 6.4];	6.54 [0.99 ; 12.1]; 0.024	0.024	0.7662
	Yes	106	10	9.43	87	4	4.60	2.05 [0.67 ; 6.32]	2.16 [0.65 ; 7.15];	4.84 [-2.26 ; 11.93]; 0.268	0.268	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	25	10.20	251	11	4.38	2.33 [1.17 ; 4.63]	2.48 [1.19 ; 5.16];	5.82 [1.26 ; 10.38]; 0.015	0.015	0.9634
	USA and Western Europe	27	3	11.11	22	1	4.55	2.44 [0.27 ; 21.89]	2.62 [0.25 ; 27.19];	6.57 [-8.14 ; 21.27]; 0.617	0.617	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Gastrointestinal disorders | Abdominal pain

5.2.55 Blood and lymphatic system disorders - Anaemia

Tabelle 246: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	5	2.84	156	7	4.49	0.63 [0.21 ; 1.95]	0.62 [0.19 ; 2];	-1.65 [-5.72 ; 2.43]; 0.559	0.559	0.9153
	>= 38 years	96	4	4.17	117	7	5.98	0.7 [0.21 ; 2.31]	0.68 [0.19 ; 2.41];	-1.82 [-7.69 ; 4.05]; 0.758	0.758	
Disease Severity at baseline (EDSS)	<=3.5	218	6	2.75	207	9	4.35	0.63 [0.23 ; 1.75]	0.62 [0.22 ; 1.78];	-1.6 [-5.12 ; 1.93]; 0.437	0.437	0.8783
	>3.5	54	3	5.56	66	5	7.58	0.73 [0.18 ; 2.93]	0.72 [0.16 ; 3.15];	-2.02 [-10.86 ; 6.82]; 0.729	0.729	
Gender	Female	178	9	5.06	176	14	7.95	0.64 [0.28 ; 1.43]	0.62 [0.26 ; 1.46];	-2.9 [-8.03 ; 2.23]; 0.289	0.289	1
	Male	94	0	0.00	97	0	0.00	1.03 [0.02 ; 51.46]	1.03 [0.02 ; 52.53];	0.02 [-2.01 ; 2.04]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	7	4.96	135	6	4.44	1.12 [0.39 ; 3.24]	1.12 [0.37 ; 3.43];	0.52 [-4.47 ; 5.51]; 1	1	0.1057
	0	131	2	1.53	136	8	5.88	0.26 [0.06 ; 1.2]	0.25 [0.05 ; 1.19];	-4.36 [-8.83 ; 0.12]; 0.103	0.103	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	3	2.56	110	7	6.36	0.4 [0.11 ; 1.52]	0.39 [0.1 ; 1.54];	-3.8 [-9.19 ; 1.59]; 0.204	0.204	0.6569
	>=3	42	3	7.14	40	3	7.50	0.95 [0.2 ; 4.45]	0.95 [0.18 ; 5];	-0.36 [-11.64 ; 10.93]; 1	1	
	2	113	3	2.65	123	4	3.25	0.82 [0.19 ; 3.57]	0.81 [0.18 ; 3.71];	-0.6 [-4.91 ; 3.72]; 1	1	
Received approved disease modifying MS drug prior to enrollment	No	166	4	2.41	186	9	4.84	0.5 [0.16 ; 1.59]	0.49 [0.15 ; 1.61];	-2.43 [-6.3 ; 1.44]; 0.268	0.268	0.5622
	Yes	106	5	4.72	87	5	5.75	0.82 [0.25 ; 2.74]	0.81 [0.23 ; 2.9];	-1.03 [-7.37 ; 5.31]; 0.756	0.756	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	9	3.67	251	14	5.58	0.66 [0.29 ; 1.49]	0.65 [0.27 ; 1.52];	-1.9 [-5.59 ; 1.78]; 0.394	0.394	0.9999
	USA and Western Europe	27	0	0.00	22	0	0.00	0.82 [0.02 ; 39.81]	0.82 [0.02 ; 42.89];	-0.39 [-8.11 ; 7.33]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Blood and lymphatic system disorders | Anaemia

5.2.56 Blood and lymphatic system disorders - Lymphopenia

Tabelle 247: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	13	7.39	156	2	1.28	5.76 [1.32 ; 25.13]	6.14 [1.36 ; 27.66];	6.1 [1.86 ; 10.35]; 0.008	0.008	0.1284
	>= 38 years	96	8	8.33	117	0	0.00	20.68 [1.21 ; 353.78]	22.57 [1.29 ; 396.28];	8.34 [2.59 ; 14.09]; 0.001	0.001	
Disease Severity at baseline (EDSS)	<=3.5	218	17	7.80	207	2	0.97	8.07 [1.89 ; 34.5]	8.67 [1.98 ; 38.01];	6.83 [3.03 ; 10.63]; 0.001	0.001	0.319
	>3.5	54	4	7.41	66	0	0.00	10.96 [0.6 ; 199.23]	11.85 [0.62 ; 225.2];	7.44 [-0.1 ; 14.97]; 0.038	0.038	
Gender	Female	178	16	8.99	176	1	0.57	15.82 [2.12 ; 118.01]	17.28 [2.27 ; 131.81];	8.42 [4.07 ; 12.77]; 0	0	0.4499
	Male	94	5	5.32	97	1	1.03	5.16 [0.61 ; 43.34]	5.39 [0.62 ; 47.06];	4.29 [-0.67 ; 9.25]; 0.114	0.114	
Number of baseline Gd-enhancing lesions	>=1	141	8	5.67	135	2	1.48	3.83 [0.83 ; 17.71]	4 [0.83 ; 19.19];	4.19 [-0.14 ; 8.52]; 0.104	0.104	0.0492
	0	131	13	9.92	136	0	0.00	28.02 [1.68 ; 466.63]	31.1 [1.83 ; 528.81];	9.86 [4.6 ; 15.13]; 0	0	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	10	8.55	110	1	0.91	9.4 [1.22 ; 72.24]	10.19 [1.28 ; 80.96];	7.64 [2.27 ; 13.01]; 0.01	0.01	0.668
	>=3	42	4	9.52	40	0	0.00	8.58 [0.48 ; 154.45]	9.47 [0.49 ; 181.77];	9.25 [-0.5 ; 18.99]; 0.116	0.116	
	2	113	7	6.19	123	1	0.81	7.62 [0.95 ; 60.97]	8.06 [0.98 ; 66.55];	5.38 [0.66 ; 10.1]; 0.03	0.03	
Received approved disease modifying MS drug prior to enrollment	No	166	7	4.22	186	0	0.00	16.8 [0.97 ; 291.86]	17.54 [0.99 ; 309.49];	4.22 [1 ; 7.45]; 0.002	0.002	0.1766
	Yes	106	14	13.21	87	2	2.30	5.75 [1.34 ; 24.6]	6.47 [1.43 ; 29.3];	10.91 [3.74 ; 18.08]; 0.007	0.007	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	20	8.16	251	2	0.80	10.24 [2.42 ; 43.36]	11.07 [2.56 ; 47.88];	7.37 [3.77 ; 10.97]; 0	0	0.7041
	USA and Western Europe	27	1	3.70	22	0	0.00	2.46 [0.11 ; 57.66]	2.55 [0.1 ; 65.66];	3.18 [-7.07 ; 13.43]; 0.497	0.497	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Blood and lymphatic system disorders | Lymphopenia

5.2.57 Infections and infestations - Respiratory tract infection viral

Tabelle 248: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	16	9.09	156	15	9.62	0.95 [0.48 ; 1.85]	0.94 [0.45 ; 1.97];	-0.52 [-6.8 ; 5.76]; 1	1	0.9594
	>= 38 years	96	6	6.25	117	8	6.84	0.91 [0.33 ; 2.54]	0.91 [0.3 ; 2.71];	-0.59 [-7.25 ; 6.07]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	218	19	8.72	207	17	8.21	1.06 [0.57 ; 1.98]	1.07 [0.54 ; 2.11];	0.5 [-4.79 ; 5.8]; 0.864	0.864	0.4556
	>3.5	54	3	5.56	66	6	9.09	0.61 [0.16 ; 2.33]	0.59 [0.14 ; 2.47];	-3.54 [-12.78 ; 5.71]; 0.512	0.512	
Gender	Female	178	16	8.99	176	18	10.23	0.88 [0.46 ; 1.67]	0.87 [0.43 ; 1.76];	-1.24 [-7.38 ; 4.9]; 0.722	0.722	0.6074
	Male	94	6	6.38	97	5	5.15	1.24 [0.39 ; 3.92]	1.25 [0.37 ; 4.26];	1.23 [-5.39 ; 7.85]; 0.765	0.765	
Number of baseline Gd-enhancing lesions	>=1	141	10	7.09	135	13	9.63	0.74 [0.33 ; 1.62]	0.72 [0.3 ; 1.69];	-2.54 [-9.07 ; 4]; 0.517	0.517	0.3588
	0	131	12	9.16	136	10	7.35	1.25 [0.56 ; 2.78]	1.27 [0.53 ; 3.05];	1.81 [-4.8 ; 8.41]; 0.66	0.66	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	9	7.69	110	8	7.27	1.06 [0.42 ; 2.64]	1.06 [0.39 ; 2.86];	0.42 [-6.43 ; 7.27]; 1	1	0.8321
	>=3	42	3	7.14	40	2	5.00	1.43 [0.25 ; 8.11]	1.46 [0.23 ; 9.24];	2.14 [-8.17 ; 12.45]; 1	1	
	2	113	10	8.85	123	13	10.57	0.84 [0.38 ; 1.83]	0.82 [0.35 ; 1.96];	-1.72 [-9.27 ; 5.83]; 0.827	0.827	
Received approved disease modifying MS drug prior to enrollment	No	166	6	3.61	186	7	3.76	0.96 [0.33 ; 2.8]	0.96 [0.32 ; 2.91];	-0.15 [-4.09 ; 3.79]; 1	1	0.7765
	Yes	106	16	15.09	87	16	18.39	0.82 [0.44 ; 1.54]	0.79 [0.37 ; 1.69];	-3.3 [-13.91 ; 7.32]; 0.565	0.565	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	22	8.98	251	23	9.16	0.98 [0.56 ; 1.71]	0.98 [0.53 ; 1.81];	-0.18 [-5.24 ; 4.87]; 1	1	1
	USA and Western Europe	27	0	0.00	22	0	0.00	0.82 [0.02 ; 39.81]	0.82 [0.02 ; 42.89];	-0.39 [-8.11 ; 7.33]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Respiratory tract infection viral

5.2.58 Gastrointestinal disorders - Dyspepsia

Tabelle 249: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	13	7.39	156	8	5.13	1.44 [0.61 ; 3.38]	1.48 [0.59 ; 3.66];	2.26 [-2.93 ; 7.45]; 0.5	0.5	0.1924
	>= 38 years	96	3	3.12	117	7	5.98	0.52 [0.14 ; 1.97]	0.51 [0.13 ; 2.02];	-2.86 [-8.39 ; 2.67]; 0.517	0.517	
Disease Severity at baseline (EDSS)	<=3.5	218	14	6.42	207	12	5.80	1.11 [0.52 ; 2.34]	1.12 [0.5 ; 2.47];	0.62 [-3.93 ; 5.18]; 0.842	0.842	0.7495
	>3.5	54	2	3.70	66	3	4.55	0.81 [0.14 ; 4.7]	0.81 [0.13 ; 5.02];	-0.84 [-7.96 ; 6.27]; 1	1	
Gender	Female	178	6	3.37	176	9	5.11	0.66 [0.24 ; 1.81]	0.65 [0.23 ; 1.86];	-1.74 [-5.94 ; 2.45]; 0.443	0.443	0.1722
	Male	94	10	10.64	97	6	6.19	1.72 [0.65 ; 4.54]	1.81 [0.63 ; 5.18];	4.45 [-3.41 ; 12.32]; 0.305	0.305	
Number of baseline Gd-enhancing lesions	>=1	141	12	8.51	135	6	4.44	1.91 [0.74 ; 4.96]	2 [0.73 ; 5.49];	4.07 [-1.7 ; 9.84]; 0.224	0.224	0.0524
	0	131	4	3.05	136	9	6.62	0.46 [0.15 ; 1.46]	0.44 [0.13 ; 1.48];	-3.56 [-8.68 ; 1.55]; 0.256	0.256	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	9	7.69	110	7	6.36	1.21 [0.47 ; 3.13]	1.23 [0.44 ; 3.41];	1.33 [-5.31 ; 7.97]; 0.798	0.798	0.7564
	>=3	42	3	7.14	40	2	5.00	1.43 [0.25 ; 8.11]	1.46 [0.23 ; 9.24];	2.14 [-8.17 ; 12.45]; 1	1	
	2	113	4	3.54	123	6	4.88	0.73 [0.21 ; 2.51]	0.72 [0.2 ; 2.6];	-1.34 [-6.45 ; 3.77]; 0.751	0.751	
Received approved disease modifying MS drug prior to enrollment	No	166	9	5.42	186	8	4.30	1.26 [0.5 ; 3.19]	1.28 [0.48 ; 3.39];	1.12 [-3.39 ; 5.63]; 0.63	0.63	0.5407
	Yes	106	7	6.60	87	7	8.05	0.82 [0.3 ; 2.25]	0.81 [0.27 ; 2.4];	-1.44 [-8.86 ; 5.98]; 0.784	0.784	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	16	6.53	251	14	5.58	1.17 [0.58 ; 2.35]	1.18 [0.56 ; 2.48];	0.95 [-3.25 ; 5.15]; 0.709	0.709	0.1833
	USA and Western Europe	27	0	0.00	22	1	4.55	0.27 [0.01 ; 6.41]	0.26 [0.01 ; 6.72];	-4.74 [-15.96 ; 6.48]; 0.208	0.208	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Gastrointestinal disorders | Dyspepsia

5.2.59 Infections and infestations - Cystitis

Tabelle 250: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	13	7.39	156	8	5.13	1.44 [0.61 ; 3.38]	1.48 [0.59 ; 3.66];	2.26 [-2.93 ; 7.45]; 0.5	0.5	0.9004
	>= 38 years	96	4	4.17	117	3	2.56	1.62 [0.37 ; 7.08]	1.65 [0.36 ; 7.57];	1.6 [-3.31 ; 6.52]; 0.703	0.703	
Disease Severity at baseline (EDSS)	<=3.5	218	13	5.96	207	8	3.86	1.54 [0.65 ; 3.65]	1.58 [0.64 ; 3.89];	2.1 [-2 ; 6.19]; 0.375	0.375	0.9449
	>3.5	54	4	7.41	66	3	4.55	1.63 [0.38 ; 6.97]	1.68 [0.36 ; 7.85];	2.86 [-5.74 ; 11.47]; 0.699	0.699	
Gender	Female	178	16	8.99	176	11	6.25	1.44 [0.69 ; 3.01]	1.48 [0.67 ; 3.29];	2.74 [-2.78 ; 8.26]; 0.424	0.424	0.3089
	Male	94	1	1.06	97	0	0.00	3.09 [0.13 ; 75.03]	3.13 [0.13 ; 77.76];	1.07 [-1.81 ; 3.95]; 0.244	0.244	
Number of baseline Gd-enhancing lesions	>=1	141	10	7.09	135	6	4.44	1.6 [0.6 ; 4.27]	1.64 [0.58 ; 4.65];	2.65 [-2.83 ; 8.13]; 0.443	0.443	0.8966
	0	131	7	5.34	136	5	3.68	1.45 [0.47 ; 4.46]	1.48 [0.46 ; 4.78];	1.67 [-3.32 ; 6.65]; 0.566	0.566	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	4	3.42	110	6	5.45	0.63 [0.18 ; 2.16]	0.61 [0.17 ; 2.24];	-2.04 [-7.41 ; 3.34]; 0.529	0.529	0.0643
	>=3	42	3	7.14	40	0	0.00	6.67 [0.36 ; 125.26]	7.18 [0.36 ; 143.5];	6.92 [-1.92 ; 15.76]; 0.118	0.118	
	2	113	10	8.85	123	5	4.07	2.18 [0.77 ; 6.18]	2.29 [0.76 ; 6.92];	4.78 [-1.51 ; 11.08]; 0.182	0.182	
Received approved disease modifying MS drug prior to enrollment	No	166	6	3.61	186	7	3.76	0.96 [0.33 ; 2.8]	0.96 [0.32 ; 2.91];	-0.15 [-4.09 ; 3.79]; 1	1	0.2593
	Yes	106	11	10.38	87	4	4.60	2.26 [0.74 ; 6.84]	2.4 [0.74 ; 7.83];	5.78 [-1.51 ; 13.06]; 0.179	0.179	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	17	6.94	251	11	4.38	1.58 [0.76 ; 3.31]	1.63 [0.75 ; 3.55];	2.56 [-1.51 ; 6.62]; 0.246	0.246	0.9999
	USA and Western Europe	27	0	0.00	22	0	0.00	0.82 [0.02 ; 39.81]	0.82 [0.02 ; 42.89];	-0.39 [-8.11 ; 7.33]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Cystitis

5.2.60 Infections and infestations - Respiratory tract infection

Tabelle 251: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	20	11.36	156	17	10.90	1.04 [0.57 ; 1.92]	1.05 [0.53 ; 2.08];	0.47 [-6.31 ; 7.24]; 1	1	0.9083
	>= 38 years	96	10	10.42	117	11	9.40	1.11 [0.49 ; 2.5]	1.12 [0.45 ; 2.76];	1.01 [-7.07 ; 9.1]; 0.821	0.821	
Disease Severity at baseline (EDSS)	<=3.5	218	26	11.93	207	20	9.66	1.23 [0.71 ; 2.14]	1.27 [0.68 ; 2.35];	2.26 [-3.63 ; 8.16]; 0.533	0.533	0.2658
	>3.5	54	4	7.41	66	8	12.12	0.61 [0.19 ; 1.92]	0.58 [0.16 ; 2.04];	-4.71 [-15.24 ; 5.81]; 0.544	0.544	
Gender	Female	178	23	12.92	176	18	10.23	1.26 [0.71 ; 2.26]	1.3 [0.68 ; 2.51];	2.69 [-3.96 ; 9.35]; 0.507	0.507	0.3093
	Male	94	7	7.45	97	10	10.31	0.72 [0.29 ; 1.82]	0.7 [0.25 ; 1.92];	-2.86 [-10.91 ; 5.19]; 0.613	0.613	
Number of baseline Gd-enhancing lesions	>=1	141	26	18.44	135	12	8.89	2.07 [1.09 ; 3.94]	2.32 [1.12 ; 4.81];	9.55 [1.55 ; 17.55]; 0.024	0.024	0.0003
	0	131	4	3.05	136	16	11.76	0.26 [0.09 ; 0.76]	0.24 [0.08 ; 0.73];	-8.71 [-14.88 ; -2.55]; 0.009	0.009	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	16	13.68	110	12	10.91	1.25 [0.62 ; 2.53]	1.29 [0.58 ; 2.87];	2.77 [-5.76 ; 11.29]; 0.552	0.552	0.7275
	>=3	42	4	9.52	40	3	7.50	1.27 [0.3 ; 5.32]	1.3 [0.27 ; 6.2];	2.02 [-10.04 ; 14.08]; 1	1	
	2	113	10	8.85	123	13	10.57	0.84 [0.38 ; 1.83]	0.82 [0.35 ; 1.96];	-1.72 [-9.27 ; 5.83]; 0.827	0.827	
Received approved disease modifying MS drug prior to enrollment	No	166	19	11.45	186	19	10.22	1.12 [0.61 ; 2.04]	1.14 [0.58 ; 2.23];	1.23 [-5.28 ; 7.74]; 0.734	0.734	0.8325
	Yes	106	11	10.38	87	9	10.34	1 [0.44 ; 2.31]	1 [0.4 ; 2.54];	0.03 [-8.61 ; 8.67]; 1	1	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	29	11.84	251	27	10.76	1.1 [0.67 ; 1.8]	1.11 [0.64 ; 1.94];	1.08 [-4.49 ; 6.65]; 0.777	0.777	0.8274
	USA and Western Europe	27	1	3.70	22	1	4.55	0.81 [0.05 ; 12.3]	0.81 [0.05 ; 13.7];	-0.84 [-12.09 ; 10.41]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Respiratory tract infection

5.2.61 Infections and infestations - Pharyngitis

Tabelle 252: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	17	9.66	156	6	3.85	2.51 [1.02 ; 6.21]	2.67 [1.03 ; 6.96];	5.81 [0.51 ; 11.12]; 0.05	0.05	0.0328
	>= 38 years	96	7	7.29	117	0	0.00	18.25 [1.06 ; 315.48]	19.69 [1.11 ; 349.37];	7.31 [1.87 ; 12.75]; 0.002	0.002	
Disease Severity at baseline (EDSS)	<=3.5	218	20	9.17	207	6	2.90	3.17 [1.3 ; 7.72]	3.38 [1.33 ; 8.6];	6.28 [1.81 ; 10.74]; 0.008	0.008	0.125
	>3.5	54	4	7.41	66	0	0.00	10.96 [0.6 ; 199.23]	11.85 [0.62 ; 225.2];	7.44 [-0.1 ; 14.97]; 0.038	0.038	
Gender	Female	178	19	10.67	176	6	3.41	3.13 [1.28 ; 7.65]	3.39 [1.32 ; 8.69];	7.27 [2 ; 12.53]; 0.011	0.011	0.1157
	Male	94	5	5.32	97	0	0.00	11.35 [0.64 ; 202.4]	11.98 [0.65 ; 219.81];	5.28 [0.38 ; 10.18]; 0.014	0.014	
Number of baseline Gd-enhancing lesions	>=1	141	11	7.80	135	3	2.22	3.51 [1 ; 12.31]	3.72 [1.02 ; 13.65];	5.58 [0.5 ; 10.66]; 0.052	0.052	0.7706
	0	131	13	9.92	136	3	2.21	4.5 [1.31 ; 15.43]	4.88 [1.36 ; 17.56];	7.72 [2.03 ; 13.4]; 0.009	0.009	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	12	10.26	110	2	1.82	5.64 [1.29 ; 24.64]	6.17 [1.35 ; 28.24];	8.44 [2.4 ; 14.48]; 0.011	0.011	0.8036
	>=3	42	6	14.29	40	2	5.00	2.86 [0.61 ; 13.34]	3.17 [0.6 ; 16.72];	9.29 [-3.27 ; 21.84]; 0.265	0.265	
	2	113	6	5.31	123	2	1.63	3.27 [0.67 ; 15.85]	3.39 [0.67 ; 17.17];	3.68 [-1.02 ; 8.38]; 0.157	0.157	
Received approved disease modifying MS drug prior to enrollment	No	166	12	7.23	186	4	2.15	3.36 [1.11 ; 10.22]	3.55 [1.12 ; 11.22];	5.08 [0.62 ; 9.54]; 0.037	0.037	0.6585
	Yes	106	12	11.32	87	2	2.30	4.92 [1.13 ; 21.41]	5.43 [1.18 ; 24.94];	9.02 [2.22 ; 15.83]; 0.023	0.023	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	23	9.39	251	6	2.39	3.93 [1.63 ; 9.48]	4.23 [1.69 ; 10.58];	7 [2.89 ; 11.11]; 0.001	0.001	0.5504
	USA and Western Europe	27	1	3.70	22	0	0.00	2.46 [0.11 ; 57.66]	2.55 [0.1 ; 65.66];	3.18 [-7.07 ; 13.43]; 0.497	0.497	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Pharyngitis

5.2.62 General disorders and administration site conditions - Influenza like illness

Tabelle 253: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	20	11.36	156	4	2.56	4.43 [1.55 ; 12.69]	4.87 [1.63 ; 14.58];	8.8 [3.5 ; 14.1]; 0.002	0.002	0.7004
	>= 38 years	96	8	8.33	117	3	2.56	3.25 [0.89 ; 11.92]	3.45 [0.89 ; 13.4];	5.77 [-0.46 ; 12]; 0.069	0.069	
Disease Severity at baseline (EDSS)	<=3.5	218	23	10.55	207	4	1.93	5.46 [1.92 ; 15.52]	5.99 [2.03 ; 17.62];	8.62 [4.13 ; 13.11]; 0	0	0.2768
	>3.5	54	5	9.26	66	3	4.55	2.04 [0.51 ; 8.14]	2.14 [0.49 ; 9.41];	4.71 [-4.51 ; 13.93]; 0.465	0.465	
Gender	Female	178	20	11.24	176	7	3.98	2.83 [1.23 ; 6.51]	3.06 [1.26 ; 7.42];	7.26 [1.79 ; 12.72]; 0.015	0.015	0.0402
	Male	94	8	8.51	97	0	0.00	17.54 [1.03 ; 299.61]	19.16 [1.09 ; 336.89];	8.44 [2.53 ; 14.35]; 0.003	0.003	
Number of baseline Gd-enhancing lesions	>=1	141	15	10.64	135	3	2.22	4.79 [1.42 ; 16.17]	5.24 [1.48 ; 18.53];	8.42 [2.75 ; 14.08]; 0.006	0.006	0.6737
	0	131	13	9.92	136	4	2.94	3.37 [1.13 ; 10.08]	3.64 [1.15 ; 11.46];	6.98 [1.13 ; 12.84]; 0.024	0.024	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	9	7.69	110	2	1.82	4.23 [0.93 ; 19.15]	4.5 [0.95 ; 21.31];	5.87 [0.44 ; 11.31]; 0.06	0.06	0.9
	>=3	42	6	14.29	40	2	5.00	2.86 [0.61 ; 13.34]	3.17 [0.6 ; 16.72];	9.29 [-3.27 ; 21.84]; 0.265	0.265	
	2	113	13	11.50	123	3	2.44	4.72 [1.38 ; 16.12]	5.2 [1.44 ; 18.76];	9.07 [2.58 ; 15.55]; 0.008	0.008	
Received approved disease modifying MS drug prior to enrollment	No	166	21	12.65	186	5	2.69	4.71 [1.82 ; 12.2]	5.24 [1.93 ; 14.24];	9.96 [4.4 ; 15.53]; 0	0	0.5719
	Yes	106	7	6.60	87	2	2.30	2.87 [0.61 ; 13.48]	3.01 [0.61 ; 14.85];	4.3 [-1.38 ; 9.99]; 0.189	0.189	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	28	11.43	251	7	2.79	4.1 [1.82 ; 9.21]	4.5 [1.93 ; 10.5];	8.64 [4.17 ; 13.11]; 0	0	0.9998
	USA and Western Europe	27	0	0.00	22	0	0.00	0.82 [0.02 ; 39.81]	0.82 [0.02 ; 42.89];	-0.39 [-8.11 ; 7.33]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - General disorders and administration site conditions | Influenza like illness

5.2.63 Respiratory, thoracic and mediastinal disorders - Cough

Tabelle 254: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	7	3.98	156	3	1.92	2.07 [0.54 ; 7.86]	2.11 [0.54 ; 8.31];	2.05 [-1.55 ; 5.66]; 0.345	0.345	0.0607
	>= 38 years	96	5	5.21	117	0	0.00	13.38 [0.75 ; 238.99]	14.13 [0.77 ; 258.77];	5.25 [0.5 ; 10]; 0.008	0.008	
Disease Severity at baseline (EDSS)	<=3.5	218	11	5.05	207	3	1.45	3.48 [0.99 ; 12.3]	3.61 [0.99 ; 13.14];	3.6 [0.27 ; 6.93]; 0.055	0.055	0.4529
	>3.5	54	1	1.85	66	0	0.00	3.65 [0.15 ; 87.94]	3.73 [0.15 ; 93.4];	1.98 [-2.79 ; 6.75]; 0.209	0.209	
Gender	Female	178	10	5.62	176	2	1.14	4.94 [1.1 ; 22.24]	5.18 [1.12 ; 23.99];	4.48 [0.75 ; 8.21]; 0.035	0.035	0.5439
	Male	94	2	2.13	97	1	1.03	2.06 [0.19 ; 22.38]	2.09 [0.19 ; 23.41];	1.1 [-2.45 ; 4.64]; 0.617	0.617	
Number of baseline Gd-enhancing lesions	>=1	141	5	3.55	135	2	1.48	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	131	7	5.34	136	1	0.74	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	8	6.84	110	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	2	4.76	40	1	2.50	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	2	1.77	123	2	1.63	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	8	4.82	186	2	1.08	4.48 [0.97 ; 20.81]	4.66 [0.97 ; 22.26];	3.74 [0.16 ; 7.32]; 0.051	0.051	0.8172
	Yes	106	4	3.77	87	1	1.15	3.28 [0.37 ; 28.84]	3.37 [0.37 ; 30.74];	2.62 [-1.64 ; 6.89]; 0.381	0.381	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	12	4.90	251	3	1.20	4.1 [1.17 ; 14.34]	4.26 [1.19 ; 15.28];	3.7 [0.68 ; 6.72]; 0.018	0.018	0.9999
	USA and Western Europe	27	0	0.00	22	0	0.00	0.82 [0.02 ; 39.81]	0.82 [0.02 ; 42.89];	-0.39 [-8.11 ; 7.33]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Respiratory, thoracic and mediastinal disorders | Cough

5.2.64 Reproductive system and breast disorders - Dysmenorrhoea

Tabelle 255: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	12	6.82	156	12	7.69	0.89 [0.41 ; 1.92]	0.88 [0.38 ; 2.02];	-0.87 [-6.47 ; 4.73]; 0.833	0.833	0.0813
	>= 38 years	96	0	0.00	117	3	2.56	0.17 [0.01 ; 3.32]	0.17 [0.01 ; 3.32];	-2.45 [-5.83 ; 0.93]; 0.129	0.129	
Disease Severity at baseline (EDSS)	<=3.5	218	12	5.50	207	14	6.76	0.81 [0.39 ; 1.72]	0.8 [0.36 ; 1.78];	-1.26 [-5.83 ; 3.31]; 0.687	0.687	0.3193
	>3.5	54	0	0.00	66	1	1.52	0.41 [0.02 ; 9.77]	0.4 [0.02 ; 10.03];	-1.33 [-5.67 ; 3.01]; 0.503	0.503	
Gender	Female	178	12	6.74	176	15	8.52	0.79 [0.38 ; 1.64]	0.78 [0.35 ; 1.71];	-1.78 [-7.31 ; 3.75]; 0.554	0.554	1
	Male	94	0	0.00	97	0	0.00	1.03 [0.02 ; 51.46]	1.03 [0.02 ; 52.53];	0.02 [-2.01 ; 2.04]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	6	4.26	135	7	5.19	0.82 [0.28 ; 2.38]	0.81 [0.27 ; 2.48];	-0.93 [-5.94 ; 4.08]; 0.782	0.782	0.9433
	0	131	6	4.58	136	8	5.88	0.78 [0.28 ; 2.18]	0.77 [0.26 ; 2.28];	-1.3 [-6.64 ; 4.03]; 0.785	0.785	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	6	5.13	110	6	5.45	0.94 [0.31 ; 2.83]	0.94 [0.29 ; 3];	-0.33 [-6.16 ; 5.5]; 1	1	0.2035
	>=3	42	1	2.38	40	5	12.50	0.19 [0.02 ; 1.56]	0.17 [0.02 ; 1.53];	-10.12 [-21.36 ; 1.12]; 0.105	0.105	
	2	113	5	4.42	123	4	3.25	1.36 [0.37 ; 4.94]	1.38 [0.36 ; 5.26];	1.17 [-3.75 ; 6.09]; 0.741	0.741	
Received approved disease modifying MS drug prior to enrollment	No	166	7	4.22	186	13	6.99	0.6 [0.25 ; 1.48]	0.59 [0.23 ; 1.51];	-2.77 [-7.54 ; 2]; 0.357	0.357	0.1728
	Yes	106	5	4.72	87	2	2.30	2.05 [0.41 ; 10.32]	2.1 [0.4 ; 11.12];	2.42 [-2.7 ; 7.54]; 0.461	0.461	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	12	4.90	251	15	5.98	0.82 [0.39 ; 1.72]	0.81 [0.37 ; 1.77];	-1.08 [-5.07 ; 2.91]; 0.694	0.694	1
	USA and Western Europe	27	0	0.00	22	0	0.00	0.82 [0.02 ; 39.81]	0.82 [0.02 ; 42.89];	-0.39 [-8.11 ; 7.33]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Reproductive system and breast disorders | Dysmenorrhoea

5.2.65 Infections and infestations - Rhinitis

Tabelle 256: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	6	3.41	156	11	7.05	0.48 [0.18 ; 1.28]	0.47 [0.17 ; 1.29];	-3.64 [-8.47 ; 1.19]; 0.144	0.144	0.8457
	>= 38 years	96	1	1.04	117	2	1.71	0.61 [0.06 ; 6.62]	0.61 [0.05 ; 6.78];	-0.67 [-3.77 ; 2.44]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	218	7	3.21	207	11	5.31	0.6 [0.24 ; 1.53]	0.59 [0.22 ; 1.56];	-2.1 [-5.95 ; 1.75]; 0.339	0.339	0.2195
	>3.5	54	0	0.00	66	2	3.03	0.24 [0.01 ; 4.97]	0.24 [0.01 ; 5.04];	-2.82 [-8.01 ; 2.36]; 0.501	0.501	
Gender	Female	178	4	2.25	176	10	5.68	0.4 [0.13 ; 1.24]	0.38 [0.12 ; 1.24];	-3.43 [-7.49 ; 0.62]; 0.11	0.11	0.3305
	Male	94	3	3.19	97	3	3.09	1.03 [0.21 ; 4.98]	1.03 [0.2 ; 5.25];	0.1 [-4.85 ; 5.05]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	4	2.84	135	6	4.44	0.64 [0.18 ; 2.21]	0.63 [0.17 ; 2.28];	-1.61 [-6.03 ; 2.82]; 0.534	0.534	0.6963
	0	131	3	2.29	136	7	5.15	0.44 [0.12 ; 1.68]	0.43 [0.11 ; 1.71];	-2.86 [-7.37 ; 1.65]; 0.335	0.335	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	2	1.71	110	8	7.27	0.24 [0.05 ; 1.08]	0.22 [0.05 ; 1.07];	-5.56 [-10.95 ; -0.17]; 0.053	0.053	0.2417
	>=3	42	2	4.76	40	1	2.50	1.9 [0.18 ; 20.19]	1.95 [0.17 ; 22.39];	2.26 [-5.79 ; 10.32]; 1	1	
	2	113	3	2.65	123	4	3.25	0.82 [0.19 ; 3.57]	0.81 [0.18 ; 3.71];	-0.6 [-4.91 ; 3.72]; 1	1	
Received approved disease modifying MS drug prior to enrollment	No	166	6	3.61	186	9	4.84	0.75 [0.27 ; 2.05]	0.74 [0.26 ; 2.12];	-1.22 [-5.42 ; 2.97]; 0.608	0.608	0.2597
	Yes	106	1	0.94	87	4	4.60	0.21 [0.02 ; 1.8]	0.2 [0.02 ; 1.8];	-3.65 [-8.42 ; 1.12]; 0.177	0.177	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	7	2.86	251	13	5.18	0.55 [0.22 ; 1.36]	0.54 [0.21 ; 1.37];	-2.32 [-5.77 ; 1.12]; 0.254	0.254	0.9999
	USA and Western Europe	27	0	0.00	22	0	0.00	0.82 [0.02 ; 39.81]	0.82 [0.02 ; 42.89];	-0.39 [-8.11 ; 7.33]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Rhinitis

5.2.66 General disorders and administration site conditions - Hyperthermia

Tabelle 257: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	18	10.23	156	2	1.28	7.98 [1.88 ; 33.83]	8.77 [2 ; 38.44];	8.95 [4.13 ; 13.76]; 0.001	0.001	0.0076
	>= 38 years	96	0	0.00	117	2	1.71	0.24 [0.01 ; 5.01]	0.24 [0.01 ; 5.05];	-1.6 [-4.57 ; 1.36]; 0.503	0.503	
Disease Severity at baseline (EDSS)	<=3.5	218	14	6.42	207	2	0.97	6.65 [1.53 ; 28.89]	7.03 [1.58 ; 31.34];	5.46 [1.94 ; 8.97]; 0.004	0.004	0.3891
	>3.5	54	4	7.41	66	2	3.03	2.44 [0.47 ; 12.84]	2.56 [0.45 ; 14.54];	4.38 [-3.74 ; 12.49]; 0.407	0.407	
Gender	Female	178	13	7.30	176	3	1.70	4.28 [1.24 ; 14.78]	4.54 [1.27 ; 16.23];	5.6 [1.32 ; 9.87]; 0.019	0.019	0.8927
	Male	94	5	5.32	97	1	1.03	5.16 [0.61 ; 43.34]	5.39 [0.62 ; 47.06];	4.29 [-0.67 ; 9.25]; 0.114	0.114	
Number of baseline Gd-enhancing lesions	>=1	141	11	7.80	135	3	2.22	3.51 [1 ; 12.31]	3.72 [1.02 ; 13.65];	5.58 [0.5 ; 10.66]; 0.052	0.052	0.557
	0	131	7	5.34	136	1	0.74	7.27 [0.91 ; 58.26]	7.62 [0.92 ; 62.82];	4.61 [0.5 ; 8.72]; 0.033	0.033	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	3	2.56	110	0	0.00	6.58 [0.34 ; 126.04]	6.76 [0.34 ; 132.3];	2.52 [-0.79 ; 5.82]; 0.123	0.123	0.4243
	>=3	42	7	16.67	40	1	2.50	6.67 [0.86 ; 51.79]	7.8 [0.91 ; 66.59];	14.17 [1.9 ; 26.43]; 0.058	0.058	
	2	113	8	7.08	123	3	2.44	2.9 [0.79 ; 10.67]	3.05 [0.79 ; 11.79];	4.64 [-0.82 ; 10.1]; 0.124	0.124	
Received approved disease modifying MS drug prior to enrollment	No	166	11	6.63	186	2	1.08	6.16 [1.39 ; 27.4]	6.53 [1.43 ; 29.9];	5.55 [1.49 ; 9.62]; 0.008	0.008	0.493
	Yes	106	7	6.60	87	2	2.30	2.87 [0.61 ; 13.48]	3.01 [0.61 ; 14.85];	4.3 [-1.38 ; 9.99]; 0.189	0.189	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	18	7.35	251	4	1.59	4.61 [1.58 ; 13.43]	4.9 [1.63 ; 14.68];	5.75 [2.14 ; 9.37]; 0.002	0.002	0.9998
	USA and Western Europe	27	0	0.00	22	0	0.00	0.82 [0.02 ; 39.81]	0.82 [0.02 ; 42.89];	-0.39 [-8.11 ; 7.33]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - General disorders and administration site conditions | Hyperthermia

5.2.67 Infections and infestations - Gastroenteritis

Tabelle 258: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	3	1.70	156	8	5.13	0.33 [0.09 ; 1.23]	0.32 [0.08 ; 1.23];	-3.42 [-7.38 ; 0.53]; 0.123	0.123	0.3504
	>= 38 years	96	0	0.00	117	2	1.71	0.24 [0.01 ; 5.01]	0.24 [0.01 ; 5.05];	-1.6 [-4.57 ; 1.36]; 0.503	0.503	
Disease Severity at baseline (EDSS)	<=3.5	218	3	1.38	207	9	4.35	0.32 [0.09 ; 1.15]	0.31 [0.08 ; 1.15];	-2.97 [-6.15 ; 0.21]; 0.081	0.081	0.5094
	>3.5	54	0	0.00	66	1	1.52	0.41 [0.02 ; 9.77]	0.4 [0.02 ; 10.03];	-1.33 [-5.67 ; 3.01]; 0.503	0.503	
Gender	Female	178	2	1.12	176	8	4.55	0.25 [0.05 ; 1.15]	0.24 [0.05 ; 1.14];	-3.42 [-6.87 ; 0.02]; 0.061	0.061	0.6114
	Male	94	1	1.06	97	2	2.06	0.52 [0.05 ; 5.6]	0.51 [0.05 ; 5.73];	-1 [-4.5 ; 2.51]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	1	0.71	135	4	2.96	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	131	2	1.53	136	6	4.41	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	2	1.71	110	4	3.64	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	0	0.00	40	1	2.50	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	1	0.88	123	5	4.07	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	2	1.20	186	6	3.23	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	Yes	106	1	0.94	87	4	4.60	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	3	1.22	251	9	3.59	0.34 [0.09 ; 1.25]	0.33 [0.09 ; 1.25];	-2.36 [-5.04 ; 0.32]; 0.141	0.141	0.4134
	USA and Western Europe	27	0	0.00	22	1	4.55	0.27 [0.01 ; 6.41]	0.26 [0.01 ; 6.72];	-4.74 [-15.96 ; 6.48]; 0.208	0.208	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Gastroenteritis

5.2.68 Blood and lymphatic system disorders - Leukocytosis

Tabelle 259: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	4	2.27	156	9	5.77	0.39 [0.12 ; 1.25]	0.38 [0.11 ; 1.26];	-3.5 [-7.77 ; 0.77]; 0.155	0.155	0.9687
	>= 38 years	96	1	1.04	117	3	2.56	0.41 [0.04 ; 3.84]	0.4 [0.04 ; 3.91];	-1.52 [-5.03 ; 1.99]; 0.629	0.629	
Disease Severity at baseline (EDSS)	<=3.5	218	3	1.38	207	9	4.35	0.32 [0.09 ; 1.15]	0.31 [0.08 ; 1.15];	-2.97 [-6.15 ; 0.21]; 0.081	0.081	0.4052
	>3.5	54	2	3.70	66	3	4.55	0.81 [0.14 ; 4.7]	0.81 [0.13 ; 5.02];	-0.84 [-7.96 ; 6.27]; 1	1	
Gender	Female	178	4	2.25	176	9	5.11	0.44 [0.14 ; 1.4]	0.43 [0.13 ; 1.41];	-2.87 [-6.78 ; 1.05]; 0.17	0.17	0.8561
	Male	94	1	1.06	97	3	3.09	0.34 [0.04 ; 3.25]	0.34 [0.03 ; 3.3];	-2.03 [-6.05 ; 1.99]; 0.621	0.621	
Number of baseline Gd-enhancing lesions	>=1	141	3	2.13	135	9	6.67	0.32 [0.09 ; 1.15]	0.3 [0.08 ; 1.15];	-4.54 [-9.37 ; 0.3]; 0.08	0.08	0.4799
	0	131	2	1.53	136	3	2.21	0.69 [0.12 ; 4.08]	0.69 [0.11 ; 4.18];	-0.68 [-3.92 ; 2.56]; 1	1	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	0	0.00	110	8	7.27	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	2	4.76	40	1	2.50	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	3	2.65	123	3	2.44	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	0	0.00	186	6	3.23	0.09 [0 ; 1.52]	0.08 [0 ; 1.49];	-3.18 [-5.93 ; -0.42]; 0.031	0.031	0.0366
	Yes	106	5	4.72	87	6	6.90	0.68 [0.22 ; 2.17]	0.67 [0.2 ; 2.27];	-2.18 [-8.86 ; 4.5]; 0.548	0.548	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	5	2.04	251	12	4.78	0.43 [0.15 ; 1.19]	0.41 [0.14 ; 1.2];	-2.74 [-5.92 ; 0.44]; 0.137	0.137	0.9999
	USA and Western Europe	27	0	0.00	22	0	0.00	0.82 [0.02 ; 39.81]	0.82 [0.02 ; 42.89];	-0.39 [-8.11 ; 7.33]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Blood and lymphatic system disorders | Leukocytosis

5.2.69 Blood and lymphatic system disorders - Neutrophilia

Tabelle 260: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	5	2.84	156	8	5.13	0.55 [0.19 ; 1.66]	0.54 [0.17 ; 1.69];	-2.29 [-6.53 ; 1.96]; 0.397	0.397	0.626
	>= 38 years	96	1	1.04	117	4	3.42	0.3 [0.03 ; 2.68]	0.3 [0.03 ; 2.71];	-2.38 [-6.25 ; 1.49]; 0.381	0.381	
Disease Severity at baseline (EDSS)	<=3.5	218	4	1.83	207	8	3.86	0.47 [0.15 ; 1.55]	0.46 [0.14 ; 1.57];	-2.03 [-5.2 ; 1.14]; 0.25	0.25	0.8191
	>3.5	54	2	3.70	66	4	6.06	0.61 [0.12 ; 3.21]	0.6 [0.1 ; 3.39];	-2.36 [-10.01 ; 5.29]; 0.689	0.689	
Gender	Female	178	5	2.81	176	8	4.55	0.62 [0.21 ; 1.85]	0.61 [0.19 ; 1.89];	-1.74 [-5.66 ; 2.18]; 0.413	0.413	0.4643
	Female	178	5	2.81	176	0	0.00	0.62 [0.21 ; 1.85]	0.61 [0.19 ; 1.89];	-1.74 [-5.66 ; 2.18]; 0.413	0.413	
	Female	178	9	5.06	176	8	4.55	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Female	178	9	5.06	176	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Male	94	1	1.06	97	4	4.12	0.26 [0.03 ; 2.27]	0.25 [0.03 ; 2.28];	-3.06 [-7.53 ; 1.41]; 0.369	0.369	
	Male	94	1	1.06	97	2	2.06	0.26 [0.03 ; 2.27]	0.25 [0.03 ; 2.28];	-3.06 [-7.53 ; 1.41]; 0.369	0.369	
	Male	94	6	6.38	97	4	4.12	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Male	94	6	6.38	97	2	2.06	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of baseline Gd-enhancing lesions	>=1	141	3	2.13	135	9	6.67	0.32 [0.09 ; 1.15]	0.3 [0.08 ; 1.15];	-4.54 [-9.37 ; 0.3]; 0.08	0.08	0.2475
	0	131	3	2.29	136	3	2.21	1.04 [0.21 ; 5.05]	1.04 [0.21 ; 5.24];	0.08 [-3.47 ; 3.64]; 1	1	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Number of relapses experienced in the 2 years prior to study start	<=1	117	0	0.00	110	9	8.18	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	3	7.14	40	1	2.50	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	3	2.65	123	2	1.63	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	1	0.60	186	5	2.69	0.22 [0.03 ; 1.9]	0.22 [0.03 ; 1.9];	-2.09 [-4.69 ; 0.52]; 0.219	0.219	0.4267
	Yes	106	5	4.72	87	7	8.05	0.59 [0.19 ; 1.78]	0.57 [0.17 ; 1.85];	-3.33 [-10.33 ; 3.67]; 0.381	0.381	
Region	Eastern Europe	245	6	2.45	251	12	4.78	0.51 [0.2 ; 1.34]	0.5 [0.18 ; 1.35];	-2.33 [-5.6 ; 0.94]; 0.23	0.23	0.9999
	USA and Western Europe	27	0	0.00	22	0	0.00	0.82 [0.02 ; 39.81]	0.82 [0.02 ; 42.89];	-0.39 [-8.11 ; 7.33]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Blood and lymphatic system disorders | Neutrophilia

5.3 Serious TEAE

5.3.1 Infections and infestations - any

Tabelle 261: Serious TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	10	5.68	156	4	2.56	2.22 [0.71 ; 6.92]	2.29 [0.7 ; 7.45];	3.12 [-1.11 ; 7.34]; 0.182	0.182	0.0685
	>= 38 years	96	2	2.08	117	6	5.13	0.41 [0.08 ; 1.97]	0.39 [0.08 ; 2];	-3.04 [-7.96 ; 1.87]; 0.299	0.299	
Disease Severity at baseline (EDSS)	<=3.5	218	11	5.05	207	8	3.86	1.31 [0.54 ; 3.18]	1.32 [0.52 ; 3.35];	1.18 [-2.74 ; 5.1]; 0.642	0.642	0.545
	>3.5	54	1	1.85	66	2	3.03	0.61 [0.06 ; 6.56]	0.6 [0.05 ; 6.84];	-1.18 [-6.66 ; 4.3]; 1	1	
Gender	Female	178	9	5.06	176	7	3.98	1.27 [0.48 ; 3.34]	1.29 [0.47 ; 3.53];	1.08 [-3.24 ; 5.4]; 0.799	0.799	0.8227
	Male	94	3	3.19	97	3	3.09	1.03 [0.21 ; 4.98]	1.03 [0.2 ; 5.25];	0.1 [-4.85 ; 5.05]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	141	6	4.26	135	4	2.96	1.44 [0.41 ; 4.98]	1.46 [0.4 ; 5.28];	1.29 [-3.1 ; 5.68]; 0.75	0.75	0.7029
	0	131	6	4.58	136	6	4.41	1.04 [0.34 ; 3.14]	1.04 [0.33 ; 3.31];	0.17 [-4.8 ; 5.14]; 1	1	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	6	5.13	110	3	2.73	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	4	9.52	40	3	7.50	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	2	1.77	123	4	3.25	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS	No	166	6	3.61	186	6	3.23	1.12 [0.37 ; 3.41]	1.12 [0.36 ; 3.56];	0.39 [-3.42 ; 4.2]; 1	1	0.9088
	Yes	106	6	5.66	87	4	4.60	1.23 [0.36 ; 4.22]	1.24 [0.34 ; 4.56];	1.06 [-5.16 ; 7.29]; 1	1	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
drug prior to enrollment												
Region	Eastern Europe	245	12	4.90	251	10	3.98	1.23 [0.54 ; 2.79]	1.24 [0.53 ; 2.93];	0.91 [-2.71 ; 4.54]; 0.667	0.667	1
	USA and Western Europe	27	0	0.00	22	0	0.00	0.82 [0.02 ; 39.81]	0.82 [0.02 ; 42.89];	-0.39 [-8.11 ; 7.33]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Serious TEAE - Infections and infestations | any

5.4 Severe TEAE

5.4.1 Investigations - any

Tabelle 262: Severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	13	7.39	156	7	4.49	1.65 [0.67 ; 4.02]	1.7 [0.66 ; 4.37];	2.9 [-2.15 ; 7.95]; 0.356	0.356	0.3054
	>= 38 years	96	9	9.38	117	3	2.56	3.66 [1.02 ; 13.13]	3.93 [1.03 ; 14.95];	6.81 [0.31 ; 13.31]; 0.039	0.039	
Disease Severity at baseline (EDSS)	<=3.5	218	18	8.26	207	9	4.35	1.9 [0.87 ; 4.13]	1.98 [0.87 ; 4.51];	3.91 [-0.68 ; 8.5]; 0.114	0.114	0.3962
	>3.5	54	4	7.41	66	1	1.52	4.89 [0.56 ; 42.46]	5.2 [0.56 ; 47.98];	5.89 [-1.69 ; 13.47]; 0.173	0.173	
Gender	Female	178	13	7.30	176	5	2.84	2.57 [0.94 ; 7.06]	2.69 [0.94 ; 7.73];	4.46 [-0.08 ; 9.01]; 0.088	0.088	0.681
	Male	94	9	9.57	97	5	5.15	1.86 [0.65 ; 5.34]	1.95 [0.63 ; 6.04];	4.42 [-2.98 ; 11.82]; 0.277	0.277	
Number of baseline Gd-enhancing lesions	>=1	141	11	7.80	135	7	5.19	1.5 [0.6 ; 3.77]	1.55 [0.58 ; 4.12];	2.62 [-3.18 ; 8.41]; 0.468	0.468	0.2335
	0	131	11	8.40	136	3	2.21	3.81 [1.09 ; 13.34]	4.06 [1.11 ; 14.92];	6.19 [0.84 ; 11.54]; 0.028	0.028	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	8	6.84	110	3	2.73	2.51 [0.68 ; 9.21]	2.62 [0.68 ; 10.13];	4.11 [-1.38 ; 9.6]; 0.218	0.218	0.9712
	>=3	42	4	9.52	40	2	5.00	1.9 [0.37 ; 9.83]	2 [0.35 ; 11.58];	4.52 [-6.63 ; 15.68]; 0.676	0.676	
	2	113	10	8.85	123	5	4.07	2.18 [0.77 ; 6.18]	2.29 [0.76 ; 6.92];	4.78 [-1.51 ; 11.08]; 0.182	0.182	
Received approved disease modifying MS	No	166	14	8.43	186	6	3.23	2.61 [1.03 ; 6.65]	2.76 [1.04 ; 7.37];	5.21 [0.28 ; 10.14]; 0.04	0.04	0.5456
	Yes	106	8	7.55	87	4	4.60	1.64 [0.51 ; 5.27]	1.69 [0.49 ; 5.83];	2.95 [-3.73 ; 9.63]; 0.552	0.552	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
drug prior to enrollment												
Region	Eastern Europe	245	21	8.57	251	9	3.59	2.39 [1.12 ; 5.12]	2.52 [1.13 ; 5.62];	4.99 [0.79 ; 9.18]; 0.023	0.023	0.4565
	USA and Western Europe	27	1	3.70	22	1	4.55	0.81 [0.05 ; 12.3]	0.81 [0.05 ; 13.7];	-0.84 [-12.09 ; 10.41]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Severe TEAE - Investigations | any

5.4.2 Blood and lymphatic system disorders - any

Tabelle 263: Severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	176	9	5.11	156	1	0.64	7.98 [1.02 ; 62.26]	8.35 [1.05 ; 66.7];	4.47 [0.99 ; 7.96]; 0.022	0.022	0.033
	>= 38 years	96	3	3.12	117	5	4.27	0.73 [0.18 ; 2.98]	0.72 [0.17 ; 3.1];	-1.15 [-6.2 ; 3.91]; 0.732	0.732	
Disease Severity at baseline (EDSS)	<=3.5	218	12	5.50	207	4	1.93	2.85 [0.93 ; 8.69]	2.96 [0.94 ; 9.32];	3.57 [0.01 ; 7.13]; 0.073	0.073	0.0365
	>3.5	54	0	0.00	66	2	3.03	0.24 [0.01 ; 4.97]	0.24 [0.01 ; 5.04];	-2.82 [-8.01 ; 2.36]; 0.501	0.501	
Gender	Female	178	7	3.93	176	6	3.41	1.15 [0.4 ; 3.36]	1.16 [0.38 ; 3.52];	0.52 [-3.39 ; 4.44]; 1	1	0.0228
	Male	94	5	5.32	97	0	0.00	11.35 [0.64 ; 202.4]	11.98 [0.65 ; 219.81];	5.28 [0.38 ; 10.18]; 0.014	0.014	
Number of baseline Gd-enhancing lesions	>=1	141	6	4.26	135	2	1.48	2.87 [0.59 ; 13.98]	2.96 [0.59 ; 14.91];	2.77 [-1.13 ; 6.68]; 0.283	0.283	0.5493
	0	131	6	4.58	136	4	2.94	1.56 [0.45 ; 5.39]	1.58 [0.44 ; 5.75];	1.64 [-2.93 ; 6.21]; 0.534	0.534	
	NA	0	0	0.00	2	0	0.00	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	9	7.69	110	2	1.82	4.23 [0.93 ; 19.15]	4.5 [0.95 ; 21.31];	5.87 [0.44 ; 11.31]; 0.06	0.06	0.1152
	>=3	42	1	2.38	40	3	7.50	0.32 [0.03 ; 2.93]	0.3 [0.03 ; 3.02];	-5.12 [-14.49 ; 4.26]; 0.353	0.353	
	2	113	2	1.77	123	1	0.81	2.18 [0.2 ; 23.68]	2.2 [0.2 ; 24.58];	0.96 [-1.95 ; 3.86]; 0.608	0.608	
Received approved disease modifying MS drug prior to enrollment	No	166	5	3.01	186	3	1.61	1.87 [0.45 ; 7.69]	1.89 [0.45 ; 8.05];	1.4 [-1.77 ; 4.57]; 0.483	0.483	0.9656
	Yes	106	7	6.60	87	3	3.45	1.92 [0.51 ; 7.19]	1.98 [0.5 ; 7.9];	3.16 [-2.93 ; 9.24]; 0.516	0.516	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	245	10	4.08	251	6	2.39	1.71 [0.63 ; 4.63]	1.74 [0.62 ; 4.86];	1.69 [-1.42 ; 4.81]; 0.319	0.319	0.2212
	USA and Western Europe	27	2	7.41	22	0	0.00	4.11 [0.21 ; 81.33]	4.41 [0.2 ; 96.84];	6.75 [-5.37 ; 18.88]; 0.497	0.497	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Severe TEAE - Blood and lymphatic system disorders | any

5.4.3 Investigations - Lymphocyte count decreased

Tabelle 264: Severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Disease Severity at baseline (EDSS)	<=3.5	218	9	4.13	207	0	0	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>3.5	54	3	5.56	66	0	0	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of baseline Gd-enhancing lesions	>=1	141	6	4.26	135	0	0	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	131	6	4.58	136	0	0	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	0	0	0.00	2	0	0	NA	NA	NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	117	3	2.56	110	0	0	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	42	3	7.14	40	0	0	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	113	6	5.31	123	0	0	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Received approved disease modifying MS drug prior to enrollment	No	166	9	5.42	186	0	0	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	Yes	106	3	2.83	87	0	0	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Region	Eastern Europe	245	12	4.90	251	0	0	25.61 [1.52 ; 430.18]	26.93 [1.59 ; 457.35];	4.88 [2.08 ; 7.68]; 0	0	0.9999
	USA and Western Europe	27	0	0.00	22	0	0	0.82 [0.02 ; 39.81]	0.82 [0.02 ; 42.89];	-0.39 [-8.11 ; 7.33]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
	p-value: fisher test; interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG; mo and m1 are logit models											
Severe TEAE - Investigations | Lymphocyte count decreased												

6 Ultimate 1 + Ultimate 2: Treatment Emergent Adverse events by SOC/PT

6.1 Any TEAE

6.1.1 Cardiac disorders - any

Tabelle 265: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	40	12.27	302	27	8.94	1,37 [0,86 ; 2,18]	1,42 [0,85 ; 2,39];	3,33 [-1,47 ; 8,13]; 0,197	0,197	0,9956
	>= 38 years	219	28	12.79	246	23	9.35	1,37 [0,81 ; 2,3]	1,42 [0,79 ; 2,55];	3,44 [-2,29 ; 9,16]; 0,298	0,298	
Disease Severity at baseline (EDSS)	<=3.5	419	54	12.89	415	35	8.43	1,53 [1,02 ; 2,29]	1,61 [1,03 ; 2,52];	4,45 [0,28 ; 8,63]; 0,043	0,043	0,2816
	>3.5	126	14	11.11	133	15	11.28	0,99 [0,5 ; 1,96]	0,98 [0,45 ; 2,13];	-0,17 [-7,85 ; 7,51]; 1	1	
Gender	Female	345	36	10.43	356	32	8.99	1,16 [0,74 ; 1,83]	1,18 [0,71 ; 1,95];	1,45 [-2,94 ; 5,83]; 0,526	0,526	0,2692
	Male	200	32	16.00	192	18	9.38	1,71 [0,99 ; 2,94]	1,84 [1 ; 3,41];	6,62 [0,08 ; 13,17]; 0,068	0,068	
Number of baseline Gd-enhancing lesions	>=1	258	45	17.44	251	18	7.17	2,43 [1,45 ; 4,08]	2,73 [1,54 ; 4,87];	10,27 [4,65 ; 15,89]; 0	0	0,0008
	0	286	23	8.04	293	32	10.92	0,74 [0,44 ; 1,23]	0,71 [0,41 ; 1,25];	-2,88 [-7,64 ; 1,88]; 0,259	0,259	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	36	16.00	202	16	7.92	2,02 [1,16 ; 3,53]	2,21 [1,19 ; 4,13];	8,08 [2,01 ; 14,15]; 0,012	0,012	0,1661
	>=3	84	11	13.10	98	12	12.24	1,07 [0,5 ; 2,3]	1,08 [0,45 ; 2,59];	0,85 [-8,85 ; 10,55]; 1	1	
	2	236	21	8.90	248	22	8.87	1 [0,57 ; 1,78]	1 [0,54 ; 1,88];	0,03 [-5,04 ; 5,1]; 1	1	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Race	Other	10	1	10.00	12	0	0.00	3,55 [0,16 ; 78,56]	3,95 [0,14 ; 108,09];	9,79 [-13,03 ; 32,61]; 0,478	0,478	0,2558
	White	535	67	12.52	536	50	9.33	1,34 [0,95 ; 1,9]	1,39 [0,94 ; 2,05];	3,2 [-0,54 ; 6,93]; 0,097	0,097	
Received approved disease modifying MS drug prior to enrollment	No	347	41	11.82	379	40	10.55	1,12 [0,74 ; 1,69]	1,14 [0,72 ; 1,8];	1,26 [-3,33 ; 5,86]; 0,638	0,638	0,0728
	Yes	198	27	13.64	169	10	5.92	2,3 [1,15 ; 4,62]	2,51 [1,18 ; 5,35];	7,72 [1,76 ; 13,68]; 0,015	0,015	
Region	Eastern Europe	492	59	11.99	495	44	8.89	1,35 [0,93 ; 1,95]	1,4 [0,92 ; 2,11];	3,1 [-0,71 ; 6,91]; 0,119	0,119	0,82
	USA and Western Europe	53	9	16.98	53	6	11.32	1,5 [0,57 ; 3,92]	1,6 [0,53 ; 4,87];	5,66 [-7,57 ; 18,89]; 0,579	0,579	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Cardiac disorders | any

6.1.2 Gastrointestinal disorders - any

Tabelle 266: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	130	39.88	302	115	38.08	1,05 [0,86 ; 1,27]	1,08 [0,78 ; 1,49];	1,8 [-5,83 ; 9,43]; 0,682	0,682	0,1014
	>= 38 years	219	61	27.85	246	87	35.37	0,79 [0,6 ; 1,03]	0,71 [0,48 ; 1,05];	-7,51 [-15,93 ; 0,91]; 0,09	0,09	
Disease Severity at baseline (EDSS)	<=3.5	419	153	36.52	415	159	38.31	0,95 [0,8 ; 1,14]	0,93 [0,7 ; 1,23];	-1,8 [-8,37 ; 4,77]; 0,617	0,617	0,9362
	>3.5	126	38	30.16	133	43	32.33	0,93 [0,65 ; 1,34]	0,9 [0,53 ; 1,53];	-2,17 [-13,46 ; 9,12]; 0,789	0,789	
Gender	Female	345	133	38.55	356	139	39.04	0,99 [0,82 ; 1,19]	0,98 [0,72 ; 1,33];	-0,49 [-7,71 ; 6,72]; 0,938	0,938	0,556
	Male	200	58	29.00	192	63	32.81	0,88 [0,66 ; 1,19]	0,84 [0,54 ; 1,28];	-3,81 [-12,96 ; 5,33]; 0,445	0,445	
Number of baseline Gd-enhancing lesions	>=1	258	100	38.76	251	97	38.65	1 [0,81 ; 1,25]	1 [0,7 ; 1,44];	0,11 [-8,35 ; 8,58]; 1	1	0,503
	0	286	91	31.82	293	104	35.49	0,9 [0,71 ; 1,13]	0,85 [0,6 ; 1,2];	-3,68 [-11,37 ; 4,01]; 0,379	0,379	
	NA	1	0	0.00	4	1	25.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	79	35.11	202	72	35.64	0,99 [0,76 ; 1,27]	0,98 [0,66 ; 1,45];	-0,53 [-9,62 ; 8,55]; 0,92	0,92	0,8359
	>=3	84	33	39.29	98	38	38.78	1,01 [0,7 ; 1,46]	1,02 [0,56 ; 1,86];	0,51 [-13,71 ; 14,73]; 1	1	
	2	236	79	33.47	248	92	37.10	0,9 [0,71 ; 1,15]	0,85 [0,59 ; 1,24];	-3,62 [-12,13 ; 4,89]; 0,447	0,447	
Race	Other	10	3	30.00	12	5	41.67	0,72 [0,23 ; 2,3]	0,6 [0,1 ; 3,54];	-11,67 [-51,48 ; 28,14]; 0,675	0,675	0,6275
	White	535	188	35.14	536	197	36.75	0,96 [0,81 ; 1,12]	0,93 [0,73 ; 1,2];	-1,61 [-7,36 ; 4,13]; 0,611	0,611	
	No	347	109	31.41	379	133	35.09	0,9 [0,73 ; 1,1]	0,85 [0,62 ; 1,15];	-3,68 [-10,53 ; 3,17]; 0,306	0,306	0,4731

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	82	41.41	169	69	40.83	1,01 [0,79 ; 1,3]	1,02 [0,68 ; 1,55];	0,59 [-9,51 ; 10,68]; 0,916	0,916	
Region	Eastern Europe	492	168	34.15	495	178	35.96	0,95 [0,8 ; 1,13]	0,92 [0,71 ; 1,2];	-1,81 [-7,77 ; 4,14]; 0,594	0,594	0,9938
	USA and Western Europe	53	23	43.40	53	24	45.28	0,96 [0,63 ; 1,47]	0,93 [0,43 ; 1,99];	-1,89 [-20,8 ; 17,02]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Gastrointestinal disorders | any

6.1.3 General disorders and administration site conditions - any

Tabelle 267: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	160	49.08	302	50	16.56	2,96 [2,25 ; 3,91]	4,86 [3,34 ; 7,05];	32,52 [25,67 ; 39,38]; 0	0	0,0001
	>= 38 years	219	73	33.33	246	58	23.58	1,41 [1,05 ; 1,89]	1,62 [1,08 ; 2,43];	9,76 [1,56 ; 17,95]; 0,023	0,023	
Disease Severity at baseline (EDSS)	<=3.5	419	190	45.35	415	79	19.04	2,38 [1,9 ; 2,98]	3,53 [2,58 ; 4,82];	26,31 [20,23 ; 32,39]; 0	0	0,049
	>3.5	126	43	34.13	133	29	21.80	1,57 [1,05 ; 2,34]	1,86 [1,07 ; 3,23];	12,32 [1,47 ; 23,18]; 0,037	0,037	
Gender	Female	345	159	46.09	356	77	21.63	2,13 [1,7 ; 2,68]	3,1 [2,23 ; 4,31];	24,46 [17,68 ; 31,24]; 0	0	0,9587
	Male	200	74	37.00	192	31	16.15	2,29 [1,58 ; 3,32]	3,05 [1,89 ; 4,93];	20,85 [12,38 ; 29,33]; 0	0	
Number of baseline Gd-enhancing lesions	>=1	258	119	46.12	251	50	19.92	2,32 [1,75 ; 3,07]	3,44 [2,32 ; 5,11];	26,2 [18,37 ; 34,04]; 0	0	0,3699
	0	286	114	39.86	293	58	19.80	2,01 [1,54 ; 2,64]	2,69 [1,85 ; 3,9];	20,06 [12,78 ; 27,35]; 0	0	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	90	40.00	202	42	20.79	1,92 [1,41 ; 2,63]	2,54 [1,65 ; 3,91];	19,21 [10,71 ; 27,71]; 0	0	0,176
	>=3	84	43	51.19	98	16	16.33	3,14 [1,91 ; 5,14]	5,38 [2,71 ; 10,67];	34,86 [21,91 ; 47,82]; 0	0	
	2	236	100	42.37	248	50	20.16	2,1 [1,57 ; 2,81]	2,91 [1,94 ; 4,36];	22,21 [14,17 ; 30,25]; 0	0	
Race	Other	10	4	40.00	12	6	50.00	0,8 [0,31 ; 2,06]	0,67 [0,12 ; 3,64];	-10 [-51,5 ; 31,5]; 0,691	0,691	0,0738
	White	535	229	42.80	536	102	19.03	2,25 [1,84 ; 2,75]	3,18 [2,42 ; 4,19];	23,77 [18,42 ; 29,12]; 0	0	
	No	347	139	40.06	379	71	18.73	2,14 [1,67 ; 2,73]	2,9 [2,07 ; 4,06];	21,32 [14,84 ; 27,81]; 0	0	0,7134

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	94	47.47	169	37	21.89	2,17 [1,57 ; 2,99]	3,22 [2,04 ; 5,1];	25,58 [16,24 ; 34,92]; 0	0	
Region	Eastern Europe	492	206	41.87	495	84	16.97	2,47 [1,98 ; 3,08]	3,52 [2,62 ; 4,73];	24,9 [19,43 ; 30,37]; 0	0	0,014
	USA and Western Europe	53	27	50.94	53	24	45.28	1,12 [0,76 ; 1,67]	1,25 [0,58 ; 2,69];	5,66 [-13,33 ; 24,65]; 0,698	0,698	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - General disorders and administration site conditions | any

6.1.4 Infections and infestations - any

Tabelle 268: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	206	63.19	302	179	59.27	1,07 [0,94 ; 1,21]	1,18 [0,86 ; 1,63];	3,92 [-3,7 ; 11,54]; 0,326	0,326	0,2103
	>= 38 years	219	98	44.75	246	119	48.37	0,93 [0,76 ; 1,13]	0,86 [0,6 ; 1,25];	-3,63 [-12,7 ; 5,45]; 0,457	0,457	
Disease Severity at baseline (EDSS)	<=3.5	419	245	58.47	415	237	57.11	1,02 [0,91 ; 1,15]	1,06 [0,8 ; 1,39];	1,36 [-5,34 ; 8,07]; 0,726	0,726	0,9518
	>3.5	126	59	46.83	133	61	45.86	1,02 [0,79 ; 1,33]	1,04 [0,64 ; 1,69];	0,96 [-11,19 ; 13,11]; 0,901	0,901	
Gender	Female	345	218	63.19	356	201	56.46	1,12 [0,99 ; 1,26]	1,32 [0,98 ; 1,79];	6,73 [-0,51 ; 13,97]; 0,077	0,077	0,0221
	Male	200	86	43.00	192	97	50.52	0,85 [0,69 ; 1,05]	0,74 [0,5 ; 1,1];	-7,52 [-17,37 ; 2,33]; 0,156	0,156	
Number of baseline Gd-enhancing lesions	>=1	258	153	59.30	251	142	56.57	1,05 [0,9 ; 1,22]	1,12 [0,79 ; 1,59];	2,73 [-5,85 ; 11,3]; 0,59	0,59	0,596
	0	286	151	52.80	293	156	53.24	0,99 [0,85 ; 1,16]	0,98 [0,71 ; 1,36];	-0,45 [-8,58 ; 7,69]; 0,934	0,934	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	119	52.89	202	105	51.98	1,02 [0,85 ; 1,22]	1,04 [0,71 ; 1,52];	0,91 [-8,58 ; 10,4]; 0,923	0,923	0,2174
	>=3	84	52	61.90	98	48	48.98	1,26 [0,97 ; 1,64]	1,69 [0,94 ; 3,06];	12,93 [-1,42 ; 27,27]; 0,1	0,1	
	2	236	133	56.36	248	145	58.47	0,96 [0,83 ; 1,12]	0,92 [0,64 ; 1,32];	-2,11 [-10,92 ; 6,7]; 0,647	0,647	
Race	Other	10	8	80.00	12	8	66.67	1,2 [0,72 ; 1,99]	2 [0,28 ; 14,2];	13,33 [-23,08 ; 49,75]; 0,646	0,646	0,5161
	White	535	296	55.33	536	290	54.10	1,02 [0,92 ; 1,14]	1,05 [0,83 ; 1,34];	1,22 [-4,74 ; 7,18]; 0,713	0,713	
	No	347	178	51.30	379	206	54.35	0,94 [0,82 ; 1,08]	0,88 [0,66 ; 1,18];	-3,06 [-10,32 ; 4,21]; 0,414	0,414	0,0526

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	126	63.64	169	92	54.44	1,17 [0,98 ; 1,39]	1,46 [0,96 ; 2,23];	9,2 [-0,87 ; 19,26]; 0,088	0,088	
Region	Eastern Europe	492	265	53.86	495	263	53.13	1,01 [0,9 ; 1,14]	1,03 [0,8 ; 1,32];	0,73 [-5,49 ; 6,95]; 0,848	0,848	0,4564
	USA and Western Europe	53	39	73.58	53	35	66.04	1,11 [0,87 ; 1,43]	1,43 [0,62 ; 3,3];	7,55 [-9,87 ; 24,97]; 0,526	0,526	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | any

6.1.5 Musculoskeletal and connective tissue disorders - any

Tabelle 269: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	77	23.62	302	53	17.55	1,35 [0,98 ; 1,84]	1,45 [0,98 ; 2,15];	6,07 [-0,23 ; 12,37]; 0,062	0,062	0,0659
	>= 38 years	219	52	23.74	246	66	26.83	0,89 [0,65 ; 1,21]	0,85 [0,56 ; 1,29];	-3,08 [-10,99 ; 4,82]; 0,457	0,457	
Disease Severity at baseline (EDSS)	<=3.5	419	108	25.78	415	87	20.96	1,23 [0,96 ; 1,57]	1,31 [0,95 ; 1,81];	4,81 [-0,92 ; 10,55]; 0,103	0,103	0,0378
	>3.5	126	21	16.67	133	32	24.06	0,69 [0,42 ; 1,13]	0,63 [0,34 ; 1,17];	-7,39 [-17,15 ; 2,36]; 0,166	0,166	
Gender	Female	345	90	26.09	356	84	23.60	1,11 [0,85 ; 1,43]	1,14 [0,81 ; 1,61];	2,49 [-3,91 ; 8,89]; 0,484	0,484	0,8715
	Male	200	39	19.50	192	35	18.23	1,07 [0,71 ; 1,61]	1,09 [0,65 ; 1,8];	1,27 [-6,47 ; 9,02]; 0,797	0,797	
Number of baseline Gd-enhancing lesions	>=1	258	68	26.36	251	56	22.31	1,18 [0,87 ; 1,61]	1,25 [0,83 ; 1,87];	4,05 [-3,4 ; 11,49]; 0,303	0,303	0,4264
	0	286	61	21.33	293	63	21.50	0,99 [0,73 ; 1,36]	0,99 [0,67 ; 1,47];	-0,17 [-6,86 ; 6,51]; 1	1	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	53	23.56	202	46	22.77	1,03 [0,73 ; 1,46]	1,04 [0,67 ; 1,64];	0,78 [-7,23 ; 8,8]; 0,909	0,909	0,6923
	>=3	84	20	23.81	98	17	17.35	1,37 [0,77 ; 2,44]	1,49 [0,72 ; 3,07];	6,46 [-5,33 ; 18,26]; 0,356	0,356	
	2	236	56	23.73	248	56	22.58	1,05 [0,76 ; 1,45]	1,07 [0,7 ; 1,63];	1,15 [-6,37 ; 8,67]; 0,829	0,829	
Race	Other	10	7	70.00	12	7	58.33	1,2 [0,64 ; 2,25]	1,67 [0,28 ; 9,82];	11,67 [-28,14 ; 51,48]; 0,675	0,675	0,6617
	White	535	122	22.80	536	112	20.90	1,09 [0,87 ; 1,37]	1,12 [0,84 ; 1,49];	1,91 [-3,04 ; 6,86]; 0,46	0,46	
	No	347	76	21.90	379	82	21.64	1,01 [0,77 ; 1,33]	1,02 [0,71 ; 1,45];	0,27 [-5,74 ; 6,28]; 1	1	0,4113

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	53	26.77	169	37	21.89	1,22 [0,85 ; 1,76]	1,3 [0,81 ; 2,11];	4,87 [-3,9 ; 13,64]; 0,33	0,33	
Region	Eastern Europe	492	99	20.12	495	94	18.99	1,06 [0,82 ; 1,36]	1,07 [0,78 ; 1,47];	1,13 [-3,82 ; 6,08]; 0,688	0,688	0,4665
	USA and Western Europe	53	30	56.60	53	25	47.17	1,2 [0,83 ; 1,74]	1,46 [0,68 ; 3,14];	9,43 [-9,5 ; 28,37]; 0,437	0,437	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Musculoskeletal and connective tissue disorders | any

6.1.6 Nervous system disorders - any

Tabelle 270: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	164	50.31	302	122	40.40	1,25 [1,05 ; 1,48]	1,49 [1,09 ; 2,05];	9,91 [2,16 ; 17,66]; 0,013	0,013	0,0748
	>= 38 years	219	75	34.25	246	87	35.37	0,97 [0,75 ; 1,24]	0,95 [0,65 ; 1,4];	-1,12 [-9,79 ; 7,55]; 0,846	0,846	
Disease Severity at baseline (EDSS)	<=3.5	419	193	46.06	415	161	38.80	1,19 [1,01 ; 1,39]	1,35 [1,02 ; 1,77];	7,27 [0,58 ; 13,96]; 0,036	0,036	0,3413
	>3.5	126	46	36.51	133	48	36.09	1,01 [0,73 ; 1,4]	1,02 [0,61 ; 1,69];	0,42 [-11,3 ; 12,13]; 1	1	
Gender	Female	345	167	48.41	356	146	41.01	1,18 [1 ; 1,39]	1,35 [1 ; 1,82];	7,39 [0,05 ; 14,74]; 0,057	0,057	0,5453
	Male	200	72	36.00	192	63	32.81	1,1 [0,83 ; 1,44]	1,15 [0,76 ; 1,75];	3,19 [-6,21 ; 12,59]; 0,525	0,525	
Number of baseline Gd-enhancing lesions	>=1	258	118	45.74	251	107	42.63	1,07 [0,88 ; 1,3]	1,13 [0,8 ; 1,61];	3,11 [-5,52 ; 11,73]; 0,532	0,532	0,4051
	0	286	121	42.31	293	101	34.47	1,23 [1 ; 1,51]	1,39 [1 ; 1,95];	7,84 [-0,06 ; 15,74]; 0,06	0,06	
	NA	1	0	0.00	4	1	25.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	95	42.22	202	85	42.08	1 [0,8 ; 1,25]	1,01 [0,68 ; 1,48];	0,14 [-9,24 ; 9,52]; 1	1	0,3279
	>=3	84	36	42.86	98	32	32.65	1,31 [0,9 ; 1,91]	1,55 [0,85 ; 2,83];	10,2 [-3,87 ; 24,28]; 0,169	0,169	
	2	236	108	45.76	248	92	37.10	1,23 [1 ; 1,53]	1,43 [0,99 ; 2,06];	8,67 [-0,08 ; 17,42]; 0,065	0,065	
Race	Other	10	8	80.00	12	6	50.00	1,6 [0,84 ; 3,05]	4 [0,59 ; 27,25];	30 [-7,62 ; 67,62]; 0,204	0,204	0,2192
	White	535	231	43.18	536	203	37.87	1,14 [0,99 ; 1,32]	1,25 [0,98 ; 1,59];	5,3 [-0,57 ; 11,18]; 0,082	0,082	
	No	347	145	41.79	379	147	38.79	1,08 [0,9 ; 1,29]	1,13 [0,84 ; 1,52];	3 [-4,14 ; 10,14]; 0,449	0,449	0,2217

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	94	47.47	169	62	36.69	1,29 [1,01 ; 1,66]	1,56 [1,03 ; 2,37];	10,79 [0,73 ; 20,85]; 0,044	0,044	
Region	Eastern Europe	492	203	41.26	495	177	35.76	1,15 [0,98 ; 1,35]	1,26 [0,98 ; 1,63];	5,5 [-0,56 ; 11,56]; 0,078	0,078	0,8214
	USA and Western Europe	53	36	67.92	53	32	60.38	1,12 [0,85 ; 1,5]	1,39 [0,63 ; 3,08];	7,55 [-10,65 ; 25,75]; 0,544	0,544	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Nervous system disorders | any

6.1.7 Renal and urinary disorders - any

Tabelle 271: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	22	6.75	302	18	5.96	1,13 [0,62 ; 2,07]	1,14 [0,6 ; 2,17];	0,79 [-3,03 ; 4,6]; 0,745	0,745	0,6767
	>= 38 years	219	15	6.85	246	18	7.32	0,94 [0,48 ; 1,81]	0,93 [0,46 ; 1,9];	-0,47 [-5,13 ; 4,2]; 0,859	0,859	
Disease Severity at baseline (EDSS)	<=3.5	419	31	7.40	415	24	5.78	1,28 [0,76 ; 2,14]	1,3 [0,75 ; 2,26];	1,62 [-1,75 ; 4,98]; 0,403	0,403	0,0993
	>3.5	126	6	4.76	133	12	9.02	0,53 [0,2 ; 1,36]	0,5 [0,18 ; 1,39];	-4,26 [-10,39 ; 1,87]; 0,224	0,224	
Gender	Female	345	27	7.83	356	22	6.18	1,27 [0,74 ; 2,18]	1,29 [0,72 ; 2,31];	1,65 [-2,13 ; 5,43]; 0,459	0,459	0,2052
	Male	200	10	5.00	192	14	7.29	0,69 [0,31 ; 1,51]	0,67 [0,29 ; 1,55];	-2,29 [-7,05 ; 2,47]; 0,402	0,402	
Number of baseline Gd-enhancing lesions	>=1	258	17	6.59	251	19	7.57	0,87 [0,46 ; 1,64]	0,86 [0,44 ; 1,7];	-0,98 [-5,44 ; 3,48]; 0,731	0,731	0,3982
	0	286	20	6.99	293	16	5.46	1,28 [0,68 ; 2,42]	1,3 [0,66 ; 2,57];	1,53 [-2,41 ; 5,47]; 0,494	0,494	
	NA	1	0	0.00	4	1	25.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	13	5.78	202	14	6.93	0,83 [0,4 ; 1,73]	0,82 [0,38 ; 1,8];	-1,15 [-5,8 ; 3,49]; 0,693	0,693	0,5198
	>=3	84	4	4.76	98	2	2.04	2,33 [0,44 ; 12,42]	2,4 [0,43 ; 13,44];	2,72 [-2,62 ; 8,07]; 0,417	0,417	
	2	236	20	8.47	248	20	8.06	1,05 [0,58 ; 1,9]	1,06 [0,55 ; 2,02];	0,41 [-4,5 ; 5,32]; 0,871	0,871	
Race	Other	10	0	0.00	12	2	16.67	0,24 [0,01 ; 4,42]	0,2 [0,01 ; 4,69];	-14,69 [-39,39 ; 10,02]; 0,481	0,481	0,0998
	White	535	37	6.92	536	34	6.34	1,09 [0,7 ; 1,71]	1,1 [0,68 ; 1,78];	0,57 [-2,41 ; 3,55]; 0,715	0,715	
	No	347	21	6.05	379	20	5.28	1,15 [0,63 ; 2,08]	1,16 [0,62 ; 2,17];	0,77 [-2,6 ; 4,15]; 0,748	0,748	0,5158

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	16	8.08	169	16	9.47	0,85 [0,44 ; 1,65]	0,84 [0,41 ; 1,74];	-1,39 [-7,21 ; 4,44]; 0,712	0,712	
Region	Eastern Europe	492	32	6.50	495	29	5.86	1,11 [0,68 ; 1,81]	1,12 [0,67 ; 1,88];	0,65 [-2,36 ; 3,65]; 0,694	0,694	0,4649
	USA and Western Europe	53	5	9.43	53	7	13.21	0,71 [0,24 ; 2,11]	0,68 [0,2 ; 2,31];	-3,77 [-15,82 ; 8,27]; 0,761	0,761	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Renal and urinary disorders | any

6.1.8 Reproductive system and breast disorders - any

Tabelle 272: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	35	10.74	302	34	11.26	0,95 [0,61 ; 1,49]	0,95 [0,57 ; 1,56];	-0,52 [-5,42 ; 4,38]; 0,899	0,899	0,6111
	>= 38 years	219	13	5.94	246	19	7.72	0,77 [0,39 ; 1,52]	0,75 [0,36 ; 1,56];	-1,79 [-6,36 ; 2,79]; 0,469	0,469	
Disease Severity at baseline (EDSS)	<=3.5	419	43	10.26	415	42	10.12	1,01 [0,68 ; 1,52]	1,02 [0,65 ; 1,59];	0,14 [-3,96 ; 4,25]; 1	1	0,1733
	>3.5	126	5	3.97	133	11	8.27	0,48 [0,17 ; 1,34]	0,46 [0,15 ; 1,36];	-4,3 [-10,09 ; 1,49]; 0,198	0,198	
Gender	Female	345	46	13.33	356	48	13.48	0,99 [0,68 ; 1,44]	0,99 [0,64 ; 1,52];	-0,15 [-5,2 ; 4,9]; 1	1	0,2488
	Male	200	2	1.00	192	5	2.60	0,38 [0,08 ; 1,96]	0,38 [0,07 ; 1,97];	-1,6 [-4,25 ; 1,04]; 0,276	0,276	
Number of baseline Gd-enhancing lesions	>=1	258	25	9.69	251	26	10.36	0,94 [0,56 ; 1,57]	0,93 [0,52 ; 1,66];	-0,67 [-5,89 ; 4,55]; 0,883	0,883	0,8581
	0	286	23	8.04	293	27	9.22	0,87 [0,51 ; 1,49]	0,86 [0,48 ; 1,54];	-1,17 [-5,74 ; 3,4]; 0,659	0,659	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	20	8.89	202	21	10.40	0,86 [0,48 ; 1,53]	0,84 [0,44 ; 1,6];	-1,51 [-7,12 ; 4,11]; 0,625	0,625	0,9142
	>=3	84	10	11.90	98	11	11.22	1,06 [0,47 ; 2,37]	1,07 [0,43 ; 2,66];	0,68 [-8,65 ; 10,01]; 1	1	
	2	236	18	7.63	248	21	8.47	0,9 [0,49 ; 1,65]	0,89 [0,46 ; 1,72];	-0,84 [-5,69 ; 4]; 0,742	0,742	
Race	Other	10	2	20.00	12	1	8.33	2,4 [0,25 ; 22,75]	2,75 [0,21 ; 35,84];	11,67 [-17,64 ; 40,98]; 0,571	0,571	0,3738
	White	535	46	8.60	536	52	9.70	0,89 [0,61 ; 1,29]	0,88 [0,58 ; 1,33];	-1,1 [-4,56 ; 2,35]; 0,596	0,596	
	No	347	33	9.51	379	36	9.50	1 [0,64 ; 1,57]	1 [0,61 ; 1,65];	0,01 [-4,26 ; 4,28]; 1	1	0,4869

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	15	7.58	169	17	10.06	0,75 [0,39 ; 1,46]	0,73 [0,35 ; 1,52];	-2,48 [-8,33 ; 3,36]; 0,46	0,46	
Region	Eastern Europe	492	40	8.13	495	45	9.09	0,89 [0,6 ; 1,34]	0,88 [0,57 ; 1,38];	-0,96 [-4,46 ; 2,54]; 0,65	0,65	0,8354
	USA and Western Europe	53	8	15.09	53	8	15.09	1 [0,41 ; 2,47]	1 [0,35 ; 2,9];	0 [-13,63 ; 13,63]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Reproductive system and breast disorders | any

6.1.9 Skin and subcutaneous tissue disorders - any

Tabelle 273: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	54	16.56	302	75	24.83	0,67 [0,49 ; 0,91]	0,6 [0,41 ; 0,89];	-8,27 [-14,6 ; -1,94]; 0,013	0,013	0,5753
	>= 38 years	219	30	13.70	246	59	23.98	0,57 [0,38 ; 0,85]	0,5 [0,31 ; 0,82];	-10,29 [-17,3 ; -3,27]; 0,006	0,006	
Disease Severity at baseline (EDSS)	<=3.5	419	73	17.42	415	108	26.02	0,67 [0,51 ; 0,87]	0,6 [0,43 ; 0,84];	-8,6 [-14,17 ; -3,03]; 0,003	0,003	0,3097
	>3.5	126	11	8.73	133	26	19.55	0,45 [0,23 ; 0,87]	0,39 [0,19 ; 0,84];	-10,82 [-19,17 ; -2,47]; 0,013	0,013	
Gender	Female	345	56	16.23	356	110	30.90	0,53 [0,39 ; 0,7]	0,43 [0,3 ; 0,62];	-14,67 [-20,85 ; -8,49]; 0	0	0,0058
	Male	200	28	14.00	192	24	12.50	1,12 [0,67 ; 1,86]	1,14 [0,63 ; 2,05];	1,5 [-5,21 ; 8,21]; 0,766	0,766	
Number of baseline Gd-enhancing lesions	>=1	258	42	16.28	251	62	24.70	0,66 [0,46 ; 0,94]	0,59 [0,38 ; 0,92];	-8,42 [-15,4 ; -1,44]; 0,021	0,021	0,7559
	0	286	42	14.69	293	71	24.23	0,61 [0,43 ; 0,86]	0,54 [0,35 ; 0,82];	-9,55 [-15,94 ; -3,15]; 0,005	0,005	
	NA	1	0	0.00	4	1	25.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	36	16.00	202	50	24.75	0,65 [0,44 ; 0,95]	0,58 [0,36 ; 0,93];	-8,75 [-16,39 ; -1,11]; 0,029	0,029	0,4311
	>=3	84	10	11.90	98	27	27.55	0,43 [0,22 ; 0,84]	0,36 [0,16 ; 0,79];	-15,65 [-26,88 ; -4,41]; 0,01	0,01	
	2	236	38	16.10	248	57	22.98	0,7 [0,48 ; 1,01]	0,64 [0,41 ; 1,01];	-6,88 [-13,91 ; 0,15]; 0,067	0,067	
Race	Other	10	4	40.00	12	6	50.00	0,8 [0,31 ; 2,06]	0,67 [0,12 ; 3,64];	-10 [-51,5 ; 31,5]; 0,691	0,691	0,844
	White	535	80	14.95	536	128	23.88	0,63 [0,49 ; 0,81]	0,56 [0,41 ; 0,76];	-8,93 [-13,63 ; -4,22]; 0	0	
	No	347	46	13.26	379	89	23.48	0,56 [0,41 ; 0,78]	0,5 [0,34 ; 0,74];	-10,23 [-15,79 ; -4,66]; 0	0	0,3935

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	38	19.19	169	45	26.63	0,72 [0,49 ; 1,05]	0,65 [0,4 ; 1,07];	-7,44 [-16,07 ; 1,2]; 0,104	0,104	
Region	Eastern Europe	492	68	13.82	495	114	23.03	0,6 [0,46 ; 0,79]	0,54 [0,39 ; 0,75];	-9,21 [-14,01 ; -4,41]; 0	0	0,5215
	USA and Western Europe	53	16	30.19	53	20	37.74	0,8 [0,47 ; 1,37]	0,71 [0,32 ; 1,6];	-7,55 [-25,52 ; 10,43]; 0,539	0,539	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Skin and subcutaneous tissue disorders | any

6.1.10 Ear and labyrinth disorders - any

Tabelle 274: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	8	2.45	302	5	1.66	1,48 [0,49 ; 4,48]	1,49 [0,48 ; 4,62];	0,8 [-1,41 ; 3,01]; 0,581	0,581	0,7198
	>= 38 years	219	15	6.85	246	9	3.66	1,87 [0,84 ; 4,19]	1,94 [0,83 ; 4,52];	3,19 [-0,9 ; 7,28]; 0,143	0,143	
Disease Severity at baseline (EDSS)	<=3.5	419	16	3.82	415	9	2.17	1,76 [0,79 ; 3,94]	1,79 [0,78 ; 4,1];	1,65 [-0,66 ; 3,96]; 0,223	0,223	0,8133
	>3.5	126	7	5.56	133	5	3.76	1,48 [0,48 ; 4,54]	1,51 [0,47 ; 4,87];	1,8 [-3,35 ; 6,94]; 0,563	0,563	
Gender	Female	345	15	4.35	356	8	2.25	1,93 [0,83 ; 4,51]	1,98 [0,83 ; 4,73];	2,1 [-0,55 ; 4,75]; 0,14	0,14	0,5475
	Male	200	8	4.00	192	6	3.12	1,28 [0,45 ; 3,62]	1,29 [0,44 ; 3,79];	0,88 [-2,79 ; 4,54]; 0,787	0,787	
Number of baseline Gd-enhancing lesions	>=1	258	6	2.33	251	7	2.79	0,83 [0,28 ; 2,45]	0,83 [0,28 ; 2,5];	-0,46 [-3,21 ; 2,28]; 0,785	0,785	0,1144
	0	286	17	5.94	293	7	2.39	2,49 [1,05 ; 5,91]	2,58 [1,05 ; 6,32];	3,55 [0,3 ; 6,81]; 0,037	0,037	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	12	5.33	202	2	0.99	5,39 [1,22 ; 23,78]	5,63 [1,25 ; 25,49];	4,34 [1,11 ; 7,58]; 0,013	0,013	0,0707
	>=3	84	3	3.57	98	2	2.04	1,75 [0,3 ; 10,23]	1,78 [0,29 ; 10,9];	1,53 [-3,33 ; 6,39]; 0,663	0,663	
	2	236	8	3.39	248	10	4.03	0,84 [0,34 ; 2,09]	0,84 [0,32 ; 2,15];	-0,64 [-4,01 ; 2,72]; 0,812	0,812	
Race	Other	10	2	20.00	12	1	8.33	2,4 [0,25 ; 22,75]	2,75 [0,21 ; 35,84];	11,67 [-17,64 ; 40,98]; 0,571	0,571	0,7001
	White	535	21	3.93	536	13	2.43	1,62 [0,82 ; 3,2]	1,64 [0,81 ; 3,32];	1,5 [-0,6 ; 3,6]; 0,168	0,168	
	No	347	14	4.03	379	7	1.85	2,18 [0,89 ; 5,35]	2,23 [0,89 ; 5,6];	2,19 [-0,29 ; 4,66]; 0,119	0,119	0,31

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	9	4.55	169	7	4.14	1,1 [0,42 ; 2,88]	1,1 [0,4 ; 3,03];	0,4 [-3,77 ; 4,58]; 1	1	
Region	Eastern Europe	492	16	3.25	495	11	2.22	1,46 [0,69 ; 3,12]	1,48 [0,68 ; 3,22];	1,03 [-1,01 ; 3,07]; 0,337	0,337	0,5054
	USA and Western Europe	53	7	13.21	53	3	5.66	2,33 [0,64 ; 8,54]	2,54 [0,62 ; 10,39];	7,55 [-3,49 ; 18,58]; 0,319	0,319	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Ear and labyrinth disorders | any

6.1.11 Respiratory, thoracic and mediastinal disorders - any

Tabelle 275: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	73	22.39	302	39	12.91	1,73 [1,21 ; 2,48]	1,95 [1,27 ; 2,98];	9,48 [3,58 ; 15,38]; 0,002	0,002	0,4065
	>= 38 years	219	37	16.89	246	30	12.20	1,39 [0,89 ; 2,16]	1,46 [0,87 ; 2,46];	4,7 [-1,73 ; 11,13]; 0,186	0,186	
Disease Severity at baseline (EDSS)	<=3.5	419	96	22.91	415	54	13.01	1,76 [1,3 ; 2,39]	1,99 [1,38 ; 2,86];	9,9 [4,74 ; 15,06]; 0	0	0,1073
	>3.5	126	14	11.11	133	15	11.28	0,99 [0,5 ; 1,96]	0,98 [0,45 ; 2,13];	-0,17 [-7,85 ; 7,51]; 1	1	
Gender	Female	345	77	22.32	356	49	13.76	1,62 [1,17 ; 2,25]	1,8 [1,21 ; 2,67];	8,55 [2,89 ; 14,22]; 0,004	0,004	0,8744
	Male	200	33	16.50	192	20	10.42	1,58 [0,94 ; 2,66]	1,7 [0,94 ; 3,08];	6,08 [-0,63 ; 12,8]; 0,103	0,103	
Number of baseline Gd-enhancing lesions	>=1	258	60	23.26	251	30	11.95	1,95 [1,3 ; 2,91]	2,23 [1,38 ; 3,6];	11,3 [4,77 ; 17,84]; 0,001	0,001	0,152
	0	286	50	17.48	293	39	13.31	1,31 [0,89 ; 1,93]	1,38 [0,88 ; 2,17];	4,17 [-1,7 ; 10,05]; 0,169	0,169	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	52	23.11	202	25	12.38	1,87 [1,21 ; 2,89]	2,13 [1,26 ; 3,58];	10,73 [3,6 ; 17,87]; 0,005	0,005	0,6018
	>=3	84	17	20.24	98	13	13.27	1,53 [0,79 ; 2,95]	1,66 [0,75 ; 3,66];	6,97 [-3,93 ; 17,88]; 0,233	0,233	
	2	236	41	17.37	248	31	12.50	1,39 [0,9 ; 2,14]	1,47 [0,89 ; 2,44];	4,87 [-1,48 ; 11,22]; 0,16	0,16	
Race	Other	10	2	20.00	12	4	33.33	0,6 [0,14 ; 2,62]	0,5 [0,07 ; 3,55];	-13,33 [-49,75 ; 23,08]; 0,646	0,646	0,1893
	White	535	108	20.19	536	65	12.13	1,66 [1,25 ; 2,21]	1,83 [1,31 ; 2,56];	8,06 [3,68 ; 12,44]; 0	0	
	No	347	59	17.00	379	47	12.40	1,37 [0,96 ; 1,95]	1,45 [0,96 ; 2,19];	4,6 [-0,56 ; 9,76]; 0,092	0,092	0,1768

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	51	25.76	169	22	13.02	1,98 [1,25 ; 3,12]	2,32 [1,34 ; 4,02];	12,74 [4,81 ; 20,67]; 0,002	0,002	
Region	Eastern Europe	492	94	19.11	495	57	11.52	1,66 [1,22 ; 2,25]	1,81 [1,27 ; 2,59];	7,59 [3,12 ; 12,06]; 0,001	0,001	0,6689
	USA and Western Europe	53	16	30.19	53	12	22.64	1,33 [0,7 ; 2,54]	1,48 [0,62 ; 3,53];	7,55 [-9,18 ; 24,27]; 0,509	0,509	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Respiratory, thoracic and mediastinal disorders | any

6.1.12 Injury, poisoning and procedural complications - any

Tabelle 276: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	47	14.42	302	33	10.93	1,32 [0,87 ; 2]	1,37 [0,85 ; 2,21];	3,49 [-1,7 ; 8,68]; 0,231	0,231	0,5463
	>= 38 years	219	29	13.24	246	30	12.20	1,09 [0,67 ; 1,75]	1,1 [0,64 ; 1,9];	1,05 [-5,03 ; 7,12]; 0,781	0,781	
Disease Severity at baseline (EDSS)	<=3.5	419	61	14.56	415	43	10.36	1,41 [0,97 ; 2,03]	1,47 [0,97 ; 2,24];	4,2 [-0,28 ; 8,67]; 0,075	0,075	0,1188
	>3.5	126	15	11.90	133	20	15.04	0,79 [0,42 ; 1,48]	0,76 [0,37 ; 1,57];	-3,13 [-11,43 ; 5,17]; 0,474	0,474	
Gender	Female	345	51	14.78	356	40	11.24	1,32 [0,89 ; 1,94]	1,37 [0,88 ; 2,14];	3,55 [-1,43 ; 8,53]; 0,178	0,178	0,4859
	Male	200	25	12.50	192	23	11.98	1,04 [0,61 ; 1,77]	1,05 [0,57 ; 1,92];	0,52 [-5,97 ; 7,01]; 0,879	0,879	
Number of baseline Gd-enhancing lesions	>=1	258	39	15.12	251	31	12.35	1,22 [0,79 ; 1,9]	1,26 [0,76 ; 2,1];	2,77 [-3,21 ; 8,74]; 0,371	0,371	0,9086
	0	286	37	12.94	293	32	10.92	1,18 [0,76 ; 1,85]	1,21 [0,73 ; 2,01];	2,02 [-3,26 ; 7,3]; 0,522	0,522	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	39	17.33	202	30	14.85	1,17 [0,75 ; 1,81]	1,2 [0,72 ; 2,02];	2,48 [-4,48 ; 9,45]; 0,513	0,513	0,3038
	>=3	84	9	10.71	98	4	4.08	2,62 [0,84 ; 8,22]	2,82 [0,84 ; 9,52];	6,63 [-1,05 ; 14,32]; 0,093	0,093	
	2	236	28	11.86	248	29	11.69	1,01 [0,62 ; 1,65]	1,02 [0,58 ; 1,77];	0,17 [-5,58 ; 5,92]; 1	1	
Race	Other	10	4	40.00	12	4	33.33	1,2 [0,4 ; 3,62]	1,33 [0,23 ; 7,63];	6,67 [-33,75 ; 47,08]; 1	1	0,9485
	White	535	72	13.46	536	59	11.01	1,22 [0,89 ; 1,69]	1,26 [0,87 ; 1,82];	2,45 [-1,47 ; 6,37]; 0,227	0,227	
	No	347	46	13.26	379	49	12.93	1,03 [0,7 ; 1,49]	1,03 [0,67 ; 1,58];	0,33 [-4,59 ; 5,24]; 0,913	0,913	0,104

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	30	15.15	169	14	8.28	1,83 [1 ; 3,33]	1,98 [1,01 ; 3,87];	6,87 [0,37 ; 13,36]; 0,053	0,053	
Region	Eastern Europe	492	57	11.59	495	48	9.70	1,19 [0,83 ; 1,72]	1,22 [0,81 ; 1,83];	1,89 [-1,96 ; 5,73]; 0,354	0,354	0,7501
	USA and Western Europe	53	19	35.85	53	15	28.30	1,27 [0,72 ; 2,22]	1,42 [0,62 ; 3,21];	7,55 [-10,17 ; 25,26]; 0,533	0,533	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Injury, poisoning and procedural complications | any

6.1.13 Investigations - any

Tabelle 277: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	105	32.21	302	74	24.50	1,31 [1,02 ; 1,69]	1,46 [1,03 ; 2,08];	7,71 [0,69 ; 14,72]; 0,034	0,034	0,9963
	>= 38 years	219	65	29.68	246	55	22.36	1,33 [0,97 ; 1,81]	1,47 [0,97 ; 2,22];	7,32 [-0,66 ; 15,3]; 0,089	0,089	
Disease Severity at baseline (EDSS)	<=3.5	419	133	31.74	415	99	23.86	1,33 [1,07 ; 1,66]	1,48 [1,09 ; 2,01];	7,89 [1,83 ; 13,94]; 0,013	0,013	0,9041
	>3.5	126	37	29.37	133	30	22.56	1,3 [0,86 ; 1,97]	1,43 [0,82 ; 2,5];	6,81 [-3,85 ; 17,47]; 0,256	0,256	
Gender	Female	345	104	30.14	356	76	21.35	1,41 [1,09 ; 1,82]	1,59 [1,13 ; 2,24];	8,8 [2,35 ; 15,24]; 0,009	0,009	0,4607
	Male	200	66	33.00	192	53	27.60	1,2 [0,88 ; 1,62]	1,29 [0,84 ; 1,99];	5,4 [-3,68 ; 14,48]; 0,272	0,272	
Number of baseline Gd-enhancing lesions	>=1	258	84	32.56	251	62	24.70	1,32 [1 ; 1,74]	1,47 [1 ; 2,17];	7,86 [0,04 ; 15,68]; 0,062	0,062	0,9856
	0	286	86	30.07	293	66	22.53	1,33 [1,01 ; 1,76]	1,48 [1,02 ; 2,15];	7,54 [0,39 ; 14,69]; 0,047	0,047	
	NA	1	0	0.00	4	1	25.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	63	28.00	202	44	21.78	1,29 [0,92 ; 1,8]	1,4 [0,9 ; 2,17];	6,22 [-1,96 ; 14,39]; 0,147	0,147	0,4234
	>=3	84	40	47.62	98	29	29.59	1,61 [1,1 ; 2,35]	2,16 [1,18 ; 3,98];	18,03 [4,04 ; 32,02]; 0,015	0,015	
	2	236	67	28.39	248	56	22.58	1,26 [0,93 ; 1,71]	1,36 [0,9 ; 2,05];	5,81 [-1,95 ; 13,57]; 0,145	0,145	
Race	Other	10	4	40.00	12	3	25.00	1,6 [0,46 ; 5,53]	2 [0,32 ; 12,33];	15 [-24,02 ; 54,02]; 0,652	0,652	0,7385
	White	535	166	31.03	536	126	23.51	1,32 [1,08 ; 1,61]	1,46 [1,12 ; 1,92];	7,52 [2,21 ; 12,84]; 0,006	0,006	
	No	347	112	32.28	379	81	21.37	1,51 [1,18 ; 1,93]	1,75 [1,26 ; 2,45];	10,9 [4,48 ; 17,33]; 0,001	0,001	0,0713

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	58	29.29	169	48	28.40	1,03 [0,75 ; 1,42]	1,04 [0,66 ; 1,64];	0,89 [-8,41 ; 10,19]; 0,908	0,908	
Region	Eastern Europe	492	151	30.69	495	116	23.43	1,31 [1,06 ; 1,61]	1,45 [1,09 ; 1,92];	7,26 [1,73 ; 12,78]; 0,012	0,012	0,7022
	USA and Western Europe	53	19	35.85	53	13	24.53	1,46 [0,81 ; 2,65]	1,72 [0,74 ; 3,99];	11,32 [-6,02 ; 28,67]; 0,29	0,29	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Investigations | any

6.1.14 Metabolism and nutrition disorders - any

Tabelle 278: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	11	3.37	302	14	4.64	0,73 [0,34 ; 1,58]	0,72 [0,32 ; 1,61];	-1,26 [-4,34 ; 1,82]; 0,541	0,541	0,6396
	>= 38 years	219	7	3.20	246	8	3.25	0,98 [0,36 ; 2,67]	0,98 [0,35 ; 2,75];	-0,06 [-3,27 ; 3,16]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	17	4.06	415	12	2.89	1,4 [0,68 ; 2,9]	1,42 [0,67 ; 3,01];	1,17 [-1,32 ; 3,65]; 0,45	0,45	0,0029
	>3.5	126	1	0.79	133	10	7.52	0,11 [0,01 ; 0,81]	0,1 [0,01 ; 0,78];	-6,73 [-11,47 ; -1,98]; 0,01	0,01	
Gender	Female	345	11	3.19	356	11	3.09	1,03 [0,45 ; 2,35]	1,03 [0,44 ; 2,41];	0,1 [-2,48 ; 2,68]; 1	1	0,4019
	Male	200	7	3.50	192	11	5.73	0,61 [0,24 ; 1,54]	0,6 [0,23 ; 1,57];	-2,23 [-6,39 ; 1,93]; 0,34	0,34	
Number of baseline Gd-enhancing lesions	>=1	258	12	4.65	251	8	3.19	1,46 [0,61 ; 3,51]	1,48 [0,6 ; 3,69];	1,46 [-1,9 ; 4,83]; 0,496	0,496	0,0609
	0	286	6	2.10	293	14	4.78	0,44 [0,17 ; 1,13]	0,43 [0,16 ; 1,13];	-2,68 [-5,63 ; 0,27]; 0,11	0,11	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	10	4.44	202	10	4.95	0,9 [0,38 ; 2,11]	0,89 [0,36 ; 2,19];	-0,51 [-4,53 ; 3,52]; 0,823	0,823	0,7501
	>=3	84	2	2.38	98	5	5.10	0,47 [0,09 ; 2,34]	0,45 [0,09 ; 2,4];	-2,72 [-8,16 ; 2,72]; 0,454	0,454	
	2	236	6	2.54	248	7	2.82	0,9 [0,31 ; 2,64]	0,9 [0,3 ; 2,71];	-0,28 [-3,16 ; 2,6]; 1	1	
Race	Other	10	1	10.00	12	2	16.67	0,6 [0,06 ; 5,69]	0,56 [0,04 ; 7,21];	-6,67 [-34,78 ; 21,45]; 1	1	0,7517
	White	535	17	3.18	536	20	3.73	0,85 [0,45 ; 1,61]	0,85 [0,44 ; 1,63];	-0,55 [-2,74 ; 1,63]; 0,738	0,738	
	No	347	10	2.88	379	15	3.96	0,73 [0,33 ; 1,6]	0,72 [0,32 ; 1,62];	-1,08 [-3,71 ; 1,56]; 0,542	0,542	0,652

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	8	4.04	169	7	4.14	0,98 [0,36 ; 2,63]	0,97 [0,35 ; 2,75];	-0,1 [-4,17 ; 3,97]; 1	1	
Region	Eastern Europe	492	13	2.64	495	17	3.43	0,77 [0,38 ; 1,57]	0,76 [0,37 ; 1,59];	-0,79 [-2,93 ; 1,35]; 0,579	0,579	0,723
	USA and Western Europe	53	5	9.43	53	5	9.43	1 [0,31 ; 3,25]	1 [0,27 ; 3,68];	0 [-11,13 ; 11,13]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Metabolism and nutrition disorders | any

6.1.15 Eye disorders - any

Tabelle 279: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	17	5.21	302	19	6.29	0,83 [0,44 ; 1,56]	0,82 [0,42 ; 1,61];	-1,08 [-4,73 ; 2,57]; 0,609	0,609	0,6756
	>= 38 years	219	11	5.02	246	12	4.88	1,03 [0,46 ; 2,29]	1,03 [0,45 ; 2,39];	0,14 [-3,81 ; 4,1]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	24	5.73	415	26	6.27	0,91 [0,53 ; 1,57]	0,91 [0,51 ; 1,61];	-0,54 [-3,76 ; 2,69]; 0,772	0,772	0,9143
	>3.5	126	4	3.17	133	5	3.76	0,84 [0,23 ; 3,07]	0,84 [0,22 ; 3,2];	-0,58 [-5,04 ; 3,87]; 1	1	
Gender	Female	345	20	5.80	356	16	4.49	1,29 [0,68 ; 2,45]	1,31 [0,67 ; 2,57];	1,3 [-1,97 ; 4,58]; 0,495	0,495	0,0797
	Male	200	8	4.00	192	15	7.81	0,51 [0,22 ; 1,18]	0,49 [0,2 ; 1,19];	-3,81 [-8,48 ; 0,85]; 0,133	0,133	
Number of baseline Gd-enhancing lesions	>=1	258	13	5.04	251	16	6.37	0,79 [0,39 ; 1,61]	0,78 [0,37 ; 1,66];	-1,34 [-5,37 ; 2,7]; 0,569	0,569	0,5206
	0	286	15	5.24	293	14	4.78	1,1 [0,54 ; 2,23]	1,1 [0,52 ; 2,33];	0,47 [-3,09 ; 4,02]; 0,85	0,85	
	NA	1	0	0.00	4	1	25.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	13	5.78	202	10	4.95	1,17 [0,52 ; 2,6]	1,18 [0,5 ; 2,75];	0,83 [-3,44 ; 5,1]; 0,831	0,831	0,6884
	>=3	84	4	4.76	98	5	5.10	0,93 [0,26 ; 3,36]	0,93 [0,24 ; 3,58];	-0,34 [-6,64 ; 5,96]; 1	1	
	2	236	11	4.66	248	16	6.45	0,72 [0,34 ; 1,52]	0,71 [0,32 ; 1,56];	-1,79 [-5,86 ; 2,28]; 0,433	0,433	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	28	5.23	536	31	5.78	0,9 [0,55 ; 1,49]	0,9 [0,53 ; 1,52];	-0,55 [-3,28 ; 2,18]; 0,789	0,789	
	No	347	16	4.61	379	15	3.96	1,17 [0,58 ; 2,32]	1,17 [0,57 ; 2,41];	0,65 [-2,3 ; 3,61]; 0,715	0,715	0,2337

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	12	6.06	169	16	9.47	0,64 [0,31 ; 1,31]	0,62 [0,28 ; 1,34];	-3,41 [-8,93 ; 2,12]; 0,241	0,241	
Region	Eastern Europe	492	24	4.88	495	25	5.05	0,97 [0,56 ; 1,67]	0,96 [0,54 ; 1,71];	-0,17 [-2,88 ; 2,54]; 1	1	0,5754
	USA and Western Europe	53	4	7.55	53	6	11.32	0,67 [0,2 ; 2,23]	0,64 [0,17 ; 2,41];	-3,77 [-14,88 ; 7,33]; 0,741	0,741	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Eye disorders | any

6.1.16 Psychiatric disorders - any

Tabelle 280: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	53	16.26	302	37	12.25	1,33 [0,9 ; 1,96]	1,39 [0,88 ; 2,19];	4,01 [-1,45 ; 9,46]; 0,172	0,172	0,5862
	>= 38 years	219	30	13.70	246	30	12.20	1,12 [0,7 ; 1,8]	1,14 [0,66 ; 1,97];	1,5 [-4,62 ; 7,62]; 0,679	0,679	
Disease Severity at baseline (EDSS)	<=3.5	419	74	17.66	415	47	11.33	1,56 [1,11 ; 2,19]	1,68 [1,13 ; 2,49];	6,34 [1,58 ; 11,09]; 0,01	0,01	0,0028
	>3.5	126	9	7.14	133	20	15.04	0,48 [0,22 ; 1]	0,43 [0,19 ; 0,99];	-7,89 [-15,45 ; -0,34]; 0,05	0,05	
Gender	Female	345	58	16.81	356	46	12.92	1,3 [0,91 ; 1,86]	1,36 [0,9 ; 2,07];	3,89 [-1,37 ; 9,15]; 0,167	0,167	0,6789
	Male	200	25	12.50	192	21	10.94	1,14 [0,66 ; 1,97]	1,16 [0,63 ; 2,16];	1,56 [-4,8 ; 7,93]; 0,642	0,642	
Number of baseline Gd-enhancing lesions	>=1	258	53	20.54	251	34	13.55	1,52 [1,02 ; 2,25]	1,65 [1,03 ; 2,64];	7 [0,5 ; 13,5]; 0,045	0,045	0,1052
	0	286	30	10.49	293	33	11.26	0,93 [0,58 ; 1,49]	0,92 [0,55 ; 1,56];	-0,77 [-5,84 ; 4,3]; 0,791	0,791	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	39	17.33	202	25	12.38	1,4 [0,88 ; 2,23]	1,48 [0,86 ; 2,55];	4,96 [-1,76 ; 11,67]; 0,175	0,175	0,511
	>=3	84	11	13.10	98	8	8.16	1,6 [0,68 ; 3,8]	1,7 [0,65 ; 4,43];	4,93 [-4,09 ; 13,96]; 0,334	0,334	
	2	236	33	13.98	248	34	13.71	1,02 [0,65 ; 1,59]	1,02 [0,61 ; 1,71];	0,27 [-5,88 ; 6,43]; 1	1	
Race	Other	10	4	40.00	12	4	33.33	1,2 [0,4 ; 3,62]	1,33 [0,23 ; 7,63];	6,67 [-33,75 ; 47,08]; 1	1	0,9782
	White	535	79	14.77	536	63	11.75	1,26 [0,92 ; 1,71]	1,3 [0,91 ; 1,86];	3,01 [-1,05 ; 7,07]; 0,15	0,15	
	No	347	50	14.41	379	41	10.82	1,33 [0,91 ; 1,96]	1,39 [0,89 ; 2,16];	3,59 [-1,25 ; 8,43]; 0,147	0,147	0,5235

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	33	16.67	169	26	15.38	1,08 [0,68 ; 1,74]	1,1 [0,63 ; 1,93];	1,28 [-6,24 ; 8,8]; 0,777	0,777	
Region	Eastern Europe	492	65	13.21	495	55	11.11	1,19 [0,85 ; 1,67]	1,22 [0,83 ; 1,79];	2,1 [-1,98 ; 6,18]; 0,331	0,331	0,4428
	USA and Western Europe	53	18	33.96	53	12	22.64	1,5 [0,8 ; 2,8]	1,76 [0,74 ; 4,15];	11,32 [-5,69 ; 28,34]; 0,281	0,281	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Psychiatric disorders | any

6.1.17 Vascular disorders - any

Tabelle 281: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	25	7.67	302	23	7.62	1,01 [0,58 ; 1,74]	1,01 [0,56 ; 1,82];	0,05 [-4,11 ; 4,21]; 1	1	0,1381
	>= 38 years	219	16	7.31	246	32	13.01	0,56 [0,32 ; 0,99]	0,53 [0,28 ; 0,99];	-5,7 [-11,14 ; -0,27]; 0,048	0,048	
Disease Severity at baseline (EDSS)	<=3.5	419	36	8.59	415	44	10.60	0,81 [0,53 ; 1,23]	0,79 [0,5 ; 1,26];	-2,01 [-6,01 ; 1,99]; 0,348	0,348	0,3544
	>3.5	126	5	3.97	133	11	8.27	0,48 [0,17 ; 1,34]	0,46 [0,15 ; 1,36];	-4,3 [-10,09 ; 1,49]; 0,198	0,198	
Gender	Female	345	29	8.41	356	37	10.39	0,81 [0,51 ; 1,28]	0,79 [0,47 ; 1,32];	-1,99 [-6,3 ; 2,33]; 0,438	0,438	0,5931
	Male	200	12	6.00	192	18	9.38	0,64 [0,32 ; 1,29]	0,62 [0,29 ; 1,32];	-3,38 [-8,65 ; 1,9]; 0,255	0,255	
Number of baseline Gd-enhancing lesions	>=1	258	21	8.14	251	26	10.36	0,79 [0,45 ; 1,36]	0,77 [0,42 ; 1,4];	-2,22 [-7,25 ; 2,82]; 0,445	0,445	0,7927
	0	286	20	6.99	293	29	9.90	0,71 [0,41 ; 1,22]	0,68 [0,38 ; 1,24];	-2,9 [-7,42 ; 1,62]; 0,234	0,234	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	21	9.33	202	22	10.89	0,86 [0,49 ; 1,51]	0,84 [0,45 ; 1,58];	-1,56 [-7,29 ; 4,18]; 0,631	0,631	0,5941
	>=3	84	7	8.33	98	9	9.18	0,91 [0,35 ; 2,33]	0,9 [0,32 ; 2,53];	-0,85 [-9,07 ; 7,37]; 1	1	
	2	236	13	5.51	248	24	9.68	0,57 [0,3 ; 1,09]	0,54 [0,27 ; 1,1];	-4,17 [-8,86 ; 0,52]; 0,09	0,09	
Race	Other	10	1	10.00	12	1	8.33	1,2 [0,09 ; 16,84]	1,22 [0,07 ; 22,4];	1,67 [-22,63 ; 25,96]; 1	1	0,7262
	White	535	40	7.48	536	54	10.07	0,74 [0,5 ; 1,1]	0,72 [0,47 ; 1,11];	-2,6 [-5,98 ; 0,79]; 0,16	0,16	
	No	347	15	4.32	379	38	10.03	0,43 [0,24 ; 0,77]	0,41 [0,22 ; 0,75];	-5,7 [-9,41 ; -2]; 0,004	0,004	0,0071

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	26	13.13	169	17	10.06	1,31 [0,73 ; 2,32]	1,35 [0,71 ; 2,59];	3,07 [-3,46 ; 9,61]; 0,417	0,417	
Region	Eastern Europe	492	36	7.32	495	47	9.49	0,77 [0,51 ; 1,17]	0,75 [0,48 ; 1,18];	-2,18 [-5,64 ; 1,28]; 0,251	0,251	0,6985
	USA and Western Europe	53	5	9.43	53	8	15.09	0,63 [0,22 ; 1,79]	0,59 [0,18 ; 1,92];	-5,66 [-18,1 ; 6,78]; 0,555	0,555	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Vascular disorders | any

6.1.18 Neoplasms benign, malignant and unspecified (incl cysts and polyps) - any

Tabelle 282: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	7	2.15	302	5	1.66	1,3 [0,42 ; 4,04]	1,3 [0,41 ; 4,15];	0,49 [-1,64 ; 2,62]; 0,774	0,774	0,8116
	>= 38 years	219	7	3.20	246	5	2.03	1,57 [0,51 ; 4,88]	1,59 [0,5 ; 5,09];	1,16 [-1,76 ; 4,09]; 0,561	0,561	
Disease Severity at baseline (EDSS)	<=3.5	419	11	2.63	415	8	1.93	1,36 [0,55 ; 3,35]	1,37 [0,55 ; 3,45];	0,7 [-1,33 ; 2,72]; 0,644	0,644	0,8825
	>3.5	126	3	2.38	133	2	1.50	1,58 [0,27 ; 9,32]	1,6 [0,26 ; 9,72];	0,88 [-2,49 ; 4,25]; 0,677	0,677	
Gender	Female	345	13	3.77	356	9	2.53	1,49 [0,65 ; 3,44]	1,51 [0,64 ; 3,58];	1,24 [-1,35 ; 3,83]; 0,391	0,391	0,761
	Male	200	1	0.50	192	1	0.52	0,96 [0,06 ; 15,24]	0,96 [0,06 ; 15,45];	-0,02 [-1,43 ; 1,39]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	258	4	1.55	251	7	2.79	0,56 [0,16 ; 1,88]	0,55 [0,16 ; 1,9];	-1,24 [-3,77 ; 1,3]; 0,377	0,377	0,0342
	0	286	10	3.50	293	3	1.02	3,41 [0,95 ; 12,28]	3,5 [0,95 ; 12,86];	2,47 [0,05 ; 4,89]; 0,052	0,052	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	6	2.67	202	4	1.98	1,35 [0,39 ; 4,7]	1,36 [0,38 ; 4,88];	0,69 [-2,16 ; 3,54]; 0,755	0,755	0,9858
	>=3	84	1	1.19	98	1	1.02	1,17 [0,07 ; 18,37]	1,17 [0,07 ; 18,98];	0,17 [-2,89 ; 3,23]; 1	1	
	2	236	7	2.97	248	5	2.02	1,47 [0,47 ; 4,57]	1,49 [0,46 ; 4,75];	0,95 [-1,83 ; 3,73]; 0,568	0,568	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	14	2.62	536	10	1.87	1,4 [0,63 ; 3,13]	1,41 [0,62 ; 3,21];	0,75 [-1,02 ; 2,52]; 0,419	0,419	
	No	347	10	2.88	379	6	1.58	1,82 [0,67 ; 4,96]	1,84 [0,66 ; 5,13];	1,3 [-0,86 ; 3,46]; 0,313	0,313	0,3818

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	4	2.02	169	4	2.37	0,85 [0,22 ; 3,36]	0,85 [0,21 ; 3,45];	-0,35 [-3,36 ; 2,67]; 1	1	
Region	Eastern Europe	492	9	1.83	495	9	1.82	1,01 [0,4 ; 2,51]	1,01 [0,4 ; 2,56];	0,01 [-1,66 ; 1,68]; 1	1	0,1242
	USA and Western Europe	53	5	9.43	53	1	1.89	5 [0,6 ; 41,37]	5,42 [0,61 ; 48,04];	7,55 [-1,13 ; 16,23]; 0,205	0,205	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Neoplasms benign, malignant and unspecified (incl cysts and polyps) | any

6.1.19 Hepatobiliary disorders - any

Tabelle 283: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	8	2.45	302	9	2.98	0,82 [0,32 ; 2,11]	0,82 [0,31 ; 2,15];	-0,53 [-3,08 ; 2,02]; 0,807	0,807	0,3386
	>= 38 years	219	5	2.28	246	3	1.22	1,87 [0,45 ; 7,74]	1,89 [0,45 ; 8,01];	1,06 [-1,34 ; 3,47]; 0,484	0,484	
Disease Severity at baseline (EDSS)	<=3.5	419	10	2.39	415	9	2.17	1,1 [0,45 ; 2,68]	1,1 [0,44 ; 2,74];	0,22 [-1,81 ; 2,24]; 1	1	0,9641
	>3.5	126	3	2.38	133	3	2.26	1,06 [0,22 ; 5,13]	1,06 [0,21 ; 5,34];	0,13 [-3,54 ; 3,79]; 1	1	
Gender	Female	345	7	2.03	356	6	1.69	1,2 [0,41 ; 3,55]	1,21 [0,4 ; 3,63];	0,34 [-1,66 ; 2,34]; 0,786	0,786	0,7758
	Male	200	6	3.00	192	6	3.12	0,96 [0,32 ; 2,93]	0,96 [0,3 ; 3,03];	-0,13 [-3,54 ; 3,29]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	258	3	1.16	251	5	1.99	0,58 [0,14 ; 2,42]	0,58 [0,14 ; 2,45];	-0,83 [-3 ; 1,34]; 0,499	0,499	0,2842
	0	286	10	3.50	293	7	2.39	1,46 [0,56 ; 3,79]	1,48 [0,56 ; 3,94];	1,11 [-1,65 ; 3,86]; 0,469	0,469	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	4	1.78	202	7	3.47	0,51 [0,15 ; 1,73]	0,5 [0,15 ; 1,75];	-1,69 [-4,74 ; 1,37]; 0,363	0,363	0,1051
	>=3	84	2	2.38	98	3	3.06	0,78 [0,13 ; 4,54]	0,77 [0,13 ; 4,74];	-0,68 [-5,4 ; 4,04]; 1	1	
	2	236	7	2.97	248	2	0.81	3,68 [0,77 ; 17,53]	3,76 [0,77 ; 18,29];	2,16 [-0,27 ; 4,59]; 0,099	0,099	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	13	2.43	536	12	2.24	1,09 [0,5 ; 2,36]	1,09 [0,49 ; 2,41];	0,19 [-1,62 ; 2]; 0,843	0,843	
	No	347	8	2.31	379	9	2.37	0,97 [0,38 ; 2,49]	0,97 [0,37 ; 2,54];	-0,07 [-2,27 ; 2,13]; 1	1	0,6576

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	5	2.53	169	3	1.78	1,42 [0,35 ; 5,87]	1,43 [0,34 ; 6,09];	0,75 [-2,21 ; 3,71]; 0,73	0,73	
Region	Eastern Europe	492	12	2.44	495	11	2.22	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	0,949
	USA and Western Europe	53	1	1.89	53	1	1.89	1 [0,06 ; 15,57]	1 [0,06 ; 16,42];	0 [-5,18 ; 5,18]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Hepatobiliary disorders | any

6.1.20 Blood and lymphatic system disorders - any

Tabelle 284: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	67	20.55	302	48	15.89	1,29 [0,92 ; 1,81]	1,37 [0,91 ; 2,06];	4,66 [-1,36 ; 10,68]; 0,148	0,148	0,1971
	>= 38 years	219	27	12.33	246	34	13.82	0,89 [0,56 ; 1,43]	0,88 [0,51 ; 1,51];	-1,49 [-7,62 ; 4,64]; 0,681	0,681	
Disease Severity at baseline (EDSS)	<=3.5	419	77	18.38	415	60	14.46	1,27 [0,93 ; 1,73]	1,33 [0,92 ; 1,93];	3,92 [-1,1 ; 8,94]; 0,135	0,135	0,1836
	>3.5	126	17	13.49	133	22	16.54	0,82 [0,45 ; 1,46]	0,79 [0,4 ; 1,56];	-3,05 [-11,74 ; 5,64]; 0,603	0,603	
Gender	Female	345	65	18.84	356	61	17.13	1,1 [0,8 ; 1,51]	1,12 [0,76 ; 1,65];	1,71 [-3,98 ; 7,39]; 0,623	0,623	0,5688
	Male	200	29	14.50	192	21	10.94	1,33 [0,78 ; 2,24]	1,38 [0,76 ; 2,52];	3,56 [-3,02 ; 10,14]; 0,364	0,364	
Number of baseline Gd-enhancing lesions	>=1	258	46	17.83	251	43	17.13	1,04 [0,71 ; 1,52]	1,05 [0,66 ; 1,66];	0,7 [-5,9 ; 7,3]; 0,907	0,907	0,4427
	0	286	48	16.78	293	38	12.97	1,29 [0,87 ; 1,92]	1,35 [0,85 ; 2,15];	3,81 [-1,98 ; 9,61]; 0,201	0,201	
	NA	1	0	0.00	4	1	25.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	36	16.00	202	30	14.85	1,08 [0,69 ; 1,68]	1,09 [0,64 ; 1,85];	1,15 [-5,71 ; 8]; 0,789	0,789	0,8657
	>=3	84	22	26.19	98	20	20.41	1,28 [0,75 ; 2,18]	1,38 [0,69 ; 2,76];	5,78 [-6,55 ; 18,11]; 0,382	0,382	
	2	236	36	15.25	248	32	12.90	1,18 [0,76 ; 1,84]	1,22 [0,73 ; 2,03];	2,35 [-3,85 ; 8,55]; 0,514	0,514	
Race	Other	10	0	0.00	12	2	16.67	0,24 [0,01 ; 4,42]	0,2 [0,01 ; 4,69];	-14,69 [-39,39 ; 10,02]; 0,481	0,481	0,0867
	White	535	94	17.57	536	80	14.93	1,18 [0,9 ; 1,55]	1,21 [0,88 ; 1,68];	2,64 [-1,77 ; 7,06]; 0,247	0,247	
	No	347	45	12.97	379	48	12.66	1,02 [0,7 ; 1,5]	1,03 [0,66 ; 1,59];	0,3 [-4,57 ; 5,17]; 0,912	0,912	0,476

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	49	24.75	169	34	20.12	1,23 [0,84 ; 1,81]	1,31 [0,8 ; 2,14];	4,63 [-3,9 ; 13,15]; 0,318	0,318	
Region	Eastern Europe	492	89	18.09	495	79	15.96	1,13 [0,86 ; 1,49]	1,16 [0,83 ; 1,62];	2,13 [-2,56 ; 6,82]; 0,397	0,397	0,6019
	USA and Western Europe	53	5	9.43	53	3	5.66	1,67 [0,42 ; 6,62]	1,74 [0,39 ; 7,67];	3,77 [-6,26 ; 13,81]; 0,716	0,716	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Blood and lymphatic system disorders | any

6.1.21 Immune system disorders - any

Tabelle 285: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	18	5.52	302	6	1.99	2,78 [1,12 ; 6,91]	2,88 [1,13 ; 7,36];	3,53 [0,6 ; 6,47]; 0,022	0,022	0,0346
	>= 38 years	219	7	3.20	246	11	4.47	0,71 [0,28 ; 1,81]	0,71 [0,27 ; 1,85];	-1,28 [-4,75 ; 2,2]; 0,631	0,631	
Disease Severity at baseline (EDSS)	<=3.5	419	22	5.25	415	11	2.65	1,98 [0,97 ; 4,03]	2,04 [0,97 ; 4,25];	2,6 [-0,04 ; 5,24]; 0,074	0,074	0,081
	>3.5	126	3	2.38	133	6	4.51	0,53 [0,13 ; 2,07]	0,52 [0,13 ; 2,11];	-2,13 [-6,55 ; 2,29]; 0,502	0,502	
Gender	Female	345	20	5.80	356	14	3.93	1,47 [0,76 ; 2,87]	1,5 [0,75 ; 3,03];	1,86 [-1,32 ; 5,05]; 0,293	0,293	0,9299
	Male	200	5	2.50	192	3	1.56	1,6 [0,39 ; 6,6]	1,62 [0,38 ; 6,85];	0,94 [-1,85 ; 3,72]; 0,724	0,724	
Number of baseline Gd-enhancing lesions	>=1	258	8	3.10	251	7	2.79	1,11 [0,41 ; 3,02]	1,12 [0,4 ; 3,12];	0,31 [-2,62 ; 3,25]; 1	1	0,4779
	0	286	17	5.94	293	10	3.41	1,74 [0,81 ; 3,74]	1,79 [0,8 ; 3,98];	2,53 [-0,91 ; 5,97]; 0,17	0,17	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	9	4.00	202	7	3.47	1,15 [0,44 ; 3,04]	1,16 [0,42 ; 3,18];	0,53 [-3,06 ; 4,13]; 0,805	0,805	0,7977
	>=3	84	2	2.38	98	1	1.02	2,33 [0,22 ; 25,28]	2,37 [0,21 ; 26,56];	1,36 [-2,46 ; 5,18]; 0,596	0,596	
	2	236	14	5.93	248	9	3.63	1,63 [0,72 ; 3,7]	1,67 [0,71 ; 3,95];	2,3 [-1,5 ; 6,11]; 0,287	0,287	
Race	Other	10	1	10.00	12	4	33.33	0,3 [0,04 ; 2,27]	0,22 [0,02 ; 2,42];	-23,33 [-55,85 ; 9,18]; 0,323	0,323	0,064
	White	535	24	4.49	536	13	2.43	1,85 [0,95 ; 3,59]	1,89 [0,95 ; 3,75];	2,06 [-0,12 ; 4,25]; 0,068	0,068	
	No	347	13	3.75	379	7	1.85	2,03 [0,82 ; 5,03]	2,07 [0,82 ; 5,25];	1,9 [-0,52 ; 4,31]; 0,172	0,172	0,277

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	12	6.06	169	10	5.92	1,02 [0,45 ; 2,31]	1,03 [0,43 ; 2,44];	0,14 [-4,72 ; 5,01]; 1	1	
Region	Eastern Europe	492	22	4.47	495	13	2.63	1,7 [0,87 ; 3,34]	1,74 [0,86 ; 3,49];	1,85 [-0,46 ; 4,15]; 0,125	0,125	0,3183
	USA and Western Europe	53	3	5.66	53	4	7.55	0,75 [0,18 ; 3,19]	0,74 [0,16 ; 3,46];	-1,89 [-11,34 ; 7,56]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Immune system disorders | any

6.1.22 Gastrointestinal disorders - Abdominal pain upper

Tabelle 286: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	16	4.91	302	12	3.97	1,24 [0,59 ; 2,57]	1,25 [0,58 ; 2,68];	0,93 [-2,28 ; 4,15]; 0,7	0,7	0,0948
	>= 38 years	219	4	1.83	246	11	4.47	0,41 [0,13 ; 1,26]	0,4 [0,12 ; 1,27];	-2,65 [-5,78 ; 0,49]; 0,122	0,122	
Disease Severity at baseline (EDSS)	<=3.5	419	19	4.53	415	21	5.06	0,9 [0,49 ; 1,64]	0,89 [0,47 ; 1,68];	-0,53 [-3,43 ; 2,38]; 0,748	0,748	0,6701
	>3.5	126	1	0.79	133	2	1.50	0,53 [0,05 ; 5,75]	0,52 [0,05 ; 5,85];	-0,71 [-3,29 ; 1,87]; 1	1	
Gender	Female	345	18	5.22	356	20	5.62	0,93 [0,5 ; 1,73]	0,92 [0,48 ; 1,78];	-0,4 [-3,75 ; 2,95]; 0,868	0,868	0,7
	Male	200	2	1.00	192	3	1.56	0,64 [0,11 ; 3,79]	0,64 [0,11 ; 3,85];	-0,56 [-2,79 ; 1,67]; 0,68	0,68	
Number of baseline Gd-enhancing lesions	>=1	258	13	5.04	251	12	4.78	1,05 [0,49 ; 2,27]	1,06 [0,47 ; 2,36];	0,26 [-3,5 ; 4,01]; 1	1	0,4353
	0	286	7	2.45	293	11	3.75	0,65 [0,26 ; 1,66]	0,64 [0,25 ; 1,68];	-1,31 [-4,13 ; 1,51]; 0,474	0,474	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	9	4.00	202	10	4.95	0,81 [0,34 ; 1,95]	0,8 [0,32 ; 2,01];	-0,95 [-4,89 ; 2,99]; 0,647	0,647	0,2087
	>=3	84	6	7.14	98	3	3.06	2,33 [0,6 ; 9,05]	2,44 [0,59 ; 10,06];	4,08 [-2,4 ; 10,56]; 0,306	0,306	
	2	236	5	2.12	248	10	4.03	0,53 [0,18 ; 1,51]	0,52 [0,17 ; 1,53];	-1,91 [-4,97 ; 1,15]; 0,296	0,296	
Race	Other	10	1	10.00	12	1	8.33	1,2 [0,09 ; 16,84]	1,22 [0,07 ; 22,4];	1,67 [-22,63 ; 25,96]; 1	1	0,8173
	White	535	19	3.55	536	22	4.10	0,87 [0,47 ; 1,58]	0,86 [0,46 ; 1,61];	-0,55 [-2,85 ; 1,74]; 0,751	0,751	
	No	347	13	3.75	379	16	4.22	0,89 [0,43 ; 1,82]	0,88 [0,42 ; 1,86];	-0,48 [-3,32 ; 2,37]; 0,85	0,85	0,9517

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	7	3.54	169	7	4.14	0,85 [0,31 ; 2,38]	0,85 [0,29 ; 2,47];	-0,61 [-4,56 ; 3,35]; 0,791	0,791	
Region	Eastern Europe	492	16	3.25	495	18	3.64	0,89 [0,46 ; 1,73]	0,89 [0,45 ; 1,77];	-0,38 [-2,66 ; 1,89]; 0,862	0,862	0,87
	USA and Western Europe	53	4	7.55	53	5	9.43	0,8 [0,23 ; 2,82]	0,78 [0,2 ; 3,1];	-1,89 [-12,49 ; 8,72]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Gastrointestinal disorders | Abdominal pain upper

6.1.23 General disorders and administration site conditions - Fatigue

Tabelle 287: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	19	5.83	302	7	2.32	2,51 [1,07 ; 5,9]	2,61 [1,08 ; 6,3];	3,51 [0,45 ; 6,57]; 0,029	0,029	0,0475
	>= 38 years	219	9	4.11	246	13	5.28	0,78 [0,34 ; 1,78]	0,77 [0,32 ; 1,83];	-1,17 [-5,01 ; 2,66]; 0,663	0,663	
Disease Severity at baseline (EDSS)	<=3.5	419	27	6.44	415	15	3.61	1,78 [0,96 ; 3,3]	1,84 [0,96 ; 3,51];	2,83 [-0,13 ; 5,79]; 0,081	0,081	0,0268
	>3.5	126	1	0.79	133	5	3.76	0,21 [0,03 ; 1,78]	0,2 [0,02 ; 1,78];	-2,97 [-6,55 ; 0,62]; 0,214	0,214	
Gender	Female	345	18	5.22	356	12	3.37	1,55 [0,76 ; 3,16]	1,58 [0,75 ; 3,33];	1,85 [-1,16 ; 4,85]; 0,265	0,265	0,6677
	Male	200	10	5.00	192	8	4.17	1,2 [0,48 ; 2,98]	1,21 [0,47 ; 3,13];	0,83 [-3,3 ; 4,97]; 0,811	0,811	
Number of baseline Gd-enhancing lesions	>=1	258	16	6.20	251	11	4.38	1,42 [0,67 ; 2,99]	1,44 [0,66 ; 3,17];	1,82 [-2,06 ; 5,7]; 0,431	0,431	0,9433
	0	286	12	4.20	293	9	3.07	1,37 [0,58 ; 3,19]	1,38 [0,57 ; 3,33];	1,12 [-1,93 ; 4,17]; 0,511	0,511	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	10	4.44	202	7	3.47	1,28 [0,5 ; 3,31]	1,3 [0,48 ; 3,47];	0,98 [-2,71 ; 4,67]; 0,631	0,631	0,9664
	>=3	84	4	4.76	98	3	3.06	1,56 [0,36 ; 6,75]	1,58 [0,34 ; 7,28];	1,7 [-3,99 ; 7,39]; 0,705	0,705	
	2	236	14	5.93	248	10	4.03	1,47 [0,67 ; 3,25]	1,5 [0,65 ; 3,45];	1,9 [-1,98 ; 5,78]; 0,404	0,404	
Race	Other	10	1	10.00	12	3	25.00	0,4 [0,05 ; 3,27]	0,33 [0,03 ; 3,84];	-15 [-45,76 ; 15,76]; 0,594	0,594	0,1906
	White	535	27	5.05	536	17	3.17	1,59 [0,88 ; 2,88]	1,62 [0,87 ; 3,01];	1,88 [-0,5 ; 4,25]; 0,127	0,127	
	No	347	17	4.90	379	13	3.43	1,43 [0,7 ; 2,9]	1,45 [0,69 ; 3,03];	1,47 [-1,45 ; 4,39]; 0,354	0,354	0,9189

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	11	5.56	169	7	4.14	1,34 [0,53 ; 3,38]	1,36 [0,52 ; 3,59];	1,41 [-2,97 ; 5,8]; 0,631	0,631	
Region	Eastern Europe	492	20	4.07	495	9	1.82	2,24 [1,03 ; 4,86]	2,29 [1,03 ; 5,08];	2,25 [0,14 ; 4,35]; 0,039	0,039	0,0595
	USA and Western Europe	53	8	15.09	53	11	20.75	0,73 [0,32 ; 1,66]	0,68 [0,25 ; 1,85];	-5,66 [-20,22 ; 8,9]; 0,613	0,613	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - General disorders and administration site conditions | Fatigue

6.1.24 Infections and infestations - Influenza

Tabelle 288: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	9	2.76	302	9	2.98	0,93 [0,37 ; 2,3]	0,92 [0,36 ; 2,36];	-0,22 [-2,83 ; 2,4]; 1	1	0,9886
	>= 38 years	219	5	2.28	246	6	2.44	0,94 [0,29 ; 3,02]	0,93 [0,28 ; 3,11];	-0,16 [-2,92 ; 2,61]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	12	2.86	415	12	2.89	0,99 [0,45 ; 2,18]	0,99 [0,44 ; 2,23];	-0,03 [-2,3 ; 2,24]; 1	1	0,7286
	>3.5	126	2	1.59	133	3	2.26	0,7 [0,12 ; 4,14]	0,7 [0,11 ; 4,25];	-0,67 [-4 ; 2,67]; 1	1	
Gender	Female	345	8	2.32	356	11	3.09	0,75 [0,31 ; 1,84]	0,74 [0,3 ; 1,87];	-0,77 [-3,17 ; 1,63]; 0,644	0,644	0,4023
	Male	200	6	3.00	192	4	2.08	1,44 [0,41 ; 5,02]	1,45 [0,4 ; 5,23];	0,92 [-2,19 ; 4,03]; 0,751	0,751	
Number of baseline Gd-enhancing lesions	>=1	258	7	2.71	251	7	2.79	0,97 [0,35 ; 2,73]	0,97 [0,34 ; 2,81];	-0,08 [-2,92 ; 2,77]; 1	1	0,9113
	0	286	7	2.45	293	8	2.73	0,9 [0,33 ; 2,44]	0,89 [0,32 ; 2,5];	-0,28 [-2,87 ; 2,3]; 1	1	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	10	4.44	202	3	1.49	2,99 [0,84 ; 10,72]	3,09 [0,84 ; 11,37];	2,96 [-0,21 ; 6,13]; 0,093	0,093	0,0191
	>=3	84	1	1.19	98	1	1.02	1,17 [0,07 ; 18,37]	1,17 [0,07 ; 18,98];	0,17 [-2,89 ; 3,23]; 1	1	
	2	236	3	1.27	248	11	4.44	0,29 [0,08 ; 1,01]	0,28 [0,08 ; 1,01];	-3,16 [-6,1 ; -0,23]; 0,055	0,055	
Race	Other	10	1	10.00	12	0	0.00	3,55 [0,16 ; 78,56]	3,95 [0,14 ; 108,09];	9,79 [-13,03 ; 32,61]; 0,478	0,478	0,1859
	White	535	13	2.43	536	15	2.80	0,87 [0,42 ; 1,81]	0,87 [0,41 ; 1,84];	-0,37 [-2,28 ; 1,54]; 0,849	0,849	
	No	347	10	2.88	379	9	2.37	1,21 [0,5 ; 2,95]	1,22 [0,49 ; 3,04];	0,51 [-1,83 ; 2,84]; 0,817	0,817	0,3286

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	4	2.02	169	6	3.55	0,57 [0,16 ; 1,98]	0,56 [0,16 ; 2,02];	-1,53 [-4,94 ; 1,88]; 0,523	0,523	
Region	Eastern Europe	492	7	1.42	495	12	2.42	0,59 [0,23 ; 1,48]	0,58 [0,23 ; 1,49];	-1 [-2,71 ; 0,71]; 0,355	0,355	0,078
	USA and Western Europe	53	7	13.21	53	3	5.66	2,33 [0,64 ; 8,54]	2,54 [0,62 ; 10,39];	7,55 [-3,49 ; 18,58]; 0,319	0,319	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Influenza

6.1.25 Musculoskeletal and connective tissue disorders - Myalgia

Tabelle 289: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	11	3.37	302	5	1.66	2,04 [0,72 ; 5,8]	2,07 [0,71 ; 6,04];	1,72 [-0,71 ; 4,15]; 0,21	0,21	0,0057
	>= 38 years	219	2	0.91	246	11	4.47	0,2 [0,05 ; 0,91]	0,2 [0,04 ; 0,9];	-3,56 [-6,43 ; -0,68]; 0,023	0,023	
Disease Severity at baseline (EDSS)	<=3.5	419	12	2.86	415	11	2.65	1,08 [0,48 ; 2,42]	1,08 [0,47 ; 2,48];	0,21 [-2,01 ; 2,44]; 1	1	0,115
	>3.5	126	1	0.79	133	5	3.76	0,21 [0,03 ; 1,78]	0,2 [0,02 ; 1,78];	-2,97 [-6,55 ; 0,62]; 0,214	0,214	
Gender	Female	345	12	3.48	356	12	3.37	1,03 [0,47 ; 2,27]	1,03 [0,46 ; 2,33];	0,11 [-2,59 ; 2,8]; 1	1	0,1775
	Male	200	1	0.50	192	4	2.08	0,24 [0,03 ; 2,13]	0,24 [0,03 ; 2,13];	-1,58 [-3,83 ; 0,66]; 0,207	0,207	
Number of baseline Gd-enhancing lesions	>=1	258	6	2.33	251	8	3.19	0,73 [0,26 ; 2,07]	0,72 [0,25 ; 2,11];	-0,86 [-3,71 ; 1,99]; 0,598	0,598	0,7798
	0	286	7	2.45	293	8	2.73	0,9 [0,33 ; 2,44]	0,89 [0,32 ; 2,5];	-0,28 [-2,87 ; 2,3]; 1	1	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	4	1.78	202	3	1.49	1,2 [0,27 ; 5,28]	1,2 [0,27 ; 5,43];	0,29 [-2,11 ; 2,69]; 1	1	0,4818
	>=3	84	2	2.38	98	1	1.02	2,33 [0,22 ; 25,28]	2,37 [0,21 ; 26,56];	1,36 [-2,46 ; 5,18]; 0,596	0,596	
	2	236	7	2.97	248	12	4.84	0,61 [0,25 ; 1,53]	0,6 [0,23 ; 1,55];	-1,87 [-5,31 ; 1,57]; 0,352	0,352	
Race	Other	10	1	10.00	12	1	8.33	1,2 [0,09 ; 16,84]	1,22 [0,07 ; 22,4];	1,67 [-22,63 ; 25,96]; 1	1	0,781
	White	535	12	2.24	536	15	2.80	0,8 [0,38 ; 1,7]	0,8 [0,37 ; 1,72];	-0,56 [-2,43 ; 1,32]; 0,697	0,697	
	No	347	7	2.02	379	9	2.37	0,85 [0,32 ; 2,26]	0,85 [0,31 ; 2,3];	-0,36 [-2,49 ; 1,77]; 0,805	0,805	0,8365

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	6	3.03	169	7	4.14	0,73 [0,25 ; 2,13]	0,72 [0,24 ; 2,2];	-1,11 [-4,95 ; 2,73]; 0,585	0,585	
Region	Eastern Europe	492	10	2.03	495	14	2.83	0,72 [0,32 ; 1,6]	0,71 [0,31 ; 1,62];	-0,8 [-2,72 ; 1,12]; 0,536	0,536	0,4509
	USA and Western Europe	53	3	5.66	53	2	3.77	1,5 [0,26 ; 8,62]	1,53 [0,25 ; 9,55];	1,89 [-6,18 ; 9,95]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Musculoskeletal and connective tissue disorders | Myalgia

6.1.26 Nervous system disorders - Paraesthesia

Tabelle 290: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	7	2.15	302	7	2.32	0,93 [0,33 ; 2,61]	0,92 [0,32 ; 2,67];	-0,17 [-2,48 ; 2,14]; 1	1	0,8262
	>= 38 years	219	4	1.83	246	4	1.63	1,12 [0,28 ; 4,44]	1,13 [0,28 ; 4,56];	0,2 [-2,18 ; 2,58]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	11	2.63	415	8	1.93	1,36 [0,55 ; 3,35]	1,37 [0,55 ; 3,45];	0,7 [-1,33 ; 2,72]; 0,644	0,644	0,0341
	>3.5	126	0	0.00	133	3	2.26	0,15 [0,01 ; 2,89]	0,15 [0,01 ; 2,88];	-2,22 [-5,13 ; 0,69]; 0,123	0,123	
Gender	Female	345	8	2.32	356	6	1.69	1,38 [0,48 ; 3,92]	1,38 [0,48 ; 4,03];	0,63 [-1,44 ; 2,71]; 0,599	0,599	0,3266
	Male	200	3	1.50	192	5	2.60	0,58 [0,14 ; 2,38]	0,57 [0,13 ; 2,42];	-1,1 [-3,92 ; 1,71]; 0,495	0,495	
Number of baseline Gd-enhancing lesions	>=1	258	7	2.71	251	4	1.59	1,7 [0,5 ; 5,74]	1,72 [0,5 ; 5,96];	1,12 [-1,4 ; 3,64]; 0,545	0,545	0,2151
	0	286	4	1.40	293	7	2.39	0,59 [0,17 ; 1,98]	0,58 [0,17 ; 2];	-0,99 [-3,21 ; 1,23]; 0,545	0,545	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	2	0.89	202	4	1.98	0,45 [0,08 ; 2,42]	0,44 [0,08 ; 2,45];	-1,09 [-3,37 ; 1,19]; 0,428	0,428	0,1319
	>=3	84	2	2.38	98	0	0.00	5,82 [0,28 ; 119,63]	5,97 [0,28 ; 126,11];	2,44 [-1,42 ; 6,29]; 0,212	0,212	
	2	236	7	2.97	248	7	2.82	1,05 [0,37 ; 2,95]	1,05 [0,36 ; 3,05];	0,14 [-2,85 ; 3,13]; 1	1	
Race	Other	10	1	10.00	12	1	8.33	1,2 [0,09 ; 16,84]	1,22 [0,07 ; 22,4];	1,67 [-22,63 ; 25,96]; 1	1	0,8981
	White	535	10	1.87	536	10	1.87	1 [0,42 ; 2,39]	1 [0,41 ; 2,43];	0 [-1,62 ; 1,62]; 1	1	
	No	347	10	2.88	379	8	2.11	1,37 [0,55 ; 3,42]	1,38 [0,54 ; 3,53];	0,77 [-1,51 ; 3,05]; 0,634	0,634	0,1752

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	1	0.51	169	3	1.78	0,28 [0,03 ; 2,71]	0,28 [0,03 ; 2,73];	-1,27 [-3,49 ; 0,95]; 0,338	0,338	
Region	Eastern Europe	492	5	1.02	495	6	1.21	0,84 [0,26 ; 2,73]	0,84 [0,25 ; 2,76];	-0,2 [-1,51 ; 1,11]; 1	1	0,665
	USA and Western Europe	53	6	11.32	53	5	9.43	1,2 [0,39 ; 3,69]	1,23 [0,35 ; 4,29];	1,89 [-9,72 ; 13,49]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Nervous system disorders | Paraesthesia

6.1.27 Gastrointestinal disorders - Nausea

Tabelle 291: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	35	10.74	302	26	8.61	1,25 [0,77 ; 2,02]	1,28 [0,75 ; 2,18];	2,13 [-2,49 ; 6,74]; 0,419	0,419	0,6201
	>= 38 years	219	23	10.50	246	17	6.91	1,52 [0,83 ; 2,77]	1,58 [0,82 ; 3,04];	3,59 [-1,56 ; 8,74]; 0,187	0,187	
Disease Severity at baseline (EDSS)	<=3.5	419	46	10.98	415	36	8.67	1,27 [0,84 ; 1,92]	1,3 [0,82 ; 2,05];	2,3 [-1,73 ; 6,34]; 0,296	0,296	0,4849
	>3.5	126	12	9.52	133	7	5.26	1,81 [0,74 ; 4,45]	1,89 [0,72 ; 4,98];	4,26 [-2,12 ; 10,64]; 0,236	0,236	
Gender	Female	345	49	14.20	356	34	9.55	1,49 [0,99 ; 2,24]	1,57 [0,98 ; 2,5];	4,65 [-0,13 ; 9,44]; 0,062	0,062	0,3607
	Male	200	9	4.50	192	9	4.69	0,96 [0,39 ; 2,37]	0,96 [0,37 ; 2,47];	-0,19 [-4,33 ; 3,96]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	258	30	11.63	251	23	9.16	1,27 [0,76 ; 2,12]	1,3 [0,74 ; 2,31];	2,46 [-2,83 ; 7,76]; 0,387	0,387	0,7634
	0	286	28	9.79	293	20	6.83	1,43 [0,83 ; 2,49]	1,48 [0,81 ; 2,7];	2,96 [-1,53 ; 7,46]; 0,228	0,228	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	25	11.11	202	15	7.43	1,5 [0,81 ; 2,76]	1,56 [0,8 ; 3,05];	3,69 [-1,79 ; 9,16]; 0,244	0,244	0,9188
	>=3	84	9	10.71	98	8	8.16	1,31 [0,53 ; 3,25]	1,35 [0,5 ; 3,67];	2,55 [-6 ; 11,1]; 0,615	0,615	
	2	236	24	10.17	248	20	8.06	1,26 [0,72 ; 2,22]	1,29 [0,69 ; 2,4];	2,1 [-3,03 ; 7,24]; 0,434	0,434	
Race	Other	10	3	30.00	12	2	16.67	1,8 [0,37 ; 8,74]	2,14 [0,28 ; 16,37];	13,33 [-22,04 ; 48,71]; 0,624	0,624	0,6775
	White	535	55	10.28	536	41	7.65	1,34 [0,91 ; 1,98]	1,38 [0,91 ; 2,11];	2,63 [-0,79 ; 6,05]; 0,136	0,136	
	No	347	36	10.37	379	29	7.65	1,36 [0,85 ; 2,16]	1,4 [0,84 ; 2,33];	2,72 [-1,46 ; 6,9]; 0,241	0,241	0,9831

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	22	11.11	169	14	8.28	1,34 [0,71 ; 2,54]	1,38 [0,68 ; 2,8];	2,83 [-3,21 ; 8,86]; 0,385	0,385	
Region	Eastern Europe	492	46	9.35	495	33	6.67	1,4 [0,91 ; 2,15]	1,44 [0,91 ; 2,3];	2,68 [-0,7 ; 6,07]; 0,128	0,128	0,7979
	USA and Western Europe	53	12	22.64	53	10	18.87	1,2 [0,57 ; 2,53]	1,26 [0,49 ; 3,23];	3,77 [-11,65 ; 19,2]; 0,811	0,811	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Gastrointestinal disorders | Nausea

6.1.28 Reproductive system and breast disorders - Dysmenorrhoea

Tabelle 292: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	16	4.91	302	18	5.96	0,82 [0,43 ; 1,59]	0,81 [0,41 ; 1,63];	-1,05 [-4,61 ; 2,5]; 0,6	0,6	0,4973
	>= 38 years	219	1	0.46	246	3	1.22	0,37 [0,04 ; 3,57]	0,37 [0,04 ; 3,6];	-0,76 [-2,4 ; 0,87]; 0,626	0,626	
Disease Severity at baseline (EDSS)	<=3.5	419	17	4.06	415	20	4.82	0,84 [0,45 ; 1,58]	0,84 [0,43 ; 1,62];	-0,76 [-3,56 ; 2,03]; 0,618	0,618	0,284
	>3.5	126	0	0.00	133	1	0.75	0,35 [0,01 ; 8,55]	0,35 [0,01 ; 8,65];	-0,73 [-2,81 ; 1,36]; 0,499	0,499	
Gender	Female	345	17	4.93	356	21	5.90	0,84 [0,45 ; 1,56]	0,83 [0,43 ; 1,6];	-0,97 [-4,32 ; 2,38]; 0,619	0,619	1
	Male	200	0	0.00	192	0	0.00	0,96 [0,02 ; 48,15]	0,96 [0,02 ; 48,63];	-0,01 [-1 ; 0,98]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	258	9	3.49	251	11	4.38	0,8 [0,34 ; 1,89]	0,79 [0,32 ; 1,94];	-0,89 [-4,27 ; 2,49]; 0,653	0,653	0,9614
	0	286	8	2.80	293	10	3.41	0,82 [0,33 ; 2,05]	0,81 [0,32 ; 2,09];	-0,62 [-3,44 ; 2,21]; 0,812	0,812	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	9	4.00	202	8	3.96	1,01 [0,4 ; 2,57]	1,01 [0,38 ; 2,67];	0,04 [-3,67 ; 3,75]; 1	1	0,3835
	>=3	84	2	2.38	98	7	7.14	0,33 [0,07 ; 1,56]	0,32 [0,06 ; 1,57];	-4,76 [-10,81 ; 1,29]; 0,181	0,181	
	2	236	6	2.54	248	6	2.42	1,05 [0,34 ; 3,21]	1,05 [0,33 ; 3,31];	0,12 [-2,65 ; 2,9]; 1	1	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	17	3.18	536	21	3.92	0,81 [0,43 ; 1,52]	0,8 [0,42 ; 1,54];	-0,74 [-2,96 ; 1,47]; 0,621	0,621	
	No	347	11	3.17	379	17	4.49	0,71 [0,34 ; 1,49]	0,7 [0,32 ; 1,51];	-1,32 [-4,1 ; 1,47]; 0,441	0,441	0,4168

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	6	3.03	169	4	2.37	1,28 [0,37 ; 4,46]	1,29 [0,36 ; 4,65];	0,66 [-2,65 ; 3,97]; 0,758	0,758	
Region	Eastern Europe	492	16	3.25	495	20	4.04	0,8 [0,42 ; 1,53]	0,8 [0,41 ; 1,56];	-0,79 [-3,13 ; 1,55]; 0,611	0,611	0,8782
	USA and Western Europe	53	1	1.89	53	1	1.89	1 [0,06 ; 15,57]	1 [0,06 ; 16,42];	0 [-5,18 ; 5,18]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Reproductive system and breast disorders | Dysmenorrhoea

6.1.29 Musculoskeletal and connective tissue disorders - Back pain

Tabelle 293: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	27	8.28	302	25	8.28	1 [0,59 ; 1,68]	1 [0,57 ; 1,77];	0 [-4,31 ; 4,32]; 1	1	0,9168
	>= 38 years	219	24	10.96	246	28	11.38	0,96 [0,58 ; 1,61]	0,96 [0,54 ; 1,71];	-0,42 [-6,16 ; 5,31]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	41	9.79	415	38	9.16	1,07 [0,7 ; 1,63]	1,08 [0,68 ; 1,71];	0,63 [-3,35 ; 4,6]; 0,813	0,813	0,3428
	>3.5	126	10	7.94	133	15	11.28	0,7 [0,33 ; 1,51]	0,68 [0,29 ; 1,57];	-3,34 [-10,5 ; 3,81]; 0,405	0,405	
Gender	Female	345	40	11.59	356	35	9.83	1,18 [0,77 ; 1,81]	1,2 [0,74 ; 1,94];	1,76 [-2,82 ; 6,34]; 0,466	0,466	0,0996
	Male	200	11	5.50	192	18	9.38	0,59 [0,28 ; 1,21]	0,56 [0,26 ; 1,22];	-3,88 [-9,07 ; 1,32]; 0,177	0,177	
Number of baseline Gd-enhancing lesions	>=1	258	32	12.40	251	28	11.16	1,11 [0,69 ; 1,79]	1,13 [0,66 ; 1,93];	1,25 [-4,35 ; 6,85]; 0,682	0,682	0,3503
	0	286	19	6.64	293	25	8.53	0,78 [0,44 ; 1,38]	0,76 [0,41 ; 1,42];	-1,89 [-6,2 ; 2,42]; 0,435	0,435	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	19	8.44	202	20	9.90	0,85 [0,47 ; 1,55]	0,84 [0,43 ; 1,62];	-1,46 [-6,95 ; 4,04]; 0,618	0,618	0,7387
	>=3	84	9	10.71	98	8	8.16	1,31 [0,53 ; 3,25]	1,35 [0,5 ; 3,67];	2,55 [-6 ; 11,1]; 0,615	0,615	
	2	236	23	9.75	248	25	10.08	0,97 [0,56 ; 1,65]	0,96 [0,53 ; 1,75];	-0,33 [-5,66 ; 4,99]; 1	1	
Race	Other	10	4	40.00	12	3	25.00	1,6 [0,46 ; 5,53]	2 [0,32 ; 12,33];	15 [-24,02 ; 54,02]; 0,652	0,652	0,4223
	White	535	47	8.79	536	50	9.33	0,94 [0,64 ; 1,38]	0,94 [0,62 ; 1,42];	-0,54 [-3,98 ; 2,89]; 0,831	0,831	
	No	347	33	9.51	379	43	11.35	0,84 [0,55 ; 1,29]	0,82 [0,51 ; 1,33];	-1,84 [-6,28 ; 2,61]; 0,467	0,467	0,1603

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	18	9.09	169	10	5.92	1,54 [0,73 ; 3,24]	1,59 [0,71 ; 3,55];	3,17 [-2,18 ; 8,53]; 0,325	0,325	
Region	Eastern Europe	492	40	8.13	495	43	8.69	0,94 [0,62 ; 1,41]	0,93 [0,59 ; 1,46];	-0,56 [-4,02 ; 2,91]; 0,819	0,819	0,7228
	USA and Western Europe	53	11	20.75	53	10	18.87	1,1 [0,51 ; 2,37]	1,13 [0,43 ; 2,93];	1,89 [-13,28 ; 17,06]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Musculoskeletal and connective tissue disorders | Back pain

6.1.30 Musculoskeletal and connective tissue disorders - Pain in extremity

Tabelle 294: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	20	6.13	302	8	2.65	2,32 [1,04 ; 5,18]	2,4 [1,04 ; 5,54];	3,49 [0,31 ; 6,66]; 0,051	0,051	0,0449
	>= 38 years	219	11	5.02	246	16	6.50	0,77 [0,37 ; 1,63]	0,76 [0,34 ; 1,68];	-1,48 [-5,71 ; 2,75]; 0,555	0,555	
Disease Severity at baseline (EDSS)	<=3.5	419	25	5.97	415	19	4.58	1,3 [0,73 ; 2,33]	1,32 [0,72 ; 2,44];	1,39 [-1,64 ; 4,42]; 0,439	0,439	0,9625
	>3.5	126	6	4.76	133	5	3.76	1,27 [0,4 ; 4,05]	1,28 [0,38 ; 4,3];	1 [-3,92 ; 5,93]; 0,764	0,764	
Gender	Female	345	22	6.38	356	20	5.62	1,14 [0,63 ; 2,04]	1,14 [0,61 ; 2,14];	0,76 [-2,76 ; 4,28]; 0,751	0,751	0,3271
	Male	200	9	4.50	192	4	2.08	2,16 [0,68 ; 6,9]	2,21 [0,67 ; 7,32];	2,42 [-1,1 ; 5,93]; 0,26	0,26	
Number of baseline Gd-enhancing lesions	>=1	258	18	6.98	251	6	2.39	2,92 [1,18 ; 7,23]	3,06 [1,2 ; 7,85];	4,59 [0,95 ; 8,22]; 0,02	0,02	0,0142
	0	286	13	4.55	293	18	6.14	0,74 [0,37 ; 1,48]	0,73 [0,35 ; 1,51];	-1,6 [-5,26 ; 2,06]; 0,462	0,462	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	14	6.22	202	9	4.46	1,4 [0,62 ; 3,16]	1,42 [0,6 ; 3,36];	1,77 [-2,48 ; 6,02]; 0,521	0,521	0,6619
	>=3	84	4	4.76	98	2	2.04	2,33 [0,44 ; 12,42]	2,4 [0,43 ; 13,44];	2,72 [-2,62 ; 8,07]; 0,417	0,417	
	2	236	13	5.51	248	13	5.24	1,05 [0,5 ; 2,22]	1,05 [0,48 ; 2,32];	0,27 [-3,75 ; 4,29]; 1	1	
Race	Other	10	4	40.00	12	0	0.00	10,64 [0,64 ; 176,54]	17,31 [0,8 ; 373,45];	37,06 [6,18 ; 67,94]; 0,029	0,029	0,0106
	White	535	27	5.05	536	24	4.48	1,13 [0,66 ; 1,93]	1,13 [0,65 ; 1,99];	0,57 [-1,98 ; 3,12]; 0,67	0,67	
	No	347	18	5.19	379	18	4.75	1,09 [0,58 ; 2,06]	1,1 [0,56 ; 2,14];	0,44 [-2,73 ; 3,6]; 0,865	0,865	0,3579

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	13	6.57	169	6	3.55	1,85 [0,72 ; 4,76]	1,91 [0,71 ; 5,14];	3,02 [-1,42 ; 7,45]; 0,241	0,241	
Region	Eastern Europe	492	19	3.86	495	19	3.84	1,01 [0,54 ; 1,88]	1,01 [0,53 ; 1,92];	0,02 [-2,38 ; 2,42]; 1	1	0,1122
	USA and Western Europe	53	12	22.64	53	5	9.43	2,4 [0,91 ; 6,34]	2,81 [0,91 ; 8,64];	13,21 [-0,54 ; 26,95]; 0,11	0,11	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Musculoskeletal and connective tissue disorders | Pain in extremity

6.1.31 Nervous system disorders - Headache

Tabelle 295: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	129	39.57	302	90	29.80	1,33 [1,07 ; 1,65]	1,54 [1,11 ; 2,15];	9,77 [2,37 ; 17,17]; 0,012	0,012	0,3962
	>= 38 years	219	58	26.48	246	56	22.76	1,16 [0,85 ; 1,6]	1,22 [0,8 ; 1,87];	3,72 [-4,13 ; 11,57]; 0,388	0,388	
Disease Severity at baseline (EDSS)	<=3.5	419	153	36.52	415	118	28.43	1,28 [1,05 ; 1,57]	1,45 [1,08 ; 1,94];	8,08 [1,75 ; 14,41]; 0,015	0,015	0,8942
	>3.5	126	34	26.98	133	28	21.05	1,28 [0,83 ; 1,98]	1,39 [0,78 ; 2,46];	5,93 [-4,46 ; 16,33]; 0,308	0,308	
Gender	Female	345	138	40.00	356	109	30.62	1,31 [1,07 ; 1,6]	1,51 [1,11 ; 2,06];	9,38 [2,34 ; 16,43]; 0,011	0,011	0,7189
	Male	200	49	24.50	192	37	19.27	1,27 [0,87 ; 1,86]	1,36 [0,84 ; 2,2];	5,23 [-2,94 ; 13,39]; 0,224	0,224	
Number of baseline Gd-enhancing lesions	>=1	258	90	34.88	251	74	29.48	1,18 [0,92 ; 1,53]	1,28 [0,88 ; 1,86];	5,4 [-2,7 ; 13,5]; 0,218	0,218	0,4358
	0	286	97	33.92	293	72	24.57	1,38 [1,07 ; 1,79]	1,58 [1,1 ; 2,26];	9,34 [1,97 ; 16,72]; 0,014	0,014	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	75	33.33	202	58	28.71	1,16 [0,87 ; 1,54]	1,24 [0,82 ; 1,87];	4,62 [-4,15 ; 13,39]; 0,346	0,346	0,4477
	>=3	84	29	34.52	98	20	20.41	1,69 [1,04 ; 2,76]	2,06 [1,06 ; 4];	14,12 [1,19 ; 27,04]; 0,044	0,044	
	2	236	83	35.17	248	68	27.42	1,28 [0,98 ; 1,67]	1,44 [0,98 ; 2,11];	7,75 [-0,49 ; 15,99]; 0,077	0,077	
Race	Other	10	5	50.00	12	2	16.67	3 [0,73 ; 12,27]	5 [0,7 ; 35,5];	33,33 [-4,15 ; 70,82]; 0,172	0,172	0,1905
	White	535	182	34.02	536	144	26.87	1,27 [1,05 ; 1,52]	1,4 [1,08 ; 1,82];	7,15 [1,66 ; 12,65]; 0,012	0,012	
	No	347	119	34.29	379	107	28.23	1,21 [0,98 ; 1,51]	1,33 [0,97 ; 1,82];	6,06 [-0,68 ; 12,81]; 0,092	0,092	0,3374

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	68	34.34	169	39	23.08	1,49 [1,06 ; 2,08]	1,74 [1,1 ; 2,77];	11,27 [2,1 ; 20,44]; 0,021	0,021	
Region	Eastern Europe	492	166	33.74	495	131	26.46	1,27 [1,05 ; 1,54]	1,41 [1,08 ; 1,86];	7,28 [1,57 ; 12,98]; 0,015	0,015	0,7119
	USA and Western Europe	53	21	39.62	53	15	28.30	1,4 [0,81 ; 2,41]	1,66 [0,74 ; 3,75];	11,32 [-6,58 ; 29,22]; 0,305	0,305	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Nervous system disorders | Headache

6.1.32 Musculoskeletal and connective tissue disorders - Neck pain

Tabelle 296: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	8	2.45	302	9	2.98	0,82 [0,32 ; 2,11]	0,82 [0,31 ; 2,15];	-0,53 [-3,08 ; 2,02]; 0,807	0,807	0,3666
	>= 38 years	219	6	2.74	246	4	1.63	1,68 [0,48 ; 5,89]	1,7 [0,47 ; 6,12];	1,11 [-1,56 ; 3,79]; 0,527	0,527	
Disease Severity at baseline (EDSS)	<=3.5	419	12	2.86	415	9	2.17	1,32 [0,56 ; 3,1]	1,33 [0,55 ; 3,19];	0,7 [-1,43 ; 2,82]; 0,66	0,66	0,3276
	>3.5	126	2	1.59	133	4	3.01	0,53 [0,1 ; 2,83]	0,52 [0,09 ; 2,89];	-1,42 [-5,05 ; 2,21]; 0,685	0,685	
Gender	Female	345	12	3.48	356	9	2.53	1,38 [0,59 ; 3,22]	1,39 [0,58 ; 3,34];	0,95 [-1,58 ; 3,48]; 0,512	0,512	0,2606
	Male	200	2	1.00	192	4	2.08	0,48 [0,09 ; 2,59]	0,47 [0,09 ; 2,62];	-1,08 [-3,53 ; 1,36]; 0,441	0,441	
Number of baseline Gd-enhancing lesions	>=1	258	10	3.88	251	5	1.99	1,95 [0,67 ; 5,61]	1,98 [0,67 ; 5,89];	1,88 [-1,04 ; 4,81]; 0,295	0,295	0,0904
	0	286	4	1.40	293	8	2.73	0,51 [0,16 ; 1,68]	0,51 [0,15 ; 1,7];	-1,33 [-3,64 ; 0,98]; 0,383	0,383	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	4	1.78	202	6	2.97	0,6 [0,17 ; 2,09]	0,59 [0,16 ; 2,13];	-1,19 [-4,1 ; 1,72]; 0,527	0,527	0,4675
	>=3	84	2	2.38	98	2	2.04	1,17 [0,17 ; 8,1]	1,17 [0,16 ; 8,5];	0,34 [-3,96 ; 4,64]; 1	1	
	2	236	8	3.39	248	5	2.02	1,68 [0,56 ; 5,07]	1,71 [0,55 ; 5,29];	1,37 [-1,52 ; 4,27]; 0,408	0,408	
Race	Other	10	0	0.00	12	3	25.00	0,17 [0,01 ; 2,93]	0,13 [0,01 ; 2,84];	-22,38 [-49,45 ; 4,69]; 0,114	0,114	0,0309
	White	535	14	2.62	536	10	1.87	1,4 [0,63 ; 3,13]	1,41 [0,62 ; 3,21];	0,75 [-1,02 ; 2,52]; 0,419	0,419	
	No	347	10	2.88	379	7	1.85	1,56 [0,6 ; 4,05]	1,58 [0,59 ; 4,19];	1,03 [-1,19 ; 3,26]; 0,463	0,463	0,2033

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	4	2.02	169	6	3.55	0,57 [0,16 ; 1,98]	0,56 [0,16 ; 2,02];	-1,53 [-4,94 ; 1,88]; 0,523	0,523	
Region	Eastern Europe	492	12	2.44	495	7	1.41	1,72 [0,68 ; 4,34]	1,74 [0,68 ; 4,46];	1,02 [-0,69 ; 2,74]; 0,257	0,257	0,0577
	USA and Western Europe	53	2	3.77	53	6	11.32	0,33 [0,07 ; 1,58]	0,31 [0,06 ; 1,6];	-7,55 [-17,5 ; 2,41]; 0,27	0,27	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Musculoskeletal and connective tissue disorders | Neck pain

6.1.33 Cardiac disorders - Tachycardia

Tabelle 297: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	14	4.29	302	9	2.98	1,44 [0,63 ; 3,28]	1,46 [0,62 ; 3,43];	1,31 [-1,6 ; 4,23]; 0,404	0,404	0,5562
	>= 38 years	219	6	2.74	246	7	2.85	0,96 [0,33 ; 2,82]	0,96 [0,32 ; 2,91];	-0,11 [-3,1 ; 2,89]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	16	3.82	415	12	2.89	1,32 [0,63 ; 2,76]	1,33 [0,62 ; 2,85];	0,93 [-1,52 ; 3,37]; 0,565	0,565	0,7765
	>3.5	126	4	3.17	133	4	3.01	1,06 [0,27 ; 4,13]	1,06 [0,26 ; 4,32];	0,17 [-4,05 ; 4,39]; 1	1	
Gender	Female	345	9	2.61	356	12	3.37	0,77 [0,33 ; 1,81]	0,77 [0,32 ; 1,85];	-0,76 [-3,28 ; 1,76]; 0,66	0,66	0,0773
	Male	200	11	5.50	192	4	2.08	2,64 [0,86 ; 8,15]	2,74 [0,86 ; 8,74];	3,42 [-0,33 ; 7,17]; 0,113	0,113	
Number of baseline Gd-enhancing lesions	>=1	258	16	6.20	251	5	1.99	3,11 [1,16 ; 8,37]	3,25 [1,17 ; 9,02];	4,21 [0,8 ; 7,62]; 0,024	0,024	0,0029
	0	286	4	1.40	293	11	3.75	0,37 [0,12 ; 1,16]	0,36 [0,11 ; 1,16];	-2,36 [-4,92 ; 0,21]; 0,114	0,114	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	11	4.89	202	4	1.98	2,47 [0,8 ; 7,63]	2,54 [0,8 ; 8,12];	2,91 [-0,5 ; 6,32]; 0,12	0,12	0,2517
	>=3	84	2	2.38	98	4	4.08	0,58 [0,11 ; 3,11]	0,57 [0,1 ; 3,21];	-1,7 [-6,8 ; 3,4]; 0,688	0,688	
	2	236	7	2.97	248	8	3.23	0,92 [0,34 ; 2,5]	0,92 [0,33 ; 2,57];	-0,26 [-3,35 ; 2,83]; 1	1	
Race	Other	10	1	10.00	12	0	0.00	3,55 [0,16 ; 78,56]	3,95 [0,14 ; 108,09];	9,79 [-13,03 ; 32,61]; 0,478	0,478	0,2339
	White	535	19	3.55	536	16	2.99	1,19 [0,62 ; 2,29]	1,2 [0,61 ; 2,35];	0,57 [-1,56 ; 2,7]; 0,612	0,612	
	No	347	9	2.59	379	13	3.43	0,76 [0,33 ; 1,75]	0,75 [0,32 ; 1,78];	-0,84 [-3,32 ; 1,64]; 0,666	0,666	0,0507

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	11	5.56	169	3	1.78	3,13 [0,89 ; 11,03]	3,25 [0,89 ; 11,87];	3,78 [0,02 ; 7,54]; 0,098	0,098	
Region	Eastern Europe	492	16	3.25	495	14	2.83	1,15 [0,57 ; 2,33]	1,15 [0,56 ; 2,39];	0,42 [-1,72 ; 2,57]; 0,715	0,715	0,5337
	USA and Western Europe	53	4	7.55	53	2	3.77	2 [0,38 ; 10,46]	2,08 [0,36 ; 11,88];	3,77 [-5 ; 12,54]; 0,678	0,678	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Cardiac disorders | Tachycardia

6.1.34 Gastrointestinal disorders - Dyspepsia

Tabelle 298: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	17	5.21	302	10	3.31	1,57 [0,73 ; 3,39]	1,61 [0,72 ; 3,57];	1,9 [-1,24 ; 5,05]; 0,325	0,325	0,1778
	>= 38 years	219	6	2.74	246	10	4.07	0,67 [0,25 ; 1,82]	0,66 [0,24 ; 1,86];	-1,33 [-4,61 ; 1,96]; 0,459	0,459	
Disease Severity at baseline (EDSS)	<=3.5	419	19	4.53	415	17	4.10	1,11 [0,58 ; 2,1]	1,11 [0,57 ; 2,17];	0,44 [-2,32 ; 3,2]; 0,865	0,865	0,7714
	>3.5	126	4	3.17	133	3	2.26	1,41 [0,32 ; 6,16]	1,42 [0,31 ; 6,48];	0,92 [-3,05 ; 4,89]; 0,716	0,716	
Gender	Female	345	9	2.61	356	12	3.37	0,77 [0,33 ; 1,81]	0,77 [0,32 ; 1,85];	-0,76 [-3,28 ; 1,76]; 0,66	0,66	0,1984
	Male	200	14	7.00	192	8	4.17	1,68 [0,72 ; 3,91]	1,73 [0,71 ; 4,23];	2,83 [-1,69 ; 7,36]; 0,275	0,275	
Number of baseline Gd-enhancing lesions	>=1	258	16	6.20	251	8	3.19	1,95 [0,85 ; 4,47]	2,01 [0,84 ; 4,78];	3,01 [-0,64 ; 6,67]; 0,143	0,143	0,0553
	0	286	7	2.45	293	12	4.10	0,6 [0,24 ; 1,5]	0,59 [0,23 ; 1,51];	-1,65 [-4,54 ; 1,24]; 0,352	0,352	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	12	5.33	202	7	3.47	1,54 [0,62 ; 3,83]	1,57 [0,61 ; 4,07];	1,87 [-2 ; 5,74]; 0,482	0,482	0,478
	>=3	84	5	5.95	98	4	4.08	1,46 [0,4 ; 5,26]	1,49 [0,39 ; 5,73];	1,87 [-4,53 ; 8,27]; 0,735	0,735	
	2	236	6	2.54	248	9	3.63	0,7 [0,25 ; 1,94]	0,69 [0,24 ; 1,98];	-1,09 [-4,16 ; 1,99]; 0,603	0,603	
Race	Other	10	1	10.00	12	0	0.00	3,55 [0,16 ; 78,56]	3,95 [0,14 ; 108,09];	9,79 [-13,03 ; 32,61]; 0,478	0,478	0,2207
	White	535	22	4.11	536	20	3.73	1,1 [0,61 ; 2]	1,11 [0,6 ; 2,05];	0,38 [-1,94 ; 2,71]; 0,756	0,756	
	No	347	10	2.88	379	12	3.17	0,91 [0,4 ; 2,08]	0,91 [0,39 ; 2,13];	-0,28 [-2,78 ; 2,21]; 1	1	0,4823

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	13	6.57	169	8	4.73	1,39 [0,59 ; 3,27]	1,41 [0,57 ; 3,5];	1,83 [-2,87 ; 6,54]; 0,505	0,505	
Region	Eastern Europe	492	21	4.27	495	18	3.64	1,17 [0,63 ; 2,18]	1,18 [0,62 ; 2,25];	0,63 [-1,8 ; 3,06]; 0,628	0,628	0,8763
	USA and Western Europe	53	2	3.77	53	2	3.77	1 [0,15 ; 6,84]	1 [0,14 ; 7,37];	0 [-7,26 ; 7,26]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Gastrointestinal disorders | Dyspepsia

6.1.35 Infections and infestations - Nasopharyngitis

Tabelle 299: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	71	21.78	302	62	20.53	1,06 [0,78 ; 1,44]	1,08 [0,73 ; 1,58];	1,25 [-5,14 ; 7,64]; 0,769	0,769	0,5652
	>= 38 years	219	29	13.24	246	36	14.63	0,9 [0,57 ; 1,42]	0,89 [0,53 ; 1,51];	-1,39 [-7,69 ; 4,91]; 0,69	0,69	
Disease Severity at baseline (EDSS)	<=3.5	419	85	20.29	415	77	18.55	1,09 [0,83 ; 1,44]	1,12 [0,79 ; 1,57];	1,73 [-3,64 ; 7,1]; 0,541	0,541	0,2753
	>3.5	126	15	11.90	133	21	15.79	0,75 [0,41 ; 1,4]	0,72 [0,35 ; 1,47];	-3,88 [-12,27 ; 4,5]; 0,377	0,377	
Gender	Female	345	74	21.45	356	65	18.26	1,17 [0,87 ; 1,58]	1,22 [0,84 ; 1,77];	3,19 [-2,71 ; 9,1]; 0,299	0,299	0,1204
	Male	200	26	13.00	192	33	17.19	0,76 [0,47 ; 1,22]	0,72 [0,41 ; 1,26];	-4,19 [-11,27 ; 2,9]; 0,261	0,261	
Number of baseline Gd-enhancing lesions	>=1	258	53	20.54	251	54	21.51	0,95 [0,68 ; 1,34]	0,94 [0,62 ; 1,44];	-0,97 [-8,05 ; 6,11]; 0,828	0,828	0,6
	0	286	47	16.43	293	44	15.02	1,09 [0,75 ; 1,6]	1,11 [0,71 ; 1,74];	1,42 [-4,51 ; 7,35]; 0,65	0,65	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	44	19.56	202	42	20.79	0,94 [0,64 ; 1,37]	0,93 [0,58 ; 1,49];	-1,24 [-8,86 ; 6,39]; 0,809	0,809	0,4103
	>=3	84	14	16.67	98	10	10.20	1,63 [0,77 ; 3,48]	1,76 [0,74 ; 4,2];	6,46 [-3,51 ; 16,43]; 0,272	0,272	
	2	236	42	17.80	248	46	18.55	0,96 [0,66 ; 1,4]	0,95 [0,6 ; 1,51];	-0,75 [-7,62 ; 6,12]; 0,906	0,906	
Race	Other	10	1	10.00	12	6	50.00	0,2 [0,03 ; 1,4]	0,11 [0,01 ; 1,17];	-40 [-73,85 ; -6,15]; 0,074	0,074	0,0308
	White	535	99	18.50	536	92	17.16	1,08 [0,83 ; 1,39]	1,1 [0,8 ; 1,5];	1,34 [-3,24 ; 5,93]; 0,577	0,577	
	No	347	67	19.31	379	71	18.73	1,03 [0,76 ; 1,39]	1,04 [0,72 ; 1,5];	0,57 [-5,14 ; 6,29]; 0,85	0,85	0,969

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	33	16.67	169	27	15.98	1,04 [0,66 ; 1,66]	1,05 [0,6 ; 1,83];	0,69 [-6,89 ; 8,27]; 0,888	0,888	
Region	Eastern Europe	492	84	17.07	495	83	16.77	1,02 [0,77 ; 1,34]	1,02 [0,73 ; 1,43];	0,31 [-4,37 ; 4,98]; 0,932	0,932	0,8799
	USA and Western Europe	53	16	30.19	53	15	28.30	1,07 [0,59 ; 1,93]	1,1 [0,47 ; 2,53];	1,89 [-15,43 ; 19,2]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Nasopharyngitis

6.1.36 Infections and infestations - Urinary tract infection

Tabelle 300: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	10	3.07	302	10	3.31	0,93 [0,39 ; 2,19]	0,92 [0,38 ; 2,25];	-0,24 [-3 ; 2,51]; 1	1	0,6265
	>= 38 years	219	12	5.48	246	19	7.72	0,71 [0,35 ; 1,43]	0,69 [0,33 ; 1,46];	-2,24 [-6,74 ; 2,25]; 0,358	0,358	
Disease Severity at baseline (EDSS)	<=3.5	419	15	3.58	415	16	3.86	0,93 [0,47 ; 1,85]	0,93 [0,45 ; 1,9];	-0,28 [-2,84 ; 2,29]; 0,857	0,857	0,3771
	>3.5	126	7	5.56	133	13	9.77	0,57 [0,23 ; 1,38]	0,54 [0,21 ; 1,41];	-4,22 [-10,66 ; 2,22]; 0,248	0,248	
Gender	Female	345	20	5.80	356	24	6.74	0,86 [0,48 ; 1,53]	0,85 [0,46 ; 1,57];	-0,94 [-4,53 ; 2,64]; 0,643	0,643	0,349
	Male	200	2	1.00	192	5	2.60	0,38 [0,08 ; 1,96]	0,38 [0,07 ; 1,97];	-1,6 [-4,25 ; 1,04]; 0,276	0,276	
Number of baseline Gd-enhancing lesions	>=1	258	8	3.10	251	10	3.98	0,78 [0,31 ; 1,94]	0,77 [0,3 ; 1,99];	-0,88 [-4,1 ; 2,33]; 0,638	0,638	0,9495
	0	286	14	4.90	293	19	6.48	0,75 [0,39 ; 1,48]	0,74 [0,36 ; 1,51];	-1,59 [-5,36 ; 2,18]; 0,475	0,475	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	10	4.44	202	14	6.93	0,64 [0,29 ; 1,41]	0,62 [0,27 ; 1,44];	-2,49 [-6,9 ; 1,93]; 0,298	0,298	0,8617
	>=3	84	2	2.38	98	3	3.06	0,78 [0,13 ; 4,54]	0,77 [0,13 ; 4,74];	-0,68 [-5,4 ; 4,04]; 1	1	
	2	236	10	4.24	248	12	4.84	0,88 [0,39 ; 1,99]	0,87 [0,37 ; 2,05];	-0,6 [-4,31 ; 3,1]; 0,829	0,829	
Race	Other	10	1	10.00	12	1	8.33	1,2 [0,09 ; 16,84]	1,22 [0,07 ; 22,4];	1,67 [-22,63 ; 25,96]; 1	1	0,7418
	White	535	21	3.93	536	28	5.22	0,75 [0,43 ; 1,31]	0,74 [0,42 ; 1,32];	-1,3 [-3,8 ; 1,2]; 0,38	0,38	
	No	347	14	4.03	379	18	4.75	0,85 [0,43 ; 1,68]	0,84 [0,41 ; 1,72];	-0,71 [-3,69 ; 2,26]; 0,719	0,719	0,5792

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	8	4.04	169	11	6.51	0,62 [0,26 ; 1,51]	0,6 [0,24 ; 1,54];	-2,47 [-7,09 ; 2,15]; 0,347	0,347	
Region	Eastern Europe	492	15	3.05	495	21	4.24	0,72 [0,37 ; 1,38]	0,71 [0,36 ; 1,39];	-1,19 [-3,53 ; 1,14]; 0,396	0,396	0,7754
	USA and Western Europe	53	7	13.21	53	8	15.09	0,88 [0,34 ; 2,24]	0,86 [0,29 ; 2,56];	-1,89 [-15,15 ; 11,38]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Urinary tract infection

6.1.37 Investigations - Lipase increased

Tabelle 301: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	10	3.07	302	10	3.31	0,93 [0,39 ; 2,19]	0,92 [0,38 ; 2,25];	-0,24 [-3 ; 2,51]; 1	1	0,5729
	>= 38 years	219	5	2.28	246	9	3.66	0,62 [0,21 ; 1,83]	0,62 [0,2 ; 1,86];	-1,38 [-4,44 ; 1,69]; 0,428	0,428	
Disease Severity at baseline (EDSS)	<=3.5	419	12	2.86	415	14	3.37	0,85 [0,4 ; 1,81]	0,84 [0,39 ; 1,85];	-0,51 [-2,87 ; 1,85]; 0,695	0,695	0,7182
	>3.5	126	3	2.38	133	5	3.76	0,63 [0,15 ; 2,6]	0,62 [0,15 ; 2,67];	-1,38 [-5,57 ; 2,81]; 0,723	0,723	
Gender	Female	345	6	1.74	356	9	2.53	0,69 [0,25 ; 1,91]	0,68 [0,24 ; 1,94];	-0,79 [-2,92 ; 1,35]; 0,604	0,604	0,7475
	Male	200	9	4.50	192	10	5.21	0,86 [0,36 ; 2,08]	0,86 [0,34 ; 2,16];	-0,71 [-4,97 ; 3,55]; 0,816	0,816	
Number of baseline Gd-enhancing lesions	>=1	258	8	3.10	251	4	1.59	1,95 [0,59 ; 6,38]	1,98 [0,59 ; 6,65];	1,51 [-1,11 ; 4,13]; 0,382	0,382	0,054
	0	286	7	2.45	293	15	5.12	0,48 [0,2 ; 1,16]	0,46 [0,19 ; 1,16];	-2,67 [-5,77 ; 0,42]; 0,127	0,127	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	5	2.22	202	6	2.97	0,75 [0,23 ; 2,41]	0,74 [0,22 ; 2,47];	-0,75 [-3,78 ; 2,28]; 0,763	0,763	0,8316
	>=3	84	4	4.76	98	4	4.08	1,17 [0,3 ; 4,52]	1,18 [0,28 ; 4,85];	0,68 [-5,33 ; 6,69]; 1	1	
	2	236	6	2.54	248	9	3.63	0,7 [0,25 ; 1,94]	0,69 [0,24 ; 1,98];	-1,09 [-4,16 ; 1,99]; 0,603	0,603	
Race	Other	10	0	0.00	12	1	8.33	0,39 [0,02 ; 8,73]	0,37 [0,01 ; 9,98];	-6,99 [-28,28 ; 14,29]; 0,493	0,493	0,3009
	White	535	15	2.80	536	18	3.36	0,83 [0,43 ; 1,64]	0,83 [0,41 ; 1,66];	-0,55 [-2,62 ; 1,51]; 0,724	0,724	
	No	347	7	2.02	379	12	3.17	0,64 [0,25 ; 1,6]	0,63 [0,25 ; 1,62];	-1,15 [-3,45 ; 1,15]; 0,362	0,362	0,5397

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	8	4.04	169	7	4.14	0,98 [0,36 ; 2,63]	0,97 [0,35 ; 2,75];	-0,1 [-4,17 ; 3,97]; 1	1	
Region	Eastern Europe	492	12	2.44	495	17	3.43	0,71 [0,34 ; 1,47]	0,7 [0,33 ; 1,49];	-1 [-3,1 ; 1,11]; 0,452	0,452	0,436
	USA and Western Europe	53	3	5.66	53	2	3.77	1,5 [0,26 ; 8,62]	1,53 [0,25 ; 9,55];	1,89 [-6,18 ; 9,95]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Investigations | Lipase increased

6.1.38 Psychiatric disorders - Anxiety

Tabelle 302: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	19	5.83	302	11	3.64	1,6 [0,77 ; 3,31]	1,64 [0,77 ; 3,5];	2,19 [-1,12 ; 5,49]; 0,261	0,261	0,0469
	>= 38 years	219	5	2.28	246	12	4.88	0,47 [0,17 ; 1,31]	0,46 [0,16 ; 1,31];	-2,59 [-5,94 ; 0,75]; 0,215	0,215	
Disease Severity at baseline (EDSS)	<=3.5	419	22	5.25	415	16	3.86	1,36 [0,73 ; 2,56]	1,38 [0,72 ; 2,67];	1,4 [-1,43 ; 4,22]; 0,407	0,407	0,055
	>3.5	126	2	1.59	133	7	5.26	0,3 [0,06 ; 1,42]	0,29 [0,06 ; 1,42];	-3,68 [-8,05 ; 0,7]; 0,173	0,173	
Gender	Female	345	18	5.22	356	20	5.62	0,93 [0,5 ; 1,73]	0,92 [0,48 ; 1,78];	-0,4 [-3,75 ; 2,95]; 0,868	0,868	0,3344
	Male	200	6	3.00	192	3	1.56	1,92 [0,49 ; 7,57]	1,95 [0,48 ; 7,9];	1,44 [-1,51 ; 4,38]; 0,504	0,504	
Number of baseline Gd-enhancing lesions	>=1	258	18	6.98	251	11	4.38	1,59 [0,77 ; 3,3]	1,64 [0,76 ; 3,54];	2,59 [-1,42 ; 6,6]; 0,252	0,252	0,0595
	0	286	6	2.10	293	12	4.10	0,51 [0,19 ; 1,35]	0,5 [0,19 ; 1,36];	-2 [-4,81 ; 0,81]; 0,231	0,231	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	15	6.67	202	8	3.96	1,68 [0,73 ; 3,89]	1,73 [0,72 ; 4,18];	2,71 [-1,52 ; 6,93]; 0,284	0,284	0,0808
	>=3	84	5	5.95	98	4	4.08	1,46 [0,4 ; 5,26]	1,49 [0,39 ; 5,73];	1,87 [-4,53 ; 8,27]; 0,735	0,735	
	2	236	4	1.69	248	11	4.44	0,38 [0,12 ; 1,18]	0,37 [0,12 ; 1,18];	-2,74 [-5,79 ; 0,31]; 0,114	0,114	
Race	Other	10	1	10.00	12	0	0.00	3,55 [0,16 ; 78,56]	3,95 [0,14 ; 108,09];	9,79 [-13,03 ; 32,61]; 0,478	0,478	0,2051
	White	535	23	4.30	536	23	4.29	1 [0,57 ; 1,76]	1 [0,55 ; 1,81];	0,01 [-2,42 ; 2,44]; 1	1	
	No	347	11	3.17	379	15	3.96	0,8 [0,37 ; 1,72]	0,79 [0,36 ; 1,75];	-0,79 [-3,48 ; 1,9]; 0,69	0,69	0,3438

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	13	6.57	169	8	4.73	1,39 [0,59 ; 3,27]	1,41 [0,57 ; 3,5];	1,83 [-2,87 ; 6,54]; 0,505	0,505	
Region	Eastern Europe	492	19	3.86	495	20	4.04	0,96 [0,52 ; 1,77]	0,95 [0,5 ; 1,81];	-0,18 [-2,61 ; 2,25]; 1	1	0,4628
	USA and Western Europe	53	5	9.43	53	3	5.66	1,67 [0,42 ; 6,62]	1,74 [0,39 ; 7,67];	3,77 [-6,26 ; 13,81]; 0,716	0,716	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Psychiatric disorders | Anxiety

6.1.39 Skin and subcutaneous tissue disorders - Alopecia

Tabelle 303: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	15	4.60	302	49	16.23	0,28 [0,16 ; 0,49]	0,25 [0,14 ; 0,45];	-11,62 [-16,36 ; -6,88]; 0	0	0,1765
	>= 38 years	219	4	1.83	246	35	14.23	0,13 [0,05 ; 0,36]	0,11 [0,04 ; 0,32];	-12,4 [-17,11 ; -7,69]; 0	0	
Disease Severity at baseline (EDSS)	<=3.5	419	14	3.34	415	73	17.59	0,19 [0,11 ; 0,33]	0,16 [0,09 ; 0,29];	-14,25 [-18,3 ; -10,2]; 0	0	0,1128
	>3.5	126	5	3.97	133	11	8.27	0,48 [0,17 ; 1,34]	0,46 [0,15 ; 1,36];	-4,3 [-10,09 ; 1,49]; 0,198	0,198	
Gender	Female	345	14	4.06	356	72	20.22	0,2 [0,12 ; 0,35]	0,17 [0,09 ; 0,3];	-16,17 [-20,83 ; -11,5]; 0	0	0,1932
	Male	200	5	2.50	192	12	6.25	0,4 [0,14 ; 1,11]	0,38 [0,13 ; 1,11];	-3,75 [-7,8 ; 0,3]; 0,084	0,084	
Number of baseline Gd-enhancing lesions	>=1	258	9	3.49	251	38	15.14	0,23 [0,11 ; 0,47]	0,2 [0,1 ; 0,43];	-11,65 [-16,62 ; -6,68]; 0	0	0,9779
	0	286	10	3.50	293	45	15.36	0,23 [0,12 ; 0,44]	0,2 [0,1 ; 0,4];	-11,86 [-16,51 ; -7,22]; 0	0	
	NA	1	0	0.00	4	1	25.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	8	3.56	202	27	13.37	0,27 [0,12 ; 0,57]	0,24 [0,11 ; 0,54];	-9,81 [-15,09 ; -4,53]; 0	0	0,6212
	>=3	84	2	2.38	98	18	18.37	0,13 [0,03 ; 0,54]	0,11 [0,02 ; 0,48];	-15,99 [-24,32 ; -7,66]; 0,001	0,001	
	2	236	9	3.81	248	39	15.73	0,24 [0,12 ; 0,49]	0,21 [0,1 ; 0,45];	-11,91 [-17,06 ; -6,76]; 0	0	
Race	Other	10	0	0.00	12	1	8.33	0,39 [0,02 ; 8,73]	0,37 [0,01 ; 9,98];	-6,99 [-28,28 ; 14,29]; 0,493	0,493	0,5659
	White	535	19	3.55	536	83	15.49	0,23 [0,14 ; 0,37]	0,2 [0,12 ; 0,34];	-11,93 [-15,37 ; -8,49]; 0	0	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	No	347	11	3.17	379	58	15.30	0,21 [0,11 ; 0,39]	0,18 [0,09 ; 0,35];	-12,13 [-16,2 ; -8,07]; 0	0	0,6498
	Yes	198	8	4.04	169	26	15.38	0,26 [0,12 ; 0,56]	0,23 [0,1 ; 0,53];	-11,34 [-17,44 ; -5,25]; 0	0	
Region	Eastern Europe	492	19	3.86	495	75	15.15	0,25 [0,16 ; 0,42]	0,22 [0,13 ; 0,38];	-11,29 [-14,88 ; -7,7]; 0	0	0,0467
	USA and Western Europe	53	0	0.00	53	9	16.98	0,05 [0 ; 0,88]	0,04 [0 ; 0,77];	-16,67 [-27,14 ; -6,19]; 0,001	0,001	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Skin and subcutaneous tissue disorders | Alopecia

6.1.40 Infections and infestations - Sinusitis

Tabelle 304: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	15	4.60	302	14	4.64	0,99 [0,49 ; 2,02]	0,99 [0,47 ; 2,09];	-0,03 [-3,32 ; 3,25]; 1	1	0,5344
	>= 38 years	219	6	2.74	246	10	4.07	0,67 [0,25 ; 1,82]	0,66 [0,24 ; 1,86];	-1,33 [-4,61 ; 1,96]; 0,459	0,459	
Disease Severity at baseline (EDSS)	<=3.5	419	17	4.06	415	21	5.06	0,8 [0,43 ; 1,5]	0,79 [0,41 ; 1,53];	-1 [-3,83 ; 1,83]; 0,511	0,511	0,487
	>3.5	126	4	3.17	133	3	2.26	1,41 [0,32 ; 6,16]	1,42 [0,31 ; 6,48];	0,92 [-3,05 ; 4,89]; 0,716	0,716	
Gender	Female	345	16	4.64	356	13	3.65	1,27 [0,62 ; 2,6]	1,28 [0,61 ; 2,71];	0,99 [-1,97 ; 3,94]; 0,572	0,572	0,0884
	Male	200	5	2.50	192	11	5.73	0,44 [0,15 ; 1,23]	0,42 [0,14 ; 1,24];	-3,23 [-7,16 ; 0,71]; 0,129	0,129	
Number of baseline Gd-enhancing lesions	>=1	258	9	3.49	251	8	3.19	1,09 [0,43 ; 2,79]	1,1 [0,42 ; 2,89];	0,3 [-2,82 ; 3,42]; 1	1	0,5563
	0	286	12	4.20	293	16	5.46	0,77 [0,37 ; 1,6]	0,76 [0,35 ; 1,63];	-1,26 [-4,75 ; 2,22]; 0,563	0,563	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	11	4.89	202	6	2.97	1,65 [0,62 ; 4,37]	1,68 [0,61 ; 4,63];	1,92 [-1,74 ; 5,58]; 0,335	0,335	0,2517
	>=3	84	3	3.57	98	7	7.14	0,5 [0,13 ; 1,87]	0,48 [0,12 ; 1,92];	-3,57 [-10,03 ; 2,89]; 0,345	0,345	
	2	236	7	2.97	248	11	4.44	0,67 [0,26 ; 1,7]	0,66 [0,25 ; 1,73];	-1,47 [-4,82 ; 1,88]; 0,475	0,475	
Race	Other	10	1	10.00	12	0	0.00	3,55 [0,16 ; 78,56]	3,95 [0,14 ; 108,09];	9,79 [-13,03 ; 32,61]; 0,478	0,478	0,1779
	White	535	20	3.74	536	24	4.48	0,83 [0,47 ; 1,49]	0,83 [0,45 ; 1,52];	-0,74 [-3,12 ; 1,64]; 0,645	0,645	
	No	347	14	4.03	379	18	4.75	0,85 [0,43 ; 1,68]	0,84 [0,41 ; 1,72];	-0,71 [-3,69 ; 2,26]; 0,719	0,719	0,8049

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	7	3.54	169	6	3.55	1 [0,34 ; 2,91]	1 [0,33 ; 3,02];	-0,01 [-3,81 ; 3,78]; 1	1	
Region	Eastern Europe	492	16	3.25	495	20	4.04	0,8 [0,42 ; 1,53]	0,8 [0,41 ; 1,56];	-0,79 [-3,13 ; 1,55]; 0,611	0,611	0,5462
	USA and Western Europe	53	5	9.43	53	4	7.55	1,25 [0,36 ; 4,4]	1,28 [0,32 ; 5,04];	1,89 [-8,72 ; 12,49]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Sinusitis

6.1.41 Infections and infestations - Upper respiratory tract infection

Tabelle 305: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	24	7.36	302	21	6.95	1,06 [0,6 ; 1,86]	1,06 [0,58 ; 1,95];	0,41 [-3,62 ; 4,44]; 0,878	0,878	0,8922
	>= 38 years	219	17	7.76	246	17	6.91	1,12 [0,59 ; 2,15]	1,13 [0,56 ; 2,28];	0,85 [-3,9 ; 5,61]; 0,726	0,726	
Disease Severity at baseline (EDSS)	<=3.5	419	33	7.88	415	30	7.23	1,09 [0,68 ; 1,75]	1,1 [0,66 ; 1,83];	0,65 [-2,94 ; 4,23]; 0,794	0,794	0,9517
	>3.5	126	8	6.35	133	8	6.02	1,06 [0,41 ; 2,73]	1,06 [0,39 ; 2,91];	0,33 [-5,54 ; 6,2]; 1	1	
Gender	Female	345	29	8.41	356	25	7.02	1,2 [0,72 ; 2]	1,22 [0,7 ; 2,12];	1,38 [-2,57 ; 5,34]; 0,571	0,571	0,5184
	Male	200	12	6.00	192	13	6.77	0,89 [0,41 ; 1,89]	0,88 [0,39 ; 1,98];	-0,77 [-5,61 ; 4,07]; 0,837	0,837	
Number of baseline Gd-enhancing lesions	>=1	258	16	6.20	251	14	5.58	1,11 [0,55 ; 2,23]	1,12 [0,53 ; 2,34];	0,62 [-3,47 ; 4,71]; 0,852	0,852	0,931
	0	286	25	8.74	293	24	8.19	1,07 [0,62 ; 1,82]	1,07 [0,6 ; 1,93];	0,55 [-3,99 ; 5,09]; 0,882	0,882	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	18	8.00	202	14	6.93	1,15 [0,59 ; 2,26]	1,17 [0,57 ; 2,41];	1,07 [-3,91 ; 6,05]; 0,716	0,716	0,9678
	>=3	84	6	7.14	98	7	7.14	1 [0,35 ; 2,86]	1 [0,32 ; 3,1];	0 [-7,51 ; 7,51]; 1	1	
	2	236	17	7.20	248	17	6.85	1,05 [0,55 ; 2,01]	1,05 [0,53 ; 2,12];	0,35 [-4,21 ; 4,91]; 1	1	
Race	Other	10	2	20.00	12	2	16.67	1,2 [0,2 ; 7,05]	1,25 [0,14 ; 10,94];	3,33 [-29,21 ; 35,88]; 1	1	0,9051
	White	535	39	7.29	536	36	6.72	1,09 [0,7 ; 1,68]	1,09 [0,68 ; 1,75];	0,57 [-2,48 ; 3,63]; 0,721	0,721	
	No	347	21	6.05	379	30	7.92	0,76 [0,45 ; 1,31]	0,75 [0,42 ; 1,34];	-1,86 [-5,56 ; 1,84]; 0,384	0,384	0,0299

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	20	10.10	169	8	4.73	2,13 [0,96 ; 4,72]	2,26 [0,97 ; 5,28];	5,37 [0,09 ; 10,65]; 0,074	0,074	
Region	Eastern Europe	492	32	6.50	495	30	6.06	1,07 [0,66 ; 1,74]	1,08 [0,64 ; 1,8];	0,44 [-2,58 ; 3,47]; 0,794	0,794	0,9126
	USA and Western Europe	53	9	16.98	53	8	15.09	1,12 [0,47 ; 2,69]	1,15 [0,41 ; 3,25];	1,89 [-12,08 ; 15,85]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Upper respiratory tract infection

6.1.42 Respiratory, thoracic and mediastinal disorders - Dyspnoea

Tabelle 306: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	7	2.15	302	2	0.66	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>= 38 years	219	5	2.28	246	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	419	11	2.63	415	2	0.48	5,45 [1,21 ; 24,43]	5,57 [1,23 ; 25,27];	2,14 [0,47 ; 3,81]; 0,021	0,021	0,5628
	>3.5	126	1	0.79	133	0	0.00	3,17 [0,13 ; 76,99]	3,19 [0,13 ; 79,07];	0,81 [-1,34 ; 2,95]; 0,238	0,238	
Gender	Female	345	9	2.61	356	2	0.56	4,64 [1,01 ; 21,34]	4,74 [1,02 ; 22,1];	2,05 [0,19 ; 3,9]; 0,035	0,035	0,3211
	Male	200	3	1.50	192	0	0.00	6,72 [0,35 ; 129,27]	6,82 [0,35 ; 132,97];	1,48 [-0,46 ; 3,43]; 0,124	0,124	
Number of baseline Gd-enhancing lesions	>=1	258	7	2.71	251	1	0.40	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	286	5	1.75	293	1	0.34	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	7	3.11	202	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	1	1.19	98	1	1.02	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	4	1.69	248	1	0.40	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	1	10.00	12	0	0.00	3,55 [0,16 ; 78,56]	3,95 [0,14 ; 108,09];	9,79 [-13,03 ; 32,61]; 0,478	0,478	0,5269
	White	535	11	2.06	536	2	0.37	5,51 [1,23 ; 24,74]	5,6 [1,24 ; 25,41];	1,68 [0,37 ; 2,99]; 0,012	0,012	
	No	347	4	1.15	379	2	0.53	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	8	4.04	169	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Region	Eastern Europe	492	9	1.83	495	2	0.40	4,53 [0,98 ; 20,85]	4,59 [0,99 ; 21,37];	1,43 [0,12 ; 2,73]; 0,037	0,037	0,2994
	USA and Western Europe	53	3	5.66	53	0	0.00	7 [0,37 ; 132,29]	7,42 [0,37 ; 147,18];	5,56 [-1,49 ; 12,6]; 0,118	0,118	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Respiratory, thoracic and mediastinal disorders | Dyspnoea

6.1.43 Infections and infestations - Bronchitis

Tabelle 307: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	15	4.60	302	16	5.30	0,87 [0,44 ; 1,73]	0,86 [0,42 ; 1,78];	-0,7 [-4,1 ; 2,7]; 0,716	0,716	0,0224
	>= 38 years	219	9	4.11	246	2	0.81	5,05 [1,1 ; 23,14]	5,23 [1,12 ; 24,47];	3,3 [0,44 ; 6,16]; 0,029	0,029	
Disease Severity at baseline (EDSS)	<=3.5	419	20	4.77	415	17	4.10	1,17 [0,62 ; 2,19]	1,17 [0,61 ; 2,27];	0,68 [-2,12 ; 3,47]; 0,737	0,737	0,2249
	>3.5	126	4	3.17	133	1	0.75	4,22 [0,48 ; 37,27]	4,33 [0,48 ; 39,26];	2,42 [-0,97 ; 5,82]; 0,203	0,203	
Gender	Female	345	22	6.38	356	13	3.65	1,75 [0,89 ; 3,41]	1,8 [0,89 ; 3,63];	2,73 [-0,51 ; 5,96]; 0,119	0,119	0,0727
	Male	200	2	1.00	192	5	2.60	0,38 [0,08 ; 1,96]	0,38 [0,07 ; 1,97];	-1,6 [-4,25 ; 1,04]; 0,276	0,276	
Number of baseline Gd-enhancing lesions	>=1	258	11	4.26	251	8	3.19	1,34 [0,55 ; 3,27]	1,35 [0,53 ; 3,42];	1,08 [-2,21 ; 4,36]; 0,642	0,642	0,9953
	0	286	13	4.55	293	10	3.41	1,33 [0,59 ; 2,99]	1,35 [0,58 ; 3,12];	1,13 [-2,05 ; 4,32]; 0,529	0,529	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	11	4.89	202	5	2.48	1,98 [0,7 ; 5,59]	2,03 [0,69 ; 5,93];	2,41 [-1,13 ; 5,95]; 0,212	0,212	0,0845
	>=3	84	2	2.38	98	7	7.14	0,33 [0,07 ; 1,56]	0,32 [0,06 ; 1,57];	-4,76 [-10,81 ; 1,29]; 0,181	0,181	
	2	236	11	4.66	248	6	2.42	1,93 [0,72 ; 5,13]	1,97 [0,72 ; 5,42];	2,24 [-1,06 ; 5,54]; 0,22	0,22	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	24	4.49	536	18	3.36	1,34 [0,73 ; 2,43]	1,35 [0,72 ; 2,52];	1,13 [-1,2 ; 3,45]; 0,35	0,35	
	No	347	15	4.32	379	11	2.90	1,49 [0,69 ; 3,2]	1,51 [0,68 ; 3,34];	1,42 [-1,31 ; 4,15]; 0,324	0,324	0,63

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	9	4.55	169	7	4.14	1,1 [0,42 ; 2,88]	1,1 [0,4 ; 3,03];	0,4 [-3,77 ; 4,58]; 1	1	
Region	Eastern Europe	492	22	4.47	495	15	3.03	1,48 [0,77 ; 2,81]	1,5 [0,77 ; 2,92];	1,44 [-0,93 ; 3,81]; 0,246	0,246	0,399
	USA and Western Europe	53	2	3.77	53	3	5.66	0,67 [0,12 ; 3,83]	0,65 [0,1 ; 4,08];	-1,89 [-9,95 ; 6,18]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Bronchitis

6.1.44 Infections and infestations - Oral herpes

Tabelle 308: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	8	2.45	302	16	5.30	0,46 [0,2 ; 1,07]	0,45 [0,19 ; 1,07];	-2,84 [-5,88 ; 0,19]; 0,094	0,094	0,0024
	>= 38 years	219	9	4.11	246	2	0.81	5,05 [1,1 ; 23,14]	5,23 [1,12 ; 24,47];	3,3 [0,44 ; 6,16]; 0,029	0,029	
Disease Severity at baseline (EDSS)	<=3.5	419	16	3.82	415	13	3.13	1,22 [0,59 ; 2,5]	1,23 [0,58 ; 2,59];	0,69 [-1,8 ; 3,17]; 0,706	0,706	0,0821
	>3.5	126	1	0.79	133	5	3.76	0,21 [0,03 ; 1,78]	0,2 [0,02 ; 1,78];	-2,97 [-6,55 ; 0,62]; 0,214	0,214	
Gender	Female	345	16	4.64	356	15	4.21	1,1 [0,55 ; 2,19]	1,11 [0,54 ; 2,27];	0,42 [-2,62 ; 3,47]; 0,855	0,855	0,2723
	Male	200	1	0.50	192	3	1.56	0,32 [0,03 ; 3,05]	0,32 [0,03 ; 3,07];	-1,06 [-3,07 ; 0,95]; 0,363	0,363	
Number of baseline Gd-enhancing lesions	>=1	258	11	4.26	251	9	3.59	1,19 [0,5 ; 2,82]	1,2 [0,49 ; 2,94];	0,68 [-2,69 ; 4,05]; 0,821	0,821	0,4139
	0	286	6	2.10	293	9	3.07	0,68 [0,25 ; 1,89]	0,68 [0,24 ; 1,92];	-0,97 [-3,55 ; 1,61]; 0,603	0,603	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	8	3.56	202	9	4.46	0,8 [0,31 ; 2,03]	0,79 [0,3 ; 2,09];	-0,9 [-4,63 ; 2,84]; 0,805	0,805	0,0689
	>=3	84	3	3.57	98	0	0.00	8,15 [0,43 ; 155,61]	8,46 [0,43 ; 166,18];	3,61 [-0,84 ; 8,06]; 0,046	0,046	
	2	236	6	2.54	248	9	3.63	0,7 [0,25 ; 1,94]	0,69 [0,24 ; 1,98];	-1,09 [-4,16 ; 1,99]; 0,603	0,603	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	17	3.18	536	18	3.36	0,95 [0,49 ; 1,82]	0,94 [0,48 ; 1,85];	-0,18 [-2,31 ; 1,95]; 1	1	
	No	347	13	3.75	379	14	3.69	1,01 [0,48 ; 2,13]	1,01 [0,47 ; 2,19];	0,05 [-2,7 ; 2,81]; 1	1	0,8287

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	4	2.02	169	4	2.37	0,85 [0,22 ; 3,36]	0,85 [0,21 ; 3,45];	-0,35 [-3,36 ; 2,67]; 1	1	
Region	Eastern Europe	492	14	2.85	495	18	3.64	0,78 [0,39 ; 1,56]	0,78 [0,38 ; 1,58];	-0,79 [-3 ; 1,42]; 0,591	0,591	0,0299
	USA and Western Europe	53	3	5.66	53	0	0.00	7 [0,37 ; 132,29]	7,42 [0,37 ; 147,18];	5,56 [-1,49 ; 12,6]; 0,118	0,118	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Oral herpes

6.1.45 Psychiatric disorders - Depression

Tabelle 309: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	6	1.84	302	3	0.99	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>= 38 years	219	2	0.91	246	7	2.85	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	419	8	1.91	415	7	1.69	1,13 [0,41 ; 3,09]	1,13 [0,41 ; 3,16];	0,22 [-1,58 ; 2,03]; 1	1	0,0493
	>3.5	126	0	0.00	133	3	2.26	0,15 [0,01 ; 2,89]	0,15 [0,01 ; 2,88];	-2,22 [-5,13 ; 0,69]; 0,123	0,123	
Gender	Female	345	7	2.03	356	8	2.25	0,9 [0,33 ; 2,46]	0,9 [0,32 ; 2,51];	-0,22 [-2,36 ; 1,92]; 1	1	0,6276
	Male	200	1	0.50	192	2	1.04	0,48 [0,04 ; 5,25]	0,48 [0,04 ; 5,31];	-0,54 [-2,28 ; 1,2]; 0,616	0,616	
Number of baseline Gd-enhancing lesions	>=1	258	5	1.94	251	7	2.79	0,69 [0,22 ; 2,16]	0,69 [0,22 ; 2,2];	-0,85 [-3,49 ; 1,79]; 0,572	0,572	0,6948
	0	286	3	1.05	293	3	1.02	1,02 [0,21 ; 5,03]	1,02 [0,21 ; 5,12];	0,03 [-1,63 ; 1,68]; 1	1	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	3	1.33	202	7	3.47	0,38 [0,1 ; 1,47]	0,38 [0,1 ; 1,48];	-2,13 [-5,07 ; 0,8]; 0,202	0,202	0,2918
	>=3	84	0	0.00	98	0	0.00	1,16 [0,02 ; 58,07]	1,17 [0,02 ; 59,38];	0,08 [-2,06 ; 2,23]; 1	1	
	2	236	5	2.12	248	3	1.21	1,75 [0,42 ; 7,25]	1,77 [0,42 ; 7,48];	0,91 [-1,38 ; 3,2]; 0,495	0,495	
Race	Other	10	1	10.00	12	3	25.00	0,4 [0,05 ; 3,27]	0,33 [0,03 ; 3,84];	-15 [-45,76 ; 15,76]; 0,594	0,594	0,3995
	White	535	7	1.31	536	7	1.31	1 [0,35 ; 2,84]	1 [0,35 ; 2,88];	0 [-1,36 ; 1,36]; 1	1	
	No	347	6	1.73	379	6	1.58	1,09 [0,36 ; 3,35]	1,09 [0,35 ; 3,42];	0,15 [-1,71 ; 2,01]; 1	1	0,3538

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	2	1.01	169	4	2.37	0,43 [0,08 ; 2,3]	0,42 [0,08 ; 2,33];	-1,36 [-4,04 ; 1,33]; 0,42	0,42	
Region	Eastern Europe	492	5	1.02	495	7	1.41	0,72 [0,23 ; 2,25]	0,72 [0,23 ; 2,27];	-0,4 [-1,76 ; 0,97]; 0,773	0,773	0,7445
	USA and Western Europe	53	3	5.66	53	3	5.66	1 [0,21 ; 4,73]	1 [0,19 ; 5,19];	0 [-8,8 ; 8,8]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Psychiatric disorders | Depression

6.1.46 Nervous system disorders - Hypoaesthesia

Tabelle 310: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	7	2.15	302	9	2.98	0,72 [0,27 ; 1,91]	0,71 [0,26 ; 1,94];	-0,83 [-3,31 ; 1,65]; 0,615	0,615	0,0268
	>= 38 years	219	0	0.00	246	6	2.44	0,09 [0 ; 1,52]	0,08 [0 ; 1,5];	-2,4 [-4,5 ; -0,31]; 0,032	0,032	
Disease Severity at baseline (EDSS)	<=3.5	419	7	1.67	415	11	2.65	0,63 [0,25 ; 1,61]	0,62 [0,24 ; 1,63];	-0,98 [-2,95 ; 0,99]; 0,352	0,352	0,0682
	>3.5	126	0	0.00	133	4	3.01	0,12 [0,01 ; 2,16]	0,11 [0,01 ; 2,13];	-2,96 [-6,2 ; 0,27]; 0,123	0,123	
Gender	Female	345	5	1.45	356	10	2.81	0,52 [0,18 ; 1,49]	0,51 [0,17 ; 1,5];	-1,36 [-3,49 ; 0,77]; 0,297	0,297	0,7659
	Male	200	2	1.00	192	5	2.60	0,38 [0,08 ; 1,96]	0,38 [0,07 ; 1,97];	-1,6 [-4,25 ; 1,04]; 0,276	0,276	
Number of baseline Gd-enhancing lesions	>=1	258	5	1.94	251	6	2.39	0,81 [0,25 ; 2,62]	0,81 [0,24 ; 2,68];	-0,45 [-2,98 ; 2,08]; 0,769	0,769	0,2287
	0	286	2	0.70	293	8	2.73	0,26 [0,05 ; 1,2]	0,25 [0,05 ; 1,19];	-2,03 [-4,13 ; 0,07]; 0,107	0,107	
	NA	1	0	0.00	4	1	25.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	2	0.89	202	6	2.97	0,3 [0,06 ; 1,47]	0,29 [0,06 ; 1,47];	-2,08 [-4,72 ; 0,56]; 0,157	0,157	0,1817
	>=3	84	0	0.00	98	3	3.06	0,17 [0,01 ; 3,18]	0,16 [0,01 ; 3,17];	-2,95 [-6,93 ; 1,04]; 0,127	0,127	
	2	236	5	2.12	248	6	2.42	0,88 [0,27 ; 2,83]	0,87 [0,26 ; 2,9];	-0,3 [-2,95 ; 2,35]; 1	1	
Race	Other	10	0	0.00	12	2	16.67	0,24 [0,01 ; 4,42]	0,2 [0,01 ; 4,69];	-14,69 [-39,39 ; 10,02]; 0,481	0,481	0,2152
	White	535	7	1.31	536	13	2.43	0,54 [0,22 ; 1,34]	0,53 [0,21 ; 1,35];	-1,12 [-2,74 ; 0,5]; 0,259	0,259	
	No	347	5	1.44	379	7	1.85	0,78 [0,25 ; 2,44]	0,78 [0,24 ; 2,47];	-0,41 [-2,25 ; 1,44]; 0,775	0,775	0,1645

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	2	1.01	169	8	4.73	0,21 [0,05 ; 0,99]	0,21 [0,04 ; 0,98];	-3,72 [-7,22 ; -0,23]; 0,049	0,049	
Region	Eastern Europe	492	7	1.42	495	8	1.62	0,88 [0,32 ; 2,41]	0,88 [0,32 ; 2,44];	-0,19 [-1,72 ; 1,33]; 1	1	0,0072
	USA and Western Europe	53	0	0.00	53	7	13.21	0,07 [0 ; 1,14]	0,06 [0 ; 1,04];	-12,96 [-22,53 ; -3,39]; 0,006	0,006	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Nervous system disorders | Hypoaesthesia

6.1.47 Investigations - Lymphocyte count decreased

Tabelle 311: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	32	9.82	302	6	1.99	4,94 [2,1 ; 11,65]	5,37 [2,21 ; 13,03];	7,83 [4,24 ; 11,42]; 0	0	0,9414
	>= 38 years	219	17	7.76	246	4	1.63	4,77 [1,63 ; 13,97]	5,09 [1,69 ; 15,37];	6,14 [2,26 ; 10,02]; 0,002	0,002	
Disease Severity at baseline (EDSS)	<=3.5	419	35	8.35	415	9	2.17	3,85 [1,88 ; 7,91]	4,11 [1,95 ; 8,67];	6,18 [3,19 ; 9,18]; 0	0	0,1513
	>3.5	126	14	11.11	133	1	0.75	14,78 [1,97 ; 110,74]	16,5 [2,14 ; 127,44];	10,36 [4,68 ; 16,04]; 0	0	
Gender	Female	345	31	8.99	356	5	1.40	6,4 [2,52 ; 16,26]	6,93 [2,66 ; 18,04];	7,58 [4,33 ; 10,84]; 0	0	0,3784
	Male	200	18	9.00	192	5	2.60	3,46 [1,31 ; 9,12]	3,7 [1,35 ; 10,17];	6,4 [1,83 ; 10,96]; 0,009	0,009	
Number of baseline Gd-enhancing lesions	>=1	258	20	7.75	251	3	1.20	6,49 [1,95 ; 21,55]	6,95 [2,04 ; 23,68];	6,56 [3,03 ; 10,09]; 0	0	0,5829
	0	286	29	10.14	293	7	2.39	4,24 [1,89 ; 9,53]	4,61 [1,99 ; 10,7];	7,75 [3,84 ; 11,66]; 0	0	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	14	6.22	202	3	1.49	4,19 [1,22 ; 14,37]	4,4 [1,25 ; 15,55];	4,74 [1,17 ; 8,31]; 0,013	0,013	0,6751
	>=3	84	14	16.67	98	2	2.04	8,17 [1,91 ; 34,91]	9,6 [2,11 ; 43,6];	14,63 [6,18 ; 23,07]; 0	0	
	2	236	21	8.90	248	5	2.02	4,41 [1,69 ; 11,51]	4,75 [1,76 ; 12,81];	6,88 [2,85 ; 10,91]; 0,001	0,001	
Race	Other	10	1	10.00	12	0	0.00	3,55 [0,16 ; 78,56]	3,95 [0,14 ; 108,09];	9,79 [-13,03 ; 32,61]; 0,478	0,478	0,5047
	White	535	48	8.97	536	10	1.87	4,81 [2,46 ; 9,4]	5,18 [2,59 ; 10,36];	7,11 [4,43 ; 9,79]; 0	0	
	No	347	38	10.95	379	8	2.11	5,19 [2,45 ; 10,97]	5,7 [2,62 ; 12,41];	8,84 [5,25 ; 12,43]; 0	0	0,8653

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	11	5.56	169	2	1.18	4,69 [1,06 ; 20,88]	4,91 [1,07 ; 22,48];	4,37 [0,79 ; 7,96]; 0,025	0,025	
Region	Eastern Europe	492	48	9.76	495	8	1.62	6,04 [2,89 ; 12,63]	6,58 [3,08 ; 14,06];	8,14 [5,29 ; 10,99]; 0	0	0,0408
	USA and Western Europe	53	1	1.89	53	2	3.77	0,5 [0,05 ; 5,35]	0,49 [0,04 ; 5,58];	-1,89 [-8,19 ; 4,42]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Investigations | Lymphocyte count decreased

6.1.48 Investigations - White blood cell count decreased

Tabelle 312: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	6	1.84	302	12	3.97	0,46 [0,18 ; 1,22]	0,45 [0,17 ; 1,22];	-2,13 [-4,78 ; 0,51]; 0,15	0,15	0,8739
	>= 38 years	219	1	0.46	246	3	1.22	0,37 [0,04 ; 3,57]	0,37 [0,04 ; 3,6];	-0,76 [-2,4 ; 0,87]; 0,626	0,626	
Disease Severity at baseline (EDSS)	<=3.5	419	6	1.43	415	13	3.13	0,46 [0,18 ; 1,19]	0,45 [0,17 ; 1,19];	-1,7 [-3,73 ; 0,33]; 0,11	0,11	0,9083
	>3.5	126	1	0.79	133	2	1.50	0,53 [0,05 ; 5,75]	0,52 [0,05 ; 5,85];	-0,71 [-3,29 ; 1,87]; 1	1	
Gender	Female	345	3	0.87	356	9	2.53	0,34 [0,09 ; 1,26]	0,34 [0,09 ; 1,26];	-1,66 [-3,56 ; 0,24]; 0,143	0,143	0,5012
	Male	200	4	2.00	192	6	3.12	0,64 [0,18 ; 2,23]	0,63 [0,18 ; 2,28];	-1,12 [-4,26 ; 2,01]; 0,536	0,536	
Number of baseline Gd-enhancing lesions	>=1	258	4	1.55	251	9	3.59	0,43 [0,13 ; 1,39]	0,42 [0,13 ; 1,39];	-2,04 [-4,79 ; 0,71]; 0,169	0,169	0,8476
	0	286	3	1.05	293	6	2.05	0,51 [0,13 ; 2,03]	0,51 [0,13 ; 2,05];	-1 [-3 ; 1,01]; 0,505	0,505	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	1	0.44	202	8	3.96	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	4	4.76	98	3	3.06	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	2	0.85	248	4	1.61	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	7	1.31	536	15	2.80	0,47 [0,19 ; 1,14]	0,46 [0,19 ; 1,14];	-1,49 [-3,19 ; 0,21]; 0,13	0,13	
	No	347	5	1.44	379	8	2.11	0,68 [0,23 ; 2,07]	0,68 [0,22 ; 2,09];	-0,67 [-2,58 ; 1,24]; 0,583	0,583	0,2741

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	2	1.01	169	7	4.14	0,24 [0,05 ; 1,16]	0,24 [0,05 ; 1,15];	-3,13 [-6,44 ; 0,18]; 0,087	0,087	
Region	Eastern Europe	492	7	1.42	495	13	2.63	0,54 [0,22 ; 1,35]	0,54 [0,21 ; 1,35];	-1,2 [-2,96 ; 0,55]; 0,258	0,258	0,1993
	USA and Western Europe	53	0	0.00	53	2	3.77	0,2 [0,01 ; 4,07]	0,19 [0,01 ; 4,11];	-3,7 [-9,86 ; 2,46]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Investigations | White blood cell count decreased

6.1.49 General disorders and administration site conditions - Pyrexia

Tabelle 313: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	52	15.95	302	13	4.30	3,71 [2,06 ; 6,67]	4,22 [2,25 ; 7,92];	11,65 [7,06 ; 16,23]; 0	0	0,1254
	>= 38 years	219	24	10.96	246	14	5.69	1,93 [1,02 ; 3,63]	2,04 [1,03 ; 4,05];	5,27 [0,22 ; 10,32]; 0,043	0,043	
Disease Severity at baseline (EDSS)	<=3.5	419	64	15.27	415	20	4.82	3,17 [1,95 ; 5,14]	3,56 [2,11 ; 6];	10,46 [6,44 ; 14,47]; 0	0	0,2675
	>3.5	126	12	9.52	133	7	5.26	1,81 [0,74 ; 4,45]	1,89 [0,72 ; 4,98];	4,26 [-2,12 ; 10,64]; 0,236	0,236	
Gender	Female	345	57	16.52	356	20	5.62	2,94 [1,81 ; 4,79]	3,33 [1,95 ; 5,67];	10,9 [6,31 ; 15,49]; 0	0	0,734
	Male	200	19	9.50	192	7	3.65	2,61 [1,12 ; 6,06]	2,77 [1,14 ; 6,76];	5,85 [1 ; 10,71]; 0,025	0,025	
Number of baseline Gd-enhancing lesions	>=1	258	33	12.79	251	9	3.59	3,57 [1,74 ; 7,3]	3,94 [1,85 ; 8,42];	9,21 [4,53 ; 13,88]; 0	0	0,4335
	0	286	43	15.03	293	18	6.14	2,45 [1,45 ; 4,14]	2,7 [1,52 ; 4,81];	8,89 [3,92 ; 13,86]; 0,001	0,001	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	30	13.33	202	12	5.94	2,24 [1,18 ; 4,26]	2,44 [1,21 ; 4,9];	7,39 [1,88 ; 12,9]; 0,014	0,014	0,6584
	>=3	84	13	15.48	98	5	5.10	3,03 [1,13 ; 8,16]	3,41 [1,16 ; 10];	10,37 [1,5 ; 19,25]; 0,025	0,025	
	2	236	33	13.98	248	10	4.03	3,47 [1,75 ; 6,88]	3,87 [1,86 ; 8,04];	9,95 [4,89 ; 15,01]; 0	0	
Race	Other	10	1	10.00	12	1	8.33	1,2 [0,09 ; 16,84]	1,22 [0,07 ; 22,4];	1,67 [-22,63 ; 25,96]; 1	1	0,5276
	White	535	75	14.02	536	26	4.85	2,89 [1,88 ; 4,44]	3,2 [2,01 ; 5,08];	9,17 [5,71 ; 12,63]; 0	0	
	No	347	45	12.97	379	17	4.49	2,89 [1,69 ; 4,95]	3,17 [1,78 ; 5,66];	8,48 [4,38 ; 12,59]; 0	0	0,8807

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	31	15.66	169	10	5.92	2,65 [1,34 ; 5,24]	2,95 [1,4 ; 6,22];	9,74 [3,55 ; 15,93]; 0,004	0,004	
Region	Eastern Europe	492	67	13.62	495	23	4.65	2,93 [1,86 ; 4,63]	3,24 [1,98 ; 5,29];	8,97 [5,42 ; 12,52]; 0	0	0,7113
	USA and Western Europe	53	9	16.98	53	4	7.55	2,25 [0,74 ; 6,86]	2,51 [0,72 ; 8,71];	9,43 [-2,93 ; 21,79]; 0,236	0,236	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - General disorders and administration site conditions | Pyrexia

6.1.50 Infections and infestations - Pneumonia

Tabelle 314: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	8	2.45	302	1	0.33	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>= 38 years	219	4	1.83	246	5	2.03	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	419	10	2.39	415	4	0.96	2,48 [0,78 ; 7,83]	2,51 [0,78 ; 8,07];	1,42 [-0,31 ; 3,16]; 0,176	0,176	0,4605
	>3.5	126	2	1.59	133	2	1.50	1,06 [0,15 ; 7,38]	1,06 [0,15 ; 7,62];	0,08 [-2,92 ; 3,09]; 1	1	
Gender	Female	345	10	2.90	356	6	1.69	1,72 [0,63 ; 4,68]	1,74 [0,63 ; 4,84];	1,21 [-1,01 ; 3,43]; 0,32	0,32	0,2002
	Male	200	2	1.00	192	0	0.00	4,8 [0,23 ; 99,36]	4,85 [0,23 ; 101,65];	0,98 [-0,71 ; 2,68]; 0,499	0,499	
Number of baseline Gd-enhancing lesions	>=1	258	7	2.71	251	3	1.20	2,27 [0,59 ; 8,68]	2,31 [0,59 ; 9,02];	1,52 [-0,88 ; 3,91]; 0,339	0,339	0,7722
	0	286	5	1.75	293	3	1.02	1,71 [0,41 ; 7,08]	1,72 [0,41 ; 7,27];	0,72 [-1,18 ; 2,63]; 0,5	0,5	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	6	2.67	202	2	0.99	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	3	3.57	98	2	2.04	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	3	1.27	248	2	0.81	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	12	2.24	536	6	1.12	2 [0,76 ; 5,3]	2,03 [0,76 ; 5,44];	1,12 [-0,42 ; 2,66]; 0,163	0,163	
	No	347	10	2.88	379	3	0.79	3,64 [1,01 ; 13,12]	3,72 [1,02 ; 13,63];	2,09 [0,12 ; 4,06]; 0,047	0,047	0,0889

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	2	1.01	169	3	1.78	0,57 [0,1 ; 3,37]	0,56 [0,09 ; 3,42];	-0,77 [-3,19 ; 1,66]; 0,665	0,665	
Region	Eastern Europe	492	9	1.83	495	5	1.01	1,81 [0,61 ; 5,37]	1,83 [0,61 ; 5,49];	0,82 [-0,66 ; 2,3]; 0,297	0,297	0,6727
	USA and Western Europe	53	3	5.66	53	1	1.89	3 [0,32 ; 27,93]	3,12 [0,31 ; 31];	3,77 [-3,45 ; 10,99]; 0,618	0,618	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Pneumonia

6.1.51 Musculoskeletal and connective tissue disorders - Arthralgia

Tabelle 315: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	12	3.68	302	7	2.32	1,59 [0,63 ; 3,98]	1,61 [0,63 ; 4,15];	1,36 [-1,29 ; 4,02]; 0,359	0,359	0,3163
	>= 38 years	219	9	4.11	246	12	4.88	0,84 [0,36 ; 1,96]	0,84 [0,35 ; 2,02];	-0,77 [-4,53 ; 2,99]; 0,824	0,824	
Disease Severity at baseline (EDSS)	<=3.5	419	20	4.77	415	15	3.61	1,32 [0,69 ; 2,54]	1,34 [0,67 ; 2,65];	1,16 [-1,56 ; 3,88]; 0,49	0,49	0,1214
	>3.5	126	1	0.79	133	4	3.01	0,26 [0,03 ; 2,33]	0,26 [0,03 ; 2,34];	-2,21 [-5,5 ; 1,08]; 0,371	0,371	
Gender	Female	345	13	3.77	356	14	3.93	0,96 [0,46 ; 2,01]	0,96 [0,44 ; 2,07];	-0,16 [-3,01 ; 2,68]; 1	1	0,4826
	Male	200	8	4.00	192	5	2.60	1,54 [0,51 ; 4,61]	1,56 [0,5 ; 4,85];	1,4 [-2,13 ; 4,92]; 0,576	0,576	
Number of baseline Gd-enhancing lesions	>=1	258	14	5.43	251	7	2.79	1,95 [0,8 ; 4,74]	2 [0,79 ; 5,04];	2,64 [-0,8 ; 6,07]; 0,181	0,181	0,0637
	0	286	7	2.45	293	12	4.10	0,6 [0,24 ; 1,5]	0,59 [0,23 ; 1,51];	-1,65 [-4,54 ; 1,24]; 0,352	0,352	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	12	5.33	202	10	4.95	1,08 [0,48 ; 2,44]	1,08 [0,46 ; 2,56];	0,38 [-3,81 ; 4,57]; 1	1	0,2405
	>=3	84	0	0.00	98	2	2.04	0,23 [0,01 ; 4,79]	0,23 [0,01 ; 4,82];	-1,94 [-5,43 ; 1,55]; 0,5	0,5	
	2	236	9	3.81	248	7	2.82	1,35 [0,51 ; 3,57]	1,37 [0,5 ; 3,73];	0,99 [-2,21 ; 4,19]; 0,616	0,616	
Race	Other	10	1	10.00	12	2	16.67	0,6 [0,06 ; 5,69]	0,56 [0,04 ; 7,21];	-6,67 [-34,78 ; 21,45]; 1	1	0,566
	White	535	20	3.74	536	17	3.17	1,18 [0,62 ; 2,22]	1,19 [0,61 ; 2,29];	0,57 [-1,62 ; 2,75]; 0,621	0,621	
	No	347	13	3.75	379	10	2.64	1,42 [0,63 ; 3,2]	1,44 [0,62 ; 3,32];	1,11 [-1,46 ; 3,68]; 0,406	0,406	0,3194

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	8	4.04	169	9	5.33	0,76 [0,3 ; 1,92]	0,75 [0,28 ; 1,99];	-1,29 [-5,64 ; 3,07]; 0,623	0,623	
Region	Eastern Europe	492	12	2.44	495	13	2.63	0,93 [0,43 ; 2,02]	0,93 [0,42 ; 2,05];	-0,19 [-2,15 ; 1,77]; 1	1	0,4302
	USA and Western Europe	53	9	16.98	53	6	11.32	1,5 [0,57 ; 3,92]	1,6 [0,53 ; 4,87];	5,66 [-7,57 ; 18,89]; 0,579	0,579	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Musculoskeletal and connective tissue disorders | Arthralgia

6.1.52 Blood and lymphatic system disorders - Leukocytosis

Tabelle 316: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	5	1.53	302	9	2.98	0,51 [0,17 ; 1,52]	0,51 [0,17 ; 1,53];	-1,45 [-3,78 ; 0,89]; 0,282	0,282	0,3757
	>= 38 years	219	1	0.46	246	6	2.44	0,19 [0,02 ; 1,54]	0,18 [0,02 ; 1,54];	-1,98 [-4,11 ; 0,14]; 0,127	0,127	
Disease Severity at baseline (EDSS)	<=3.5	419	4	0.95	415	10	2.41	0,4 [0,13 ; 1,25]	0,39 [0,12 ; 1,25];	-1,45 [-3,2 ; 0,29]; 0,114	0,114	0,9568
	>3.5	126	2	1.59	133	5	3.76	0,42 [0,08 ; 2,14]	0,41 [0,08 ; 2,17];	-2,17 [-6,07 ; 1,73]; 0,448	0,448	
Gender	Female	345	4	1.16	356	10	2.81	0,41 [0,13 ; 1,3]	0,41 [0,13 ; 1,31];	-1,65 [-3,7 ; 0,41]; 0,176	0,176	0,9445
	Male	200	2	1.00	192	5	2.60	0,38 [0,08 ; 1,96]	0,38 [0,07 ; 1,97];	-1,6 [-4,25 ; 1,04]; 0,276	0,276	
Number of baseline Gd-enhancing lesions	>=1	258	3	1.16	251	10	3.98	0,29 [0,08 ; 1,05]	0,28 [0,08 ; 1,04];	-2,82 [-5,57 ; -0,07]; 0,051	0,051	0,439
	0	286	3	1.05	293	5	1.71	0,61 [0,15 ; 2,55]	0,61 [0,14 ; 2,58];	-0,66 [-2,55 ; 1,24]; 0,725	0,725	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	1	0.44	202	9	4.46	0,1 [0,01 ; 0,78]	0,1 [0,01 ; 0,76];	-4,01 [-6,99 ; -1,04]; 0,008	0,008	0,1093
	>=3	84	2	2.38	98	2	2.04	1,17 [0,17 ; 8,1]	1,17 [0,16 ; 8,5];	0,34 [-3,96 ; 4,64]; 1	1	
	2	236	3	1.27	248	4	1.61	0,79 [0,18 ; 3,48]	0,79 [0,17 ; 3,55];	-0,34 [-2,46 ; 1,78]; 1	1	
Race	Other	10	0	0.00	12	1	8.33	0,39 [0,02 ; 8,73]	0,37 [0,01 ; 9,98];	-6,99 [-28,28 ; 14,29]; 0,493	0,493	0,4312
	White	535	6	1.12	536	14	2.61	0,43 [0,17 ; 1,11]	0,42 [0,16 ; 1,11];	-1,49 [-3,11 ; 0,13]; 0,112	0,112	
	No	347	1	0.29	379	7	1.85	0,16 [0,02 ; 1,26]	0,15 [0,02 ; 1,25];	-1,56 [-3,03 ; -0,09]; 0,071	0,071	0,2794

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	5	2.53	169	8	4.73	0,53 [0,18 ; 1,6]	0,52 [0,17 ; 1,62];	-2,21 [-6,08 ; 1,67]; 0,273	0,273	
Region	Eastern Europe	492	6	1.22	495	14	2.83	0,43 [0,17 ; 1,11]	0,42 [0,16 ; 1,11];	-1,61 [-3,36 ; 0,14]; 0,112	0,112	0,4047
	USA and Western Europe	53	0	0.00	53	1	1.89	0,33 [0,01 ; 8]	0,33 [0,01 ; 8,21];	-1,85 [-6,93 ; 3,22]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Blood and lymphatic system disorders | Leukocytosis

6.1.53 Investigations - Weight decreased

Tabelle 317: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	3	0.92	302	6	1.99	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>= 38 years	219	2	0.91	246	4	1.63	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	419	4	0.95	415	7	1.69	0,57 [0,17 ; 1,92]	0,56 [0,16 ; 1,93];	-0,73 [-2,28 ; 0,82]; 0,382	0,382	0,7094
	>3.5	126	1	0.79	133	3	2.26	0,35 [0,04 ; 3,34]	0,35 [0,04 ; 3,38];	-1,46 [-4,42 ; 1,5]; 0,623	0,623	
Gender	Female	345	2	0.58	356	7	1.97	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	Male	200	3	1.50	192	3	1.56	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of baseline Gd-enhancing lesions	>=1	258	1	0.39	251	6	2.39	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	286	4	1.40	293	3	1.02	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	1	0	0.00	4	1	25.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	2	0.89	202	4	1.98	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	0	0.00	98	5	5.10	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	3	1.27	248	1	0.40	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	0	0.00	12	1	8.33	0,39 [0,02 ; 8,73]	0,37 [0,01 ; 9,98];	-6,99 [-28,28 ; 14,29]; 0,493	0,493	0,3825
	White	535	5	0.93	536	9	1.68	0,56 [0,19 ; 1,65]	0,55 [0,18 ; 1,66];	-0,74 [-2,1 ; 0,61]; 0,421	0,421	
	No	347	5	1.44	379	5	1.32	1,09 [0,32 ; 3,74]	1,09 [0,31 ; 3,81];	0,12 [-1,58 ; 1,82]; 1	1	0,0131

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	0	0.00	169	5	2.96	0,08 [0 ; 1,39]	0,08 [0 ; 1,37];	-2,98 [-5,73 ; -0,23]; 0,009	0,009	
Region	Eastern Europe	492	4	0.81	495	9	1.82	0,45 [0,14 ; 1,44]	0,44 [0,14 ; 1,45];	-1,01 [-2,42 ; 0,41]; 0,264	0,264	0,6016
	USA and Western Europe	53	1	1.89	53	1	1.89	1 [0,06 ; 15,57]	1 [0,06 ; 16,42];	0 [-5,18 ; 5,18]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Investigations | Weight decreased

6.1.54 Psychiatric disorders - Insomnia

Tabelle 318: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	20	6.13	302	11	3.64	1,68 [0,82 ; 3,46]	1,73 [0,81 ; 3,67];	2,49 [-0,86 ; 5,85]; 0,197	0,197	0,3853
	>= 38 years	219	13	5.94	246	5	2.03	2,92 [1,06 ; 8,06]	3,04 [1,07 ; 8,68];	3,9 [0,31 ; 7,5]; 0,032	0,032	
Disease Severity at baseline (EDSS)	<=3.5	419	31	7.40	415	12	2.89	2,56 [1,33 ; 4,91]	2,68 [1,36 ; 5,3];	4,51 [1,53 ; 7,49]; 0,004	0,004	0,0711
	>3.5	126	2	1.59	133	4	3.01	0,53 [0,1 ; 2,83]	0,52 [0,09 ; 2,89];	-1,42 [-5,05 ; 2,21]; 0,685	0,685	
Gender	Female	345	22	6.38	356	7	1.97	3,24 [1,4 ; 7,49]	3,4 [1,43 ; 8,06];	4,41 [1,46 ; 7,36]; 0,004	0,004	0,0956
	Male	200	11	5.50	192	9	4.69	1,17 [0,5 ; 2,77]	1,18 [0,48 ; 2,92];	0,81 [-3,54 ; 5,16]; 0,82	0,82	
Number of baseline Gd-enhancing lesions	>=1	258	20	7.75	251	8	3.19	2,43 [1,09 ; 5,42]	2,55 [1,1 ; 5,91];	4,56 [0,64 ; 8,49]; 0,031	0,031	0,5141
	0	286	13	4.55	293	8	2.73	1,66 [0,7 ; 3,96]	1,7 [0,69 ; 4,16];	1,82 [-1,24 ; 4,87]; 0,272	0,272	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	15	6.67	202	2	0.99	6,73 [1,56 ; 29,08]	7,14 [1,61 ; 31,63];	5,68 [2,14 ; 9,21]; 0,002	0,002	0,0626
	>=3	84	3	3.57	98	1	1.02	3,5 [0,37 ; 33,02]	3,59 [0,37 ; 35,21];	2,55 [-1,89 ; 6,99]; 0,336	0,336	
	2	236	15	6.36	248	13	5.24	1,21 [0,59 ; 2,49]	1,23 [0,57 ; 2,64];	1,11 [-3,06 ; 5,28]; 0,698	0,698	
Race	Other	10	2	20.00	12	0	0.00	5,91 [0,32 ; 110,47]	7,35 [0,31 ; 173,13];	18,88 [-8 ; 45,76]; 0,195	0,195	0,1529
	White	535	31	5.79	536	16	2.99	1,94 [1,07 ; 3,51]	2 [1,08 ; 3,7];	2,81 [0,36 ; 5,26]; 0,026	0,026	
	No	347	22	6.34	379	11	2.90	2,18 [1,08 ; 4,44]	2,26 [1,08 ; 4,74];	3,44 [0,37 ; 6,51]; 0,032	0,032	0,8108

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	11	5.56	169	5	2.96	1,88 [0,67 ; 5,3]	1,93 [0,66 ; 5,67];	2,6 [-1,49 ; 6,68]; 0,307	0,307	
Region	Eastern Europe	492	23	4.67	495	16	3.23	1,45 [0,77 ; 2,7]	1,47 [0,77 ; 2,81];	1,44 [-0,99 ; 3,87]; 0,257	0,257	0,0017
	USA and Western Europe	53	10	18.87	53	0	0.00	21 [1,26 ; 349,45]	25,83 [1,47 ; 453,3];	18,52 [7,66 ; 29,38]; 0,001	0,001	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Psychiatric disorders | Insomnia

6.1.55 Respiratory, thoracic and mediastinal disorders - Cough

Tabelle 319: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	13	3.99	302	8	2.65	1,51 [0,63 ; 3,58]	1,53 [0,62 ; 3,74];	1,34 [-1,45 ; 4,13]; 0,383	0,383	0,0863
	>= 38 years	219	11	5.02	246	2	0.81	6,18 [1,38 ; 27,57]	6,45 [1,41 ; 29,44];	4,21 [1,11 ; 7,31]; 0,009	0,009	
Disease Severity at baseline (EDSS)	<=3.5	419	21	5.01	415	10	2.41	2,08 [0,99 ; 4,36]	2,14 [0,99 ; 4,6];	2,6 [0,04 ; 5,16]; 0,066	0,066	0,1293
	>3.5	126	3	2.38	133	0	0.00	7,39 [0,39 ; 141,57]	7,57 [0,39 ; 147,98];	2,38 [-0,65 ; 5,41]; 0,056	0,056	
Gender	Female	345	20	5.80	356	8	2.25	2,58 [1,15 ; 5,78]	2,68 [1,16 ; 6,16];	3,55 [0,64 ; 6,46]; 0,02	0,02	0,7424
	Male	200	4	2.00	192	2	1.04	1,92 [0,36 ; 10,36]	1,94 [0,35 ; 10,71];	0,96 [-1,46 ; 3,37]; 0,685	0,685	
Number of baseline Gd-enhancing lesions	>=1	258	12	4.65	251	5	1.99	2,33 [0,83 ; 6,53]	2,4 [0,83 ; 6,91];	2,66 [-0,44 ; 5,76]; 0,137	0,137	0,9479
	0	286	12	4.20	293	5	1.71	2,46 [0,88 ; 6,89]	2,52 [0,88 ; 7,25];	2,49 [-0,27 ; 5,25]; 0,088	0,088	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	17	7.56	202	3	1.49	5,09 [1,51 ; 17,1]	5,42 [1,56 ; 18,78];	6,07 [2,24 ; 9,91]; 0,003	0,003	0,1302
	>=3	84	2	2.38	98	2	2.04	1,17 [0,17 ; 8,1]	1,17 [0,16 ; 8,5];	0,34 [-3,96 ; 4,64]; 1	1	
	2	236	5	2.12	248	5	2.02	1,05 [0,31 ; 3,58]	1,05 [0,3 ; 3,68];	0,1 [-2,43 ; 2,64]; 1	1	
Race	Other	10	1	10.00	12	0	0.00	3,55 [0,16 ; 78,56]	3,95 [0,14 ; 108,09];	9,79 [-13,03 ; 32,61]; 0,478	0,478	0,3555
	White	535	23	4.30	536	10	1.87	2,3 [1,11 ; 4,79]	2,36 [1,11 ; 5,01];	2,43 [0,37 ; 4,5]; 0,022	0,022	
	No	347	15	4.32	379	8	2.11	2,05 [0,88 ; 4,77]	2,1 [0,88 ; 5];	2,21 [-0,37 ; 4,8]; 0,095	0,095	0,4649

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	9	4.55	169	2	1.18	3,84 [0,84 ; 17,53]	3,98 [0,85 ; 18,66];	3,36 [0,03 ; 6,69]; 0,071	0,071	
Region	Eastern Europe	492	20	4.07	495	9	1.82	2,24 [1,03 ; 4,86]	2,29 [1,03 ; 5,08];	2,25 [0,14 ; 4,35]; 0,039	0,039	0,5933
	USA and Western Europe	53	4	7.55	53	1	1.89	4 [0,46 ; 34,61]	4,24 [0,46 ; 39,31];	5,66 [-2,34 ; 13,66]; 0,363	0,363	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Respiratory, thoracic and mediastinal disorders | Cough

6.1.56 Skin and subcutaneous tissue disorders - Erythema

Tabelle 320: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	6	1.84	302	1	0.33	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>= 38 years	219	6	2.74	246	3	1.22	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	419	11	2.63	415	2	0.48	5,45 [1,21 ; 24,43]	5,57 [1,23 ; 25,27];	2,14 [0,47 ; 3,81]; 0,021	0,021	0,0888
	>3.5	126	1	0.79	133	2	1.50	0,53 [0,05 ; 5,75]	0,52 [0,05 ; 5,85];	-0,71 [-3,29 ; 1,87]; 1	1	
Gender	Female	345	4	1.16	356	3	0.84	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	Male	200	8	4.00	192	1	0.52	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of baseline Gd-enhancing lesions	>=1	258	10	3.88	251	2	0.80	4,86 [1,08 ; 21,98]	5,02 [1,09 ; 23,15];	3,08 [0,48 ; 5,68]; 0,037	0,037	0,2086
	0	286	2	0.70	293	2	0.68	1,02 [0,15 ; 7,22]	1,02 [0,14 ; 7,32];	0,02 [-1,33 ; 1,37]; 1	1	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	7	3.11	202	2	0.99	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	0	0.00	98	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	5	2.12	248	2	0.81	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	12	2.24	536	4	0.75	3,01 [0,98 ; 9,26]	3,05 [0,98 ; 9,52];	1,5 [0,05 ; 2,95]; 0,047	0,047	
	No	347	6	1.73	379	4	1.06	1,64 [0,47 ; 5,76]	1,65 [0,46 ; 5,9];	0,67 [-1,04 ; 2,39]; 0,532	0,532	0,0491

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	6	3.03	169	0	0.00	11,11 [0,63 ; 195,7]	11,45 [0,64 ; 204,7];	2,97 [0,37 ; 5,57]; 0,033	0,033	
Region	Eastern Europe	492	11	2.24	495	3	0.61	3,69 [1,04 ; 13,14]	3,75 [1,04 ; 13,53];	1,63 [0,16 ; 3,1]; 0,033	0,033	0,4076
	USA and Western Europe	53	1	1.89	53	1	1.89	1 [0,06 ; 15,57]	1 [0,06 ; 16,42];	0 [-5,18 ; 5,18]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Skin and subcutaneous tissue disorders | Erythema

6.1.57 General disorders and administration site conditions - Chills

Tabelle 321: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	33	10.12	302	1	0.33	30,57 [4,21 ; 222,14]	33,9 [4,61 ; 249,48];	9,79 [6,45 ; 13,13]; 0	0	0,0629
	>= 38 years	219	11	5.02	246	3	1.22	4,12 [1,16 ; 14,57]	4,28 [1,18 ; 15,56];	3,8 [0,6 ; 7]; 0,026	0,026	
Disease Severity at baseline (EDSS)	<=3.5	419	38	9.07	415	2	0.48	18,82 [4,57 ; 77,5]	20,6 [4,94 ; 85,95];	8,59 [5,76 ; 11,42]; 0	0	0,1067
	>3.5	126	6	4.76	133	2	1.50	3,17 [0,65 ; 15,4]	3,28 [0,65 ; 16,54];	3,26 [-1 ; 7,51]; 0,163	0,163	
Gender	Female	345	18	5.22	356	3	0.84	6,19 [1,84 ; 20,83]	6,48 [1,89 ; 22,19];	4,37 [1,84 ; 6,91]; 0,001	0,001	0,1831
	Male	200	26	13.00	192	1	0.52	24,96 [3,42 ; 182,13]	28,54 [3,83 ; 212,54];	12,48 [7,71 ; 17,25]; 0	0	
Number of baseline Gd-enhancing lesions	>=1	258	23	8.91	251	4	1.59	5,59 [1,96 ; 15,95]	6,04 [2,06 ; 17,74];	7,32 [3,51 ; 11,13]; 0	0	0,0251
	0	286	21	7.34	293	0	0.00	44,05 [2,68 ; 723,74]	47,53 [2,87 ; 788,57];	7,32 [4,24 ; 10,4]; 0	0	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	13	5.78	202	2	0.99	5,84 [1,33 ; 25,55]	6,13 [1,37 ; 27,51];	4,79 [1,45 ; 8,13]; 0,008	0,008	0,384
	>=3	84	6	7.14	98	0	0.00	15,14 [0,87 ; 264,87]	16,31 [0,91 ; 294];	7,14 [1,32 ; 12,96]; 0,009	0,009	
	2	236	25	10.59	248	2	0.81	13,14 [3,15 ; 54,85]	14,57 [3,41 ; 62,25];	9,79 [5,71 ; 13,87]; 0	0	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9997
	White	535	44	8.22	536	4	0.75	11,02 [3,99 ; 30,46]	11,92 [4,25 ; 33,41];	7,48 [5,04 ; 9,92]; 0	0	
	No	347	27	7.78	379	2	0.53	14,74 [3,53 ; 61,55]	15,9 [3,75 ; 67,4];	7,25 [4,34 ; 10,16]; 0	0	0,5059

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	17	8.59	169	2	1.18	7,26 [1,7 ; 30,95]	7,84 [1,78 ; 34,46];	7,4 [3,17 ; 11,63]; 0,001	0,001	
Region	Eastern Europe	492	38	7.72	495	3	0.61	12,74 [3,96 ; 41,01]	13,73 [4,21 ; 44,78];	7,12 [4,66 ; 9,57]; 0	0	0,5804
	USA and Western Europe	53	6	11.32	53	1	1.89	6 [0,75 ; 48,15]	6,64 [0,77 ; 57,19];	9,43 [0,15 ; 18,72]; 0,113	0,113	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - General disorders and administration site conditions | Chills

6.1.58 Gastrointestinal disorders - Constipation

Tabelle 322: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	16	4.91	302	11	3.64	1,35 [0,64 ; 2,86]	1,37 [0,62 ; 2,99];	1,27 [-1,89 ; 4,42]; 0,556	0,556	0,2265
	>= 38 years	219	7	3.20	246	12	4.88	0,66 [0,26 ; 1,63]	0,64 [0,25 ; 1,67];	-1,68 [-5,24 ; 1,88]; 0,483	0,483	
Disease Severity at baseline (EDSS)	<=3.5	419	19	4.53	415	18	4.34	1,05 [0,56 ; 1,96]	1,05 [0,54 ; 2,03];	0,2 [-2,6 ; 2,99]; 1	1	0,7704
	>3.5	126	4	3.17	133	5	3.76	0,84 [0,23 ; 3,07]	0,84 [0,22 ; 3,2];	-0,58 [-5,04 ; 3,87]; 1	1	
Gender	Female	345	16	4.64	356	14	3.93	1,18 [0,58 ; 2,38]	1,19 [0,57 ; 2,47];	0,71 [-2,3 ; 3,71]; 0,711	0,711	0,452
	Male	200	7	3.50	192	9	4.69	0,75 [0,28 ; 1,97]	0,74 [0,27 ; 2,02];	-1,19 [-5,12 ; 2,74]; 0,616	0,616	
Number of baseline Gd-enhancing lesions	>=1	258	13	5.04	251	11	4.38	1,15 [0,52 ; 2,52]	1,16 [0,51 ; 2,63];	0,66 [-3,02 ; 4,34]; 0,835	0,835	0,6071
	0	286	10	3.50	293	12	4.10	0,85 [0,37 ; 1,94]	0,85 [0,36 ; 2];	-0,6 [-3,71 ; 2,51]; 0,829	0,829	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	10	4.44	202	8	3.96	1,12 [0,45 ; 2,79]	1,13 [0,44 ; 2,92];	0,48 [-3,32 ; 4,29]; 1	1	0,25
	>=3	84	1	1.19	98	5	5.10	0,23 [0,03 ; 1,96]	0,22 [0,03 ; 1,96];	-3,91 [-8,85 ; 1,02]; 0,219	0,219	
	2	236	12	5.08	248	10	4.03	1,26 [0,56 ; 2,86]	1,27 [0,54 ; 3,01];	1,05 [-2,67 ; 4,77]; 0,665	0,665	
Race	Other	10	1	10.00	12	0	0.00	3,55 [0,16 ; 78,56]	3,95 [0,14 ; 108,09];	9,79 [-13,03 ; 32,61]; 0,478	0,478	0,1983
	White	535	22	4.11	536	23	4.29	0,96 [0,54 ; 1,7]	0,96 [0,53 ; 1,74];	-0,18 [-2,58 ; 2,22]; 1	1	
	No	347	16	4.61	379	12	3.17	1,46 [0,7 ; 3,03]	1,48 [0,69 ; 3,17];	1,44 [-1,38 ; 4,27]; 0,34	0,34	0,0975

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	7	3.54	169	11	6.51	0,54 [0,22 ; 1,37]	0,53 [0,2 ; 1,39];	-2,97 [-7,5 ; 1,55]; 0,229	0,229	
Region	Eastern Europe	492	19	3.86	495	22	4.44	0,87 [0,48 ; 1,58]	0,86 [0,46 ; 1,62];	-0,58 [-3,07 ; 1,91]; 0,75	0,75	0,1356
	USA and Western Europe	53	4	7.55	53	1	1.89	4 [0,46 ; 34,61]	4,24 [0,46 ; 39,31];	5,66 [-2,34 ; 13,66]; 0,363	0,363	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Gastrointestinal disorders | Constipation

6.1.59 Gastrointestinal disorders - Vomiting

Tabelle 323: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	9	2.76	302	11	3.64	0,76 [0,32 ; 1,8]	0,75 [0,31 ; 1,84];	-0,88 [-3,64 ; 1,88]; 0,651	0,651	0,1847
	>= 38 years	219	1	0.46	246	6	2.44	0,19 [0,02 ; 1,54]	0,18 [0,02 ; 1,54];	-1,98 [-4,11 ; 0,14]; 0,127	0,127	
Disease Severity at baseline (EDSS)	<=3.5	419	8	1.91	415	15	3.61	0,53 [0,23 ; 1,23]	0,52 [0,22 ; 1,24];	-1,71 [-3,93 ; 0,52]; 0,144	0,144	0,5208
	>3.5	126	2	1.59	133	2	1.50	1,06 [0,15 ; 7,38]	1,06 [0,15 ; 7,62];	0,08 [-2,92 ; 3,09]; 1	1	
Gender	Female	345	8	2.32	356	14	3.93	0,59 [0,25 ; 1,39]	0,58 [0,24 ; 1,4];	-1,61 [-4,18 ; 0,96]; 0,28	0,28	0,9278
	Male	200	2	1.00	192	3	1.56	0,64 [0,11 ; 3,79]	0,64 [0,11 ; 3,85];	-0,56 [-2,79 ; 1,67]; 0,68	0,68	
Number of baseline Gd-enhancing lesions	>=1	258	8	3.10	251	11	4.38	0,71 [0,29 ; 1,73]	0,7 [0,28 ; 1,77];	-1,28 [-4,58 ; 2,02]; 0,49	0,49	0,429
	0	286	2	0.70	293	6	2.05	0,34 [0,07 ; 1,68]	0,34 [0,07 ; 1,68];	-1,35 [-3,24 ; 0,54]; 0,286	0,286	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	5	2.22	202	7	3.47	0,64 [0,21 ; 1,99]	0,63 [0,2 ; 2,03];	-1,24 [-4,42 ; 1,93]; 0,561	0,561	0,6477
	>=3	84	2	2.38	98	2	2.04	1,17 [0,17 ; 8,1]	1,17 [0,16 ; 8,5];	0,34 [-3,96 ; 4,64]; 1	1	
	2	236	3	1.27	248	8	3.23	0,39 [0,11 ; 1,47]	0,39 [0,1 ; 1,47];	-1,95 [-4,58 ; 0,67]; 0,223	0,223	
Race	Other	10	1	10.00	12	1	8.33	1,2 [0,09 ; 16,84]	1,22 [0,07 ; 22,4];	1,67 [-22,63 ; 25,96]; 1	1	0,6123
	White	535	9	1.68	536	16	2.99	0,56 [0,25 ; 1,26]	0,56 [0,24 ; 1,27];	-1,3 [-3,11 ; 0,5]; 0,224	0,224	
	No	347	7	2.02	379	13	3.43	0,59 [0,24 ; 1,46]	0,58 [0,23 ; 1,47];	-1,41 [-3,77 ; 0,94]; 0,266	0,266	0,9204

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	3	1.52	169	4	2.37	0,64 [0,15 ; 2,82]	0,63 [0,14 ; 2,88];	-0,85 [-3,71 ; 2]; 0,708	0,708	
Region	Eastern Europe	492	8	1.63	495	12	2.42	0,67 [0,28 ; 1,63]	0,67 [0,27 ; 1,64];	-0,8 [-2,55 ; 0,96]; 0,499	0,499	0,5525
	USA and Western Europe	53	2	3.77	53	5	9.43	0,4 [0,08 ; 1,97]	0,38 [0,07 ; 2,03];	-5,66 [-15,05 ; 3,73]; 0,437	0,437	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Gastrointestinal disorders | Vomiting

6.1.60 Injury, poisoning and procedural complications - Infusion related reaction

Tabelle 324: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	19	5.83	302	2	0.66	8,8 [2,07 ; 37,47]	9,28 [2,14 ; 40,2];	5,17 [2,46 ; 7,87]; 0	0	0,9996
	>= 38 years	219	8	3.65	246	1	0.41	8,99 [1,13 ; 71,28]	9,29 [1,15 ; 74,88];	3,25 [0,64 ; 5,86]; 0,015	0,015	
Disease Severity at baseline (EDSS)	<=3.5	419	24	5.73	415	2	0.48	11,89 [2,83 ; 49,97]	12,55 [2,95 ; 53,44];	5,25 [2,92 ; 7,57]; 0	0	0,352
	>3.5	126	3	2.38	133	1	0.75	3,17 [0,33 ; 30,04]	3,22 [0,33 ; 31,36];	1,63 [-1,41 ; 4,67]; 0,359	0,359	
Gender	Female	345	19	5.51	356	2	0.56	9,8 [2,3 ; 41,77]	10,32 [2,38 ; 44,63];	4,95 [2,42 ; 7,47]; 0	0	0,8438
	Male	200	8	4.00	192	1	0.52	7,68 [0,97 ; 60,83]	7,96 [0,99 ; 64,24];	3,48 [0,58 ; 6,38]; 0,037	0,037	
Number of baseline Gd-enhancing lesions	>=1	258	14	5.43	251	1	0.40	13,62 [1,8 ; 102,81]	14,34 [1,87 ; 109,92];	5,03 [2,16 ; 7,9]; 0,001	0,001	0,5627
	0	286	13	4.55	293	2	0.68	6,66 [1,52 ; 29,25]	6,93 [1,55 ; 30,98];	3,86 [1,27 ; 6,45]; 0,003	0,003	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	18	8.00	202	1	0.50	16,16 [2,18 ; 119,97]	17,48 [2,31 ; 132,15];	7,5 [3,83 ; 11,18]; 0	0	0,3698
	>=3	84	2	2.38	98	0	0.00	5,82 [0,28 ; 119,63]	5,97 [0,28 ; 126,11];	2,44 [-1,42 ; 6,29]; 0,212	0,212	
	2	236	7	2.97	248	2	0.81	3,68 [0,77 ; 17,53]	3,76 [0,77 ; 18,29];	2,16 [-0,27 ; 4,59]; 0,099	0,099	
Race	Other	10	2	20.00	12	0	0.00	5,91 [0,32 ; 110,47]	7,35 [0,31 ; 173,13];	18,88 [-8 ; 45,76]; 0,195	0,195	0,4421
	White	535	25	4.67	536	3	0.56	8,35 [2,54 ; 27,49]	8,71 [2,61 ; 29,02];	4,11 [2,22 ; 6,01]; 0	0	
	No	347	16	4.61	379	2	0.53	8,74 [2,02 ; 37,73]	9,11 [2,08 ; 39,92];	4,08 [1,76 ; 6,41]; 0	0	0,9497

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	11	5.56	169	1	0.59	9,39 [1,22 ; 71,98]	9,88 [1,26 ; 77,36];	4,96 [1,57 ; 8,36]; 0,007	0,007	
Region	Eastern Europe	492	21	4.27	495	3	0.61	7,04 [2,11 ; 23,46]	7,31 [2,17 ; 24,68];	3,66 [1,75 ; 5,57]; 0	0	0,2211
	USA and Western Europe	53	6	11.32	53	0	0.00	13 [0,75 ; 225,1]	14,64 [0,8 ; 266,87];	11,11 [2,06 ; 20,16]; 0,027	0,027	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Injury, poisoning and procedural complications | Infusion related reaction

6.1.61 Nervous system disorders - Dizziness

Tabelle 325: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	19	5.83	302	7	2.32	2,51 [1,07 ; 5,9]	2,61 [1,08 ; 6,3];	3,51 [0,45 ; 6,57]; 0,029	0,029	0,0243
	>= 38 years	219	5	2.28	246	10	4.07	0,56 [0,19 ; 1,62]	0,55 [0,19 ; 1,64];	-1,78 [-4,94 ; 1,38]; 0,306	0,306	
Disease Severity at baseline (EDSS)	<=3.5	419	24	5.73	415	11	2.65	2,16 [1,07 ; 4,35]	2,23 [1,08 ; 4,62];	3,08 [0,37 ; 5,79]; 0,037	0,037	0,0006
	>3.5	126	0	0.00	133	6	4.51	0,08 [0 ; 1,43]	0,08 [0 ; 1,39];	-4,46 [-8,25 ; -0,66]; 0,03	0,03	
Gender	Female	345	18	5.22	356	10	2.81	1,86 [0,87 ; 3,97]	1,9 [0,87 ; 4,19];	2,41 [-0,5 ; 5,32]; 0,124	0,124	0,2209
	Male	200	6	3.00	192	7	3.65	0,82 [0,28 ; 2,4]	0,82 [0,27 ; 2,48];	-0,65 [-4,2 ; 2,91]; 0,783	0,783	
Number of baseline Gd-enhancing lesions	>=1	258	16	6.20	251	11	4.38	1,42 [0,67 ; 2,99]	1,44 [0,66 ; 3,17];	1,82 [-2,06 ; 5,7]; 0,431	0,431	
	0	286	8	2.80	293	6	2.05	1,37 [0,48 ; 3,89]	1,38 [0,47 ; 4,02];	0,75 [-1,76 ; 3,26]; 0,599	0,599	0,945
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	11	4.89	202	8	3.96	1,23 [0,51 ; 3,01]	1,25 [0,49 ; 3,16];	0,93 [-2,97 ; 4,82]; 0,815	0,815	
	>=3	84	2	2.38	98	0	0.00	5,82 [0,28 ; 119,63]	5,97 [0,28 ; 126,11];	2,44 [-1,42 ; 6,29]; 0,212	0,212	0,2814
	2	236	11	4.66	248	9	3.63	1,28 [0,54 ; 3,04]	1,3 [0,53 ; 3,19];	1,03 [-2,52 ; 4,59]; 0,651	0,651	
Race	Other	10	2	20.00	12	0	0.00	5,91 [0,32 ; 110,47]	7,35 [0,31 ; 173,13];	18,88 [-8 ; 45,76]; 0,195	0,195	0,0976
	White	535	22	4.11	536	17	3.17	1,3 [0,7 ; 2,41]	1,31 [0,69 ; 2,49];	0,94 [-1,3 ; 3,18]; 0,421	0,421	
	No	347	16	4.61	379	13	3.43	1,34 [0,66 ; 2,75]	1,36 [0,64 ; 2,87];	1,18 [-1,69 ; 4,05]; 0,452	0,452	0,7364

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	8	4.04	169	4	2.37	1,71 [0,52 ; 5,57]	1,74 [0,51 ; 5,87];	1,67 [-1,9 ; 5,25]; 0,558	0,558	
Region	Eastern Europe	492	18	3.66	495	12	2.42	1,51 [0,73 ; 3,1]	1,53 [0,73 ; 3,21];	1,23 [-0,91 ; 3,38]; 0,272	0,272	0,7665
	USA and Western Europe	53	6	11.32	53	5	9.43	1,2 [0,39 ; 3,69]	1,23 [0,35 ; 4,29];	1,89 [-9,72 ; 13,49]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Nervous system disorders | Dizziness

6.1.62 Gastrointestinal disorders - Abdominal pain

Tabelle 326: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	31	9.51	302	13	4.30	2,21 [1,18 ; 4,14]	2,34 [1,2 ; 4,55];	5,2 [1,28 ; 9,13]; 0,012	0,012	0,6
	>= 38 years	219	12	5.48	246	8	3.25	1,68 [0,7 ; 4,05]	1,72 [0,69 ; 4,3];	2,23 [-1,51 ; 5,97]; 0,26	0,26	
Disease Severity at baseline (EDSS)	<=3.5	419	32	7.64	415	18	4.34	1,76 [1 ; 3,09]	1,82 [1,01 ; 3,3];	3,3 [0,09 ; 6,51]; 0,057	0,057	0,2405
	>3.5	126	11	8.73	133	3	2.26	3,87 [1,11 ; 13,55]	4,14 [1,13 ; 15,22];	6,47 [0,94 ; 12,01]; 0,027	0,027	
Gender	Female	345	32	9.28	356	16	4.49	2,06 [1,15 ; 3,69]	2,17 [1,17 ; 4,04];	4,78 [1,04 ; 8,52]; 0,016	0,016	0,9976
	Male	200	11	5.50	192	5	2.60	2,11 [0,75 ; 5,97]	2,18 [0,74 ; 6,39];	2,9 [-0,98 ; 6,78]; 0,202	0,202	
Number of baseline Gd-enhancing lesions	>=1	258	25	9.69	251	5	1.99	4,86 [1,89 ; 12,51]	5,28 [1,99 ; 14,02];	7,7 [3,7 ; 11,7]; 0	0	0,0091
	0	286	18	6.29	293	16	5.46	1,15 [0,6 ; 2,22]	1,16 [0,58 ; 2,33];	0,83 [-3 ; 4,67]; 0,726	0,726	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	13	5.78	202	9	4.46	1,3 [0,57 ; 2,97]	1,31 [0,55 ; 3,14];	1,32 [-2,85 ; 5,49]; 0,662	0,662	0,2451
	>=3	84	11	13.10	98	3	3.06	4,28 [1,23 ; 14,83]	4,77 [1,28 ; 17,73];	10,03 [2,05 ; 18,01]; 0,013	0,013	
	2	236	19	8.05	248	9	3.63	2,22 [1,02 ; 4,8]	2,33 [1,03 ; 5,25];	4,42 [0,24 ; 8,6]; 0,05	0,05	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	43	8.04	536	21	3.92	2,05 [1,23 ; 3,41]	2,14 [1,25 ; 3,66];	4,12 [1,29 ; 6,95]; 0,005	0,005	
	No	347	26	7.49	379	15	3.96	1,89 [1,02 ; 3,51]	1,97 [1,02 ; 3,78];	3,54 [0,14 ; 6,93]; 0,052	0,052	0,656

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	17	8.59	169	6	3.55	2,42 [0,98 ; 5,99]	2,55 [0,98 ; 6,63];	5,04 [0,24 ; 9,83]; 0,053	0,053	
Region	Eastern Europe	492	40	8.13	495	19	3.84	2,12 [1,24 ; 3,6]	2,22 [1,27 ; 3,89];	4,29 [1,34 ; 7,24]; 0,005	0,005	0,7074
	USA and Western Europe	53	3	5.66	53	2	3.77	1,5 [0,26 ; 8,62]	1,53 [0,25 ; 9,55];	1,89 [-6,18 ; 9,95]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Gastrointestinal disorders | Abdominal pain

6.1.63 Gastrointestinal disorders - Diarrhoea

Tabelle 327: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	26	7.98	302	32	10.60	0,75 [0,46 ; 1,23]	0,73 [0,42 ; 1,26];	-2,62 [-7,17 ; 1,93]; 0,272	0,272	0,9332
	>= 38 years	219	18	8.22	246	26	10.57	0,78 [0,44 ; 1,38]	0,76 [0,4 ; 1,42];	-2,35 [-7,64 ; 2,94]; 0,43	0,43	
Disease Severity at baseline (EDSS)	<=3.5	419	34	8.11	415	43	10.36	0,78 [0,51 ; 1,2]	0,76 [0,48 ; 1,22];	-2,25 [-6,18 ; 1,68]; 0,283	0,283	0,8081
	>3.5	126	10	7.94	133	15	11.28	0,7 [0,33 ; 1,51]	0,68 [0,29 ; 1,57];	-3,34 [-10,5 ; 3,81]; 0,405	0,405	
Gender	Female	345	32	9.28	356	40	11.24	0,83 [0,53 ; 1,28]	0,81 [0,49 ; 1,32];	-1,96 [-6,45 ; 2,53]; 0,456	0,456	0,558
	Male	200	12	6.00	192	18	9.38	0,64 [0,32 ; 1,29]	0,62 [0,29 ; 1,32];	-3,38 [-8,65 ; 1,9]; 0,255	0,255	
Number of baseline Gd-enhancing lesions	>=1	258	27	10.47	251	29	11.55	0,91 [0,55 ; 1,49]	0,89 [0,51 ; 1,56];	-1,09 [-6,53 ; 4,35]; 0,777	0,777	0,344
	0	286	17	5.94	293	28	9.56	0,62 [0,35 ; 1,11]	0,6 [0,32 ; 1,12];	-3,61 [-7,95 ; 0,73]; 0,121	0,121	
	NA	1	0	0.00	4	1	25.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	17	7.56	202	21	10.40	0,73 [0,39 ; 1,34]	0,7 [0,36 ; 1,38];	-2,84 [-8,28 ; 2,6]; 0,313	0,313	0,9814
	>=3	84	6	7.14	98	9	9.18	0,78 [0,29 ; 2,1]	0,76 [0,26 ; 2,23];	-2,04 [-9,98 ; 5,9]; 0,788	0,788	
	2	236	21	8.90	248	28	11.29	0,79 [0,46 ; 1,35]	0,77 [0,42 ; 1,39];	-2,39 [-7,75 ; 2,97]; 0,452	0,452	
Race	Other	10	1	10.00	12	0	0.00	3,55 [0,16 ; 78,56]	3,95 [0,14 ; 108,09];	9,79 [-13,03 ; 32,61]; 0,478	0,478	0,1573
	White	535	43	8.04	536	58	10.82	0,74 [0,51 ; 1,08]	0,72 [0,48 ; 1,09];	-2,78 [-6,28 ; 0,71]; 0,143	0,143	
	No	347	24	6.92	379	39	10.29	0,67 [0,41 ; 1,09]	0,65 [0,38 ; 1,1];	-3,37 [-7,43 ; 0,69]; 0,115	0,115	0,4681

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	20	10.10	169	19	11.24	0,9 [0,5 ; 1,63]	0,89 [0,46 ; 1,72];	-1,14 [-7,49 ; 5,21]; 0,737	0,737	
Region	Eastern Europe	492	39	7.93	495	52	10.51	0,75 [0,51 ; 1,12]	0,73 [0,47 ; 1,13];	-2,58 [-6,18 ; 1,03]; 0,187	0,187	0,875
	USA and Western Europe	53	5	9.43	53	6	11.32	0,83 [0,27 ; 2,56]	0,82 [0,23 ; 2,86];	-1,89 [-13,49 ; 9,72]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Gastrointestinal disorders | Diarrhoea

6.1.64 Skin and subcutaneous tissue disorders - Pruritus

Tabelle 328: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	4	1.23	302	2	0.66	1,85 [0,34 ; 10,04]	1,86 [0,34 ; 10,25];	0,56 [-0,94 ; 2,07]; 0,687	0,687	0,9345
	>= 38 years	219	6	2.74	246	4	1.63	1,68 [0,48 ; 5,89]	1,7 [0,47 ; 6,12];	1,11 [-1,56 ; 3,79]; 0,527	0,527	
Disease Severity at baseline (EDSS)	<=3.5	419	8	1.91	415	4	0.96	1,98 [0,6 ; 6,53]	2 [0,6 ; 6,69];	0,95 [-0,67 ; 2,56]; 0,384	0,384	0,5893
	>3.5	126	2	1.59	133	2	1.50	1,06 [0,15 ; 7,38]	1,06 [0,15 ; 7,62];	0,08 [-2,92 ; 3,09]; 1	1	
Gender	Female	345	9	2.61	356	5	1.40	1,86 [0,63 ; 5,49]	1,88 [0,62 ; 5,67];	1,2 [-0,88 ; 3,28]; 0,29	0,29	0,6611
	Male	200	1	0.50	192	1	0.52	0,96 [0,06 ; 15,24]	0,96 [0,06 ; 15,45];	-0,02 [-1,43 ; 1,39]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	258	5	1.94	251	4	1.59	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	286	5	1.75	293	2	0.68	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	5	2.22	202	2	0.99	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	2	2.38	98	3	3.06	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	3	1.27	248	1	0.40	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	1	10.00	12	0	0.00	3,55 [0,16 ; 78,56]	3,95 [0,14 ; 108,09];	9,79 [-13,03 ; 32,61]; 0,478	0,478	0,2792
	White	535	9	1.68	536	6	1.12	1,5 [0,54 ; 4,19]	1,51 [0,53 ; 4,28];	0,56 [-0,84 ; 1,97]; 0,451	0,451	
	No	347	7	2.02	379	4	1.06	1,91 [0,56 ; 6,47]	1,93 [0,56 ; 6,65];	0,96 [-0,84 ; 2,76]; 0,368	0,368	0,7165

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	3	1.52	169	2	1.18	1,28 [0,22 ; 7,57]	1,28 [0,21 ; 7,78];	0,33 [-2,02 ; 2,69]; 1	1	
Region	Eastern Europe	492	8	1.63	495	6	1.21	1,34 [0,47 ; 3,84]	1,35 [0,46 ; 3,91];	0,41 [-1,06 ; 1,89]; 0,604	0,604	0,1505
	USA and Western Europe	53	2	3.77	53	0	0.00	5 [0,25 ; 101,73]	5,19 [0,24 ; 110,82];	3,7 [-2,46 ; 9,86]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Skin and subcutaneous tissue disorders | Pruritus

6.1.65 Infections and infestations - Gastroenteritis

Tabelle 329: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	4	1.23	302	9	2.98	0,41 [0,13 ; 1,32]	0,4 [0,12 ; 1,33];	-1,75 [-4,01 ; 0,51]; 0,162	0,162	0,2849
	>= 38 years	219	0	0.00	246	2	0.81	0,22 [0,01 ; 4,65]	0,22 [0,01 ; 4,67];	-0,78 [-2,18 ; 0,61]; 0,5	0,5	
Disease Severity at baseline (EDSS)	<=3.5	419	4	0.95	415	10	2.41	0,4 [0,13 ; 1,25]	0,39 [0,12 ; 1,25];	-1,45 [-3,2 ; 0,29]; 0,114	0,114	0,4357
	>3.5	126	0	0.00	133	1	0.75	0,35 [0,01 ; 8,55]	0,35 [0,01 ; 8,65];	-0,73 [-2,81 ; 1,36]; 0,499	0,499	
Gender	Female	345	3	0.87	356	9	2.53	0,34 [0,09 ; 1,26]	0,34 [0,09 ; 1,26];	-1,66 [-3,56 ; 0,24]; 0,143	0,143	0,8076
	Male	200	1	0.50	192	2	1.04	0,48 [0,04 ; 5,25]	0,48 [0,04 ; 5,31];	-0,54 [-2,28 ; 1,2]; 0,616	0,616	
Number of baseline Gd-enhancing lesions	>=1	258	2	0.78	251	5	1.99	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	286	2	0.70	293	6	2.05	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	2	0.89	202	5	2.48	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	0	0.00	98	1	1.02	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	2	0.85	248	5	2.02	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	1	10.00	12	0	0.00	3,55 [0,16 ; 78,56]	3,95 [0,14 ; 108,09];	9,79 [-13,03 ; 32,61]; 0,478	0,478	0,0741
	White	535	3	0.56	536	11	2.05	0,27 [0,08 ; 0,97]	0,27 [0,07 ; 0,97];	-1,49 [-2,85 ; -0,13]; 0,056	0,056	
	No	347	3	0.86	379	7	1.85	0,47 [0,12 ; 1,8]	0,46 [0,12 ; 1,81];	-0,98 [-2,65 ; 0,69]; 0,345	0,345	0,5347

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	1	0.51	169	4	2.37	0,21 [0,02 ; 1,89]	0,21 [0,02 ; 1,89];	-1,86 [-4,36 ; 0,63]; 0,185	0,185	
Region	Eastern Europe	492	3	0.61	495	10	2.02	0,3 [0,08 ; 1,09]	0,3 [0,08 ; 1,09];	-1,41 [-2,83 ; 0,01]; 0,09	0,09	0,4471
	USA and Western Europe	53	1	1.89	53	1	1.89	1 [0,06 ; 15,57]	1 [0,06 ; 16,42];	0 [-5,18 ; 5,18]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Gastroenteritis

6.1.66 General disorders and administration site conditions - Chest pain

Tabelle 330: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	6	1.84	302	0	0.00	12,05 [0,68 ; 212,92]	12,27 [0,69 ; 218,74];	1,82 [0,24 ; 3,4]; 0,031	0,031	0,021
	>= 38 years	219	5	2.28	246	5	2.03	1,12 [0,33 ; 3,83]	1,13 [0,32 ; 3,94];	0,25 [-2,4 ; 2,9]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	10	2.39	415	5	1.20	1,98 [0,68 ; 5,75]	2 [0,68 ; 5,92];	1,18 [-0,62 ; 2,98]; 0,297	0,297	0,3666
	>3.5	126	1	0.79	133	0	0.00	3,17 [0,13 ; 76,99]	3,19 [0,13 ; 79,07];	0,81 [-1,34 ; 2,95]; 0,238	0,238	
Gender	Female	345	10	2.90	356	4	1.12	2,58 [0,82 ; 8,15]	2,63 [0,82 ; 8,46];	1,77 [-0,31 ; 3,86]; 0,11	0,11	0,5175
	Male	200	1	0.50	192	1	0.52	0,96 [0,06 ; 15,24]	0,96 [0,06 ; 15,45];	-0,02 [-1,43 ; 1,39]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	258	4	1.55	251	2	0.80	1,95 [0,36 ; 10,53]	1,96 [0,36 ; 10,8];	0,75 [-1,11 ; 2,62]; 0,686	0,686	0,849
	0	286	7	2.45	293	3	1.02	2,39 [0,62 ; 9,15]	2,43 [0,62 ; 9,47];	1,42 [-0,71 ; 3,55]; 0,217	0,217	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	4	1.78	202	3	1.49	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	4	4.76	98	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	3	1.27	248	2	0.81	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	11	2.06	536	5	0.93	2,2 [0,77 ; 6,3]	2,23 [0,77 ; 6,46];	1,12 [-0,33 ; 2,58]; 0,14	0,14	
	No	347	5	1.44	379	4	1.06	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	6	3.03	169	1	0.59	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Region	Eastern Europe	492	10	2.03	495	2	0.40	5,03 [1,11 ; 22,84]	5,11 [1,11 ; 23,46];	1,63 [0,26 ; 2,99]; 0,021	0,021	0,0311
	USA and Western Europe	53	1	1.89	53	3	5.66	0,33 [0,04 ; 3,1]	0,32 [0,03 ; 3,18];	-3,77 [-10,99 ; 3,45]; 0,618	0,618	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - General disorders and administration site conditions | Chest pain

6.1.67 Blood and lymphatic system disorders - Leukopenia

Tabelle 331: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	7	2.15	302	15	4.97	0,43 [0,18 ; 1,05]	0,42 [0,17 ; 1,04];	-2,82 [-5,73 ; 0,09]; 0,08	0,08	0,2479
	>= 38 years	219	4	1.83	246	4	1.63	1,12 [0,28 ; 4,44]	1,13 [0,28 ; 4,56];	0,2 [-2,18 ; 2,58]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	9	2.15	415	18	4.34	0,5 [0,23 ; 1,09]	0,48 [0,21 ; 1,09];	-2,19 [-4,59 ; 0,21]; 0,081	0,081	0,2374
	>3.5	126	2	1.59	133	1	0.75	2,11 [0,19 ; 22,99]	2,13 [0,19 ; 23,77];	0,84 [-1,79 ; 3,47]; 0,614	0,614	
Gender	Female	345	7	2.03	356	14	3.93	0,52 [0,21 ; 1,26]	0,51 [0,2 ; 1,27];	-1,9 [-4,41 ; 0,6]; 0,184	0,184	0,619
	Male	200	4	2.00	192	5	2.60	0,77 [0,21 ; 2,82]	0,76 [0,2 ; 2,89];	-0,6 [-3,58 ; 2,37]; 0,747	0,747	
Number of baseline Gd-enhancing lesions	>=1	258	3	1.16	251	8	3.19	0,36 [0,1 ; 1,36]	0,36 [0,09 ; 1,36];	-2,02 [-4,56 ; 0,51]; 0,137	0,137	0,3144
	0	286	8	2.80	293	10	3.41	0,82 [0,33 ; 2,05]	0,81 [0,32 ; 2,09];	-0,62 [-3,44 ; 2,21]; 0,812	0,812	
	NA	1	0	0.00	4	1	25.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	5	2.22	202	4	1.98	1,12 [0,31 ; 4,12]	1,12 [0,3 ; 4,25];	0,24 [-2,48 ; 2,96]; 1	1	0,3788
	>=3	84	2	2.38	98	8	8.16	0,29 [0,06 ; 1,34]	0,27 [0,06 ; 1,33];	-5,78 [-12,11 ; 0,54]; 0,11	0,11	
	2	236	4	1.69	248	7	2.82	0,6 [0,18 ; 2,02]	0,59 [0,17 ; 2,05];	-1,13 [-3,77 ; 1,51]; 0,546	0,546	
Race	Other	10	0	0.00	12	1	8.33	0,39 [0,02 ; 8,73]	0,37 [0,01 ; 9,98];	-6,99 [-28,28 ; 14,29]; 0,493	0,493	0,3607
	White	535	11	2.06	536	18	3.36	0,61 [0,29 ; 1,28]	0,6 [0,28 ; 1,29];	-1,3 [-3,24 ; 0,64]; 0,258	0,258	
	No	347	9	2.59	379	8	2.11	1,23 [0,48 ; 3,15]	1,23 [0,47 ; 3,24];	0,48 [-1,73 ; 2,69]; 0,807	0,807	0,0111

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	2	1.01	169	11	6.51	0,16 [0,03 ; 0,69]	0,15 [0,03 ; 0,67];	-5,5 [-9,47 ; -1,53]; 0,008	0,008	
Region	Eastern Europe	492	11	2.24	495	18	3.64	0,61 [0,29 ; 1,29]	0,61 [0,28 ; 1,3];	-1,4 [-3,5 ; 0,7]; 0,258	0,258	0,3334
	USA and Western Europe	53	0	0.00	53	1	1.89	0,33 [0,01 ; 8]	0,33 [0,01 ; 8,21];	-1,85 [-6,93 ; 3,22]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Blood and lymphatic system disorders | Leukopenia

6.1.68 Blood and lymphatic system disorders - Neutropenia

Tabelle 332: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	14	4.29	302	16	5.30	0,81 [0,4 ; 1,63]	0,8 [0,38 ; 1,67];	-1 [-4,35 ; 2,35]; 0,579	0,579	0,7503
	>= 38 years	219	4	1.83	246	7	2.85	0,64 [0,19 ; 2,16]	0,64 [0,18 ; 2,2];	-1,02 [-3,75 ; 1,71]; 0,552	0,552	
Disease Severity at baseline (EDSS)	<=3.5	419	16	3.82	415	19	4.58	0,83 [0,43 ; 1,6]	0,83 [0,42 ; 1,63];	-0,76 [-3,48 ; 1,96]; 0,609	0,609	0,6163
	>3.5	126	2	1.59	133	4	3.01	0,53 [0,1 ; 2,83]	0,52 [0,09 ; 2,89];	-1,42 [-5,05 ; 2,21]; 0,685	0,685	
Gender	Female	345	11	3.19	356	17	4.78	0,67 [0,32 ; 1,4]	0,66 [0,3 ; 1,42];	-1,59 [-4,48 ; 1,3]; 0,337	0,337	0,4343
	Male	200	7	3.50	192	6	3.12	1,12 [0,38 ; 3,27]	1,12 [0,37 ; 3,41];	0,38 [-3,17 ; 3,92]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	258	6	2.33	251	13	5.18	0,45 [0,17 ; 1,16]	0,44 [0,16 ; 1,17];	-2,85 [-6,15 ; 0,45]; 0,104	0,104	0,1101
	0	286	12	4.20	293	10	3.41	1,23 [0,54 ; 2,8]	1,24 [0,53 ; 2,92];	0,78 [-2,34 ; 3,9]; 0,668	0,668	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	10	4.44	202	8	3.96	1,12 [0,45 ; 2,79]	1,13 [0,44 ; 2,92];	0,48 [-3,32 ; 4,29]; 1	1	0,3744
	>=3	84	3	3.57	98	9	9.18	0,39 [0,11 ; 1,39]	0,37 [0,1 ; 1,4];	-5,61 [-12,57 ; 1,35]; 0,147	0,147	
	2	236	5	2.12	248	6	2.42	0,88 [0,27 ; 2,83]	0,87 [0,26 ; 2,9];	-0,3 [-2,95 ; 2,35]; 1	1	
Race	Other	10	0	0.00	12	1	8.33	0,39 [0,02 ; 8,73]	0,37 [0,01 ; 9,98];	-6,99 [-28,28 ; 14,29]; 0,493	0,493	0,3038
	White	535	18	3.36	536	22	4.10	0,82 [0,44 ; 1,51]	0,81 [0,43 ; 1,53];	-0,74 [-3,01 ; 1,53]; 0,629	0,629	
	No	347	9	2.59	379	16	4.22	0,61 [0,28 ; 1,37]	0,6 [0,26 ; 1,39];	-1,63 [-4,25 ; 1]; 0,309	0,309	0,3642

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	9	4.55	169	7	4.14	1,1 [0,42 ; 2,88]	1,1 [0,4 ; 3,03];	0,4 [-3,77 ; 4,58]; 1	1	
Region	Eastern Europe	492	16	3.25	495	22	4.44	0,73 [0,39 ; 1,38]	0,72 [0,37 ; 1,39];	-1,19 [-3,59 ; 1,21]; 0,409	0,409	0,4045
	USA and Western Europe	53	2	3.77	53	1	1.89	2 [0,19 ; 21,4]	2,04 [0,18 ; 23,19];	1,89 [-4,42 ; 8,19]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Blood and lymphatic system disorders | Neutropenia

6.1.69 Respiratory, thoracic and mediastinal disorders - Oropharyngeal pain

Tabelle 333: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	21	6.44	302	12	3.97	1,62 [0,81 ; 3,24]	1,66 [0,8 ; 3,44];	2,47 [-0,99 ; 5,93]; 0,21	0,21	0,9765
	>= 38 years	219	10	4.57	246	7	2.85	1,6 [0,62 ; 4,14]	1,63 [0,61 ; 4,37];	1,72 [-1,74 ; 5,18]; 0,336	0,336	
Disease Severity at baseline (EDSS)	<=3.5	419	25	5.97	415	15	3.61	1,65 [0,88 ; 3,09]	1,69 [0,88 ; 3,26];	2,35 [-0,54 ; 5,24]; 0,144	0,144	0,948
	>3.5	126	6	4.76	133	4	3.01	1,58 [0,46 ; 5,48]	1,61 [0,44 ; 5,85];	1,75 [-2,96 ; 6,47]; 0,531	0,531	
Gender	Female	345	24	6.96	356	17	4.78	1,46 [0,8 ; 2,66]	1,49 [0,79 ; 2,83];	2,18 [-1,3 ; 5,66]; 0,26	0,26	0,3133
	Male	200	7	3.50	192	2	1.04	3,36 [0,71 ; 15,97]	3,45 [0,71 ; 16,8];	2,46 [-0,47 ; 5,38]; 0,175	0,175	
Number of baseline Gd-enhancing lesions	>=1	258	17	6.59	251	5	1.99	3,31 [1,24 ; 8,83]	3,47 [1,26 ; 9,56];	4,6 [1,11 ; 8,08]; 0,015	0,015	0,051
	0	286	14	4.90	293	14	4.78	1,02 [0,5 ; 2,11]	1,03 [0,48 ; 2,19];	0,12 [-3,38 ; 3,61]; 1	1	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	14	6.22	202	5	2.48	2,51 [0,92 ; 6,86]	2,61 [0,92 ; 7,39];	3,75 [-0,07 ; 7,56]; 0,098	0,098	0,342
	>=3	84	6	7.14	98	3	3.06	2,33 [0,6 ; 9,05]	2,44 [0,59 ; 10,06];	4,08 [-2,4 ; 10,56]; 0,306	0,306	
	2	236	11	4.66	248	11	4.44	1,05 [0,46 ; 2,38]	1,05 [0,45 ; 2,48];	0,23 [-3,49 ; 3,94]; 1	1	
Race	Other	10	0	0.00	12	2	16.67	0,24 [0,01 ; 4,42]	0,2 [0,01 ; 4,69];	-14,69 [-39,39 ; 10,02]; 0,481	0,481	0,0516
	White	535	31	5.79	536	17	3.17	1,83 [1,02 ; 3,26]	1,88 [1,03 ; 3,44];	2,62 [0,15 ; 5,1]; 0,04	0,04	
	No	347	16	4.61	379	13	3.43	1,34 [0,66 ; 2,75]	1,36 [0,64 ; 2,87];	1,18 [-1,69 ; 4,05]; 0,452	0,452	0,4258

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	15	7.58	169	6	3.55	2,13 [0,85 ; 5,38]	2,23 [0,84 ; 5,87];	4,03 [-0,6 ; 8,65]; 0,117	0,117	
Region	Eastern Europe	492	26	5.28	495	16	3.23	1,63 [0,89 ; 3,01]	1,67 [0,88 ; 3,15];	2,05 [-0,46 ; 4,57]; 0,117	0,117	0,9626
	USA and Western Europe	53	5	9.43	53	3	5.66	1,67 [0,42 ; 6,62]	1,74 [0,39 ; 7,67];	3,77 [-6,26 ; 13,81]; 0,716	0,716	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Respiratory, thoracic and mediastinal disorders | Oropharyngeal pain

6.1.70 Skin and subcutaneous tissue disorders - Rash

Tabelle 334: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	3	0.92	302	7	2.32	0,4 [0,1 ; 1,52]	0,39 [0,1 ; 1,53];	-1,4 [-3,39 ; 0,59]; 0,208	0,208	0,3898
	>= 38 years	219	4	1.83	246	5	2.03	0,9 [0,24 ; 3,3]	0,9 [0,24 ; 3,38];	-0,21 [-2,71 ; 2,29]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	5	1.19	415	8	1.93	0,62 [0,2 ; 1,88]	0,61 [0,2 ; 1,89];	-0,73 [-2,42 ; 0,95]; 0,418	0,418	0,8731
	>3.5	126	2	1.59	133	4	3.01	0,53 [0,1 ; 2,83]	0,52 [0,09 ; 2,89];	-1,42 [-5,05 ; 2,21]; 0,685	0,685	
Gender	Female	345	6	1.74	356	8	2.25	0,77 [0,27 ; 2,21]	0,77 [0,26 ; 2,24];	-0,51 [-2,58 ; 1,56]; 0,789	0,789	0,3136
	Male	200	1	0.50	192	4	2.08	0,24 [0,03 ; 2,13]	0,24 [0,03 ; 2,13];	-1,58 [-3,83 ; 0,66]; 0,207	0,207	
Number of baseline Gd-enhancing lesions	>=1	258	3	1.16	251	3	1.20	0,97 [0,2 ; 4,77]	0,97 [0,19 ; 4,86];	-0,03 [-1,91 ; 1,84]; 1	1	0,4464
	0	286	4	1.40	293	9	3.07	0,46 [0,14 ; 1,46]	0,45 [0,14 ; 1,47];	-1,67 [-4,07 ; 0,73]; 0,262	0,262	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	2	0.89	202	4	1.98	0,45 [0,08 ; 2,42]	0,44 [0,08 ; 2,45];	-1,09 [-3,37 ; 1,19]; 0,428	0,428	0,5815
	>=3	84	0	0.00	98	1	1.02	0,39 [0,02 ; 9,41]	0,38 [0,02 ; 9,57];	-0,93 [-3,83 ; 1,98]; 0,501	0,501	
	2	236	5	2.12	248	7	2.82	0,75 [0,24 ; 2,33]	0,75 [0,23 ; 2,38];	-0,7 [-3,47 ; 2,06]; 0,772	0,772	
Race	Other	10	0	0.00	12	2	16.67	0,24 [0,01 ; 4,42]	0,2 [0,01 ; 4,69];	-14,69 [-39,39 ; 10,02]; 0,481	0,481	0,1719
	White	535	7	1.31	536	10	1.87	0,7 [0,27 ; 1,83]	0,7 [0,26 ; 1,85];	-0,56 [-2,05 ; 0,94]; 0,626	0,626	
	No	347	4	1.15	379	6	1.58	0,73 [0,21 ; 2,56]	0,72 [0,2 ; 2,59];	-0,43 [-2,12 ; 1,26]; 0,755	0,755	0,5674

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	3	1.52	169	6	3.55	0,43 [0,11 ; 1,68]	0,42 [0,1 ; 1,7];	-2,04 [-5,3 ; 1,23]; 0,312	0,312	
Region	Eastern Europe	492	4	0.81	495	8	1.62	0,5 [0,15 ; 1,66]	0,5 [0,15 ; 1,67];	-0,8 [-2,17 ; 0,56]; 0,385	0,385	0,6992
	USA and Western Europe	53	3	5.66	53	4	7.55	0,75 [0,18 ; 3,19]	0,74 [0,16 ; 3,46];	-1,89 [-11,34 ; 7,56]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Skin and subcutaneous tissue disorders | Rash

6.1.71 Investigations - Amylase increased

Tabelle 335: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	6	1.84	302	1	0.33	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>= 38 years	219	5	2.28	246	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	419	9	2.15	415	1	0.24	8,91 [1,13 ; 70,05]	9,09 [1,15 ; 72,05];	1,91 [0,44 ; 3,37]; 0,021	0,021	0,5259
	>3.5	126	2	1.59	133	0	0.00	5,28 [0,26 ; 108,82]	5,36 [0,25 ; 112,78];	1,6 [-1,03 ; 4,22]; 0,234	0,234	
Number of baseline Gd-enhancing lesions	>=1	258	6	2.33	251	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	286	5	1.75	293	1	0.34	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	4	1.78	202	1	0.50	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	4	4.76	98	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	3	1.27	248	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9998
	White	535	11	2.06	536	1	0.19	11,02 [1,43 ; 85,06]	11,23 [1,44 ; 87,3];	1,87 [0,61 ; 3,13]; 0,003	0,003	
Received approved disease modifying MS drug prior to enrollment	No	347	5	1.44	379	1	0.26	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	Yes	198	6	3.03	169	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	492	9	1.83	495	1	0.20	9,05 [1,15 ; 71,2]	9,2 [1,16 ; 72,93];	1,63 [0,38 ; 2,88]; 0,011	0,011	0,5341
	USA and Western Europe	53	2	3.77	53	0	0.00	5 [0,25 ; 101,73]	5,19 [0,24 ; 110,82];	3,7 [-2,46 ; 9,86]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Investigations | Amylase increased

6.1.72 Infections and infestations - Respiratory tract infection

Tabelle 336: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	28	8.59	302	24	7.95	1,08 [0,64 ; 1,82]	1,09 [0,62 ; 1,92];	0,64 [-3,67 ; 4,95]; 0,885	0,885	0,936
	>= 38 years	219	14	6.39	246	14	5.69	1,12 [0,55 ; 2,3]	1,13 [0,53 ; 2,43];	0,7 [-3,64 ; 5,05]; 0,846	0,846	
Disease Severity at baseline (EDSS)	<=3.5	419	35	8.35	415	30	7.23	1,16 [0,72 ; 1,85]	1,17 [0,7 ; 1,94];	1,12 [-2,51 ; 4,76]; 0,606	0,606	0,6839
	>3.5	126	7	5.56	133	8	6.02	0,92 [0,35 ; 2,47]	0,92 [0,32 ; 2,61];	-0,46 [-6,14 ; 5,23]; 1	1	
Gender	Female	345	31	8.99	356	25	7.02	1,28 [0,77 ; 2,12]	1,31 [0,75 ; 2,26];	1,96 [-2,06 ; 5,98]; 0,403	0,403	0,3337
	Male	200	11	5.50	192	13	6.77	0,81 [0,37 ; 1,77]	0,8 [0,35 ; 1,84];	-1,27 [-6,03 ; 3,48]; 0,676	0,676	
Number of baseline Gd-enhancing lesions	>=1	258	31	12.02	251	17	6.77	1,77 [1,01 ; 3,12]	1,88 [1,01 ; 3,49];	5,24 [0,2 ; 10,28]; 0,049	0,049	0,0078
	0	286	11	3.85	293	21	7.17	0,54 [0,26 ; 1,09]	0,52 [0,25 ; 1,1];	-3,32 [-7,02 ; 0,38]; 0,101	0,101	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	17	7.56	202	12	5.94	1,27 [0,62 ; 2,6]	1,29 [0,6 ; 2,78];	1,61 [-3,13 ; 6,36]; 0,567	0,567	0,6004
	>=3	84	9	10.71	98	7	7.14	1,5 [0,58 ; 3,85]	1,56 [0,55 ; 4,39];	3,57 [-4,78 ; 11,92]; 0,44	0,44	
	2	236	16	6.78	248	19	7.66	0,88 [0,47 ; 1,68]	0,88 [0,44 ; 1,75];	-0,88 [-5,49 ; 3,73]; 0,729	0,729	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	42	7.85	536	38	7.09	1,11 [0,73 ; 1,69]	1,12 [0,71 ; 1,76];	0,76 [-2,39 ; 3,91]; 0,644	0,644	
	No	347	22	6.34	379	24	6.33	1 [0,57 ; 1,75]	1 [0,55 ; 1,82];	0,01 [-3,54 ; 3,56]; 1	1	0,6478

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	20	10.10	169	14	8.28	1,22 [0,64 ; 2,34]	1,24 [0,61 ; 2,55];	1,82 [-4,09 ; 7,72]; 0,592	0,592	
Region	Eastern Europe	492	41	8.33	495	36	7.27	1,15 [0,75 ; 1,76]	1,16 [0,73 ; 1,85];	1,06 [-2,29 ; 4,41]; 0,555	0,555	0,4826
	USA and Western Europe	53	1	1.89	53	2	3.77	0,5 [0,05 ; 5,35]	0,49 [0,04 ; 5,58];	-1,89 [-8,19 ; 4,42]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Respiratory tract infection

6.1.73 Vascular disorders - Hypertension

Tabelle 337: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	13	3.99	302	14	4.64	0,86 [0,41 ; 1,8]	0,85 [0,39 ; 1,85];	-0,65 [-3,83 ; 2,54]; 0,699	0,699	0,1387
	>= 38 years	219	8	3.65	246	23	9.35	0,39 [0,18 ; 0,86]	0,37 [0,16 ; 0,84];	-5,7 [-10,1 ; -1,29]; 0,015	0,015	
Disease Severity at baseline (EDSS)	<=3.5	419	17	4.06	415	29	6.99	0,58 [0,32 ; 1,04]	0,56 [0,3 ; 1,04];	-2,93 [-6,03 ; 0,17]; 0,07	0,07	0,8927
	>3.5	126	4	3.17	133	8	6.02	0,53 [0,16 ; 1,71]	0,51 [0,15 ; 1,75];	-2,84 [-7,91 ; 2,23]; 0,378	0,378	
Gender	Female	345	15	4.35	356	23	6.46	0,67 [0,36 ; 1,27]	0,66 [0,34 ; 1,28];	-2,11 [-5,45 ; 1,23]; 0,245	0,245	0,3888
	Male	200	6	3.00	192	14	7.29	0,41 [0,16 ; 1,05]	0,39 [0,15 ; 1,05];	-4,29 [-8,66 ; 0,08]; 0,066	0,066	
Number of baseline Gd-enhancing lesions	>=1	258	9	3.49	251	17	6.77	0,52 [0,23 ; 1,13]	0,5 [0,22 ; 1,14];	-3,28 [-7,12 ; 0,55]; 0,109	0,109	0,7447
	0	286	12	4.20	293	20	6.83	0,61 [0,31 ; 1,23]	0,6 [0,29 ; 1,25];	-2,63 [-6,34 ; 1,08]; 0,203	0,203	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	9	4.00	202	14	6.93	0,58 [0,26 ; 1,3]	0,56 [0,24 ; 1,32];	-2,93 [-7,27 ; 1,41]; 0,202	0,202	0,8379
	>=3	84	4	4.76	98	6	6.12	0,78 [0,23 ; 2,66]	0,77 [0,21 ; 2,81];	-1,36 [-7,94 ; 5,22]; 0,755	0,755	
	2	236	8	3.39	248	17	6.85	0,49 [0,22 ; 1,12]	0,48 [0,2 ; 1,13];	-3,47 [-7,37 ; 0,44]; 0,101	0,101	
Race	Other	10	0	0.00	12	1	8.33	0,39 [0,02 ; 8,73]	0,37 [0,01 ; 9,98];	-6,99 [-28,28 ; 14,29]; 0,493	0,493	0,3704
	White	535	21	3.93	536	36	6.72	0,58 [0,35 ; 0,99]	0,57 [0,33 ; 0,99];	-2,79 [-5,47 ; -0,11]; 0,056	0,056	
	No	347	8	2.31	379	25	6.60	0,35 [0,16 ; 0,76]	0,33 [0,15 ; 0,75];	-4,29 [-7,25 ; -1,33]; 0,007	0,007	0,0789

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	13	6.57	169	12	7.10	0,92 [0,43 ; 1,97]	0,92 [0,41 ; 2,07];	-0,53 [-5,72 ; 4,65]; 0,839	0,839	
Region	Eastern Europe	492	21	4.27	495	34	6.87	0,62 [0,37 ; 1,06]	0,6 [0,35 ; 1,06];	-2,6 [-5,46 ; 0,26]; 0,095	0,095	0,0932
	USA and Western Europe	53	0	0.00	53	3	5.66	0,14 [0,01 ; 2,7]	0,13 [0,01 ; 2,68];	-5,56 [-12,6 ; 1,49]; 0,118	0,118	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Vascular disorders | Hypertension

6.1.74 General disorders and administration site conditions - Asthenia

Tabelle 338: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	18	5.52	302	18	5.96	0,93 [0,49 ; 1,75]	0,92 [0,47 ; 1,81];	-0,44 [-4,08 ; 3,2]; 0,865	0,865	0,8246
	>= 38 years	219	8	3.65	246	11	4.47	0,82 [0,33 ; 1,99]	0,81 [0,32 ; 2,05];	-0,82 [-4,4 ; 2,77]; 0,815	0,815	
Disease Severity at baseline (EDSS)	<=3.5	419	22	5.25	415	20	4.82	1,09 [0,6 ; 1,97]	1,09 [0,59 ; 2,04];	0,43 [-2,54 ; 3,4]; 0,874	0,874	0,1889
	>3.5	126	4	3.17	133	9	6.77	0,47 [0,15 ; 1,49]	0,45 [0,14 ; 1,51];	-3,59 [-8,85 ; 1,66]; 0,257	0,257	
Gender	Female	345	17	4.93	356	17	4.78	1,03 [0,54 ; 1,99]	1,03 [0,52 ; 2,06];	0,15 [-3,03 ; 3,33]; 1	1	0,5066
	Male	200	9	4.50	192	12	6.25	0,72 [0,31 ; 1,67]	0,71 [0,29 ; 1,72];	-1,75 [-6,22 ; 2,72]; 0,505	0,505	
Number of baseline Gd-enhancing lesions	>=1	258	11	4.26	251	14	5.58	0,76 [0,35 ; 1,65]	0,75 [0,34 ; 1,69];	-1,31 [-5,07 ; 2,45]; 0,543	0,543	0,5804
	0	286	15	5.24	293	15	5.12	1,02 [0,51 ; 2,06]	1,03 [0,49 ; 2,14];	0,13 [-3,49 ; 3,74]; 1	1	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	13	5.78	202	7	3.47	1,67 [0,68 ; 4,1]	1,71 [0,67 ; 4,37];	2,31 [-1,64 ; 6,27]; 0,359	0,359	0,2057
	>=3	84	2	2.38	98	5	5.10	0,47 [0,09 ; 2,34]	0,45 [0,09 ; 2,4];	-2,72 [-8,16 ; 2,72]; 0,454	0,454	
	2	236	11	4.66	248	17	6.85	0,68 [0,33 ; 1,42]	0,66 [0,3 ; 1,45];	-2,19 [-6,33 ; 1,94]; 0,335	0,335	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	26	4.86	536	29	5.41	0,9 [0,54 ; 1,5]	0,89 [0,52 ; 1,54];	-0,55 [-3,19 ; 2,09]; 0,782	0,782	
	No	347	14	4.03	379	19	5.01	0,8 [0,41 ; 1,58]	0,8 [0,39 ; 1,61];	-0,98 [-4 ; 2,04]; 0,595	0,595	0,6567

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	12	6.06	169	10	5.92	1,02 [0,45 ; 2,31]	1,03 [0,43 ; 2,44];	0,14 [-4,72 ; 5,01]; 1	1	
Region	Eastern Europe	492	25	5.08	495	28	5.66	0,9 [0,53 ; 1,52]	0,89 [0,51 ; 1,55];	-0,58 [-3,39 ; 2,24]; 0,778	0,778	0,938
	USA and Western Europe	53	1	1.89	53	1	1.89	1 [0,06 ; 15,57]	1 [0,06 ; 16,42];	0 [-5,18 ; 5,18]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - General disorders and administration site conditions | Asthenia

6.1.75 Blood and lymphatic system disorders - Lymphopenia

Tabelle 339: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	36	11.04	302	3	0.99	11,12 [3,46 ; 35,72]	12,37 [3,77 ; 40,62];	10,05 [6,47 ; 13,63]; 0	0	0,4986
	>= 38 years	219	17	7.76	246	3	1.22	6,37 [1,89 ; 21,43]	6,82 [1,97 ; 23,59];	6,54 [2,74 ; 10,34]; 0,001	0,001	
Disease Severity at baseline (EDSS)	<=3.5	419	45	10.74	415	3	0.72	14,86 [4,65 ; 47,43]	16,52 [5,09 ; 53,62];	10,02 [6,94 ; 13,09]; 0	0	0,0657
	>3.5	126	8	6.35	133	3	2.26	2,81 [0,76 ; 10,37]	2,94 [0,76 ; 11,33];	4,09 [-0,86 ; 9,04]; 0,129	0,129	
Gender	Female	345	32	9.28	356	4	1.12	8,26 [2,95 ; 23,1]	9 [3,15 ; 25,72];	8,15 [4,9 ; 11,4]; 0	0	0,8143
	Male	200	21	10.50	192	2	1.04	10,08 [2,4 ; 42,41]	11,15 [2,58 ; 48,22];	9,46 [4,97 ; 13,94]; 0	0	
Number of baseline Gd-enhancing lesions	>=1	258	27	10.47	251	3	1.20	8,76 [2,69 ; 28,5]	9,66 [2,89 ; 32,28];	9,27 [5,3 ; 13,24]; 0	0	0,9996
	0	286	26	9.09	293	3	1.02	8,88 [2,72 ; 29,01]	9,67 [2,89 ; 32,31];	8,07 [4,54 ; 11,59]; 0	0	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	21	9.33	202	1	0.50	18,85 [2,56 ; 138,9]	20,69 [2,76 ; 155,28];	8,84 [4,92 ; 12,76]; 0	0	0,5121
	>=3	84	10	11.90	98	1	1.02	11,67 [1,52 ; 89,26]	13,11 [1,64 ; 104,69];	10,88 [3,68 ; 18,09]; 0,003	0,003	
	2	236	22	9.32	248	4	1.61	5,78 [2,02 ; 16,52]	6,27 [2,13 ; 18,49];	7,71 [3,68 ; 11,74]; 0	0	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9997
	White	535	53	9.91	536	6	1.12	8,85 [3,84 ; 20,41]	9,71 [4,14 ; 22,8];	8,79 [6,1 ; 11,47]; 0	0	
	No	347	22	6.34	379	2	0.53	12,01 [2,85 ; 50,72]	12,76 [2,98 ; 54,68];	5,81 [3,15 ; 8,48]; 0	0	0,5715

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	31	15.66	169	4	2.37	6,61 [2,38 ; 18,36]	7,66 [2,64 ; 22,17];	13,29 [7,73 ; 18,85]; 0	0	
Region	Eastern Europe	492	52	10.57	495	6	1.21	8,72 [3,78 ; 20,11]	9,63 [4,1 ; 22,64];	9,36 [6,47 ; 12,24]; 0	0	0,6554
	USA and Western Europe	53	1	1.89	53	0	0.00	3 [0,12 ; 72,02]	3,06 [0,12 ; 76,76];	1,85 [-3,22 ; 6,93]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Blood and lymphatic system disorders | Lymphopenia

6.1.76 Infections and infestations - Respiratory tract infection viral

Tabelle 340: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	33	10.12	302	21	6.95	1,46 [0,86 ; 2,46]	1,51 [0,85 ; 2,67];	3,17 [-1,18 ; 7,52]; 0,2	0,2	0,4696
	>= 38 years	219	9	4.11	246	10	4.07	1,01 [0,42 ; 2,44]	1,01 [0,4 ; 2,54];	0,04 [-3,56 ; 3,65]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	35	8.35	415	25	6.02	1,39 [0,85 ; 2,27]	1,42 [0,84 ; 2,42];	2,33 [-1,17 ; 5,83]; 0,228	0,228	0,8338
	>3.5	126	7	5.56	133	6	4.51	1,23 [0,43 ; 3,56]	1,25 [0,41 ; 3,81];	1,04 [-4,29 ; 6,38]; 0,78	0,78	
Gender	Female	345	26	7.54	356	21	5.90	1,28 [0,73 ; 2,23]	1,3 [0,72 ; 2,36];	1,64 [-2,07 ; 5,35]; 0,451	0,451	0,7023
	Male	200	16	8.00	192	10	5.21	1,54 [0,71 ; 3,3]	1,58 [0,7 ; 3,58];	2,79 [-2,11 ; 7,69]; 0,313	0,313	
Number of baseline Gd-enhancing lesions	>=1	258	17	6.59	251	16	6.37	1,03 [0,53 ; 2]	1,04 [0,51 ; 2,1];	0,21 [-4,06 ; 4,49]; 1	1	0,2743
	0	286	25	8.74	293	15	5.12	1,71 [0,92 ; 3,17]	1,78 [0,92 ; 3,44];	3,62 [-0,51 ; 7,75]; 0,101	0,101	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	17	7.56	202	9	4.46	1,7 [0,77 ; 3,72]	1,75 [0,76 ; 4,02];	3,1 [-1,37 ; 7,57]; 0,225	0,225	0,3502
	>=3	84	8	9.52	98	4	4.08	2,33 [0,73 ; 7,48]	2,47 [0,72 ; 8,53];	5,44 [-1,96 ; 12,84]; 0,23	0,23	
	2	236	17	7.20	248	18	7.26	0,99 [0,52 ; 1,88]	0,99 [0,5 ; 1,97];	-0,05 [-4,67 ; 4,56]; 1	1	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	42	7.85	536	31	5.78	1,36 [0,87 ; 2,13]	1,39 [0,86 ; 2,24];	2,07 [-0,95 ; 5,08]; 0,185	0,185	
	No	347	13	3.75	379	13	3.43	1,09 [0,51 ; 2,32]	1,1 [0,5 ; 2,4];	0,32 [-2,39 ; 3,03]; 0,844	0,844	0,5938

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	29	14.65	169	18	10.65	1,38 [0,79 ; 2,39]	1,44 [0,77 ; 2,7];	4 [-2,78 ; 10,77]; 0,276	0,276	
Region	Eastern Europe	492	42	8.54	495	31	6.26	1,36 [0,87 ; 2,13]	1,4 [0,86 ; 2,26];	2,27 [-0,99 ; 5,54]; 0,183	0,183	0,9999
	USA and Western Europe	53	0	0.00	53	0	0.00	1 [0,02 ; 49,49]	1 [0,02 ; 51,33];	0 [-3,61 ; 3,61]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Respiratory tract infection viral

6.1.77 General disorders and administration site conditions - Hyperthermia

Tabelle 341: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	25	7.67	302	2	0.66	11,58 [2,77 ; 48,47]	12,46 [2,92 ; 53,07];	7,01 [3,98 ; 10,04]; 0	0	0,036
	>= 38 years	219	6	2.74	246	4	1.63	1,68 [0,48 ; 5,89]	1,7 [0,47 ; 6,12];	1,11 [-1,56 ; 3,79]; 0,527	0,527	
Disease Severity at baseline (EDSS)	<=3.5	419	22	5.25	415	3	0.72	7,26 [2,19 ; 24,08]	7,61 [2,26 ; 25,63];	4,53 [2,24 ; 6,81]; 0	0	0,3715
	>3.5	126	9	7.14	133	3	2.26	3,17 [0,88 ; 11,43]	3,33 [0,88 ; 12,61];	4,89 [-0,27 ; 10,04]; 0,078	0,078	
Gender	Female	345	22	6.38	356	5	1.40	4,54 [1,74 ; 11,85]	4,78 [1,79 ; 12,77];	4,97 [2,12 ; 7,83]; 0,001	0,001	0,5706
	Male	200	9	4.50	192	1	0.52	8,64 [1,11 ; 67,55]	9 [1,13 ; 71,73];	3,98 [0,93 ; 7,03]; 0,02	0,02	
Number of baseline Gd-enhancing lesions	>=1	258	17	6.59	251	4	1.59	4,13 [1,41 ; 12,12]	4,36 [1,44 ; 13,13];	5 [1,59 ; 8,4]; 0,006	0,006	
	0	286	14	4.90	293	2	0.68	7,17 [1,64 ; 31,27]	7,49 [1,69 ; 33,26];	4,21 [1,54 ; 6,88]; 0,002	0,002	0,56
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	8	3.56	202	2	0.99	3,59 [0,77 ; 16,71]	3,69 [0,77 ; 17,57];	2,57 [-0,21 ; 5,34]; 0,11	0,11	
	>=3	84	13	15.48	98	1	1.02	15,17 [2,03 ; 113,53]	17,76 [2,27 ; 138,91];	14,46 [6,47 ; 22,44]; 0	0	0,3158
	2	236	10	4.24	248	3	1.21	3,5 [0,98 ; 12,57]	3,61 [0,98 ; 13,3];	3,03 [0,12 ; 5,94]; 0,049	0,049	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9998
	White	535	31	5.79	536	6	1.12	5,18 [2,18 ; 12,31]	5,43 [2,25 ; 13,13];	4,67 [2,5 ; 6,85]; 0	0	
	No	347	17	4.90	379	4	1.06	4,64 [1,58 ; 13,66]	4,83 [1,61 ; 14,5];	3,84 [1,35 ; 6,34]; 0,003	0,003	0,7701

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	14	7.07	169	2	1.18	5,97 [1,38 ; 25,92]	6,35 [1,42 ; 28,37];	5,89 [1,96 ; 9,81]; 0,008	0,008	
Region	Eastern Europe	492	31	6.30	495	6	1.21	5,2 [2,19 ; 12,35]	5,48 [2,27 ; 13,26];	5,09 [2,74 ; 7,44]; 0	0	0,9998
	USA and Western Europe	53	0	0.00	53	0	0.00	1 [0,02 ; 49,49]	1 [0,02 ; 51,33];	0 [-3,61 ; 3,61]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - General disorders and administration site conditions | Hyperthermia

6.1.78 General disorders and administration site conditions - Influenza like illness

Tabelle 342: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	28	8.59	302	5	1.66	5,19 [2,03 ; 13,26]	5,58 [2,13 ; 14,65];	6,93 [3,57 ; 10,3]; 0	0	0,1721
	>= 38 years	219	11	5.02	246	6	2.44	2,06 [0,77 ; 5,48]	2,12 [0,77 ; 5,82];	2,58 [-0,89 ; 6,06]; 0,148	0,148	
Disease Severity at baseline (EDSS)	<=3.5	419	32	7.64	415	6	1.45	5,28 [2,23 ; 12,5]	5,64 [2,33 ; 13,63];	6,19 [3,4 ; 8,98]; 0	0	0,0809
	>3.5	126	7	5.56	133	5	3.76	1,48 [0,48 ; 4,54]	1,51 [0,47 ; 4,87];	1,8 [-3,35 ; 6,94]; 0,563	0,563	
Gender	Female	345	27	7.83	356	11	3.09	2,53 [1,28 ; 5,03]	2,66 [1,3 ; 5,46];	4,74 [1,38 ; 8,09]; 0,007	0,007	0,0105
	Male	200	12	6.00	192	0	0.00	24 [1,43 ; 402,64]	25,53 [1,5 ; 434,28];	5,96 [2,55 ; 9,37]; 0	0	
Number of baseline Gd-enhancing lesions	>=1	258	18	6.98	251	5	1.99	3,5 [1,32 ; 9,29]	3,69 [1,35 ; 10,1];	4,98 [1,43 ; 8,54]; 0,009	0,009	0,9692
	0	286	21	7.34	293	6	2.05	3,59 [1,47 ; 8,75]	3,79 [1,51 ; 9,54];	5,29 [1,86 ; 8,73]; 0,003	0,003	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	14	6.22	202	4	1.98	3,14 [1,05 ; 9,39]	3,28 [1,06 ; 10,15];	4,24 [0,55 ; 7,94]; 0,032	0,032	0,9074
	>=3	84	8	9.52	98	2	2.04	4,67 [1,02 ; 21,38]	5,05 [1,04 ; 24,49];	7,48 [0,61 ; 14,36]; 0,046	0,046	
	2	236	17	7.20	248	5	2.02	3,57 [1,34 ; 9,53]	3,77 [1,37 ; 10,4];	5,19 [1,45 ; 8,92]; 0,008	0,008	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9998
	White	535	39	7.29	536	11	2.05	3,55 [1,84 ; 6,86]	3,75 [1,9 ; 7,41];	5,24 [2,73 ; 7,75]; 0	0	
	No	347	26	7.49	379	7	1.85	4,06 [1,78 ; 9,23]	4,3 [1,84 ; 10,05];	5,65 [2,56 ; 8,73]; 0	0	0,5893

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	13	6.57	169	4	2.37	2,77 [0,92 ; 8,35]	2,9 [0,93 ; 9,06];	4,2 [0,06 ; 8,34]; 0,079	0,079	
Region	Eastern Europe	492	39	7.93	495	11	2.22	3,57 [1,85 ; 6,88]	3,79 [1,92 ; 7,49];	5,7 [2,99 ; 8,42]; 0	0	0,9998
	USA and Western Europe	53	0	0.00	53	0	0.00	1 [0,02 ; 49,49]	1 [0,02 ; 51,33];	0 [-3,61 ; 3,61]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - General disorders and administration site conditions | Influenza like illness

6.1.79 Investigations - Alanine aminotransferase increased

Tabelle 343: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	12	3.68	302	16	5.30	0,69 [0,33 ; 1,44]	0,68 [0,32 ; 1,47];	-1,62 [-4,87 ; 1,63]; 0,341	0,341	0,5205
	>= 38 years	219	9	4.11	246	10	4.07	1,01 [0,42 ; 2,44]	1,01 [0,4 ; 2,54];	0,04 [-3,56 ; 3,65]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	17	4.06	415	19	4.58	0,89 [0,47 ; 1,68]	0,88 [0,45 ; 1,72];	-0,52 [-3,28 ; 2,24]; 0,736	0,736	0,5768
	>3.5	126	4	3.17	133	7	5.26	0,6 [0,18 ; 2,01]	0,59 [0,17 ; 2,07];	-2,09 [-6,96 ; 2,79]; 0,542	0,542	
Gender	Female	345	11	3.19	356	13	3.65	0,87 [0,4 ; 1,92]	0,87 [0,38 ; 1,97];	-0,46 [-3,15 ; 2,23]; 0,836	0,836	0,7626
	Male	200	10	5.00	192	13	6.77	0,74 [0,33 ; 1,64]	0,72 [0,31 ; 1,69];	-1,77 [-6,43 ; 2,89]; 0,522	0,522	
Number of baseline Gd-enhancing lesions	>=1	258	15	5.81	251	14	5.58	1,04 [0,51 ; 2,11]	1,04 [0,49 ; 2,21];	0,24 [-3,79 ; 4,26]; 1	1	0,242
	0	286	6	2.10	293	12	4.10	0,51 [0,19 ; 1,35]	0,5 [0,19 ; 1,36];	-2 [-4,81 ; 0,81]; 0,231	0,231	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	9	4.00	202	6	2.97	1,35 [0,49 ; 3,72]	1,36 [0,48 ; 3,89];	1,03 [-2,44 ; 4,5]; 0,609	0,609	0,4917
	>=3	84	4	4.76	98	8	8.16	0,58 [0,18 ; 1,87]	0,56 [0,16 ; 1,94];	-3,4 [-10,48 ; 3,68]; 0,389	0,389	
	2	236	8	3.39	248	12	4.84	0,7 [0,29 ; 1,68]	0,69 [0,28 ; 1,72];	-1,45 [-4,98 ; 2,08]; 0,497	0,497	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	21	3.93	536	26	4.85	0,81 [0,46 ; 1,42]	0,8 [0,45 ; 1,44];	-0,93 [-3,38 ; 1,53]; 0,551	0,551	
	No	347	13	3.75	379	15	3.96	0,95 [0,46 ; 1,96]	0,94 [0,44 ; 2,01];	-0,21 [-3,01 ; 2,59]; 1	1	0,4668

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	8	4.04	169	11	6.51	0,62 [0,26 ; 1,51]	0,6 [0,24 ; 1,54];	-2,47 [-7,09 ; 2,15]; 0,347	0,347	
Region	Eastern Europe	492	19	3.86	495	25	5.05	0,76 [0,43 ; 1,37]	0,76 [0,41 ; 1,39];	-1,19 [-3,76 ; 1,38]; 0,441	0,441	0,4227
	USA and Western Europe	53	2	3.77	53	1	1.89	2 [0,19 ; 21,4]	2,04 [0,18 ; 23,19];	1,89 [-4,42 ; 8,19]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Investigations | Alanine aminotransferase increased

6.1.80 Investigations - Body temperature increased

Tabelle 344: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	16	4.91	302	4	1.32	3,71 [1,25 ; 10,96]	3,85 [1,27 ; 11,63];	3,58 [0,91 ; 6,26]; 0,012	0,012	0,849
	>= 38 years	219	8	3.65	246	2	0.81	4,49 [0,96 ; 20,93]	4,63 [0,97 ; 22,02];	2,84 [0,11 ; 5,57]; 0,052	0,052	
Disease Severity at baseline (EDSS)	<=3.5	419	18	4.30	415	4	0.96	4,46 [1,52 ; 13,06]	4,61 [1,55 ; 13,75];	3,33 [1,18 ; 5,49]; 0,004	0,004	0,7339
	>3.5	126	6	4.76	133	2	1.50	3,17 [0,65 ; 15,4]	3,28 [0,65 ; 16,54];	3,26 [-1 ; 7,51]; 0,163	0,163	
Gender	Female	345	16	4.64	356	3	0.84	5,5 [1,62 ; 18,72]	5,72 [1,65 ; 19,82];	3,79 [1,38 ; 6,21]; 0,002	0,002	0,4054
	Male	200	8	4.00	192	3	1.56	2,56 [0,69 ; 9,51]	2,62 [0,69 ; 10,05];	2,44 [-0,8 ; 5,67]; 0,221	0,221	
Number of baseline Gd-enhancing lesions	>=1	258	7	2.71	251	4	1.59	1,7 [0,5 ; 5,74]	1,72 [0,5 ; 5,96];	1,12 [-1,4 ; 3,64]; 0,545	0,545	0,0777
	0	286	17	5.94	293	2	0.68	8,71 [2,03 ; 37,35]	9,2 [2,1 ; 40,17];	5,26 [2,36 ; 8,16]; 0	0	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	8	3.56	202	1	0.50	7,18 [0,91 ; 56,93]	7,41 [0,92 ; 59,77];	3,06 [0,45 ; 5,67]; 0,04	0,04	0,7707
	>=3	84	4	4.76	98	1	1.02	4,67 [0,53 ; 40,95]	4,85 [0,53 ; 44,26];	3,74 [-1,23 ; 8,71]; 0,183	0,183	
	2	236	12	5.08	248	4	1.61	3,15 [1,03 ; 9,64]	3,27 [1,04 ; 10,28];	3,47 [0,26 ; 6,68]; 0,041	0,041	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9998
	White	535	24	4.49	536	6	1.12	4,01 [1,65 ; 9,73]	4,15 [1,68 ; 10,23];	3,37 [1,4 ; 5,33]; 0,001	0,001	
	No	347	12	3.46	379	3	0.79	4,37 [1,24 ; 15,35]	4,49 [1,26 ; 16,05];	2,67 [0,55 ; 4,79]; 0,016	0,016	0,8038

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	12	6.06	169	3	1.78	3,41 [0,98 ; 11,9]	3,57 [0,99 ; 12,87];	4,29 [0,41 ; 8,16]; 0,061	0,061	
Region	Eastern Europe	492	22	4.47	495	6	1.21	3,69 [1,51 ; 9,02]	3,81 [1,53 ; 9,49];	3,26 [1,19 ; 5,32]; 0,002	0,002	0,3375
	USA and Western Europe	53	2	3.77	53	0	0.00	5 [0,25 ; 101,73]	5,19 [0,24 ; 110,82];	3,7 [-2,46 ; 9,86]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Investigations | Body temperature increased

6.1.81 Investigations - Aspartate aminotransferase increased

Tabelle 345: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	14	4.29	302	8	2.65	1,62 [0,69 ; 3,81]	1,65 [0,68 ; 3,99];	1,65 [-1,2 ; 4,5]; 0,286	0,286	0,1366
	>= 38 years	219	10	4.57	246	2	0.81	5,62 [1,24 ; 25,35]	5,84 [1,26 ; 26,94];	3,75 [0,77 ; 6,74]; 0,016	0,016	
Disease Severity at baseline (EDSS)	<=3.5	419	16	3.82	415	9	2.17	1,76 [0,79 ; 3,94]	1,79 [0,78 ; 4,1];	1,65 [-0,66 ; 3,96]; 0,223	0,223	0,1111
	>3.5	126	8	6.35	133	1	0.75	8,44 [1,07 ; 66,56]	8,95 [1,1 ; 72,62];	5,6 [1,09 ; 10,1]; 0,017	0,017	
Gender	Female	345	14	4.06	356	5	1.40	2,89 [1,05 ; 7,94]	2,97 [1,06 ; 8,33];	2,65 [0,24 ; 5,07]; 0,036	0,036	0,592
	Male	200	10	5.00	192	5	2.60	1,92 [0,67 ; 5,51]	1,97 [0,66 ; 5,87];	2,4 [-1,37 ; 6,16]; 0,294	0,294	
Number of baseline Gd-enhancing lesions	>=1	258	14	5.43	251	5	1.99	2,72 [1 ; 7,45]	2,82 [1 ; 7,96];	3,43 [0,17 ; 6,69]; 0,059	0,059	0,6933
	0	286	10	3.50	293	5	1.71	2,05 [0,71 ; 5,92]	2,09 [0,7 ; 6,18];	1,79 [-0,8 ; 4,38]; 0,199	0,199	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	8	3.56	202	1	0.50	7,18 [0,91 ; 56,93]	7,41 [0,92 ; 59,77];	3,06 [0,45 ; 5,67]; 0,04	0,04	0,4121
	>=3	84	8	9.52	98	4	4.08	2,33 [0,73 ; 7,48]	2,47 [0,72 ; 8,53];	5,44 [-1,96 ; 12,84]; 0,23	0,23	
	2	236	8	3.39	248	5	2.02	1,68 [0,56 ; 5,07]	1,71 [0,55 ; 5,29];	1,37 [-1,52 ; 4,27]; 0,408	0,408	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	24	4.49	536	10	1.87	2,4 [1,16 ; 4,98]	2,47 [1,17 ; 5,22];	2,62 [0,53 ; 4,72]; 0,015	0,015	
	No	347	15	4.32	379	7	1.85	2,34 [0,97 ; 5,67]	2,4 [0,97 ; 5,96];	2,48 [-0,06 ; 5,01]; 0,081	0,081	0,9094

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	9	4.55	169	3	1.78	2,56 [0,7 ; 9,31]	2,63 [0,7 ; 9,89];	2,77 [-0,75 ; 6,29]; 0,155	0,155	
Region	Eastern Europe	492	23	4.67	495	9	1.82	2,57 [1,2 ; 5,5]	2,65 [1,21 ; 5,78];	2,86 [0,65 ; 5,06]; 0,012	0,012	0,5172
	USA and Western Europe	53	1	1.89	53	1	1.89	1 [0,06 ; 15,57]	1 [0,06 ; 16,42];	0 [-5,18 ; 5,18]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Investigations | Aspartate aminotransferase increased

6.1.82 Gastrointestinal disorders - Toothache

Tabelle 346: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	20	6.13	302	14	4.64	1,32 [0,68 ; 2,57]	1,34 [0,67 ; 2,71];	1,5 [-2,02 ; 5,02]; 0,482	0,482	0,1688
	>= 38 years	219	3	1.37	246	7	2.85	0,48 [0,13 ; 1,84]	0,47 [0,12 ; 1,86];	-1,48 [-4,06 ; 1,11]; 0,347	0,347	
Disease Severity at baseline (EDSS)	<=3.5	419	21	5.01	415	18	4.34	1,16 [0,62 ; 2,14]	1,16 [0,61 ; 2,22];	0,67 [-2,19 ; 3,54]; 0,743	0,743	0,5989
	>3.5	126	2	1.59	133	3	2.26	0,7 [0,12 ; 4,14]	0,7 [0,11 ; 4,25];	-0,67 [-4 ; 2,67]; 1	1	
Gender	Female	345	12	3.48	356	17	4.78	0,73 [0,35 ; 1,5]	0,72 [0,34 ; 1,53];	-1,3 [-4,24 ; 1,64]; 0,45	0,45	0,049
	Male	200	11	5.50	192	4	2.08	2,64 [0,86 ; 8,15]	2,74 [0,86 ; 8,74];	3,42 [-0,33 ; 7,17]; 0,113	0,113	
Number of baseline Gd-enhancing lesions	>=1	258	9	3.49	251	11	4.38	0,8 [0,34 ; 1,89]	0,79 [0,32 ; 1,94];	-0,89 [-4,27 ; 2,49]; 0,653	0,653	0,323
	0	286	14	4.90	293	10	3.41	1,43 [0,65 ; 3,18]	1,46 [0,64 ; 3,34];	1,48 [-1,77 ; 4,73]; 0,41	0,41	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	9	4.00	202	10	4.95	0,81 [0,34 ; 1,95]	0,8 [0,32 ; 2,01];	-0,95 [-4,89 ; 2,99]; 0,647	0,647	0,5179
	>=3	84	4	4.76	98	2	2.04	2,33 [0,44 ; 12,42]	2,4 [0,43 ; 13,44];	2,72 [-2,62 ; 8,07]; 0,417	0,417	
	2	236	10	4.24	248	9	3.63	1,17 [0,48 ; 2,82]	1,18 [0,47 ; 2,94];	0,61 [-2,86 ; 4,08]; 0,817	0,817	
Race	Other	10	0	0.00	12	1	8.33	0,39 [0,02 ; 8,73]	0,37 [0,01 ; 9,98];	-6,99 [-28,28 ; 14,29]; 0,493	0,493	0,2421
	White	535	23	4.30	536	20	3.73	1,15 [0,64 ; 2,07]	1,16 [0,63 ; 2,14];	0,57 [-1,78 ; 2,92]; 0,645	0,645	
	No	347	13	3.75	379	17	4.49	0,84 [0,41 ; 1,69]	0,83 [0,4 ; 1,73];	-0,74 [-3,63 ; 2,15]; 0,71	0,71	0,1577

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	10	5.05	169	4	2.37	2,13 [0,68 ; 6,68]	2,19 [0,68 ; 7,13];	2,68 [-1,13 ; 6,5]; 0,274	0,274	
Region	Eastern Europe	492	21	4.27	495	20	4.04	1,06 [0,58 ; 1,92]	1,06 [0,57 ; 1,98];	0,23 [-2,26 ; 2,72]; 0,875	0,875	0,6002
	USA and Western Europe	53	2	3.77	53	1	1.89	2 [0,19 ; 21,4]	2,04 [0,18 ; 23,19];	1,89 [-4,42 ; 8,19]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Gastrointestinal disorders | Toothache

6.1.83 Infections and infestations - Acute sinusitis

Tabelle 347: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	13	3.99	302	5	1.66	2,41 [0,87 ; 6,68]	2,47 [0,87 ; 7];	2,33 [-0,23 ; 4,9]; 0,096	0,096	0,2511
	>= 38 years	219	1	0.46	246	2	0.81	0,56 [0,05 ; 6,15]	0,56 [0,05 ; 6,21];	-0,36 [-1,79 ; 1,08]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	13	3.10	415	6	1.45	2,15 [0,82 ; 5,59]	2,18 [0,82 ; 5,8];	1,66 [-0,36 ; 3,68]; 0,162	0,162	0,6318
	>3.5	126	1	0.79	133	1	0.75	1,06 [0,07 ; 16,7]	1,06 [0,07 ; 17,07];	0,04 [-2,09 ; 2,18]; 1	1	
Gender	Female	345	13	3.77	356	6	1.69	2,24 [0,86 ; 5,82]	2,28 [0,86 ; 6,08];	2,08 [-0,33 ; 4,5]; 0,106	0,106	0,568
	Male	200	1	0.50	192	1	0.52	0,96 [0,06 ; 15,24]	0,96 [0,06 ; 15,45];	-0,02 [-1,43 ; 1,39]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	258	5	1.94	251	3	1.20	1,62 [0,39 ; 6,71]	1,63 [0,39 ; 6,91];	0,74 [-1,41 ; 2,9]; 0,725	0,725	0,7046
	0	286	9	3.15	293	4	1.37	2,31 [0,72 ; 7,4]	2,35 [0,71 ; 7,71];	1,78 [-0,64 ; 4,2]; 0,17	0,17	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	8	3.56	202	2	0.99	3,59 [0,77 ; 16,71]	3,69 [0,77 ; 17,57];	2,57 [-0,21 ; 5,34]; 0,11	0,11	0,1868
	>=3	84	2	2.38	98	4	4.08	0,58 [0,11 ; 3,11]	0,57 [0,1 ; 3,21];	-1,7 [-6,8 ; 3,4]; 0,688	0,688	
	2	236	4	1.69	248	1	0.40	4,2 [0,47 ; 37,34]	4,26 [0,47 ; 38,38];	1,29 [-0,53 ; 3,12]; 0,206	0,206	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	14	2.62	536	7	1.31	2 [0,82 ; 4,93]	2,03 [0,81 ; 5,07];	1,31 [-0,35 ; 2,97]; 0,13	0,13	
	No	347	8	2.31	379	3	0.79	2,91 [0,78 ; 10,89]	2,96 [0,78 ; 11,24];	1,51 [-0,3 ; 3,33]; 0,129	0,129	0,3763

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	6	3.03	169	4	2.37	1,28 [0,37 ; 4,46]	1,29 [0,36 ; 4,65];	0,66 [-2,65 ; 3,97]; 0,758	0,758	
Region	Eastern Europe	492	14	2.85	495	7	1.41	2,01 [0,82 ; 4,94]	2,04 [0,82 ; 5,1];	1,43 [-0,37 ; 3,23]; 0,129	0,129	0,9999
	USA and Western Europe	53	0	0.00	53	0	0.00	1 [0,02 ; 49,49]	1 [0,02 ; 51,33];	0 [-3,61 ; 3,61]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Acute sinusitis

6.1.84 Infections and infestations - Pharyngitis

Tabelle 348: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	22	6.75	302	9	2.98	2,26 [1,06 ; 4,84]	2,36 [1,07 ; 5,2];	3,77 [0,44 ; 7,1]; 0,041	0,041	0,5147
	>= 38 years	219	10	4.57	246	3	1.22	3,74 [1,04 ; 13,43]	3,88 [1,05 ; 14,27];	3,35 [0,26 ; 6,43]; 0,045	0,045	
Disease Severity at baseline (EDSS)	<=3.5	419	24	5.73	415	12	2.89	1,98 [1 ; 3,91]	2,04 [1,01 ; 4,14];	2,84 [0,09 ; 5,58]; 0,06	0,06	0,0137
	>3.5	126	8	6.35	133	0	0.00	17,94 [1,05 ; 307,56]	19,15 [1,09 ; 335,38];	6,32 [1,85 ; 10,79]; 0,003	0,003	
Gender	Female	345	26	7.54	356	11	3.09	2,44 [1,22 ; 4,86]	2,56 [1,24 ; 5,26];	4,45 [1,13 ; 7,76]; 0,011	0,011	0,4318
	Male	200	6	3.00	192	1	0.52	5,76 [0,7 ; 47,4]	5,91 [0,7 ; 49,53];	2,48 [-0,09 ; 5,05]; 0,122	0,122	
Number of baseline Gd-enhancing lesions	>=1	258	16	6.20	251	5	1.99	3,11 [1,16 ; 8,37]	3,25 [1,17 ; 9,02];	4,21 [0,8 ; 7,62]; 0,024	0,024	0,6699
	0	286	16	5.59	293	7	2.39	2,34 [0,98 ; 5,61]	2,42 [0,98 ; 5,98];	3,21 [0,02 ; 6,39]; 0,056	0,056	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	13	5.78	202	5	2.48	2,33 [0,85 ; 6,43]	2,42 [0,85 ; 6,9];	3,3 [-0,42 ; 7,03]; 0,098	0,098	0,929
	>=3	84	7	8.33	98	3	3.06	2,72 [0,73 ; 10,2]	2,88 [0,72 ; 11,51];	5,27 [-1,55 ; 12,1]; 0,191	0,191	
	2	236	12	5.08	248	4	1.61	3,15 [1,03 ; 9,64]	3,27 [1,04 ; 10,28];	3,47 [0,26 ; 6,68]; 0,041	0,041	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	32	5.98	536	12	2.24	2,67 [1,39 ; 5,13]	2,78 [1,41 ; 5,45];	3,74 [1,37 ; 6,11]; 0,002	0,002	
	No	347	18	5.19	379	8	2.11	2,46 [1,08 ; 5,58]	2,54 [1,09 ; 5,91];	3,08 [0,33 ; 5,82]; 0,029	0,029	0,7666

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	14	7.07	169	4	2.37	2,99 [1 ; 8,9]	3,14 [1,01 ; 9,72];	4,7 [0,46 ; 8,95]; 0,051	0,051	
Region	Eastern Europe	492	31	6.30	495	12	2.42	2,6 [1,35 ; 5]	2,71 [1,37 ; 5,33];	3,88 [1,34 ; 6,42]; 0,003	0,003	0,4282
	USA and Western Europe	53	1	1.89	53	0	0.00	3 [0,12 ; 72,02]	3,06 [0,12 ; 76,76];	1,85 [-3,22 ; 6,93]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Pharyngitis

6.1.85 Blood and lymphatic system disorders - Anaemia

Tabelle 349: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	11	3.37	302	11	3.64	0,93 [0,41 ; 2,11]	0,92 [0,39 ; 2,16];	-0,27 [-3,15 ; 2,61]; 1	1	0,4603
	>= 38 years	219	5	2.28	246	10	4.07	0,56 [0,19 ; 1,62]	0,55 [0,19 ; 1,64];	-1,78 [-4,94 ; 1,38]; 0,306	0,306	
Disease Severity at baseline (EDSS)	<=3.5	419	11	2.63	415	14	3.37	0,78 [0,36 ; 1,69]	0,77 [0,35 ; 1,72];	-0,75 [-3,06 ; 1,57]; 0,549	0,549	0,9587
	>3.5	126	5	3.97	133	7	5.26	0,75 [0,25 ; 2,31]	0,74 [0,23 ; 2,41];	-1,29 [-6,4 ; 3,81]; 0,77	0,77	
Gender	Female	345	16	4.64	356	21	5.90	0,79 [0,42 ; 1,48]	0,78 [0,4 ; 1,51];	-1,26 [-4,56 ; 2,04]; 0,502	0,502	1
	Male	200	0	0.00	192	0	0.00	0,96 [0,02 ; 48,15]	0,96 [0,02 ; 48,63];	-0,01 [-1 ; 0,98]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	258	9	3.49	251	7	2.79	1,25 [0,47 ; 3,31]	1,26 [0,46 ; 3,44];	0,7 [-2,33 ; 3,73]; 0,801	0,801	0,1789
	0	286	7	2.45	293	14	4.78	0,51 [0,21 ; 1,25]	0,5 [0,2 ; 1,26];	-2,33 [-5,36 ; 0,7]; 0,182	0,182	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	6	2.67	202	9	4.46	0,6 [0,22 ; 1,65]	0,59 [0,21 ; 1,68];	-1,79 [-5,33 ; 1,75]; 0,431	0,431	0,8162
	>=3	84	4	4.76	98	5	5.10	0,93 [0,26 ; 3,36]	0,93 [0,24 ; 3,58];	-0,34 [-6,64 ; 5,96]; 1	1	
	2	236	6	2.54	248	7	2.82	0,9 [0,31 ; 2,64]	0,9 [0,3 ; 2,71];	-0,28 [-3,16 ; 2,6]; 1	1	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	16	2.99	536	21	3.92	0,76 [0,4 ; 1,45]	0,76 [0,39 ; 1,47];	-0,93 [-3,11 ; 1,26]; 0,504	0,504	
	No	347	9	2.59	379	15	3.96	0,66 [0,29 ; 1,48]	0,65 [0,28 ; 1,5];	-1,36 [-3,94 ; 1,21]; 0,407	0,407	0,5414

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	7	3.54	169	6	3.55	1 [0,34 ; 2,91]	1 [0,33 ; 3,02];	-0,01 [-3,81 ; 3,78]; 1	1	
Region	Eastern Europe	492	16	3.25	495	20	4.04	0,8 [0,42 ; 1,53]	0,8 [0,41 ; 1,56];	-0,79 [-3,13 ; 1,55]; 0,611	0,611	0,2813
	USA and Western Europe	53	0	0.00	53	1	1.89	0,33 [0,01 ; 8]	0,33 [0,01 ; 8,21];	-1,85 [-6,93 ; 3,22]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Blood and lymphatic system disorders | Anaemia

6.1.86 Infections and infestations - Rhinitis

Tabelle 350: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	20	6.13	302	14	4.64	1,32 [0,68 ; 2,57]	1,34 [0,67 ; 2,71];	1,5 [-2,02 ; 5,02]; 0,482	0,482	0,2956
	>= 38 years	219	4	1.83	246	7	2.85	0,64 [0,19 ; 2,16]	0,64 [0,18 ; 2,2];	-1,02 [-3,75 ; 1,71]; 0,552	0,552	
Disease Severity at baseline (EDSS)	<=3.5	419	19	4.53	415	18	4.34	1,05 [0,56 ; 1,96]	1,05 [0,54 ; 2,03];	0,2 [-2,6 ; 2,99]; 1	1	0,5054
	>3.5	126	5	3.97	133	3	2.26	1,76 [0,43 ; 7,21]	1,79 [0,42 ; 7,65];	1,71 [-2,53 ; 5,95]; 0,491	0,491	
Gender	Female	345	10	2.90	356	16	4.49	0,64 [0,3 ; 1,4]	0,63 [0,28 ; 1,42];	-1,6 [-4,38 ; 1,19]; 0,319	0,319	0,021
	Male	200	14	7.00	192	5	2.60	2,69 [0,99 ; 7,32]	2,82 [0,99 ; 7,97];	4,4 [0,2 ; 8,59]; 0,058	0,058	
Number of baseline Gd-enhancing lesions	>=1	258	12	4.65	251	11	4.38	1,06 [0,48 ; 2,36]	1,06 [0,46 ; 2,46];	0,27 [-3,34 ; 3,88]; 1	1	0,803
	0	286	12	4.20	293	10	3.41	1,23 [0,54 ; 2,8]	1,24 [0,53 ; 2,92];	0,78 [-2,34 ; 3,9]; 0,668	0,668	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	3	1.33	202	12	5.94	0,22 [0,06 ; 0,78]	0,21 [0,06 ; 0,77];	-4,61 [-8,2 ; -1,02]; 0,015	0,015	0,0009
	>=3	84	3	3.57	98	3	3.06	1,17 [0,24 ; 5,63]	1,17 [0,23 ; 5,97];	0,51 [-4,72 ; 5,74]; 1	1	
	2	236	18	7.63	248	6	2.42	3,15 [1,27 ; 7,81]	3,33 [1,3 ; 8,54];	5,21 [1,32 ; 9,1]; 0,011	0,011	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	24	4.49	536	21	3.92	1,14 [0,65 ; 2,03]	1,15 [0,63 ; 2,1];	0,57 [-1,83 ; 2,97]; 0,652	0,652	
	No	347	17	4.90	379	16	4.22	1,16 [0,6 ; 2,26]	1,17 [0,58 ; 2,35];	0,68 [-2,36 ; 3,72]; 0,723	0,723	0,9676

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	7	3.54	169	5	2.96	1,19 [0,39 ; 3,7]	1,2 [0,37 ; 3,86];	0,58 [-3,05 ; 4,2]; 1	1	
Region	Eastern Europe	492	24	4.88	495	21	4.24	1,15 [0,65 ; 2,04]	1,16 [0,64 ; 2,11];	0,64 [-1,97 ; 3,24]; 0,65	0,65	1
	USA and Western Europe	53	0	0.00	53	0	0.00	1 [0,02 ; 49,49]	1 [0,02 ; 51,33];	0 [-3,61 ; 3,61]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Rhinitis

6.1.87 Infections and infestations - Vaginal infection

Tabelle 351: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	7	2.15	302	7	2.32	0,93 [0,33 ; 2,61]	0,92 [0,32 ; 2,67];	-0,17 [-2,48 ; 2,14]; 1	1	0,3059
	>= 38 years	219	6	2.74	246	3	1.22	2,25 [0,57 ; 8,88]	2,28 [0,56 ; 9,23];	1,52 [-1,04 ; 4,08]; 0,317	0,317	
Disease Severity at baseline (EDSS)	<=3.5	419	6	1.43	415	8	1.93	0,74 [0,26 ; 2,12]	0,74 [0,25 ; 2,15];	-0,5 [-2,24 ; 1,25]; 0,603	0,603	0,0741
	>3.5	126	7	5.56	133	2	1.50	3,69 [0,78 ; 17,45]	3,85 [0,78 ; 18,91];	4,05 [-0,45 ; 8,55]; 0,095	0,095	
Gender	Female	345	13	3.77	356	10	2.81	1,34 [0,6 ; 3,02]	1,35 [0,59 ; 3,13];	0,96 [-1,68 ; 3,6]; 0,529	0,529	1
	Male	200	0	0.00	192	0	0.00	0,96 [0,02 ; 48,15]	0,96 [0,02 ; 48,63];	-0,01 [-1 ; 0,98]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	258	6	2.33	251	4	1.59	1,46 [0,42 ; 5,11]	1,47 [0,41 ; 5,27];	0,73 [-1,67 ; 3,14]; 0,752	0,752	0,8133
	0	286	7	2.45	293	6	2.05	1,2 [0,41 ; 3,51]	1,2 [0,4 ; 3,62];	0,4 [-2,02 ; 2,82]; 0,786	0,786	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	3	1.33	202	5	2.48	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	3	3.57	98	3	3.06	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	7	2.97	248	2	0.81	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	13	2.43	536	10	1.87	1,3 [0,58 ; 2,94]	1,31 [0,57 ; 3,01];	0,56 [-1,17 ; 2,3]; 0,537	0,537	
	No	347	9	2.59	379	8	2.11	1,23 [0,48 ; 3,15]	1,23 [0,47 ; 3,24];	0,48 [-1,73 ; 2,69]; 0,807	0,807	0,7377

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	4	2.02	169	2	1.18	1,71 [0,32 ; 9,2]	1,72 [0,31 ; 9,52];	0,84 [-1,71 ; 3,39]; 0,691	0,691	
Region	Eastern Europe	492	12	2.44	495	10	2.02	1,21 [0,53 ; 2,77]	1,21 [0,52 ; 2,83];	0,42 [-1,42 ; 2,26]; 0,673	0,673	0,2783
	USA and Western Europe	53	1	1.89	53	0	0.00	3 [0,12 ; 72,02]	3,06 [0,12 ; 76,76];	1,85 [-3,22 ; 6,93]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Vaginal infection

6.1.88 Infections and infestations - Conjunctivitis

Tabelle 352: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	9	2.76	302	6	1.99	1,39 [0,5 ; 3,86]	1,4 [0,49 ; 3,98];	0,77 [-1,6 ; 3,15]; 0,607	0,607	0,0197
	>= 38 years	219	0	0.00	246	4	1.63	0,12 [0,01 ; 2,3]	0,12 [0,01 ; 2,29];	-1,59 [-3,38 ; 0,19]; 0,126	0,126	
Disease Severity at baseline (EDSS)	<=3.5	419	9	2.15	415	10	2.41	0,89 [0,37 ; 2,17]	0,89 [0,36 ; 2,21];	-0,26 [-2,29 ; 1,76]; 0,821	0,821	1
	>3.5	126	0	0.00	133	0	0.00	1,06 [0,02 ; 52,78]	1,06 [0,02 ; 53,59];	0,02 [-1,48 ; 1,52]; 1	1	
Gender	Female	345	7	2.03	356	5	1.40	1,44 [0,46 ; 4,51]	1,45 [0,46 ; 4,63];	0,62 [-1,3 ; 2,55]; 0,572	0,572	0,1752
	Male	200	2	1.00	192	5	2.60	0,38 [0,08 ; 1,96]	0,38 [0,07 ; 1,97];	-1,6 [-4,25 ; 1,04]; 0,276	0,276	
Number of baseline Gd-enhancing lesions	>=1	258	4	1.55	251	5	1.99	0,78 [0,21 ; 2,87]	0,77 [0,21 ; 2,92];	-0,44 [-2,74 ; 1,85]; 0,749	0,749	0,7633
	0	286	5	1.75	293	5	1.71	1,02 [0,3 ; 3,5]	1,02 [0,29 ; 3,58];	0,04 [-2,08 ; 2,16]; 1	1	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	3	1.33	202	3	1.49	0,9 [0,18 ; 4,4]	0,9 [0,18 ; 4,49];	-0,15 [-2,39 ; 2,09]; 1	1	0,1499
	>=3	84	2	2.38	98	0	0.00	5,82 [0,28 ; 119,63]	5,97 [0,28 ; 126,11];	2,44 [-1,42 ; 6,29]; 0,212	0,212	
	2	236	4	1.69	248	7	2.82	0,6 [0,18 ; 2,02]	0,59 [0,17 ; 2,05];	-1,13 [-3,77 ; 1,51]; 0,546	0,546	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	9	1.68	536	10	1.87	0,9 [0,37 ; 2,2]	0,9 [0,36 ; 2,23];	-0,18 [-1,76 ; 1,4]; 1	1	
	No	347	5	1.44	379	7	1.85	0,78 [0,25 ; 2,44]	0,78 [0,24 ; 2,47];	-0,41 [-2,25 ; 1,44]; 0,775	0,775	0,6912

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	4	2.02	169	3	1.78	1,14 [0,26 ; 5,01]	1,14 [0,25 ; 5,17];	0,25 [-2,55 ; 3,04]; 1	1	
Region	Eastern Europe	492	9	1.83	495	8	1.62	1,13 [0,44 ; 2,91]	1,13 [0,43 ; 2,96];	0,21 [-1,41 ; 1,84]; 0,812	0,812	0,0926
	USA and Western Europe	53	0	0.00	53	2	3.77	0,2 [0,01 ; 4,07]	0,19 [0,01 ; 4,11];	-3,7 [-9,86 ; 2,46]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Conjunctivitis

6.1.89 Immune system disorders - Hypersensitivity

Tabelle 353: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	8	2.45	302	1	0.33	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>= 38 years	219	5	2.28	246	4	1.63	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	419	11	2.63	415	3	0.72	3,63 [1,02 ; 12,92]	3,7 [1,03 ; 13,37];	1,9 [0,17 ; 3,64]; 0,055	0,055	0,2981
	>3.5	126	2	1.59	133	2	1.50	1,06 [0,15 ; 7,38]	1,06 [0,15 ; 7,62];	0,08 [-2,92 ; 3,09]; 1	1	
Gender	Female	345	9	2.61	356	5	1.40	1,86 [0,63 ; 5,49]	1,88 [0,62 ; 5,67];	1,2 [-0,88 ; 3,28]; 0,29	0,29	0,0907
	Male	200	4	2.00	192	0	0.00	8,64 [0,47 ; 159,44]	8,82 [0,47 ; 164,87];	1,98 [-0,19 ; 4,15]; 0,123	0,123	
Number of baseline Gd-enhancing lesions	>=1	258	6	2.33	251	1	0.40	5,84 [0,71 ; 48,14]	5,95 [0,71 ; 49,8];	1,93 [-0,07 ; 3,92]; 0,123	0,123	0,3135
	0	286	7	2.45	293	4	1.37	1,79 [0,53 ; 6,06]	1,81 [0,52 ; 6,26];	1,08 [-1,15 ; 3,31]; 0,378	0,378	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	5	2.22	202	3	1.49	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	1	1.19	98	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	7	2.97	248	2	0.81	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	0	0.00	12	2	16.67	0,24 [0,01 ; 4,42]	0,2 [0,01 ; 4,69];	-14,69 [-39,39 ; 10,02]; 0,481	0,481	0,0192
	White	535	13	2.43	536	3	0.56	4,34 [1,24 ; 15,15]	4,42 [1,25 ; 15,62];	1,87 [0,42 ; 3,32]; 0,012	0,012	
	No	347	8	2.31	379	1	0.26	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	5	2.53	169	4	2.37	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Region	Eastern Europe	492	13	2.64	495	3	0.61	4,36 [1,25 ; 15,2]	4,45 [1,26 ; 15,72];	2,04 [0,46 ; 3,61]; 0,012	0,012	0,0149
	USA and Western Europe	53	0	0.00	53	2	3.77	0,2 [0,01 ; 4,07]	0,19 [0,01 ; 4,11];	-3,7 [-9,86 ; 2,46]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Immune system disorders | Hypersensitivity

6.1.90 Infections and infestations - Cystitis

Tabelle 354: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	19	5.83	302	14	4.64	1,26 [0,64 ; 2,46]	1,27 [0,63 ; 2,59];	1,19 [-2,28 ; 4,67]; 0,592	0,592	0,859
	>= 38 years	219	6	2.74	246	6	2.44	1,12 [0,37 ; 3,43]	1,13 [0,36 ; 3,55];	0,3 [-2,6 ; 3,2]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	20	4.77	415	14	3.37	1,41 [0,72 ; 2,76]	1,44 [0,72 ; 2,88];	1,4 [-1,28 ; 4,08]; 0,382	0,382	0,4862
	>3.5	126	5	3.97	133	6	4.51	0,88 [0,28 ; 2,81]	0,87 [0,26 ; 2,94];	-0,54 [-5,45 ; 4,36]; 1	1	
Gender	Female	345	23	6.67	356	20	5.62	1,19 [0,66 ; 2,12]	1,2 [0,65 ; 2,23];	1,05 [-2,51 ; 4,61]; 0,638	0,638	0,1306
	Male	200	2	1.00	192	0	0.00	4,8 [0,23 ; 99,36]	4,85 [0,23 ; 101,65];	0,98 [-0,71 ; 2,68]; 0,499	0,499	
Number of baseline Gd-enhancing lesions	>=1	258	15	5.81	251	9	3.59	1,62 [0,72 ; 3,64]	1,66 [0,71 ; 3,87];	2,23 [-1,44 ; 5,89]; 0,297	0,297	0,3466
	0	286	10	3.50	293	11	3.75	0,93 [0,4 ; 2,16]	0,93 [0,39 ; 2,22];	-0,26 [-3,3 ; 2,79]; 1	1	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	7	3.11	202	8	3.96	0,79 [0,29 ; 2,13]	0,78 [0,28 ; 2,19];	-0,85 [-4,37 ; 2,67]; 0,794	0,794	0,2678
	>=3	84	4	4.76	98	1	1.02	4,67 [0,53 ; 40,95]	4,85 [0,53 ; 44,26];	3,74 [-1,23 ; 8,71]; 0,183	0,183	
	2	236	14	5.93	248	11	4.44	1,34 [0,62 ; 2,89]	1,36 [0,6 ; 3,06];	1,5 [-2,46 ; 5,45]; 0,54	0,54	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	25	4.67	536	20	3.73	1,25 [0,7 ; 2,23]	1,26 [0,69 ; 2,31];	0,94 [-1,46 ; 3,34]; 0,451	0,451	
	No	347	10	2.88	379	13	3.43	0,84 [0,37 ; 1,89]	0,84 [0,36 ; 1,93];	-0,55 [-3,09 ; 1,99]; 0,833	0,833	0,1907

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	15	7.58	169	7	4.14	1,83 [0,76 ; 4,38]	1,9 [0,75 ; 4,77];	3,43 [-1,32 ; 8,19]; 0,191	0,191	
Region	Eastern Europe	492	25	5.08	495	20	4.04	1,26 [0,71 ; 2,23]	1,27 [0,7 ; 2,32];	1,04 [-1,56 ; 3,64]; 0,45	0,45	1
	USA and Western Europe	53	0	0.00	53	0	0.00	1 [0,02 ; 49,49]	1 [0,02 ; 51,33];	0 [-3,61 ; 3,61]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Cystitis

6.1.91 Renal and urinary disorders - Leukocyturia

Tabelle 355: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	6	1.84	302	4	1.32	1,39 [0,4 ; 4,88]	1,4 [0,39 ; 5];	0,52 [-1,43 ; 2,46]; 0,754	0,754	0,9899
	>= 38 years	219	5	2.28	246	4	1.63	1,4 [0,38 ; 5,16]	1,41 [0,37 ; 5,33];	0,66 [-1,87 ; 3,19]; 0,741	0,741	
Disease Severity at baseline (EDSS)	<=3.5	419	8	1.91	415	4	0.96	1,98 [0,6 ; 6,53]	2 [0,6 ; 6,69];	0,95 [-0,67 ; 2,56]; 0,384	0,384	0,3405
	>3.5	126	3	2.38	133	4	3.01	0,79 [0,18 ; 3,47]	0,79 [0,17 ; 3,59];	-0,63 [-4,57 ; 3,31]; 1	1	
Gender	Female	345	10	2.90	356	6	1.69	1,72 [0,63 ; 4,68]	1,74 [0,63 ; 4,84];	1,21 [-1,01 ; 3,43]; 0,32	0,32	0,3167
	Male	200	1	0.50	192	2	1.04	0,48 [0,04 ; 5,25]	0,48 [0,04 ; 5,31];	-0,54 [-2,28 ; 1,2]; 0,616	0,616	
Number of baseline Gd-enhancing lesions	>=1	258	5	1.94	251	5	1.99	0,97 [0,29 ; 3,32]	0,97 [0,28 ; 3,4];	-0,05 [-2,47 ; 2,36]; 1	1	0,4248
	0	286	6	2.10	293	3	1.02	2,05 [0,52 ; 8,11]	2,07 [0,51 ; 8,36];	1,07 [-0,95 ; 3,1]; 0,335	0,335	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	1	0.44	202	3	1.49	0,3 [0,03 ; 2,85]	0,3 [0,03 ; 2,87];	-1,04 [-2,92 ; 0,84]; 0,348	0,348	0,0538
	>=3	84	3	3.57	98	0	0.00	8,15 [0,43 ; 155,61]	8,46 [0,43 ; 166,18];	3,61 [-0,84 ; 8,06]; 0,046	0,046	
	2	236	7	2.97	248	5	2.02	1,47 [0,47 ; 4,57]	1,49 [0,46 ; 4,75];	0,95 [-1,83 ; 3,73]; 0,568	0,568	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	11	2.06	536	8	1.49	1,38 [0,56 ; 3,4]	1,39 [0,55 ; 3,47];	0,56 [-1,02 ; 2,14]; 0,499	0,499	
	No	347	5	1.44	379	3	0.79	1,82 [0,44 ; 7,56]	1,83 [0,43 ; 7,72];	0,65 [-0,89 ; 2,19]; 0,489	0,489	0,5421

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	6	3.03	169	5	2.96	1,02 [0,32 ; 3,3]	1,03 [0,31 ; 3,42];	0,07 [-3,42 ; 3,57]; 1	1	
Region	Eastern Europe	492	11	2.24	495	8	1.62	1,38 [0,56 ; 3,41]	1,39 [0,56 ; 3,49];	0,62 [-1,1 ; 2,33]; 0,498	0,498	1
	USA and Western Europe	53	0	0.00	53	0	0.00	1 [0,02 ; 49,49]	1 [0,02 ; 51,33];	0 [-3,61 ; 3,61]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Renal and urinary disorders | Leukocyturia

6.1.92 Gastrointestinal disorders - Chronic gastritis

Tabelle 356: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	2	0.61	302	5	1.66	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>= 38 years	219	2	0.91	246	5	2.03	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	419	2	0.48	415	5	1.20	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>3.5	126	2	1.59	133	5	3.76	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Gender	Female	345	4	1.16	356	6	1.69	0,69 [0,2 ; 2,42]	0,68 [0,19 ; 2,45];	-0,53 [-2,28 ; 1,22]; 0,752	0,752	0,0623
	Male	200	0	0.00	192	4	2.08	0,11 [0,01 ; 1,97]	0,1 [0,01 ; 1,95];	-2,08 [-4,32 ; 0,15]; 0,057	0,057	
Number of baseline Gd-enhancing lesions	>=1	258	2	0.78	251	3	1.20	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	286	2	0.70	293	7	2.39	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	1	0.44	202	1	0.50	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	1	1.19	98	6	6.12	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	2	0.85	248	3	1.21	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	4	0.75	536	10	1.87	0,4 [0,13 ; 1,27]	0,4 [0,12 ; 1,27];	-1,12 [-2,48 ; 0,24]; 0,177	0,177	
	No	347	2	0.58	379	5	1.32	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	2	1.01	169	5	2.96	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Region	Eastern Europe	492	4	0.81	495	10	2.02	0,4 [0,13 ; 1,27]	0,4 [0,12 ; 1,28];	-1,21 [-2,68 ; 0,26]; 0,176	0,176	0,9999
	USA and Western Europe	53	0	0.00	53	0	0.00	1 [0,02 ; 49,49]	1 [0,02 ; 51,33];	0 [-3,61 ; 3,61]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Gastrointestinal disorders | Chronic gastritis

6.1.93 Infections and infestations - Tonsillitis

Tabelle 357: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	8	2.45	302	10	3.31	0,74 [0,3 ; 1,85]	0,73 [0,29 ; 1,89];	-0,86 [-3,48 ; 1,77]; 0,634	0,634	0,7769
	>= 38 years	219	1	0.46	246	1	0.41	1,12 [0,07 ; 17,85]	1,12 [0,07 ; 18,08];	0,05 [-1,15 ; 1,25]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	7	1.67	415	9	2.17	0,77 [0,29 ; 2,05]	0,77 [0,28 ; 2,08];	-0,5 [-2,36 ; 1,36]; 0,624	0,624	0,7764
	>3.5	126	2	1.59	133	2	1.50	1,06 [0,15 ; 7,38]	1,06 [0,15 ; 7,62];	0,08 [-2,92 ; 3,09]; 1	1	
Gender	Female	345	8	2.32	356	9	2.53	0,92 [0,36 ; 2,35]	0,92 [0,35 ; 2,4];	-0,21 [-2,49 ; 2,07]; 1	1	0,6155
	Male	200	1	0.50	192	2	1.04	0,48 [0,04 ; 5,25]	0,48 [0,04 ; 5,31];	-0,54 [-2,28 ; 1,2]; 0,616	0,616	
Number of baseline Gd-enhancing lesions	>=1	258	5	1.94	251	8	3.19	0,61 [0,2 ; 1,83]	0,6 [0,19 ; 1,86];	-1,25 [-4 ; 1,5]; 0,412	0,412	0,3864
	0	286	4	1.40	293	3	1.02	1,37 [0,31 ; 6,05]	1,37 [0,3 ; 6,18];	0,37 [-1,41 ; 2,16]; 0,722	0,722	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	2	0.89	202	3	1.49	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	5	5.95	98	4	4.08	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	2	0.85	248	4	1.61	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	9	1.68	536	11	2.05	0,82 [0,34 ; 1,96]	0,82 [0,34 ; 1,99];	-0,37 [-1,99 ; 1,25]; 0,822	0,822	
	No	347	5	1.44	379	9	2.37	0,61 [0,21 ; 1,79]	0,6 [0,2 ; 1,81];	-0,93 [-2,91 ; 1,05]; 0,426	0,426	0,2987

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	4	2.02	169	2	1.18	1,71 [0,32 ; 9,2]	1,72 [0,31 ; 9,52];	0,84 [-1,71 ; 3,39]; 0,691	0,691	
Region	Eastern Europe	492	9	1.83	495	10	2.02	0,91 [0,37 ; 2,21]	0,9 [0,36 ; 2,24];	-0,19 [-1,91 ; 1,52]; 1	1	0,2634
	USA and Western Europe	53	0	0.00	53	1	1.89	0,33 [0,01 ; 8]	0,33 [0,01 ; 8,21];	-1,85 [-6,93 ; 3,22]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Infections and infestations | Tonsillitis

6.1.94 Respiratory, thoracic and mediastinal disorders - Rhinitis allergic

Tabelle 358: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	9	2.76	302	6	1.99	1,39 [0,5 ; 3,86]	1,4 [0,49 ; 3,98];	0,77 [-1,6 ; 3,15]; 0,607	0,607	0,0926
	>= 38 years	219	1	0.46	246	5	2.03	0,22 [0,03 ; 1,91]	0,22 [0,03 ; 1,91];	-1,58 [-3,55 ; 0,4]; 0,22	0,22	
Disease Severity at baseline (EDSS)	<=3.5	419	9	2.15	415	9	2.17	0,99 [0,4 ; 2,47]	0,99 [0,39 ; 2,52];	-0,02 [-1,99 ; 1,95]; 1	1	0,6224
	>3.5	126	1	0.79	133	2	1.50	0,53 [0,05 ; 5,75]	0,52 [0,05 ; 5,85];	-0,71 [-3,29 ; 1,87]; 1	1	
Gender	Female	345	8	2.32	356	10	2.81	0,83 [0,33 ; 2,07]	0,82 [0,32 ; 2,11];	-0,49 [-2,83 ; 1,85]; 0,813	0,813	0,5064
	Male	200	2	1.00	192	1	0.52	1,92 [0,18 ; 21]	1,93 [0,17 ; 21,45];	0,48 [-1,23 ; 2,19]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	258	4	1.55	251	8	3.19	0,49 [0,15 ; 1,6]	0,48 [0,14 ; 1,61];	-1,64 [-4,28 ; 1,01]; 0,255	0,255	0,1094
	0	286	6	2.10	293	3	1.02	2,05 [0,52 ; 8,11]	2,07 [0,51 ; 8,36];	1,07 [-0,95 ; 3,1]; 0,335	0,335	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	3	1.33	202	6	2.97	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	2	2.38	98	3	3.06	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	5	2.12	248	2	0.81	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	10	1.87	536	11	2.05	0,91 [0,39 ; 2,13]	0,91 [0,38 ; 2,16];	-0,18 [-1,84 ; 1,48]; 1	1	
	No	347	5	1.44	379	9	2.37	0,61 [0,21 ; 1,79]	0,6 [0,2 ; 1,81];	-0,93 [-2,91 ; 1,05]; 0,426	0,426	0,1896

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	5	2.53	169	2	1.18	2,13 [0,42 ; 10,86]	2,16 [0,41 ; 11,3];	1,34 [-1,38 ; 4,07]; 0,459	0,459	
Region	Eastern Europe	492	10	2.03	495	11	2.22	0,91 [0,39 ; 2,13]	0,91 [0,38 ; 2,17];	-0,19 [-1,99 ; 1,61]; 1	1	1
	USA and Western Europe	53	0	0.00	53	0	0.00	1 [0,02 ; 49,49]	1 [0,02 ; 51,33];	0 [-3,61 ; 3,61]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Respiratory, thoracic and mediastinal disorders | Rhinitis allergic

6.1.95 Cardiac disorders - Sinus tachycardia

Tabelle 359: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	13	3.99	302	8	2.65	1,51 [0,63 ; 3,58]	1,53 [0,62 ; 3,74];	1,34 [-1,45 ; 4,13]; 0,383	0,383	0,0654
	>= 38 years	219	12	5.48	246	2	0.81	6,74 [1,53 ; 29,78]	7,07 [1,56 ; 31,96];	4,67 [1,45 ; 7,88]; 0,005	0,005	
Disease Severity at baseline (EDSS)	<=3.5	419	18	4.30	415	6	1.45	2,97 [1,19 ; 7,41]	3,06 [1,2 ; 7,79];	2,85 [0,59 ; 5,11]; 0,021	0,021	0,551
	>3.5	126	7	5.56	133	4	3.01	1,85 [0,55 ; 6,16]	1,9 [0,54 ; 6,64];	2,55 [-2,39 ; 7,49]; 0,366	0,366	
Gender	Female	345	18	5.22	356	4	1.12	4,64 [1,59 ; 13,58]	4,84 [1,62 ; 14,46];	4,09 [1,5 ; 6,68]; 0,002	0,002	0,0614
	Male	200	7	3.50	192	6	3.12	1,12 [0,38 ; 3,27]	1,12 [0,37 ; 3,41];	0,38 [-3,17 ; 3,92]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	258	15	5.81	251	4	1.59	3,65 [1,23 ; 10,84]	3,81 [1,25 ; 11,65];	4,22 [0,97 ; 7,47]; 0,017	0,017	0,3034
	0	286	10	3.50	293	6	2.05	1,71 [0,63 ; 4,64]	1,73 [0,62 ; 4,83];	1,45 [-1,23 ; 4,12]; 0,32	0,32	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	13	5.78	202	3	1.49	3,89 [1,12 ; 13,46]	4,07 [1,14 ; 14,49];	4,29 [0,82 ; 7,77]; 0,022	0,022	0,585
	>=3	84	6	7.14	98	3	3.06	2,33 [0,6 ; 9,05]	2,44 [0,59 ; 10,06];	4,08 [-2,4 ; 10,56]; 0,306	0,306	
	2	236	6	2.54	248	4	1.61	1,58 [0,45 ; 5,52]	1,59 [0,44 ; 5,71];	0,93 [-1,62 ; 3,48]; 0,536	0,536	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	25	4.67	536	10	1.87	2,5 [1,21 ; 5,16]	2,58 [1,23 ; 5,42];	2,81 [0,68 ; 4,93]; 0,01	0,01	
	No	347	16	4.61	379	8	2.11	2,18 [0,95 ; 5,04]	2,24 [0,95 ; 5,31];	2,5 [-0,14 ; 5,14]; 0,064	0,064	0,5134

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	9	4.55	169	2	1.18	3,84 [0,84 ; 17,53]	3,98 [0,85 ; 18,66];	3,36 [0,03 ; 6,69]; 0,071	0,071	
Region	Eastern Europe	492	24	4.88	495	10	2.02	2,41 [1,17 ; 5]	2,49 [1,18 ; 5,26];	2,86 [0,59 ; 5,13]; 0,015	0,015	0,4124
	USA and Western Europe	53	1	1.89	53	0	0.00	3 [0,12 ; 72,02]	3,06 [0,12 ; 76,76];	1,85 [-3,22 ; 6,93]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Cardiac disorders | Sinus tachycardia

6.1.96 Blood and lymphatic system disorders - Neutrophilia

Tabelle 360: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	6	1.84	302	8	2.65	0,69 [0,24 ; 1,98]	0,69 [0,24 ; 2,01];	-0,81 [-3,13 ; 1,52]; 0,593	0,593	0,3217
	>= 38 years	219	1	0.46	246	5	2.03	0,22 [0,03 ; 1,91]	0,22 [0,03 ; 1,91];	-1,58 [-3,55 ; 0,4]; 0,22	0,22	
Disease Severity at baseline (EDSS)	<=3.5	419	5	1.19	415	8	1.93	0,62 [0,2 ; 1,88]	0,61 [0,2 ; 1,89];	-0,73 [-2,42 ; 0,95]; 0,418	0,418	0,6946
	>3.5	126	2	1.59	133	5	3.76	0,42 [0,08 ; 2,14]	0,41 [0,08 ; 2,17];	-2,17 [-6,07 ; 1,73]; 0,448	0,448	
Gender	Female	345	5	1.45	356	9	2.53	0,57 [0,19 ; 1,69]	0,57 [0,19 ; 1,71];	-1,08 [-3,14 ; 0,98]; 0,42	0,42	0,8636
	Male	200	2	1.00	192	4	2.08	0,48 [0,09 ; 2,59]	0,47 [0,09 ; 2,62];	-1,08 [-3,53 ; 1,36]; 0,441	0,441	
Number of baseline Gd-enhancing lesions	>=1	258	3	1.16	251	9	3.59	0,32 [0,09 ; 1,18]	0,32 [0,08 ; 1,18];	-2,42 [-5,07 ; 0,22]; 0,085	0,085	0,2241
	0	286	4	1.40	293	4	1.37	1,02 [0,26 ; 4,06]	1,02 [0,25 ; 4,14];	0,03 [-1,87 ; 1,94]; 1	1	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	1	0.44	202	9	4.46	0,1 [0,01 ; 0,78]	0,1 [0,01 ; 0,76];	-4,01 [-6,99 ; -1,04]; 0,008	0,008	0,0275
	>=3	84	3	3.57	98	2	2.04	1,75 [0,3 ; 10,23]	1,78 [0,29 ; 10,9];	1,53 [-3,33 ; 6,39]; 0,663	0,663	
	2	236	3	1.27	248	2	0.81	1,58 [0,27 ; 9,35]	1,58 [0,26 ; 9,56];	0,46 [-1,35 ; 2,28]; 0,679	0,679	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	7	1.31	536	13	2.43	0,54 [0,22 ; 1,34]	0,53 [0,21 ; 1,35];	-1,12 [-2,74 ; 0,5]; 0,259	0,259	
	No	347	2	0.58	379	6	1.58	0,36 [0,07 ; 1,79]	0,36 [0,07 ; 1,8];	-1,01 [-2,49 ; 0,48]; 0,29	0,29	0,6103

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	5	2.53	169	7	4.14	0,61 [0,2 ; 1,89]	0,6 [0,19 ; 1,92];	-1,62 [-5,33 ; 2,1]; 0,398	0,398	
Region	Eastern Europe	492	7	1.42	495	13	2.63	0,54 [0,22 ; 1,35]	0,54 [0,21 ; 1,35];	-1,2 [-2,96 ; 0,55]; 0,258	0,258	0,9999
	USA and Western Europe	53	0	0.00	53	0	0.00	1 [0,02 ; 49,49]	1 [0,02 ; 51,33];	0 [-3,61 ; 3,61]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Blood and lymphatic system disorders | Neutrophilia

6.1.97 Respiratory, thoracic and mediastinal disorders - Throat irritation

Tabelle 361: Any TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	11	3.37	302	0	0.00	21,31 [1,26 ; 360,1]	22,05 [1,29 ; 375,86];	3,35 [1,3 ; 5,4]; 0	0	0,1603
	>= 38 years	219	5	2.28	246	1	0.41	5,62 [0,66 ; 47,7]	5,72 [0,66 ; 49,38];	1,88 [-0,26 ; 4,01]; 0,104	0,104	
Disease Severity at baseline (EDSS)	<=3.5	419	14	3.34	415	0	0.00	28,72 [1,72 ; 479,94]	29,72 [1,77 ; 499,78];	3,33 [1,55 ; 5,11]; 0	0	0,0541
	>3.5	126	2	1.59	133	1	0.75	2,11 [0,19 ; 22,99]	2,13 [0,19 ; 23,77];	0,84 [-1,79 ; 3,47]; 0,614	0,614	
Gender	Female	345	12	3.48	356	1	0.28	12,38 [1,62 ; 94,72]	12,79 [1,65 ; 98,92];	3,2 [1,19 ; 5,21]; 0,001	0,001	0,4725
	Male	200	4	2.00	192	0	0.00	8,64 [0,47 ; 159,44]	8,82 [0,47 ; 164,87];	1,98 [-0,19 ; 4,15]; 0,123	0,123	
Number of baseline Gd-enhancing lesions	>=1	258	10	3.88	251	0	0.00	20,43 [1,2 ; 346,84]	21,25 [1,24 ; 364,66];	3,86 [1,39 ; 6,32]; 0,002	0,002	
	0	286	6	2.10	293	1	0.34	6,15 [0,74 ; 50,74]	6,26 [0,75 ; 52,3];	1,76 [-0,03 ; 3,55]; 0,066	0,066	0,1768
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	8	3.56	202	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	>=3	84	6	7.14	98	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	2	236	2	0.85	248	1	0.40	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9998
	White	535	16	2.99	536	1	0.19	16,03 [2,13 ; 120,44]	16,49 [2,18 ; 124,82];	2,8 [1,32 ; 4,29]; 0	0	
	No	347	9	2.59	379	1	0.26	9,83 [1,25 ; 77,19]	10,07 [1,27 ; 79,86];	2,33 [0,58 ; 4,08]; 0,009	0,009	0,3369

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	7	3.54	169	0	0.00	12,81 [0,74 ; 222,72]	13,28 [0,75 ; 234,2];	3,47 [0,71 ; 6,24]; 0,009	0,009	
Region	Eastern Europe	492	13	2.64	495	1	0.20	13,08 [1,72 ; 99,6]	13,41 [1,75 ; 102,89];	2,44 [0,97 ; 3,91]; 0,001	0,001	0,522
	USA and Western Europe	53	3	5.66	53	0	0.00	7 [0,37 ; 132,29]	7,42 [0,37 ; 147,18];	5,56 [-1,49 ; 12,6]; 0,118	0,118	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Any TEAE - Respiratory, thoracic and mediastinal disorders | Throat irritation

6.2 Non-severe TEAE

6.2.1 Cardiac disorders - any

Tabelle 362: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	40	12.27	302	27	8.94	1,37 [0,86 ; 2,18]	1,42 [0,85 ; 2,39];	3,33 [-1,47 ; 8,13]; 0,197	0,197	0,9956
	>= 38 years	219	28	12.79	246	23	9.35	1,37 [0,81 ; 2,3]	1,42 [0,79 ; 2,55];	3,44 [-2,29 ; 9,16]; 0,298	0,298	
Disease Severity at baseline (EDSS)	<=3.5	419	54	12.89	415	35	8.43	1,53 [1,02 ; 2,29]	1,61 [1,03 ; 2,52];	4,45 [0,28 ; 8,63]; 0,043	0,043	0,2816
	>3.5	126	14	11.11	133	15	11.28	0,99 [0,5 ; 1,96]	0,98 [0,45 ; 2,13];	-0,17 [-7,85 ; 7,51]; 1	1	
Gender	Female	345	36	10.43	356	32	8.99	1,16 [0,74 ; 1,83]	1,18 [0,71 ; 1,95];	1,45 [-2,94 ; 5,83]; 0,526	0,526	0,2692
	Male	200	32	16.00	192	18	9.38	1,71 [0,99 ; 2,94]	1,84 [1 ; 3,41];	6,62 [0,08 ; 13,17]; 0,068	0,068	
Number of baseline Gd-enhancing lesions	>=1	258	45	17.44	251	18	7.17	2,43 [1,45 ; 4,08]	2,73 [1,54 ; 4,87];	10,27 [4,65 ; 15,89]; 0	0	0,0008
	0	286	23	8.04	293	32	10.92	0,74 [0,44 ; 1,23]	0,71 [0,41 ; 1,25];	-2,88 [-7,64 ; 1,88]; 0,259	0,259	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	36	16.00	202	16	7.92	2,02 [1,16 ; 3,53]	2,21 [1,19 ; 4,13];	8,08 [2,01 ; 14,15]; 0,012	0,012	0,1661
	>=3	84	11	13.10	98	12	12.24	1,07 [0,5 ; 2,3]	1,08 [0,45 ; 2,59];	0,85 [-8,85 ; 10,55]; 1	1	
	2	236	21	8.90	248	22	8.87	1 [0,57 ; 1,78]	1 [0,54 ; 1,88];	0,03 [-5,04 ; 5,1]; 1	1	
Race	Other	10	1	10.00	12	0	0.00	3,55 [0,16 ; 78,56]	3,95 [0,14 ; 108,09];	9,79 [-13,03 ; 32,61]; 0,478	0,478	0,2558
	White	535	67	12.52	536	50	9.33	1,34 [0,95 ; 1,9]	1,39 [0,94 ; 2,05];	3,2 [-0,54 ; 6,93]; 0,097	0,097	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	No	347	41	11.82	379	40	10.55	1,12 [0,74 ; 1,69]	1,14 [0,72 ; 1,8];	1,26 [-3,33 ; 5,86]; 0,638	0,638	0,0728
	Yes	198	27	13.64	169	10	5.92	2,3 [1,15 ; 4,62]	2,51 [1,18 ; 5,35];	7,72 [1,76 ; 13,68]; 0,015	0,015	
Region	Eastern Europe	492	59	11.99	495	44	8.89	1,35 [0,93 ; 1,95]	1,4 [0,92 ; 2,11];	3,1 [-0,71 ; 6,91]; 0,119	0,119	0,82
	USA and Western Europe	53	9	16.98	53	6	11.32	1,5 [0,57 ; 3,92]	1,6 [0,53 ; 4,87];	5,66 [-7,57 ; 18,89]; 0,579	0,579	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Cardiac disorders | any

6.2.2 Gastrointestinal disorders - any

Tabelle 363: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	129	39.57	302	113	37.42	1,06 [0,87 ; 1,29]	1,1 [0,79 ; 1,51];	2,15 [-5,46 ; 9,77]; 0,623	0,623	0,1039
	>= 38 years	219	61	27.85	246	86	34.96	0,8 [0,61 ; 1,05]	0,72 [0,48 ; 1,07];	-7,11 [-15,52 ; 1,31]; 0,11	0,11	
Disease Severity at baseline (EDSS)	<=3.5	419	152	36.28	415	156	37.59	0,97 [0,81 ; 1,15]	0,95 [0,71 ; 1,25];	-1,31 [-7,86 ; 5,24]; 0,72	0,72	0,8831
	>3.5	126	38	30.16	133	43	32.33	0,93 [0,65 ; 1,34]	0,9 [0,53 ; 1,53];	-2,17 [-13,46 ; 9,12]; 0,789	0,789	
Gender	Female	345	132	38.26	356	138	38.76	0,99 [0,82 ; 1,19]	0,98 [0,72 ; 1,33];	-0,5 [-7,71 ; 6,7]; 0,938	0,938	0,6832
	Male	200	58	29.00	192	61	31.77	0,91 [0,68 ; 1,23]	0,88 [0,57 ; 1,35];	-2,77 [-11,88 ; 6,34]; 0,584	0,584	
Number of baseline Gd-enhancing lesions	>=1	258	99	38.37	251	95	37.85	1,01 [0,81 ; 1,27]	1,02 [0,71 ; 1,46];	0,52 [-7,92 ; 8,96]; 0,927	0,927	0,4978
	0	286	91	31.82	293	103	35.15	0,91 [0,72 ; 1,14]	0,86 [0,61 ; 1,22];	-3,34 [-11,02 ; 4,35]; 0,428	0,428	
	NA	1	0	0.00	4	1	25.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	78	34.67	202	72	35.64	0,97 [0,75 ; 1,26]	0,96 [0,64 ; 1,43];	-0,98 [-10,05 ; 8,09]; 0,84	0,84	0,9334
	>=3	84	33	39.29	98	38	38.78	1,01 [0,7 ; 1,46]	1,02 [0,56 ; 1,86];	0,51 [-13,71 ; 14,73]; 1	1	
	2	236	79	33.47	248	89	35.89	0,93 [0,73 ; 1,19]	0,9 [0,62 ; 1,31];	-2,41 [-10,89 ; 6,07]; 0,633	0,633	
Race	Other	10	3	30.00	12	5	41.67	0,72 [0,23 ; 2,3]	0,6 [0,1 ; 3,54];	-11,67 [-51,48 ; 28,14]; 0,675	0,675	0,615
	White	535	187	34.95	536	194	36.19	0,97 [0,82 ; 1,13]	0,95 [0,74 ; 1,22];	-1,24 [-6,97 ; 4,49]; 0,702	0,702	
	No	347	109	31.41	379	131	34.56	0,91 [0,74 ; 1,12]	0,87 [0,64 ; 1,18];	-3,15 [-9,99 ; 3,69]; 0,386	0,386	0,5206

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	81	40.91	169	68	40.24	1,02 [0,79 ; 1,3]	1,03 [0,68 ; 1,56];	0,67 [-9,41 ; 10,75]; 0,915	0,915	
Region	Eastern Europe	492	167	33.94	495	175	35.35	0,96 [0,81 ; 1,14]	0,94 [0,72 ; 1,22];	-1,41 [-7,35 ; 4,53]; 0,688	0,688	0,9727
	USA and Western Europe	53	23	43.40	53	24	45.28	0,96 [0,63 ; 1,47]	0,93 [0,43 ; 1,99];	-1,89 [-20,8 ; 17,02]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Gastrointestinal disorders | any

6.2.3 General disorders and administration site conditions - any

Tabelle 364: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	159	48.77	302	50	16.56	2,95 [2,23 ; 3,88]	4,8 [3,3 ; 6,97];	32,22 [25,36 ; 39,07]; 0	0	0,0001
	>= 38 years	219	73	33.33	246	58	23.58	1,41 [1,05 ; 1,89]	1,62 [1,08 ; 2,43];	9,76 [1,56 ; 17,95]; 0,023	0,023	
Disease Severity at baseline (EDSS)	<=3.5	419	189	45.11	415	79	19.04	2,37 [1,89 ; 2,97]	3,49 [2,56 ; 4,77];	26,07 [19,99 ; 32,15]; 0	0	0,0524
	>3.5	126	43	34.13	133	29	21.80	1,57 [1,05 ; 2,34]	1,86 [1,07 ; 3,23];	12,32 [1,47 ; 23,18]; 0,037	0,037	
Gender	Female	345	158	45.80	356	77	21.63	2,12 [1,68 ; 2,66]	3,06 [2,2 ; 4,26];	24,17 [17,39 ; 30,95]; 0	0	0,9901
	Male	200	74	37.00	192	31	16.15	2,29 [1,58 ; 3,32]	3,05 [1,89 ; 4,93];	20,85 [12,38 ; 29,33]; 0	0	
Number of baseline Gd-enhancing lesions	>=1	258	118	45.74	251	50	19.92	2,3 [1,73 ; 3,04]	3,39 [2,28 ; 5,03];	25,82 [17,98 ; 33,65]; 0	0	0,4009
	0	286	114	39.86	293	58	19.80	2,01 [1,54 ; 2,64]	2,69 [1,85 ; 3,9];	20,06 [12,78 ; 27,35]; 0	0	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	90	40.00	202	42	20.79	1,92 [1,41 ; 2,63]	2,54 [1,65 ; 3,91];	19,21 [10,71 ; 27,71]; 0	0	0,2206
	>=3	84	42	50.00	98	16	16.33	3,06 [1,86 ; 5,03]	5,12 [2,58 ; 10,17];	33,67 [20,72 ; 46,63]; 0	0	
	2	236	100	42.37	248	50	20.16	2,1 [1,57 ; 2,81]	2,91 [1,94 ; 4,36];	22,21 [14,17 ; 30,25]; 0	0	
Race	Other	10	4	40.00	12	6	50.00	0,8 [0,31 ; 2,06]	0,67 [0,12 ; 3,64];	-10 [-51,5 ; 31,5]; 0,691	0,691	0,0753
	White	535	228	42.62	536	102	19.03	2,24 [1,83 ; 2,74]	3,16 [2,4 ; 4,16];	23,59 [18,24 ; 28,94]; 0	0	
	No	347	139	40.06	379	71	18.73	2,14 [1,67 ; 2,73]	2,9 [2,07 ; 4,06];	21,32 [14,84 ; 27,81]; 0	0	0,7663

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	93	46.97	169	37	21.89	2,15 [1,56 ; 2,96]	3,16 [2 ; 5];	25,08 [15,74 ; 34,41]; 0	0	
Region	Eastern Europe	492	205	41.67	495	84	16.97	2,46 [1,97 ; 3,06]	3,49 [2,6 ; 4,7];	24,7 [19,23 ; 30,17]; 0	0	0,0148
	USA and Western Europe	53	27	50.94	53	24	45.28	1,12 [0,76 ; 1,67]	1,25 [0,58 ; 2,69];	5,66 [-13,33 ; 24,65]; 0,698	0,698	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - General disorders and administration site conditions | any

6.2.4 Infections and infestations - any

Tabelle 365: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	204	62.58	302	178	58.94	1,06 [0,94 ; 1,2]	1,16 [0,85 ; 1,61];	3,64 [-4 ; 11,28]; 0,369	0,369	0,2256
	>= 38 years	219	97	44.29	246	118	47.97	0,92 [0,76 ; 1,12]	0,86 [0,6 ; 1,24];	-3,68 [-12,74 ; 5,39]; 0,457	0,457	
Disease Severity at baseline (EDSS)	<=3.5	419	243	58.00	415	236	56.87	1,02 [0,91 ; 1,15]	1,05 [0,8 ; 1,38];	1,13 [-5,58 ; 7,84]; 0,779	0,779	0,9747
	>3.5	126	58	46.03	133	60	45.11	1,02 [0,78 ; 1,33]	1,04 [0,64 ; 1,69];	0,92 [-11,22 ; 13,05]; 0,901	0,901	
Gender	Female	345	216	62.61	356	201	56.46	1,11 [0,98 ; 1,25]	1,29 [0,95 ; 1,75];	6,15 [-1,1 ; 13,4]; 0,106	0,106	0,0351
	Male	200	85	42.50	192	95	49.48	0,86 [0,69 ; 1,07]	0,75 [0,51 ; 1,12];	-6,98 [-16,83 ; 2,87]; 0,188	0,188	
Number of baseline Gd-enhancing lesions	>=1	258	151	58.53	251	141	56.18	1,04 [0,9 ; 1,21]	1,1 [0,77 ; 1,56];	2,35 [-6,24 ; 10,94]; 0,654	0,654	0,6402
	0	286	150	52.45	293	155	52.90	0,99 [0,85 ; 1,16]	0,98 [0,71 ; 1,36];	-0,45 [-8,59 ; 7,68]; 0,934	0,934	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	118	52.44	202	105	51.98	1,01 [0,84 ; 1,21]	1,02 [0,7 ; 1,49];	0,46 [-9,03 ; 9,95]; 1	1	0,2226
	>=3	84	51	60.71	98	47	47.96	1,27 [0,97 ; 1,66]	1,68 [0,93 ; 3,03];	12,76 [-1,63 ; 27,14]; 0,101	0,101	
	2	236	132	55.93	248	144	58.06	0,96 [0,83 ; 1,12]	0,92 [0,64 ; 1,31];	-2,13 [-10,95 ; 6,69]; 0,647	0,647	
Race	Other	10	8	80.00	12	8	66.67	1,2 [0,72 ; 1,99]	2 [0,28 ; 14,2];	13,33 [-23,08 ; 49,75]; 0,646	0,646	0,5111
	White	535	293	54.77	536	288	53.73	1,02 [0,91 ; 1,14]	1,04 [0,82 ; 1,33];	1,04 [-4,93 ; 7]; 0,759	0,759	
	No	347	177	51.01	379	204	53.83	0,95 [0,82 ; 1,09]	0,89 [0,67 ; 1,2];	-2,82 [-10,09 ; 4,45]; 0,458	0,458	0,0824

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	124	62.63	169	92	54.44	1,15 [0,97 ; 1,37]	1,4 [0,92 ; 2,13];	8,19 [-1,9 ; 18,28]; 0,136	0,136	
Region	Eastern Europe	492	262	53.25	495	261	52.73	1,01 [0,9 ; 1,14]	1,02 [0,8 ; 1,31];	0,52 [-5,7 ; 6,75]; 0,899	0,899	0,4451
	USA and Western Europe	53	39	73.58	53	35	66.04	1,11 [0,87 ; 1,43]	1,43 [0,62 ; 3,3];	7,55 [-9,87 ; 24,97]; 0,526	0,526	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | any

6.2.5 Musculoskeletal and connective tissue disorders - any

Tabelle 366: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	76	23.31	302	53	17.55	1,33 [0,97 ; 1,82]	1,43 [0,96 ; 2,11];	5,76 [-0,52 ; 12,05]; 0,076	0,076	0,0753
	>= 38 years	219	52	23.74	246	66	26.83	0,89 [0,65 ; 1,21]	0,85 [0,56 ; 1,29];	-3,08 [-10,99 ; 4,82]; 0,457	0,457	
Disease Severity at baseline (EDSS)	<=3.5	419	107	25.54	415	87	20.96	1,22 [0,95 ; 1,56]	1,29 [0,94 ; 1,79];	4,57 [-1,15 ; 10,3]; 0,12	0,12	0,0413
	>3.5	126	21	16.67	133	32	24.06	0,69 [0,42 ; 1,13]	0,63 [0,34 ; 1,17];	-7,39 [-17,15 ; 2,36]; 0,166	0,166	
Gender	Female	345	90	26.09	356	84	23.60	1,11 [0,85 ; 1,43]	1,14 [0,81 ; 1,61];	2,49 [-3,91 ; 8,89]; 0,484	0,484	0,7919
	Male	200	38	19.00	192	35	18.23	1,04 [0,69 ; 1,58]	1,05 [0,63 ; 1,75];	0,77 [-6,94 ; 8,48]; 0,897	0,897	
Number of baseline Gd-enhancing lesions	>=1	258	68	26.36	251	56	22.31	1,18 [0,87 ; 1,61]	1,25 [0,83 ; 1,87];	4,05 [-3,4 ; 11,49]; 0,303	0,303	0,3862
	0	286	60	20.98	293	63	21.50	0,98 [0,71 ; 1,34]	0,97 [0,65 ; 1,44];	-0,52 [-7,19 ; 6,14]; 0,919	0,919	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	53	23.56	202	46	22.77	1,03 [0,73 ; 1,46]	1,04 [0,67 ; 1,64];	0,78 [-7,23 ; 8,8]; 0,909	0,909	0,6752
	>=3	84	20	23.81	98	17	17.35	1,37 [0,77 ; 2,44]	1,49 [0,72 ; 3,07];	6,46 [-5,33 ; 18,26]; 0,356	0,356	
	2	236	55	23.31	248	56	22.58	1,03 [0,74 ; 1,43]	1,04 [0,68 ; 1,59];	0,72 [-6,77 ; 8,22]; 0,914	0,914	
Race	Other	10	7	70.00	12	7	58.33	1,2 [0,64 ; 2,25]	1,67 [0,28 ; 9,82];	11,67 [-28,14 ; 51,48]; 0,675	0,675	0,6532
	White	535	121	22.62	536	112	20.90	1,08 [0,86 ; 1,36]	1,11 [0,83 ; 1,48];	1,72 [-3,22 ; 6,66]; 0,506	0,506	
	No	347	75	21.61	379	82	21.64	1 [0,76 ; 1,32]	1 [0,7 ; 1,42];	-0,02 [-6,02 ; 5,97]; 1	1	0,3807

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	53	26.77	169	37	21.89	1,22 [0,85 ; 1,76]	1,3 [0,81 ; 2,11];	4,87 [-3,9 ; 13,64]; 0,33	0,33	
Region	Eastern Europe	492	98	19.92	495	94	18.99	1,05 [0,81 ; 1,35]	1,06 [0,77 ; 1,45];	0,93 [-4,01 ; 5,87]; 0,748	0,748	0,4484
	USA and Western Europe	53	30	56.60	53	25	47.17	1,2 [0,83 ; 1,74]	1,46 [0,68 ; 3,14];	9,43 [-9,5 ; 28,37]; 0,437	0,437	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Musculoskeletal and connective tissue disorders | any

6.2.6 Nervous system disorders - any

Tabelle 367: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	164	50.31	302	121	40.07	1,26 [1,05 ; 1,5]	1,51 [1,1 ; 2,08];	10,24 [2,49 ; 17,99]; 0,01	0,01	0,1221
	>= 38 years	219	75	34.25	246	83	33.74	1,02 [0,79 ; 1,31]	1,02 [0,7 ; 1,5];	0,51 [-8,12 ; 9,13]; 0,922	0,922	
Disease Severity at baseline (EDSS)	<=3.5	419	193	46.06	415	157	37.83	1,22 [1,04 ; 1,43]	1,4 [1,06 ; 1,85];	8,23 [1,56 ; 14,91]; 0,017	0,017	0,3288
	>3.5	126	46	36.51	133	47	35.34	1,03 [0,75 ; 1,43]	1,05 [0,63 ; 1,75];	1,17 [-10,52 ; 12,86]; 0,897	0,897	
Gender	Female	345	167	48.41	356	144	40.45	1,2 [1,01 ; 1,41]	1,38 [1,02 ; 1,86];	7,96 [0,62 ; 15,29]; 0,04	0,04	0,6762
	Male	200	72	36.00	192	60	31.25	1,15 [0,87 ; 1,52]	1,24 [0,81 ; 1,88];	4,75 [-4,59 ; 14,09]; 0,337	0,337	
Number of baseline Gd-enhancing lesions	>=1	258	118	45.74	251	104	41.43	1,1 [0,91 ; 1,35]	1,19 [0,84 ; 1,69];	4,3 [-4,31 ; 12,91]; 0,371	0,371	0,45
	0	286	121	42.31	293	99	33.79	1,25 [1,02 ; 1,54]	1,44 [1,03 ; 2,01];	8,52 [0,64 ; 16,4]; 0,04	0,04	
	NA	1	0	0.00	4	1	25.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	95	42.22	202	81	40.10	1,05 [0,84 ; 1,32]	1,09 [0,74 ; 1,61];	2,12 [-7,22 ; 11,47]; 0,694	0,694	0,4593
	>=3	84	36	42.86	98	31	31.63	1,35 [0,92 ; 1,98]	1,62 [0,88 ; 2,97];	11,22 [-2,8 ; 25,25]; 0,126	0,126	
	2	236	108	45.76	248	92	37.10	1,23 [1 ; 1,53]	1,43 [0,99 ; 2,06];	8,67 [-0,08 ; 17,42]; 0,065	0,065	
Race	Other	10	8	80.00	12	6	50.00	1,6 [0,84 ; 3,05]	4 [0,59 ; 27,25];	30 [-7,62 ; 67,62]; 0,204	0,204	0,2359
	White	535	231	43.18	536	198	36.94	1,17 [1,01 ; 1,35]	1,3 [1,02 ; 1,66];	6,24 [0,38 ; 12,09]; 0,04	0,04	
	No	347	145	41.79	379	143	37.73	1,11 [0,93 ; 1,32]	1,18 [0,88 ; 1,6];	4,06 [-3,07 ; 11,18]; 0,288	0,288	0,2516

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	94	47.47	169	61	36.09	1,32 [1,03 ; 1,69]	1,6 [1,05 ; 2,44];	11,38 [1,34 ; 21,42]; 0,034	0,034	
Region	Eastern Europe	492	203	41.26	495	173	34.95	1,18 [1,01 ; 1,39]	1,31 [1,01 ; 1,69];	6,31 [0,26 ; 12,36]; 0,042	0,042	0,7434
	USA and Western Europe	53	36	67.92	53	31	58.49	1,16 [0,87 ; 1,56]	1,5 [0,68 ; 3,33];	9,43 [-8,84 ; 27,71]; 0,421	0,421	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Nervous system disorders | any

6.2.7 Renal and urinary disorders - any

Tabelle 368: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	22	6.75	302	18	5.96	1,13 [0,62 ; 2,07]	1,14 [0,6 ; 2,17];	0,79 [-3,03 ; 4,6]; 0,745	0,745	0,6767
	>= 38 years	219	15	6.85	246	18	7.32	0,94 [0,48 ; 1,81]	0,93 [0,46 ; 1,9];	-0,47 [-5,13 ; 4,2]; 0,859	0,859	
Disease Severity at baseline (EDSS)	<=3.5	419	31	7.40	415	24	5.78	1,28 [0,76 ; 2,14]	1,3 [0,75 ; 2,26];	1,62 [-1,75 ; 4,98]; 0,403	0,403	0,0993
	>3.5	126	6	4.76	133	12	9.02	0,53 [0,2 ; 1,36]	0,5 [0,18 ; 1,39];	-4,26 [-10,39 ; 1,87]; 0,224	0,224	
Gender	Female	345	27	7.83	356	22	6.18	1,27 [0,74 ; 2,18]	1,29 [0,72 ; 2,31];	1,65 [-2,13 ; 5,43]; 0,459	0,459	0,2052
	Male	200	10	5.00	192	14	7.29	0,69 [0,31 ; 1,51]	0,67 [0,29 ; 1,55];	-2,29 [-7,05 ; 2,47]; 0,402	0,402	
Number of baseline Gd-enhancing lesions	>=1	258	17	6.59	251	19	7.57	0,87 [0,46 ; 1,64]	0,86 [0,44 ; 1,7];	-0,98 [-5,44 ; 3,48]; 0,731	0,731	0,3982
	0	286	20	6.99	293	16	5.46	1,28 [0,68 ; 2,42]	1,3 [0,66 ; 2,57];	1,53 [-2,41 ; 5,47]; 0,494	0,494	
	NA	1	0	0.00	4	1	25.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	13	5.78	202	14	6.93	0,83 [0,4 ; 1,73]	0,82 [0,38 ; 1,8];	-1,15 [-5,8 ; 3,49]; 0,693	0,693	0,5198
	>=3	84	4	4.76	98	2	2.04	2,33 [0,44 ; 12,42]	2,4 [0,43 ; 13,44];	2,72 [-2,62 ; 8,07]; 0,417	0,417	
	2	236	20	8.47	248	20	8.06	1,05 [0,58 ; 1,9]	1,06 [0,55 ; 2,02];	0,41 [-4,5 ; 5,32]; 0,871	0,871	
Race	Other	10	0	0.00	12	2	16.67	0,24 [0,01 ; 4,42]	0,2 [0,01 ; 4,69];	-14,69 [-39,39 ; 10,02]; 0,481	0,481	0,0998
	White	535	37	6.92	536	34	6.34	1,09 [0,7 ; 1,71]	1,1 [0,68 ; 1,78];	0,57 [-2,41 ; 3,55]; 0,715	0,715	
	No	347	21	6.05	379	20	5.28	1,15 [0,63 ; 2,08]	1,16 [0,62 ; 2,17];	0,77 [-2,6 ; 4,15]; 0,748	0,748	0,5158

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	16	8.08	169	16	9.47	0,85 [0,44 ; 1,65]	0,84 [0,41 ; 1,74];	-1,39 [-7,21 ; 4,44]; 0,712	0,712	
Region	Eastern Europe	492	32	6.50	495	29	5.86	1,11 [0,68 ; 1,81]	1,12 [0,67 ; 1,88];	0,65 [-2,36 ; 3,65]; 0,694	0,694	0,4649
	USA and Western Europe	53	5	9.43	53	7	13.21	0,71 [0,24 ; 2,11]	0,68 [0,2 ; 2,31];	-3,77 [-15,82 ; 8,27]; 0,761	0,761	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Renal and urinary disorders | any

6.2.8 Reproductive system and breast disorders - any

Tabelle 369: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	35	10.74	302	34	11.26	0,95 [0,61 ; 1,49]	0,95 [0,57 ; 1,56];	-0,52 [-5,42 ; 4,38]; 0,899	0,899	0,8117
	>= 38 years	219	13	5.94	246	17	6.91	0,86 [0,43 ; 1,73]	0,85 [0,4 ; 1,79];	-0,97 [-5,43 ; 3,48]; 0,709	0,709	
Disease Severity at baseline (EDSS)	<=3.5	419	43	10.26	415	41	9.88	1,04 [0,69 ; 1,56]	1,04 [0,66 ; 1,64];	0,38 [-3,7 ; 4,47]; 0,909	0,909	0,227
	>3.5	126	5	3.97	133	10	7.52	0,53 [0,19 ; 1,5]	0,51 [0,17 ; 1,53];	-3,55 [-9,18 ; 2,08]; 0,29	0,29	
Gender	Female	345	46	13.33	356	47	13.20	1,01 [0,69 ; 1,47]	1,01 [0,65 ; 1,56];	0,13 [-4,89 ; 5,15]; 1	1	0,3877
	Male	200	2	1.00	192	4	2.08	0,48 [0,09 ; 2,59]	0,47 [0,09 ; 2,62];	-1,08 [-3,53 ; 1,36]; 0,441	0,441	
Number of baseline Gd-enhancing lesions	>=1	258	25	9.69	251	25	9.96	0,97 [0,57 ; 1,65]	0,97 [0,54 ; 1,74];	-0,27 [-5,44 ; 4,9]; 1	1	0,8552
	0	286	23	8.04	293	26	8.87	0,91 [0,53 ; 1,55]	0,9 [0,5 ; 1,61];	-0,83 [-5,36 ; 3,7]; 0,766	0,766	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	20	8.89	202	21	10.40	0,86 [0,48 ; 1,53]	0,84 [0,44 ; 1,6];	-1,51 [-7,12 ; 4,11]; 0,625	0,625	0,8963
	>=3	84	10	11.90	98	11	11.22	1,06 [0,47 ; 2,37]	1,07 [0,43 ; 2,66];	0,68 [-8,65 ; 10,01]; 1	1	
	2	236	18	7.63	248	19	7.66	1 [0,54 ; 1,85]	1 [0,51 ; 1,95];	-0,03 [-4,77 ; 4,7]; 1	1	
Race	Other	10	2	20.00	12	1	8.33	2,4 [0,25 ; 22,75]	2,75 [0,21 ; 35,84];	11,67 [-17,64 ; 40,98]; 0,571	0,571	0,3925
	White	535	46	8.60	536	50	9.33	0,92 [0,63 ; 1,35]	0,91 [0,6 ; 1,39];	-0,73 [-4,15 ; 2,69]; 0,748	0,748	
	No	347	33	9.51	379	35	9.23	1,03 [0,65 ; 1,62]	1,03 [0,63 ; 1,7];	0,28 [-3,97 ; 4,52]; 0,899	0,899	0,5432

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	15	7.58	169	16	9.47	0,8 [0,41 ; 1,57]	0,78 [0,38 ; 1,64];	-1,89 [-7,64 ; 3,86]; 0,574	0,574	
Region	Eastern Europe	492	40	8.13	495	44	8.89	0,91 [0,61 ; 1,38]	0,91 [0,58 ; 1,42];	-0,76 [-4,24 ; 2,72]; 0,732	0,732	0,6746
	USA and Western Europe	53	8	15.09	53	7	13.21	1,14 [0,45 ; 2,93]	1,17 [0,39 ; 3,49];	1,89 [-11,38 ; 15,15]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Reproductive system and breast disorders | any

6.2.9 Skin and subcutaneous tissue disorders - any

Tabelle 370: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	54	16.56	302	75	24.83	0,67 [0,49 ; 0,91]	0,6 [0,41 ; 0,89];	-8,27 [-14,6 ; -1,94]; 0,013	0,013	0,5753
	>= 38 years	219	30	13.70	246	59	23.98	0,57 [0,38 ; 0,85]	0,5 [0,31 ; 0,82];	-10,29 [-17,3 ; -3,27]; 0,006	0,006	
Disease Severity at baseline (EDSS)	<=3.5	419	73	17.42	415	108	26.02	0,67 [0,51 ; 0,87]	0,6 [0,43 ; 0,84];	-8,6 [-14,17 ; -3,03]; 0,003	0,003	0,3097
	>3.5	126	11	8.73	133	26	19.55	0,45 [0,23 ; 0,87]	0,39 [0,19 ; 0,84];	-10,82 [-19,17 ; -2,47]; 0,013	0,013	
Gender	Female	345	56	16.23	356	110	30.90	0,53 [0,39 ; 0,7]	0,43 [0,3 ; 0,62];	-14,67 [-20,85 ; -8,49]; 0	0	0,0058
	Male	200	28	14.00	192	24	12.50	1,12 [0,67 ; 1,86]	1,14 [0,63 ; 2,05];	1,5 [-5,21 ; 8,21]; 0,766	0,766	
Number of baseline Gd-enhancing lesions	>=1	258	42	16.28	251	62	24.70	0,66 [0,46 ; 0,94]	0,59 [0,38 ; 0,92];	-8,42 [-15,4 ; -1,44]; 0,021	0,021	0,7559
	0	286	42	14.69	293	71	24.23	0,61 [0,43 ; 0,86]	0,54 [0,35 ; 0,82];	-9,55 [-15,94 ; -3,15]; 0,005	0,005	
	NA	1	0	0.00	4	1	25.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	36	16.00	202	50	24.75	0,65 [0,44 ; 0,95]	0,58 [0,36 ; 0,93];	-8,75 [-16,39 ; -1,11]; 0,029	0,029	0,4311
	>=3	84	10	11.90	98	27	27.55	0,43 [0,22 ; 0,84]	0,36 [0,16 ; 0,79];	-15,65 [-26,88 ; -4,41]; 0,01	0,01	
	2	236	38	16.10	248	57	22.98	0,7 [0,48 ; 1,01]	0,64 [0,41 ; 1,01];	-6,88 [-13,91 ; 0,15]; 0,067	0,067	
Race	Other	10	4	40.00	12	6	50.00	0,8 [0,31 ; 2,06]	0,67 [0,12 ; 3,64];	-10 [-51,5 ; 31,5]; 0,691	0,691	0,844
	White	535	80	14.95	536	128	23.88	0,63 [0,49 ; 0,81]	0,56 [0,41 ; 0,76];	-8,93 [-13,63 ; -4,22]; 0	0	
	No	347	46	13.26	379	89	23.48	0,56 [0,41 ; 0,78]	0,5 [0,34 ; 0,74];	-10,23 [-15,79 ; -4,66]; 0	0	0,3935

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	38	19.19	169	45	26.63	0,72 [0,49 ; 1,05]	0,65 [0,4 ; 1,07];	-7,44 [-16,07 ; 1,2]; 0,104	0,104	
Region	Eastern Europe	492	68	13.82	495	114	23.03	0,6 [0,46 ; 0,79]	0,54 [0,39 ; 0,75];	-9,21 [-14,01 ; -4,41]; 0	0	0,5215
	USA and Western Europe	53	16	30.19	53	20	37.74	0,8 [0,47 ; 1,37]	0,71 [0,32 ; 1,6];	-7,55 [-25,52 ; 10,43]; 0,539	0,539	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Skin and subcutaneous tissue disorders | any

6.2.10 Ear and labyrinth disorders - any

Tabelle 371: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	8	2.45	302	5	1.66	1,48 [0,49 ; 4,48]	1,49 [0,48 ; 4,62];	0,8 [-1,41 ; 3,01]; 0,581	0,581	0,6029
	>= 38 years	219	15	6.85	246	8	3.25	2,11 [0,91 ; 4,87]	2,19 [0,91 ; 5,26];	3,6 [-0,42 ; 7,61]; 0,088	0,088	
Disease Severity at baseline (EDSS)	<=3.5	419	16	3.82	415	9	2.17	1,76 [0,79 ; 3,94]	1,79 [0,78 ; 4,1];	1,65 [-0,66 ; 3,96]; 0,223	0,223	0,9401
	>3.5	126	7	5.56	133	4	3.01	1,85 [0,55 ; 6,16]	1,9 [0,54 ; 6,64];	2,55 [-2,39 ; 7,49]; 0,366	0,366	
Gender	Female	345	15	4.35	356	8	2.25	1,93 [0,83 ; 4,51]	1,98 [0,83 ; 4,73];	2,1 [-0,55 ; 4,75]; 0,14	0,14	0,7449
	Male	200	8	4.00	192	5	2.60	1,54 [0,51 ; 4,61]	1,56 [0,5 ; 4,85];	1,4 [-2,13 ; 4,92]; 0,576	0,576	
Number of baseline Gd-enhancing lesions	>=1	258	6	2.33	251	6	2.39	0,97 [0,32 ; 2,98]	0,97 [0,31 ; 3,06];	-0,06 [-2,7 ; 2,57]; 1	1	0,1865
	0	286	17	5.94	293	7	2.39	2,49 [1,05 ; 5,91]	2,58 [1,05 ; 6,32];	3,55 [0,3 ; 6,81]; 0,037	0,037	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	12	5.33	202	2	0.99	5,39 [1,22 ; 23,78]	5,63 [1,25 ; 25,49];	4,34 [1,11 ; 7,58]; 0,013	0,013	0,102
	>=3	84	3	3.57	98	2	2.04	1,75 [0,3 ; 10,23]	1,78 [0,29 ; 10,9];	1,53 [-3,33 ; 6,39]; 0,663	0,663	
	2	236	8	3.39	248	9	3.63	0,93 [0,37 ; 2,38]	0,93 [0,35 ; 2,46];	-0,24 [-3,52 ; 3,04]; 1	1	
Race	Other	10	2	20.00	12	1	8.33	2,4 [0,25 ; 22,75]	2,75 [0,21 ; 35,84];	11,67 [-17,64 ; 40,98]; 0,571	0,571	0,747
	White	535	21	3.93	536	12	2.24	1,75 [0,87 ; 3,53]	1,78 [0,87 ; 3,66];	1,69 [-0,38 ; 3,75]; 0,116	0,116	
	No	347	14	4.03	379	6	1.58	2,55 [0,99 ; 6,56]	2,61 [0,99 ; 6,88];	2,45 [0,03 ; 4,87]; 0,067	0,067	0,2244

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	9	4.55	169	7	4.14	1,1 [0,42 ; 2,88]	1,1 [0,4 ; 3,03];	0,4 [-3,77 ; 4,58]; 1	1	
Region	Eastern Europe	492	16	3.25	495	10	2.02	1,61 [0,74 ; 3,51]	1,63 [0,73 ; 3,63];	1,23 [-0,77 ; 3,23]; 0,24	0,24	0,5889
	USA and Western Europe	53	7	13.21	53	3	5.66	2,33 [0,64 ; 8,54]	2,54 [0,62 ; 10,39];	7,55 [-3,49 ; 18,58]; 0,319	0,319	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Ear and labyrinth disorders | any

6.2.11 Respiratory, thoracic and mediastinal disorders - any

Tabelle 372: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	73	22.39	302	39	12.91	1,73 [1,21 ; 2,48]	1,95 [1,27 ; 2,98];	9,48 [3,58 ; 15,38]; 0,002	0,002	0,4751
	>= 38 years	219	37	16.89	246	29	11.79	1,43 [0,91 ; 2,25]	1,52 [0,9 ; 2,57];	5,11 [-1,29 ; 11,5]; 0,143	0,143	
Disease Severity at baseline (EDSS)	<=3.5	419	96	22.91	415	54	13.01	1,76 [1,3 ; 2,39]	1,99 [1,38 ; 2,86];	9,9 [4,74 ; 15,06]; 0	0	0,1574
	>3.5	126	14	11.11	133	14	10.53	1,06 [0,52 ; 2,12]	1,06 [0,48 ; 2,33];	0,58 [-6,99 ; 8,16]; 1	1	
Gender	Female	345	77	22.32	356	49	13.76	1,62 [1,17 ; 2,25]	1,8 [1,21 ; 2,67];	8,55 [2,89 ; 14,22]; 0,004	0,004	0,999
	Male	200	33	16.50	192	19	9.90	1,67 [0,98 ; 2,83]	1,8 [0,98 ; 3,29];	6,6 [-0,05 ; 13,26]; 0,073	0,073	
Number of baseline Gd-enhancing lesions	>=1	258	60	23.26	251	30	11.95	1,95 [1,3 ; 2,91]	2,23 [1,38 ; 3,6];	11,3 [4,77 ; 17,84]; 0,001	0,001	0,1805
	0	286	50	17.48	293	38	12.97	1,35 [0,91 ; 1,99]	1,42 [0,9 ; 2,25];	4,51 [-1,33 ; 10,36]; 0,134	0,134	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	52	23.11	202	24	11.88	1,95 [1,25 ; 3,03]	2,23 [1,32 ; 3,78];	11,23 [4,14 ; 18,32]; 0,003	0,003	0,5261
	>=3	84	17	20.24	98	13	13.27	1,53 [0,79 ; 2,95]	1,66 [0,75 ; 3,66];	6,97 [-3,93 ; 17,88]; 0,233	0,233	
	2	236	41	17.37	248	31	12.50	1,39 [0,9 ; 2,14]	1,47 [0,89 ; 2,44];	4,87 [-1,48 ; 11,22]; 0,16	0,16	
Race	Other	10	2	20.00	12	3	25.00	0,8 [0,16 ; 3,88]	0,75 [0,1 ; 5,69];	-5 [-39,85 ; 29,85]; 1	1	0,3895
	White	535	108	20.19	536	65	12.13	1,66 [1,25 ; 2,21]	1,83 [1,31 ; 2,56];	8,06 [3,68 ; 12,44]; 0	0	
	No	347	59	17.00	379	47	12.40	1,37 [0,96 ; 1,95]	1,45 [0,96 ; 2,19];	4,6 [-0,56 ; 9,76]; 0,092	0,092	0,1354

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	51	25.76	169	21	12.43	2,07 [1,3 ; 3,3]	2,45 [1,4 ; 4,27];	13,33 [5,47 ; 21,2]; 0,001	0,001	
Region	Eastern Europe	492	94	19.11	495	57	11.52	1,66 [1,22 ; 2,25]	1,81 [1,27 ; 2,59];	7,59 [3,12 ; 12,06]; 0,001	0,001	0,8462
	USA and Western Europe	53	16	30.19	53	11	20.75	1,45 [0,75 ; 2,83]	1,65 [0,68 ; 4];	9,43 [-7,06 ; 25,93]; 0,373	0,373	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Respiratory, thoracic and mediastinal disorders | any

6.2.12 Injury, poisoning and procedural complications - any

Tabelle 373: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	46	14.11	302	33	10.93	1,29 [0,85 ; 1,96]	1,34 [0,83 ; 2,16];	3,18 [-1,98 ; 8,35]; 0,278	0,278	0,5216
	>= 38 years	219	28	12.79	246	30	12.20	1,05 [0,65 ; 1,7]	1,06 [0,61 ; 1,83];	0,59 [-5,43 ; 6,61]; 0,889	0,889	
Disease Severity at baseline (EDSS)	<=3.5	419	60	14.32	415	43	10.36	1,38 [0,96 ; 2]	1,45 [0,95 ; 2,2];	3,96 [-0,5 ; 8,41]; 0,092	0,092	0,0931
	>3.5	126	14	11.11	133	20	15.04	0,74 [0,39 ; 1,4]	0,71 [0,34 ; 1,47];	-3,93 [-12,11 ; 4,26]; 0,365	0,365	
Gender	Female	345	50	14.49	356	40	11.24	1,29 [0,87 ; 1,9]	1,34 [0,86 ; 2,09];	3,26 [-1,7 ; 8,21]; 0,215	0,215	0,4516
	Male	200	24	12.00	192	23	11.98	1 [0,59 ; 1,71]	1 [0,54 ; 1,84];	0,02 [-6,41 ; 6,45]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	258	37	14.34	251	31	12.35	1,16 [0,74 ; 1,81]	1,19 [0,71 ; 1,98];	1,99 [-3,91 ; 7,89]; 0,518	0,518	0,9568
	0	286	37	12.94	293	32	10.92	1,18 [0,76 ; 1,85]	1,21 [0,73 ; 2,01];	2,02 [-3,26 ; 7,3]; 0,522	0,522	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	38	16.89	202	30	14.85	1,14 [0,73 ; 1,76]	1,17 [0,69 ; 1,96];	2,04 [-4,89 ; 8,97]; 0,598	0,598	0,2759
	>=3	84	9	10.71	98	4	4.08	2,62 [0,84 ; 8,22]	2,82 [0,84 ; 9,52];	6,63 [-1,05 ; 14,32]; 0,093	0,093	
	2	236	27	11.44	248	29	11.69	0,98 [0,6 ; 1,6]	0,98 [0,56 ; 1,7];	-0,25 [-5,95 ; 5,45]; 1	1	
Race	Other	10	3	30.00	12	4	33.33	0,9 [0,26 ; 3,11]	0,86 [0,14 ; 5,23];	-3,33 [-42,3 ; 35,63]; 1	1	0,696
	White	535	71	13.27	536	59	11.01	1,21 [0,87 ; 1,67]	1,24 [0,86 ; 1,79];	2,26 [-1,65 ; 6,17]; 0,263	0,263	
	No	347	44	12.68	379	49	12.93	0,98 [0,67 ; 1,43]	0,98 [0,63 ; 1,51];	-0,25 [-5,11 ; 4,62]; 1	1	0,0802

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	30	15.15	169	14	8.28	1,83 [1 ; 3,33]	1,98 [1,01 ; 3,87];	6,87 [0,37 ; 13,36]; 0,053	0,053	
Region	Eastern Europe	492	56	11.38	495	48	9.70	1,17 [0,82 ; 1,69]	1,2 [0,8 ; 1,8];	1,69 [-2,15 ; 5,52]; 0,408	0,408	0,8554
	USA and Western Europe	53	18	33.96	53	15	28.30	1,2 [0,68 ; 2,12]	1,3 [0,57 ; 2,97];	5,66 [-11,94 ; 23,26]; 0,675	0,675	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Injury, poisoning and procedural complications | any

6.2.13 Investigations - any

Tabelle 374: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	87	26.69	302	71	23.51	1,14 [0,87 ; 1,49]	1,18 [0,82 ; 1,7];	3,18 [-3,6 ; 9,95]; 0,408	0,408	0,8747
	>= 38 years	219	50	22.83	246	51	20.73	1,1 [0,78 ; 1,55]	1,13 [0,73 ; 1,76];	2,1 [-5,42 ; 9,62]; 0,652	0,652	
Disease Severity at baseline (EDSS)	<=3.5	419	107	25.54	415	95	22.89	1,12 [0,88 ; 1,42]	1,16 [0,84 ; 1,59];	2,65 [-3,17 ; 8,46]; 0,375	0,375	0,86
	>3.5	126	30	23.81	133	27	20.30	1,17 [0,74 ; 1,86]	1,23 [0,68 ; 2,21];	3,51 [-6,59 ; 13,61]; 0,55	0,55	
Gender	Female	345	81	23.48	356	71	19.94	1,18 [0,89 ; 1,56]	1,23 [0,86 ; 1,77];	3,53 [-2,57 ; 9,64]; 0,272	0,272	0,6418
	Male	200	56	28.00	192	51	26.56	1,05 [0,76 ; 1,46]	1,08 [0,69 ; 1,68];	1,44 [-7,38 ; 10,26]; 0,821	0,821	
Number of baseline Gd-enhancing lesions	>=1	258	66	25.58	251	57	22.71	1,13 [0,83 ; 1,53]	1,17 [0,78 ; 1,76];	2,87 [-4,56 ; 10,3]; 0,47	0,47	0,9723
	0	286	71	24.83	293	64	21.84	1,14 [0,85 ; 1,53]	1,18 [0,8 ; 1,74];	2,98 [-3,91 ; 9,87]; 0,432	0,432	
	NA	1	0	0.00	4	1	25.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	52	23.11	202	44	21.78	1,06 [0,74 ; 1,51]	1,08 [0,68 ; 1,7];	1,33 [-6,59 ; 9,25]; 0,817	0,817	0,8089
	>=3	84	31	36.90	98	29	29.59	1,25 [0,82 ; 1,89]	1,39 [0,75 ; 2,59];	7,31 [-6,4 ; 21,03]; 0,344	0,344	
	2	236	54	22.88	248	49	19.76	1,16 [0,82 ; 1,63]	1,2 [0,78 ; 1,86];	3,12 [-4,18 ; 10,42]; 0,437	0,437	
Race	Other	10	4	40.00	12	2	16.67	2,4 [0,55 ; 10,49]	3,33 [0,46 ; 24,05];	23,33 [-13,63 ; 60,3]; 0,348	0,348	0,2827
	White	535	133	24.86	536	120	22.39	1,11 [0,89 ; 1,38]	1,15 [0,86 ; 1,52];	2,47 [-2,61 ; 7,56]; 0,35	0,35	
	No	347	90	25.94	379	76	20.05	1,29 [0,99 ; 1,69]	1,4 [0,99 ; 1,98];	5,88 [-0,24 ; 12,01]; 0,064	0,064	0,0834

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	47	23.74	169	46	27.22	0,87 [0,61 ; 1,24]	0,83 [0,52 ; 1,33];	-3,48 [-12,43 ; 5,47]; 0,471	0,471	
Region	Eastern Europe	492	118	23.98	495	111	22.42	1,07 [0,85 ; 1,34]	1,09 [0,81 ; 1,47];	1,56 [-3,71 ; 6,83]; 0,598	0,598	0,1482
	USA and Western Europe	53	19	35.85	53	11	20.75	1,73 [0,91 ; 3,27]	2,13 [0,89 ; 5,09];	15,09 [-1,81 ; 32]; 0,13	0,13	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Investigations | any

6.2.14 Metabolism and nutrition disorders - any

Tabelle 375: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	11	3.37	302	10	3.31	1,02 [0,44 ; 2,37]	1,02 [0,43 ; 2,44];	0,06 [-2,75 ; 2,88]; 1	1	0,7807
	>= 38 years	219	6	2.74	246	8	3.25	0,84 [0,3 ; 2,39]	0,84 [0,29 ; 2,45];	-0,51 [-3,61 ; 2,58]; 0,792	0,792	
Disease Severity at baseline (EDSS)	<=3.5	419	17	4.06	415	9	2.17	1,87 [0,84 ; 4,15]	1,91 [0,84 ; 4,33];	1,89 [-0,46 ; 4,24]; 0,162	0,162	0,0001
	>3.5	126	0	0.00	133	9	6.77	0,06 [0 ; 0,94]	0,05 [0 ; 0,9];	-6,7 [-11,18 ; -2,22]; 0,002	0,002	
Gender	Female	345	10	2.90	356	9	2.53	1,15 [0,47 ; 2,79]	1,15 [0,46 ; 2,87];	0,37 [-2,04 ; 2,78]; 0,819	0,819	0,5203
	Male	200	7	3.50	192	9	4.69	0,75 [0,28 ; 1,97]	0,74 [0,27 ; 2,02];	-1,19 [-5,12 ; 2,74]; 0,616	0,616	
Number of baseline Gd-enhancing lesions	>=1	258	12	4.65	251	8	3.19	1,46 [0,61 ; 3,51]	1,48 [0,6 ; 3,69];	1,46 [-1,9 ; 4,83]; 0,496	0,496	0,1282
	0	286	5	1.75	293	10	3.41	0,51 [0,18 ; 1,48]	0,5 [0,17 ; 1,49];	-1,66 [-4,24 ; 0,91]; 0,296	0,296	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	9	4.00	202	9	4.46	0,9 [0,36 ; 2,22]	0,89 [0,35 ; 2,3];	-0,46 [-4,28 ; 3,37]; 0,815	0,815	0,955
	>=3	84	2	2.38	98	3	3.06	0,78 [0,13 ; 4,54]	0,77 [0,13 ; 4,74];	-0,68 [-5,4 ; 4,04]; 1	1	
	2	236	6	2.54	248	6	2.42	1,05 [0,34 ; 3,21]	1,05 [0,33 ; 3,31];	0,12 [-2,65 ; 2,9]; 1	1	
Race	Other	10	1	10.00	12	2	16.67	0,6 [0,06 ; 5,69]	0,56 [0,04 ; 7,21];	-6,67 [-34,78 ; 21,45]; 1	1	0,658
	White	535	16	2.99	536	16	2.99	1 [0,51 ; 1,98]	1 [0,5 ; 2,02];	0,01 [-2,03 ; 2,04]; 1	1	
	No	347	9	2.59	379	11	2.90	0,89 [0,37 ; 2,13]	0,89 [0,36 ; 2,18];	-0,31 [-2,69 ; 2,07]; 0,825	0,825	0,8976

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	8	4.04	169	7	4.14	0,98 [0,36 ; 2,63]	0,97 [0,35 ; 2,75];	-0,1 [-4,17 ; 3,97]; 1	1	
Region	Eastern Europe	492	12	2.44	495	13	2.63	0,93 [0,43 ; 2,02]	0,93 [0,42 ; 2,05];	-0,19 [-2,15 ; 1,77]; 1	1	0,9224
	USA and Western Europe	53	5	9.43	53	5	9.43	1 [0,31 ; 3,25]	1 [0,27 ; 3,68];	0 [-11,13 ; 11,13]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Metabolism and nutrition disorders | any

6.2.15 Eye disorders - any

Tabelle 376: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	16	4.91	302	19	6.29	0,78 [0,41 ; 1,49]	0,77 [0,39 ; 1,52];	-1,38 [-4,99 ; 2,22]; 0,489	0,489	0,5951
	>= 38 years	219	11	5.02	246	12	4.88	1,03 [0,46 ; 2,29]	1,03 [0,45 ; 2,39];	0,14 [-3,81 ; 4,1]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	23	5.49	415	26	6.27	0,88 [0,51 ; 1,51]	0,87 [0,49 ; 1,55];	-0,78 [-3,97 ; 2,42]; 0,661	0,661	0,9628
	>3.5	126	4	3.17	133	5	3.76	0,84 [0,23 ; 3,07]	0,84 [0,22 ; 3,2];	-0,58 [-5,04 ; 3,87]; 1	1	
Gender	Female	345	20	5.80	356	16	4.49	1,29 [0,68 ; 2,45]	1,31 [0,67 ; 2,57];	1,3 [-1,97 ; 4,58]; 0,495	0,495	0,05
	Male	200	7	3.50	192	15	7.81	0,45 [0,19 ; 1,07]	0,43 [0,17 ; 1,07];	-4,31 [-8,88 ; 0,26]; 0,079	0,079	
Number of baseline Gd-enhancing lesions	>=1	258	13	5.04	251	16	6.37	0,79 [0,39 ; 1,61]	0,78 [0,37 ; 1,66];	-1,34 [-5,37 ; 2,7]; 0,569	0,569	0,6145
	0	286	14	4.90	293	14	4.78	1,02 [0,5 ; 2,11]	1,03 [0,48 ; 2,19];	0,12 [-3,38 ; 3,61]; 1	1	
	NA	1	0	0.00	4	1	25.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	13	5.78	202	10	4.95	1,17 [0,52 ; 2,6]	1,18 [0,5 ; 2,75];	0,83 [-3,44 ; 5,1]; 0,831	0,831	0,6523
	>=3	84	3	3.57	98	5	5.10	0,7 [0,17 ; 2,84]	0,69 [0,16 ; 2,97];	-1,53 [-7,42 ; 4,36]; 0,727	0,727	
	2	236	11	4.66	248	16	6.45	0,72 [0,34 ; 1,52]	0,71 [0,32 ; 1,56];	-1,79 [-5,86 ; 2,28]; 0,433	0,433	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	27	5.05	536	31	5.78	0,87 [0,53 ; 1,44]	0,87 [0,51 ; 1,47];	-0,74 [-3,45 ; 1,97]; 0,686	0,686	
	No	347	16	4.61	379	15	3.96	1,17 [0,58 ; 2,32]	1,17 [0,57 ; 2,41];	0,65 [-2,3 ; 3,61]; 0,715	0,715	0,178

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	11	5.56	169	16	9.47	0,59 [0,28 ; 1,23]	0,56 [0,25 ; 1,25];	-3,91 [-9,36 ; 1,53]; 0,165	0,165	
Region	Eastern Europe	492	23	4.67	495	25	5.05	0,93 [0,53 ; 1,61]	0,92 [0,52 ; 1,65];	-0,38 [-3,06 ; 2,31]; 0,883	0,883	0,6185
	USA and Western Europe	53	4	7.55	53	6	11.32	0,67 [0,2 ; 2,23]	0,64 [0,17 ; 2,41];	-3,77 [-14,88 ; 7,33]; 0,741	0,741	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Eye disorders | any

6.2.16 Psychiatric disorders - any

Tabelle 377: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	52	15.95	302	37	12.25	1,3 [0,88 ; 1,93]	1,36 [0,86 ; 2,14];	3,7 [-1,73 ; 9,13]; 0,208	0,208	0,6308
	>= 38 years	219	30	13.70	246	30	12.20	1,12 [0,7 ; 1,8]	1,14 [0,66 ; 1,97];	1,5 [-4,62 ; 7,62]; 0,679	0,679	
Disease Severity at baseline (EDSS)	<=3.5	419	73	17.42	415	47	11.33	1,54 [1,09 ; 2,16]	1,65 [1,11 ; 2,45];	6,1 [1,36 ; 10,84]; 0,014	0,014	0,0032
	>3.5	126	9	7.14	133	20	15.04	0,48 [0,22 ; 1]	0,43 [0,19 ; 0,99];	-7,89 [-15,45 ; -0,34]; 0,05	0,05	
Gender	Female	345	58	16.81	356	46	12.92	1,3 [0,91 ; 1,86]	1,36 [0,9 ; 2,07];	3,89 [-1,37 ; 9,15]; 0,167	0,167	0,594
	Male	200	24	12.00	192	21	10.94	1,1 [0,63 ; 1,9]	1,11 [0,6 ; 2,07];	1,06 [-5,24 ; 7,37]; 0,754	0,754	
Number of baseline Gd-enhancing lesions	>=1	258	52	20.16	251	34	13.55	1,49 [1 ; 2,21]	1,61 [1 ; 2,58];	6,61 [0,14 ; 13,08]; 0,058	0,058	0,1208
	0	286	30	10.49	293	33	11.26	0,93 [0,58 ; 1,49]	0,92 [0,55 ; 1,56];	-0,77 [-5,84 ; 4,3]; 0,791	0,791	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	38	16.89	202	25	12.38	1,36 [0,85 ; 2,18]	1,44 [0,83 ; 2,48];	4,51 [-2,16 ; 11,19]; 0,219	0,219	0,5424
	>=3	84	11	13.10	98	8	8.16	1,6 [0,68 ; 3,8]	1,7 [0,65 ; 4,43];	4,93 [-4,09 ; 13,96]; 0,334	0,334	
	2	236	33	13.98	248	34	13.71	1,02 [0,65 ; 1,59]	1,02 [0,61 ; 1,71];	0,27 [-5,88 ; 6,43]; 1	1	
Race	Other	10	4	40.00	12	4	33.33	1,2 [0,4 ; 3,62]	1,33 [0,23 ; 7,63];	6,67 [-33,75 ; 47,08]; 1	1	0,9651
	White	535	78	14.58	536	63	11.75	1,24 [0,91 ; 1,69]	1,28 [0,9 ; 1,83];	2,83 [-1,22 ; 6,87]; 0,176	0,176	
	No	347	49	14.12	379	41	10.82	1,31 [0,89 ; 1,92]	1,36 [0,87 ; 2,11];	3,3 [-1,51 ; 8,12]; 0,215	0,215	0,567

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	33	16.67	169	26	15.38	1,08 [0,68 ; 1,74]	1,1 [0,63 ; 1,93];	1,28 [-6,24 ; 8,8]; 0,777	0,777	
Region	Eastern Europe	492	65	13.21	495	55	11.11	1,19 [0,85 ; 1,67]	1,22 [0,83 ; 1,79];	2,1 [-1,98 ; 6,18]; 0,331	0,331	0,5586
	USA and Western Europe	53	17	32.08	53	12	22.64	1,42 [0,75 ; 2,67]	1,61 [0,68 ; 3,83];	9,43 [-7,44 ; 26,31]; 0,384	0,384	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Psychiatric disorders | any

6.2.17 Vascular disorders - any

Tabelle 378: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	25	7.67	302	22	7.28	1,05 [0,61 ; 1,83]	1,06 [0,58 ; 1,92];	0,38 [-3,73 ; 4,5]; 0,88	0,88	0,134
	>= 38 years	219	16	7.31	246	31	12.60	0,58 [0,33 ; 1,03]	0,55 [0,29 ; 1,03];	-5,3 [-10,69 ; 0,1]; 0,065	0,065	
Disease Severity at baseline (EDSS)	<=3.5	419	36	8.59	415	42	10.12	0,85 [0,56 ; 1,3]	0,83 [0,52 ; 1,33];	-1,53 [-5,48 ; 2,42]; 0,477	0,477	0,3107
	>3.5	126	5	3.97	133	11	8.27	0,48 [0,17 ; 1,34]	0,46 [0,15 ; 1,36];	-4,3 [-10,09 ; 1,49]; 0,198	0,198	
Gender	Female	345	29	8.41	356	37	10.39	0,81 [0,51 ; 1,28]	0,79 [0,47 ; 1,32];	-1,99 [-6,3 ; 2,33]; 0,438	0,438	0,8008
	Male	200	12	6.00	192	16	8.33	0,72 [0,35 ; 1,48]	0,7 [0,32 ; 1,53];	-2,33 [-7,44 ; 2,78]; 0,435	0,435	
Number of baseline Gd-enhancing lesions	>=1	258	21	8.14	251	25	9.96	0,82 [0,47 ; 1,42]	0,8 [0,44 ; 1,47];	-1,82 [-6,81 ; 3,17]; 0,537	0,537	0,7857
	0	286	20	6.99	293	28	9.56	0,73 [0,42 ; 1,27]	0,71 [0,39 ; 1,29];	-2,56 [-7,04 ; 1,92]; 0,293	0,293	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	21	9.33	202	22	10.89	0,86 [0,49 ; 1,51]	0,84 [0,45 ; 1,58];	-1,56 [-7,29 ; 4,18]; 0,631	0,631	0,4447
	>=3	84	7	8.33	98	7	7.14	1,17 [0,43 ; 3,19]	1,18 [0,4 ; 3,52];	1,19 [-6,62 ; 9]; 0,787	0,787	
	2	236	13	5.51	248	24	9.68	0,57 [0,3 ; 1,09]	0,54 [0,27 ; 1,1];	-4,17 [-8,86 ; 0,52]; 0,09	0,09	
Race	Other	10	1	10.00	12	1	8.33	1,2 [0,09 ; 16,84]	1,22 [0,07 ; 22,4];	1,67 [-22,63 ; 25,96]; 1	1	0,747
	White	535	40	7.48	536	52	9.70	0,77 [0,52 ; 1,14]	0,75 [0,49 ; 1,16];	-2,22 [-5,58 ; 1,13]; 0,23	0,23	
	No	347	15	4.32	379	37	9.76	0,44 [0,25 ; 0,79]	0,42 [0,22 ; 0,78];	-5,44 [-9,12 ; -1,76]; 0,006	0,006	0,0059

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	26	13.13	169	16	9.47	1,39 [0,77 ; 2,5]	1,45 [0,75 ; 2,8];	3,66 [-2,79 ; 10,11]; 0,325	0,325	
Region	Eastern Europe	492	36	7.32	495	45	9.09	0,8 [0,53 ; 1,23]	0,79 [0,5 ; 1,25];	-1,77 [-5,2 ; 1,65]; 0,354	0,354	0,6445
	USA and Western Europe	53	5	9.43	53	8	15.09	0,63 [0,22 ; 1,79]	0,59 [0,18 ; 1,92];	-5,66 [-18,1 ; 6,78]; 0,555	0,555	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Vascular disorders | any

6.2.18 Neoplasms benign, malignant and unspecified (incl cysts and polyps) - any

Tabelle 379: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	6	1.84	302	5	1.66	1,11 [0,34 ; 3,6]	1,11 [0,34 ; 3,69];	0,18 [-1,86 ; 2,23]; 1	1	0,675
	>= 38 years	219	7	3.20	246	5	2.03	1,57 [0,51 ; 4,88]	1,59 [0,5 ; 5,09];	1,16 [-1,76 ; 4,09]; 0,561	0,561	
Disease Severity at baseline (EDSS)	<=3.5	419	10	2.39	415	8	1.93	1,24 [0,49 ; 3,11]	1,24 [0,49 ; 3,18];	0,46 [-1,51 ; 2,43]; 0,813	0,813	0,8089
	>3.5	126	3	2.38	133	2	1.50	1,58 [0,27 ; 9,32]	1,6 [0,26 ; 9,72];	0,88 [-2,49 ; 4,25]; 0,677	0,677	
Gender	Female	345	12	3.48	356	9	2.53	1,38 [0,59 ; 3,22]	1,39 [0,58 ; 3,34];	0,95 [-1,58 ; 3,48]; 0,512	0,512	0,8039
	Male	200	1	0.50	192	1	0.52	0,96 [0,06 ; 15,24]	0,96 [0,06 ; 15,45];	-0,02 [-1,43 ; 1,39]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	258	4	1.55	251	7	2.79	0,56 [0,16 ; 1,88]	0,55 [0,16 ; 1,9];	-1,24 [-3,77 ; 1,3]; 0,377	0,377	0,0487
	0	286	9	3.15	293	3	1.02	3,07 [0,84 ; 11,24]	3,14 [0,84 ; 11,72];	2,12 [-0,21 ; 4,45]; 0,086	0,086	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	5	2.22	202	4	1.98	1,12 [0,31 ; 4,12]	1,12 [0,3 ; 4,25];	0,24 [-2,48 ; 2,96]; 1	1	0,9504
	>=3	84	1	1.19	98	1	1.02	1,17 [0,07 ; 18,37]	1,17 [0,07 ; 18,98];	0,17 [-2,89 ; 3,23]; 1	1	
	2	236	7	2.97	248	5	2.02	1,47 [0,47 ; 4,57]	1,49 [0,46 ; 4,75];	0,95 [-1,83 ; 3,73]; 0,568	0,568	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	13	2.43	536	10	1.87	1,3 [0,58 ; 2,94]	1,31 [0,57 ; 3,01];	0,56 [-1,17 ; 2,3]; 0,537	0,537	
	No	347	9	2.59	379	6	1.58	1,64 [0,59 ; 4,56]	1,66 [0,58 ; 4,7];	1,01 [-1,08 ; 3,1]; 0,436	0,436	0,4551

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	4	2.02	169	4	2.37	0,85 [0,22 ; 3,36]	0,85 [0,21 ; 3,45];	-0,35 [-3,36 ; 2,67]; 1	1	
Region	Eastern Europe	492	8	1.63	495	9	1.82	0,89 [0,35 ; 2,3]	0,89 [0,34 ; 2,33];	-0,19 [-1,82 ; 1,43]; 1	1	0,0999
	USA and Western Europe	53	5	9.43	53	1	1.89	5 [0,6 ; 41,37]	5,42 [0,61 ; 48,04];	7,55 [-1,13 ; 16,23]; 0,205	0,205	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Neoplasms benign, malignant and unspecified (incl cysts and polyps) | any

6.2.19 Hepatobiliary disorders - any

Tabelle 380: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	7	2.15	302	9	2.98	0,72 [0,27 ; 1,91]	0,71 [0,26 ; 1,94];	-0,83 [-3,31 ; 1,65]; 0,615	0,615	0,4162
	>= 38 years	219	4	1.83	246	3	1.22	1,5 [0,34 ; 6,62]	1,51 [0,33 ; 6,81];	0,61 [-1,63 ; 2,85]; 0,712	0,712	
Disease Severity at baseline (EDSS)	<=3.5	419	8	1.91	415	9	2.17	0,88 [0,34 ; 2,26]	0,88 [0,34 ; 2,3];	-0,26 [-2,18 ; 1,66]; 0,812	0,812	0,8471
	>3.5	126	3	2.38	133	3	2.26	1,06 [0,22 ; 5,13]	1,06 [0,21 ; 5,34];	0,13 [-3,54 ; 3,79]; 1	1	
Gender	Female	345	5	1.45	356	6	1.69	0,86 [0,26 ; 2,79]	0,86 [0,26 ; 2,84];	-0,24 [-2,07 ; 1,6]; 1	1	0,8954
	Male	200	6	3.00	192	6	3.12	0,96 [0,32 ; 2,93]	0,96 [0,3 ; 3,03];	-0,13 [-3,54 ; 3,29]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	258	3	1.16	251	5	1.99	0,58 [0,14 ; 2,42]	0,58 [0,14 ; 2,45];	-0,83 [-3 ; 1,34]; 0,499	0,499	0,4281
	0	286	8	2.80	293	7	2.39	1,17 [0,43 ; 3,19]	1,18 [0,42 ; 3,29];	0,41 [-2,18 ; 3]; 0,799	0,799	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	3	1.33	202	7	3.47	0,38 [0,1 ; 1,47]	0,38 [0,1 ; 1,48];	-2,13 [-5,07 ; 0,8]; 0,202	0,202	0,104
	>=3	84	2	2.38	98	3	3.06	0,78 [0,13 ; 4,54]	0,77 [0,13 ; 4,74];	-0,68 [-5,4 ; 4,04]; 1	1	
	2	236	6	2.54	248	2	0.81	3,15 [0,64 ; 15,46]	3,21 [0,64 ; 16,06];	1,74 [-0,56 ; 4,03]; 0,167	0,167	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	11	2.06	536	12	2.24	0,92 [0,41 ; 2,06]	0,92 [0,4 ; 2,1];	-0,18 [-1,92 ; 1,55]; 1	1	
	No	347	6	1.73	379	9	2.37	0,73 [0,26 ; 2,02]	0,72 [0,25 ; 2,05];	-0,65 [-2,7 ; 1,41]; 0,609	0,609	0,447

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	5	2.53	169	3	1.78	1,42 [0,35 ; 5,87]	1,43 [0,34 ; 6,09];	0,75 [-2,21 ; 3,71]; 0,73	0,73	
Region	Eastern Europe	492	10	2.03	495	11	2.22	0,91 [0,39 ; 2,13]	0,91 [0,38 ; 2,17];	-0,19 [-1,99 ; 1,61]; 1	1	0,9514
	USA and Western Europe	53	1	1.89	53	1	1.89	1 [0,06 ; 15,57]	1 [0,06 ; 16,42];	0 [-5,18 ; 5,18]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Hepatobiliary disorders | any

6.2.20 Blood and lymphatic system disorders - any

Tabelle 381: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	53	16.26	302	45	14.90	1,09 [0,76 ; 1,57]	1,11 [0,72 ; 1,71];	1,36 [-4,32 ; 7,03]; 0,661	0,661	0,1777
	>= 38 years	219	20	9.13	246	32	13.01	0,7 [0,41 ; 1,19]	0,67 [0,37 ; 1,21];	-3,88 [-9,55 ; 1,8]; 0,238	0,238	
Disease Severity at baseline (EDSS)	<=3.5	419	58	13.84	415	55	13.25	1,04 [0,74 ; 1,47]	1,05 [0,71 ; 1,56];	0,59 [-4,06 ; 5,23]; 0,84	0,84	0,2925
	>3.5	126	15	11.90	133	22	16.54	0,72 [0,39 ; 1,32]	0,68 [0,34 ; 1,38];	-4,64 [-13,11 ; 3,84]; 0,375	0,375	
Gender	Female	345	54	15.65	356	56	15.73	1 [0,71 ; 1,4]	0,99 [0,66 ; 1,49];	-0,08 [-5,46 ; 5,31]; 1	1	0,701
	Male	200	19	9.50	192	21	10.94	0,87 [0,48 ; 1,56]	0,85 [0,44 ; 1,65];	-1,44 [-7,44 ; 4,56]; 0,739	0,739	
Number of baseline Gd-enhancing lesions	>=1	258	33	12.79	251	42	16.73	0,76 [0,5 ; 1,17]	0,73 [0,45 ; 1,2];	-3,94 [-10,1 ; 2,22]; 0,214	0,214	0,1348
	0	286	40	13.99	293	34	11.60	1,21 [0,79 ; 1,85]	1,24 [0,76 ; 2,02];	2,38 [-3,06 ; 7,82]; 0,455	0,455	
	NA	1	0	0.00	4	1	25.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	25	11.11	202	27	13.37	0,83 [0,5 ; 1,38]	0,81 [0,45 ; 1,45];	-2,26 [-8,49 ; 3,98]; 0,554	0,554	0,7483
	>=3	84	18	21.43	98	19	19.39	1,11 [0,62 ; 1,96]	1,13 [0,55 ; 2,34];	2,04 [-9,72 ; 13,8]; 0,854	0,854	
	2	236	30	12.71	248	31	12.50	1,02 [0,64 ; 1,63]	1,02 [0,6 ; 1,74];	0,21 [-5,7 ; 6,13]; 1	1	
Race	Other	10	0	0.00	12	2	16.67	0,24 [0,01 ; 4,42]	0,2 [0,01 ; 4,69];	-14,69 [-39,39 ; 10,02]; 0,481	0,481	0,1129
	White	535	73	13.64	536	75	13.99	0,98 [0,72 ; 1,32]	0,97 [0,69 ; 1,37];	-0,35 [-4,48 ; 3,79]; 0,929	0,929	
	No	347	37	10.66	379	44	11.61	0,92 [0,61 ; 1,39]	0,91 [0,57 ; 1,44];	-0,95 [-5,52 ; 3,63]; 0,724	0,724	0,9826

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	36	18.18	169	33	19.53	0,93 [0,61 ; 1,42]	0,92 [0,54 ; 1,55];	-1,34 [-9,38 ; 6,69]; 0,789	0,789	
Region	Eastern Europe	492	71	14.43	495	74	14.95	0,97 [0,71 ; 1,3]	0,96 [0,67 ; 1,36];	-0,52 [-4,94 ; 3,9]; 0,857	0,857	0,6841
	USA and Western Europe	53	2	3.77	53	3	5.66	0,67 [0,12 ; 3,83]	0,65 [0,1 ; 4,08];	-1,89 [-9,95 ; 6,18]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Blood and lymphatic system disorders | any

6.2.21 Immune system disorders - any

Tabelle 382: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	17	5.21	302	6	1.99	2,62 [1,05 ; 6,57]	2,71 [1,06 ; 6,98];	3,23 [0,35 ; 6,11]; 0,034	0,034	0,0663
	>= 38 years	219	7	3.20	246	10	4.07	0,79 [0,3 ; 2,03]	0,78 [0,29 ; 2,08];	-0,87 [-4,26 ; 2,53]; 0,805	0,805	
Disease Severity at baseline (EDSS)	<=3.5	419	21	5.01	415	11	2.65	1,89 [0,92 ; 3,87]	1,94 [0,92 ; 4,07];	2,36 [-0,24 ; 4,96]; 0,103	0,103	0,1658
	>3.5	126	3	2.38	133	5	3.76	0,63 [0,15 ; 2,6]	0,62 [0,15 ; 2,67];	-1,38 [-5,57 ; 2,81]; 0,723	0,723	
Gender	Female	345	19	5.51	356	14	3.93	1,4 [0,71 ; 2,75]	1,42 [0,7 ; 2,89];	1,57 [-1,57 ; 4,72]; 0,374	0,374	0,5488
	Male	200	5	2.50	192	2	1.04	2,4 [0,47 ; 12,22]	2,44 [0,47 ; 12,71];	1,46 [-1,14 ; 4,06]; 0,45	0,45	
Number of baseline Gd-enhancing lesions	>=1	258	8	3.10	251	7	2.79	1,11 [0,41 ; 3,02]	1,12 [0,4 ; 3,12];	0,31 [-2,62 ; 3,25]; 1	1	0,4446
	0	286	16	5.59	293	9	3.07	1,82 [0,82 ; 4,05]	1,87 [0,81 ; 4,3];	2,52 [-0,79 ; 5,84]; 0,155	0,155	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	9	4.00	202	6	2.97	1,35 [0,49 ; 3,72]	1,36 [0,48 ; 3,89];	1,03 [-2,44 ; 4,5]; 0,609	0,609	0,915
	>=3	84	2	2.38	98	1	1.02	2,33 [0,22 ; 25,28]	2,37 [0,21 ; 26,56];	1,36 [-2,46 ; 5,18]; 0,596	0,596	
	2	236	13	5.51	248	9	3.63	1,52 [0,66 ; 3,48]	1,55 [0,65 ; 3,69];	1,88 [-1,85 ; 5,61]; 0,385	0,385	
Race	Other	10	1	10.00	12	3	25.00	0,4 [0,05 ; 3,27]	0,33 [0,03 ; 3,84];	-15 [-45,76 ; 15,76]; 0,594	0,594	0,1648
	White	535	23	4.30	536	13	2.43	1,77 [0,91 ; 3,46]	1,81 [0,91 ; 3,61];	1,87 [-0,28 ; 4,03]; 0,093	0,093	
	No	347	12	3.46	379	7	1.85	1,87 [0,75 ; 4,7]	1,9 [0,74 ; 4,89];	1,61 [-0,74 ; 3,96]; 0,244	0,244	0,4429

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	12	6.06	169	9	5.33	1,14 [0,49 ; 2,63]	1,15 [0,47 ; 2,79];	0,74 [-4,01 ; 5,48]; 0,825	0,825	
Region	Eastern Europe	492	21	4.27	495	13	2.63	1,63 [0,82 ; 3,21]	1,65 [0,82 ; 3,34];	1,64 [-0,63 ; 3,92]; 0,167	0,167	0,5832
	USA and Western Europe	53	3	5.66	53	3	5.66	1 [0,21 ; 4,73]	1 [0,19 ; 5,19];	0 [-8,8 ; 8,8]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Immune system disorders | any

6.2.22 Gastrointestinal disorders - Abdominal pain upper

Tabelle 383: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	16	4.91	302	12	3.97	1,24 [0,59 ; 2,57]	1,25 [0,58 ; 2,68];	0,93 [-2,28 ; 4,15]; 0,7	0,7	0,0948
	>= 38 years	219	4	1.83	246	11	4.47	0,41 [0,13 ; 1,26]	0,4 [0,12 ; 1,27];	-2,65 [-5,78 ; 0,49]; 0,122	0,122	
Disease Severity at baseline (EDSS)	<=3.5	419	19	4.53	415	21	5.06	0,9 [0,49 ; 1,64]	0,89 [0,47 ; 1,68];	-0,53 [-3,43 ; 2,38]; 0,748	0,748	0,6701
	>3.5	126	1	0.79	133	2	1.50	0,53 [0,05 ; 5,75]	0,52 [0,05 ; 5,85];	-0,71 [-3,29 ; 1,87]; 1	1	
Gender	Female	345	18	5.22	356	20	5.62	0,93 [0,5 ; 1,73]	0,92 [0,48 ; 1,78];	-0,4 [-3,75 ; 2,95]; 0,868	0,868	0,7
	Male	200	2	1.00	192	3	1.56	0,64 [0,11 ; 3,79]	0,64 [0,11 ; 3,85];	-0,56 [-2,79 ; 1,67]; 0,68	0,68	
Number of baseline Gd-enhancing lesions	>=1	258	13	5.04	251	12	4.78	1,05 [0,49 ; 2,27]	1,06 [0,47 ; 2,36];	0,26 [-3,5 ; 4,01]; 1	1	0,4353
	0	286	7	2.45	293	11	3.75	0,65 [0,26 ; 1,66]	0,64 [0,25 ; 1,68];	-1,31 [-4,13 ; 1,51]; 0,474	0,474	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	9	4.00	202	10	4.95	0,81 [0,34 ; 1,95]	0,8 [0,32 ; 2,01];	-0,95 [-4,89 ; 2,99]; 0,647	0,647	0,2087
	>=3	84	6	7.14	98	3	3.06	2,33 [0,6 ; 9,05]	2,44 [0,59 ; 10,06];	4,08 [-2,4 ; 10,56]; 0,306	0,306	
	2	236	5	2.12	248	10	4.03	0,53 [0,18 ; 1,51]	0,52 [0,17 ; 1,53];	-1,91 [-4,97 ; 1,15]; 0,296	0,296	
Race	Other	10	1	10.00	12	1	8.33	1,2 [0,09 ; 16,84]	1,22 [0,07 ; 22,4];	1,67 [-22,63 ; 25,96]; 1	1	0,8173
	White	535	19	3.55	536	22	4.10	0,87 [0,47 ; 1,58]	0,86 [0,46 ; 1,61];	-0,55 [-2,85 ; 1,74]; 0,751	0,751	
	No	347	13	3.75	379	16	4.22	0,89 [0,43 ; 1,82]	0,88 [0,42 ; 1,86];	-0,48 [-3,32 ; 2,37]; 0,85	0,85	0,9517

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	7	3.54	169	7	4.14	0,85 [0,31 ; 2,38]	0,85 [0,29 ; 2,47];	-0,61 [-4,56 ; 3,35]; 0,791	0,791	
Region	Eastern Europe	492	16	3.25	495	18	3.64	0,89 [0,46 ; 1,73]	0,89 [0,45 ; 1,77];	-0,38 [-2,66 ; 1,89]; 0,862	0,862	0,87
	USA and Western Europe	53	4	7.55	53	5	9.43	0,8 [0,23 ; 2,82]	0,78 [0,2 ; 3,1];	-1,89 [-12,49 ; 8,72]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Gastrointestinal disorders | Abdominal pain upper

6.2.23 General disorders and administration site conditions - Fatigue

Tabelle 384: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	19	5.83	302	7	2.32	2,51 [1,07 ; 5,9]	2,61 [1,08 ; 6,3];	3,51 [0,45 ; 6,57]; 0,029	0,029	0,0475
	>= 38 years	219	9	4.11	246	13	5.28	0,78 [0,34 ; 1,78]	0,77 [0,32 ; 1,83];	-1,17 [-5,01 ; 2,66]; 0,663	0,663	
Disease Severity at baseline (EDSS)	<=3.5	419	27	6.44	415	15	3.61	1,78 [0,96 ; 3,3]	1,84 [0,96 ; 3,51];	2,83 [-0,13 ; 5,79]; 0,081	0,081	0,0268
	>3.5	126	1	0.79	133	5	3.76	0,21 [0,03 ; 1,78]	0,2 [0,02 ; 1,78];	-2,97 [-6,55 ; 0,62]; 0,214	0,214	
Gender	Female	345	18	5.22	356	12	3.37	1,55 [0,76 ; 3,16]	1,58 [0,75 ; 3,33];	1,85 [-1,16 ; 4,85]; 0,265	0,265	0,6677
	Male	200	10	5.00	192	8	4.17	1,2 [0,48 ; 2,98]	1,21 [0,47 ; 3,13];	0,83 [-3,3 ; 4,97]; 0,811	0,811	
Number of baseline Gd-enhancing lesions	>=1	258	16	6.20	251	11	4.38	1,42 [0,67 ; 2,99]	1,44 [0,66 ; 3,17];	1,82 [-2,06 ; 5,7]; 0,431	0,431	0,9433
	0	286	12	4.20	293	9	3.07	1,37 [0,58 ; 3,19]	1,38 [0,57 ; 3,33];	1,12 [-1,93 ; 4,17]; 0,511	0,511	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	10	4.44	202	7	3.47	1,28 [0,5 ; 3,31]	1,3 [0,48 ; 3,47];	0,98 [-2,71 ; 4,67]; 0,631	0,631	0,9664
	>=3	84	4	4.76	98	3	3.06	1,56 [0,36 ; 6,75]	1,58 [0,34 ; 7,28];	1,7 [-3,99 ; 7,39]; 0,705	0,705	
	2	236	14	5.93	248	10	4.03	1,47 [0,67 ; 3,25]	1,5 [0,65 ; 3,45];	1,9 [-1,98 ; 5,78]; 0,404	0,404	
Race	Other	10	1	10.00	12	3	25.00	0,4 [0,05 ; 3,27]	0,33 [0,03 ; 3,84];	-15 [-45,76 ; 15,76]; 0,594	0,594	0,1906
	White	535	27	5.05	536	17	3.17	1,59 [0,88 ; 2,88]	1,62 [0,87 ; 3,01];	1,88 [-0,5 ; 4,25]; 0,127	0,127	
	No	347	17	4.90	379	13	3.43	1,43 [0,7 ; 2,9]	1,45 [0,69 ; 3,03];	1,47 [-1,45 ; 4,39]; 0,354	0,354	0,9189

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	11	5.56	169	7	4.14	1,34 [0,53 ; 3,38]	1,36 [0,52 ; 3,59];	1,41 [-2,97 ; 5,8]; 0,631	0,631	
Region	Eastern Europe	492	20	4.07	495	9	1.82	2,24 [1,03 ; 4,86]	2,29 [1,03 ; 5,08];	2,25 [0,14 ; 4,35]; 0,039	0,039	0,0595
	USA and Western Europe	53	8	15.09	53	11	20.75	0,73 [0,32 ; 1,66]	0,68 [0,25 ; 1,85];	-5,66 [-20,22 ; 8,9]; 0,613	0,613	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - General disorders and administration site conditions | Fatigue

6.2.24 Infections and infestations - Influenza

Tabelle 385: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	9	2.76	302	9	2.98	0,93 [0,37 ; 2,3]	0,92 [0,36 ; 2,36];	-0,22 [-2,83 ; 2,4]; 1	1	0,9886
	>= 38 years	219	5	2.28	246	6	2.44	0,94 [0,29 ; 3,02]	0,93 [0,28 ; 3,11];	-0,16 [-2,92 ; 2,61]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	12	2.86	415	12	2.89	0,99 [0,45 ; 2,18]	0,99 [0,44 ; 2,23];	-0,03 [-2,3 ; 2,24]; 1	1	0,7286
	>3.5	126	2	1.59	133	3	2.26	0,7 [0,12 ; 4,14]	0,7 [0,11 ; 4,25];	-0,67 [-4 ; 2,67]; 1	1	
Gender	Female	345	8	2.32	356	11	3.09	0,75 [0,31 ; 1,84]	0,74 [0,3 ; 1,87];	-0,77 [-3,17 ; 1,63]; 0,644	0,644	0,4023
	Male	200	6	3.00	192	4	2.08	1,44 [0,41 ; 5,02]	1,45 [0,4 ; 5,23];	0,92 [-2,19 ; 4,03]; 0,751	0,751	
Number of baseline Gd-enhancing lesions	>=1	258	7	2.71	251	7	2.79	0,97 [0,35 ; 2,73]	0,97 [0,34 ; 2,81];	-0,08 [-2,92 ; 2,77]; 1	1	0,9113
	0	286	7	2.45	293	8	2.73	0,9 [0,33 ; 2,44]	0,89 [0,32 ; 2,5];	-0,28 [-2,87 ; 2,3]; 1	1	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	10	4.44	202	3	1.49	2,99 [0,84 ; 10,72]	3,09 [0,84 ; 11,37];	2,96 [-0,21 ; 6,13]; 0,093	0,093	0,0191
	>=3	84	1	1.19	98	1	1.02	1,17 [0,07 ; 18,37]	1,17 [0,07 ; 18,98];	0,17 [-2,89 ; 3,23]; 1	1	
	2	236	3	1.27	248	11	4.44	0,29 [0,08 ; 1,01]	0,28 [0,08 ; 1,01];	-3,16 [-6,1 ; -0,23]; 0,055	0,055	
Race	Other	10	1	10.00	12	0	0.00	3,55 [0,16 ; 78,56]	3,95 [0,14 ; 108,09];	9,79 [-13,03 ; 32,61]; 0,478	0,478	0,1859
	White	535	13	2.43	536	15	2.80	0,87 [0,42 ; 1,81]	0,87 [0,41 ; 1,84];	-0,37 [-2,28 ; 1,54]; 0,849	0,849	
	No	347	10	2.88	379	9	2.37	1,21 [0,5 ; 2,95]	1,22 [0,49 ; 3,04];	0,51 [-1,83 ; 2,84]; 0,817	0,817	0,3286

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	4	2.02	169	6	3.55	0,57 [0,16 ; 1,98]	0,56 [0,16 ; 2,02];	-1,53 [-4,94 ; 1,88]; 0,523	0,523	
Region	Eastern Europe	492	7	1.42	495	12	2.42	0,59 [0,23 ; 1,48]	0,58 [0,23 ; 1,49];	-1 [-2,71 ; 0,71]; 0,355	0,355	0,078
	USA and Western Europe	53	7	13.21	53	3	5.66	2,33 [0,64 ; 8,54]	2,54 [0,62 ; 10,39];	7,55 [-3,49 ; 18,58]; 0,319	0,319	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Influenza

6.2.25 Musculoskeletal and connective tissue disorders - Myalgia

Tabelle 386: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	11	3.37	302	5	1.66	2,04 [0,72 ; 5,8]	2,07 [0,71 ; 6,04];	1,72 [-0,71 ; 4,15]; 0,21	0,21	0,0057
	>= 38 years	219	2	0.91	246	11	4.47	0,2 [0,05 ; 0,91]	0,2 [0,04 ; 0,9];	-3,56 [-6,43 ; -0,68]; 0,023	0,023	
Disease Severity at baseline (EDSS)	<=3.5	419	12	2.86	415	11	2.65	1,08 [0,48 ; 2,42]	1,08 [0,47 ; 2,48];	0,21 [-2,01 ; 2,44]; 1	1	0,115
	>3.5	126	1	0.79	133	5	3.76	0,21 [0,03 ; 1,78]	0,2 [0,02 ; 1,78];	-2,97 [-6,55 ; 0,62]; 0,214	0,214	
Gender	Female	345	12	3.48	356	12	3.37	1,03 [0,47 ; 2,27]	1,03 [0,46 ; 2,33];	0,11 [-2,59 ; 2,8]; 1	1	0,1775
	Male	200	1	0.50	192	4	2.08	0,24 [0,03 ; 2,13]	0,24 [0,03 ; 2,13];	-1,58 [-3,83 ; 0,66]; 0,207	0,207	
Number of baseline Gd-enhancing lesions	>=1	258	6	2.33	251	8	3.19	0,73 [0,26 ; 2,07]	0,72 [0,25 ; 2,11];	-0,86 [-3,71 ; 1,99]; 0,598	0,598	0,7798
	0	286	7	2.45	293	8	2.73	0,9 [0,33 ; 2,44]	0,89 [0,32 ; 2,5];	-0,28 [-2,87 ; 2,3]; 1	1	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	4	1.78	202	3	1.49	1,2 [0,27 ; 5,28]	1,2 [0,27 ; 5,43];	0,29 [-2,11 ; 2,69]; 1	1	0,4818
	>=3	84	2	2.38	98	1	1.02	2,33 [0,22 ; 25,28]	2,37 [0,21 ; 26,56];	1,36 [-2,46 ; 5,18]; 0,596	0,596	
	2	236	7	2.97	248	12	4.84	0,61 [0,25 ; 1,53]	0,6 [0,23 ; 1,55];	-1,87 [-5,31 ; 1,57]; 0,352	0,352	
Race	Other	10	1	10.00	12	1	8.33	1,2 [0,09 ; 16,84]	1,22 [0,07 ; 22,4];	1,67 [-22,63 ; 25,96]; 1	1	0,781
	White	535	12	2.24	536	15	2.80	0,8 [0,38 ; 1,7]	0,8 [0,37 ; 1,72];	-0,56 [-2,43 ; 1,32]; 0,697	0,697	
	No	347	7	2.02	379	9	2.37	0,85 [0,32 ; 2,26]	0,85 [0,31 ; 2,3];	-0,36 [-2,49 ; 1,77]; 0,805	0,805	0,8365

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	6	3.03	169	7	4.14	0,73 [0,25 ; 2,13]	0,72 [0,24 ; 2,2];	-1,11 [-4,95 ; 2,73]; 0,585	0,585	
Region	Eastern Europe	492	10	2.03	495	14	2.83	0,72 [0,32 ; 1,6]	0,71 [0,31 ; 1,62];	-0,8 [-2,72 ; 1,12]; 0,536	0,536	0,4509
	USA and Western Europe	53	3	5.66	53	2	3.77	1,5 [0,26 ; 8,62]	1,53 [0,25 ; 9,55];	1,89 [-6,18 ; 9,95]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Musculoskeletal and connective tissue disorders | Myalgia

6.2.26 Nervous system disorders - Paraesthesia

Tabelle 387: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	7	2.15	302	7	2.32	0,93 [0,33 ; 2,61]	0,92 [0,32 ; 2,67];	-0,17 [-2,48 ; 2,14]; 1	1	0,8262
	>= 38 years	219	4	1.83	246	4	1.63	1,12 [0,28 ; 4,44]	1,13 [0,28 ; 4,56];	0,2 [-2,18 ; 2,58]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	11	2.63	415	8	1.93	1,36 [0,55 ; 3,35]	1,37 [0,55 ; 3,45];	0,7 [-1,33 ; 2,72]; 0,644	0,644	0,0341
	>3.5	126	0	0.00	133	3	2.26	0,15 [0,01 ; 2,89]	0,15 [0,01 ; 2,88];	-2,22 [-5,13 ; 0,69]; 0,123	0,123	
Gender	Female	345	8	2.32	356	6	1.69	1,38 [0,48 ; 3,92]	1,38 [0,48 ; 4,03];	0,63 [-1,44 ; 2,71]; 0,599	0,599	0,3266
	Male	200	3	1.50	192	5	2.60	0,58 [0,14 ; 2,38]	0,57 [0,13 ; 2,42];	-1,1 [-3,92 ; 1,71]; 0,495	0,495	
Number of baseline Gd-enhancing lesions	>=1	258	7	2.71	251	4	1.59	1,7 [0,5 ; 5,74]	1,72 [0,5 ; 5,96];	1,12 [-1,4 ; 3,64]; 0,545	0,545	0,2151
	0	286	4	1.40	293	7	2.39	0,59 [0,17 ; 1,98]	0,58 [0,17 ; 2];	-0,99 [-3,21 ; 1,23]; 0,545	0,545	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	2	0.89	202	4	1.98	0,45 [0,08 ; 2,42]	0,44 [0,08 ; 2,45];	-1,09 [-3,37 ; 1,19]; 0,428	0,428	0,1319
	>=3	84	2	2.38	98	0	0.00	5,82 [0,28 ; 119,63]	5,97 [0,28 ; 126,11];	2,44 [-1,42 ; 6,29]; 0,212	0,212	
	2	236	7	2.97	248	7	2.82	1,05 [0,37 ; 2,95]	1,05 [0,36 ; 3,05];	0,14 [-2,85 ; 3,13]; 1	1	
Race	Other	10	1	10.00	12	1	8.33	1,2 [0,09 ; 16,84]	1,22 [0,07 ; 22,4];	1,67 [-22,63 ; 25,96]; 1	1	0,8981
	White	535	10	1.87	536	10	1.87	1 [0,42 ; 2,39]	1 [0,41 ; 2,43];	0 [-1,62 ; 1,62]; 1	1	
	No	347	10	2.88	379	8	2.11	1,37 [0,55 ; 3,42]	1,38 [0,54 ; 3,53];	0,77 [-1,51 ; 3,05]; 0,634	0,634	0,1752

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	1	0.51	169	3	1.78	0,28 [0,03 ; 2,71]	0,28 [0,03 ; 2,73];	-1,27 [-3,49 ; 0,95]; 0,338	0,338	
Region	Eastern Europe	492	5	1.02	495	6	1.21	0,84 [0,26 ; 2,73]	0,84 [0,25 ; 2,76];	-0,2 [-1,51 ; 1,11]; 1	1	0,665
	USA and Western Europe	53	6	11.32	53	5	9.43	1,2 [0,39 ; 3,69]	1,23 [0,35 ; 4,29];	1,89 [-9,72 ; 13,49]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Nervous system disorders | Paraesthesia

6.2.27 Gastrointestinal disorders - Nausea

Tabelle 388: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	35	10.74	302	26	8.61	1,25 [0,77 ; 2,02]	1,28 [0,75 ; 2,18];	2,13 [-2,49 ; 6,74]; 0,419	0,419	0,6201
	>= 38 years	219	23	10.50	246	17	6.91	1,52 [0,83 ; 2,77]	1,58 [0,82 ; 3,04];	3,59 [-1,56 ; 8,74]; 0,187	0,187	
Disease Severity at baseline (EDSS)	<=3.5	419	46	10.98	415	36	8.67	1,27 [0,84 ; 1,92]	1,3 [0,82 ; 2,05];	2,3 [-1,73 ; 6,34]; 0,296	0,296	0,4849
	>3.5	126	12	9.52	133	7	5.26	1,81 [0,74 ; 4,45]	1,89 [0,72 ; 4,98];	4,26 [-2,12 ; 10,64]; 0,236	0,236	
Gender	Female	345	49	14.20	356	34	9.55	1,49 [0,99 ; 2,24]	1,57 [0,98 ; 2,5];	4,65 [-0,13 ; 9,44]; 0,062	0,062	0,3607
	Male	200	9	4.50	192	9	4.69	0,96 [0,39 ; 2,37]	0,96 [0,37 ; 2,47];	-0,19 [-4,33 ; 3,96]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	258	30	11.63	251	23	9.16	1,27 [0,76 ; 2,12]	1,3 [0,74 ; 2,31];	2,46 [-2,83 ; 7,76]; 0,387	0,387	0,7634
	0	286	28	9.79	293	20	6.83	1,43 [0,83 ; 2,49]	1,48 [0,81 ; 2,7];	2,96 [-1,53 ; 7,46]; 0,228	0,228	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	25	11.11	202	15	7.43	1,5 [0,81 ; 2,76]	1,56 [0,8 ; 3,05];	3,69 [-1,79 ; 9,16]; 0,244	0,244	0,9188
	>=3	84	9	10.71	98	8	8.16	1,31 [0,53 ; 3,25]	1,35 [0,5 ; 3,67];	2,55 [-6 ; 11,1]; 0,615	0,615	
	2	236	24	10.17	248	20	8.06	1,26 [0,72 ; 2,22]	1,29 [0,69 ; 2,4];	2,1 [-3,03 ; 7,24]; 0,434	0,434	
Race	Other	10	3	30.00	12	2	16.67	1,8 [0,37 ; 8,74]	2,14 [0,28 ; 16,37];	13,33 [-22,04 ; 48,71]; 0,624	0,624	0,6775
	White	535	55	10.28	536	41	7.65	1,34 [0,91 ; 1,98]	1,38 [0,91 ; 2,11];	2,63 [-0,79 ; 6,05]; 0,136	0,136	
	No	347	36	10.37	379	29	7.65	1,36 [0,85 ; 2,16]	1,4 [0,84 ; 2,33];	2,72 [-1,46 ; 6,9]; 0,241	0,241	0,9831

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	22	11.11	169	14	8.28	1,34 [0,71 ; 2,54]	1,38 [0,68 ; 2,8];	2,83 [-3,21 ; 8,86]; 0,385	0,385	
Region	Eastern Europe	492	46	9.35	495	33	6.67	1,4 [0,91 ; 2,15]	1,44 [0,91 ; 2,3];	2,68 [-0,7 ; 6,07]; 0,128	0,128	0,7979
	USA and Western Europe	53	12	22.64	53	10	18.87	1,2 [0,57 ; 2,53]	1,26 [0,49 ; 3,23];	3,77 [-11,65 ; 19,2]; 0,811	0,811	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Gastrointestinal disorders | Nausea

6.2.28 Reproductive system and breast disorders - Dysmenorrhoea

Tabelle 389: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	16	4.91	302	18	5.96	0,82 [0,43 ; 1,59]	0,81 [0,41 ; 1,63];	-1,05 [-4,61 ; 2,5]; 0,6	0,6	0,4973
	>= 38 years	219	1	0.46	246	3	1.22	0,37 [0,04 ; 3,57]	0,37 [0,04 ; 3,6];	-0,76 [-2,4 ; 0,87]; 0,626	0,626	
Disease Severity at baseline (EDSS)	<=3.5	419	17	4.06	415	20	4.82	0,84 [0,45 ; 1,58]	0,84 [0,43 ; 1,62];	-0,76 [-3,56 ; 2,03]; 0,618	0,618	0,284
	>3.5	126	0	0.00	133	1	0.75	0,35 [0,01 ; 8,55]	0,35 [0,01 ; 8,65];	-0,73 [-2,81 ; 1,36]; 0,499	0,499	
Gender	Female	345	17	4.93	356	21	5.90	0,84 [0,45 ; 1,56]	0,83 [0,43 ; 1,6];	-0,97 [-4,32 ; 2,38]; 0,619	0,619	1
	Male	200	0	0.00	192	0	0.00	0,96 [0,02 ; 48,15]	0,96 [0,02 ; 48,63];	-0,01 [-1 ; 0,98]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	258	9	3.49	251	11	4.38	0,8 [0,34 ; 1,89]	0,79 [0,32 ; 1,94];	-0,89 [-4,27 ; 2,49]; 0,653	0,653	0,9614
	0	286	8	2.80	293	10	3.41	0,82 [0,33 ; 2,05]	0,81 [0,32 ; 2,09];	-0,62 [-3,44 ; 2,21]; 0,812	0,812	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	9	4.00	202	8	3.96	1,01 [0,4 ; 2,57]	1,01 [0,38 ; 2,67];	0,04 [-3,67 ; 3,75]; 1	1	0,3835
	>=3	84	2	2.38	98	7	7.14	0,33 [0,07 ; 1,56]	0,32 [0,06 ; 1,57];	-4,76 [-10,81 ; 1,29]; 0,181	0,181	
	2	236	6	2.54	248	6	2.42	1,05 [0,34 ; 3,21]	1,05 [0,33 ; 3,31];	0,12 [-2,65 ; 2,9]; 1	1	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	17	3.18	536	21	3.92	0,81 [0,43 ; 1,52]	0,8 [0,42 ; 1,54];	-0,74 [-2,96 ; 1,47]; 0,621	0,621	
	No	347	11	3.17	379	17	4.49	0,71 [0,34 ; 1,49]	0,7 [0,32 ; 1,51];	-1,32 [-4,1 ; 1,47]; 0,441	0,441	0,4168

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	6	3.03	169	4	2.37	1,28 [0,37 ; 4,46]	1,29 [0,36 ; 4,65];	0,66 [-2,65 ; 3,97]; 0,758	0,758	
Region	Eastern Europe	492	16	3.25	495	20	4.04	0,8 [0,42 ; 1,53]	0,8 [0,41 ; 1,56];	-0,79 [-3,13 ; 1,55]; 0,611	0,611	0,8782
	USA and Western Europe	53	1	1.89	53	1	1.89	1 [0,06 ; 15,57]	1 [0,06 ; 16,42];	0 [-5,18 ; 5,18]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Reproductive system and breast disorders | Dysmenorrhoea

6.2.29 Musculoskeletal and connective tissue disorders - Back pain

Tabelle 390: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	27	8.28	302	25	8.28	1 [0,59 ; 1,68]	1 [0,57 ; 1,77];	0 [-4,31 ; 4,32]; 1	1	0,9168
	>= 38 years	219	24	10.96	246	28	11.38	0,96 [0,58 ; 1,61]	0,96 [0,54 ; 1,71];	-0,42 [-6,16 ; 5,31]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	41	9.79	415	38	9.16	1,07 [0,7 ; 1,63]	1,08 [0,68 ; 1,71];	0,63 [-3,35 ; 4,6]; 0,813	0,813	0,3428
	>3.5	126	10	7.94	133	15	11.28	0,7 [0,33 ; 1,51]	0,68 [0,29 ; 1,57];	-3,34 [-10,5 ; 3,81]; 0,405	0,405	
Gender	Female	345	40	11.59	356	35	9.83	1,18 [0,77 ; 1,81]	1,2 [0,74 ; 1,94];	1,76 [-2,82 ; 6,34]; 0,466	0,466	0,0996
	Male	200	11	5.50	192	18	9.38	0,59 [0,28 ; 1,21]	0,56 [0,26 ; 1,22];	-3,88 [-9,07 ; 1,32]; 0,177	0,177	
Number of baseline Gd-enhancing lesions	>=1	258	32	12.40	251	28	11.16	1,11 [0,69 ; 1,79]	1,13 [0,66 ; 1,93];	1,25 [-4,35 ; 6,85]; 0,682	0,682	0,3503
	0	286	19	6.64	293	25	8.53	0,78 [0,44 ; 1,38]	0,76 [0,41 ; 1,42];	-1,89 [-6,2 ; 2,42]; 0,435	0,435	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	19	8.44	202	20	9.90	0,85 [0,47 ; 1,55]	0,84 [0,43 ; 1,62];	-1,46 [-6,95 ; 4,04]; 0,618	0,618	0,7387
	>=3	84	9	10.71	98	8	8.16	1,31 [0,53 ; 3,25]	1,35 [0,5 ; 3,67];	2,55 [-6 ; 11,1]; 0,615	0,615	
	2	236	23	9.75	248	25	10.08	0,97 [0,56 ; 1,65]	0,96 [0,53 ; 1,75];	-0,33 [-5,66 ; 4,99]; 1	1	
Race	Other	10	4	40.00	12	3	25.00	1,6 [0,46 ; 5,53]	2 [0,32 ; 12,33];	15 [-24,02 ; 54,02]; 0,652	0,652	0,4223
	White	535	47	8.79	536	50	9.33	0,94 [0,64 ; 1,38]	0,94 [0,62 ; 1,42];	-0,54 [-3,98 ; 2,89]; 0,831	0,831	
	No	347	33	9.51	379	43	11.35	0,84 [0,55 ; 1,29]	0,82 [0,51 ; 1,33];	-1,84 [-6,28 ; 2,61]; 0,467	0,467	0,1603

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	18	9.09	169	10	5.92	1,54 [0,73 ; 3,24]	1,59 [0,71 ; 3,55];	3,17 [-2,18 ; 8,53]; 0,325	0,325	
Region	Eastern Europe	492	40	8.13	495	43	8.69	0,94 [0,62 ; 1,41]	0,93 [0,59 ; 1,46];	-0,56 [-4,02 ; 2,91]; 0,819	0,819	0,7228
	USA and Western Europe	53	11	20.75	53	10	18.87	1,1 [0,51 ; 2,37]	1,13 [0,43 ; 2,93];	1,89 [-13,28 ; 17,06]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Musculoskeletal and connective tissue disorders | Back pain

6.2.30 Musculoskeletal and connective tissue disorders - Pain in extremity

Tabelle 391: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	20	6.13	302	8	2.65	2,32 [1,04 ; 5,18]	2,4 [1,04 ; 5,54];	3,49 [0,31 ; 6,66]; 0,051	0,051	0,0449
	>= 38 years	219	11	5.02	246	16	6.50	0,77 [0,37 ; 1,63]	0,76 [0,34 ; 1,68];	-1,48 [-5,71 ; 2,75]; 0,555	0,555	
Disease Severity at baseline (EDSS)	<=3.5	419	25	5.97	415	19	4.58	1,3 [0,73 ; 2,33]	1,32 [0,72 ; 2,44];	1,39 [-1,64 ; 4,42]; 0,439	0,439	0,9625
	>3.5	126	6	4.76	133	5	3.76	1,27 [0,4 ; 4,05]	1,28 [0,38 ; 4,3];	1 [-3,92 ; 5,93]; 0,764	0,764	
Gender	Female	345	22	6.38	356	20	5.62	1,14 [0,63 ; 2,04]	1,14 [0,61 ; 2,14];	0,76 [-2,76 ; 4,28]; 0,751	0,751	0,3271
	Male	200	9	4.50	192	4	2.08	2,16 [0,68 ; 6,9]	2,21 [0,67 ; 7,32];	2,42 [-1,1 ; 5,93]; 0,26	0,26	
Number of baseline Gd-enhancing lesions	>=1	258	18	6.98	251	6	2.39	2,92 [1,18 ; 7,23]	3,06 [1,2 ; 7,85];	4,59 [0,95 ; 8,22]; 0,02	0,02	0,0142
	0	286	13	4.55	293	18	6.14	0,74 [0,37 ; 1,48]	0,73 [0,35 ; 1,51];	-1,6 [-5,26 ; 2,06]; 0,462	0,462	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	14	6.22	202	9	4.46	1,4 [0,62 ; 3,16]	1,42 [0,6 ; 3,36];	1,77 [-2,48 ; 6,02]; 0,521	0,521	0,6619
	>=3	84	4	4.76	98	2	2.04	2,33 [0,44 ; 12,42]	2,4 [0,43 ; 13,44];	2,72 [-2,62 ; 8,07]; 0,417	0,417	
	2	236	13	5.51	248	13	5.24	1,05 [0,5 ; 2,22]	1,05 [0,48 ; 2,32];	0,27 [-3,75 ; 4,29]; 1	1	
Race	Other	10	4	40.00	12	0	0.00	10,64 [0,64 ; 176,54]	17,31 [0,8 ; 373,45];	37,06 [6,18 ; 67,94]; 0,029	0,029	0,0106
	White	535	27	5.05	536	24	4.48	1,13 [0,66 ; 1,93]	1,13 [0,65 ; 1,99];	0,57 [-1,98 ; 3,12]; 0,67	0,67	
	No	347	18	5.19	379	18	4.75	1,09 [0,58 ; 2,06]	1,1 [0,56 ; 2,14];	0,44 [-2,73 ; 3,6]; 0,865	0,865	0,3579

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	13	6.57	169	6	3.55	1,85 [0,72 ; 4,76]	1,91 [0,71 ; 5,14];	3,02 [-1,42 ; 7,45]; 0,241	0,241	
Region	Eastern Europe	492	19	3.86	495	19	3.84	1,01 [0,54 ; 1,88]	1,01 [0,53 ; 1,92];	0,02 [-2,38 ; 2,42]; 1	1	0,1122
	USA and Western Europe	53	12	22.64	53	5	9.43	2,4 [0,91 ; 6,34]	2,81 [0,91 ; 8,64];	13,21 [-0,54 ; 26,95]; 0,11	0,11	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Musculoskeletal and connective tissue disorders | Pain in extremity

6.2.31 Nervous system disorders - Headache

Tabelle 392: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	129	39.57	302	90	29.80	1,33 [1,07 ; 1,65]	1,54 [1,11 ; 2,15];	9,77 [2,37 ; 17,17]; 0,012	0,012	0,3962
	>= 38 years	219	58	26.48	246	56	22.76	1,16 [0,85 ; 1,6]	1,22 [0,8 ; 1,87];	3,72 [-4,13 ; 11,57]; 0,388	0,388	
Disease Severity at baseline (EDSS)	<=3.5	419	153	36.52	415	118	28.43	1,28 [1,05 ; 1,57]	1,45 [1,08 ; 1,94];	8,08 [1,75 ; 14,41]; 0,015	0,015	0,8942
	>3.5	126	34	26.98	133	28	21.05	1,28 [0,83 ; 1,98]	1,39 [0,78 ; 2,46];	5,93 [-4,46 ; 16,33]; 0,308	0,308	
Gender	Female	345	138	40.00	356	109	30.62	1,31 [1,07 ; 1,6]	1,51 [1,11 ; 2,06];	9,38 [2,34 ; 16,43]; 0,011	0,011	0,7189
	Male	200	49	24.50	192	37	19.27	1,27 [0,87 ; 1,86]	1,36 [0,84 ; 2,2];	5,23 [-2,94 ; 13,39]; 0,224	0,224	
Number of baseline Gd-enhancing lesions	>=1	258	90	34.88	251	74	29.48	1,18 [0,92 ; 1,53]	1,28 [0,88 ; 1,86];	5,4 [-2,7 ; 13,5]; 0,218	0,218	0,4358
	0	286	97	33.92	293	72	24.57	1,38 [1,07 ; 1,79]	1,58 [1,1 ; 2,26];	9,34 [1,97 ; 16,72]; 0,014	0,014	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	75	33.33	202	58	28.71	1,16 [0,87 ; 1,54]	1,24 [0,82 ; 1,87];	4,62 [-4,15 ; 13,39]; 0,346	0,346	0,4477
	>=3	84	29	34.52	98	20	20.41	1,69 [1,04 ; 2,76]	2,06 [1,06 ; 4];	14,12 [1,19 ; 27,04]; 0,044	0,044	
	2	236	83	35.17	248	68	27.42	1,28 [0,98 ; 1,67]	1,44 [0,98 ; 2,11];	7,75 [-0,49 ; 15,99]; 0,077	0,077	
Race	Other	10	5	50.00	12	2	16.67	3 [0,73 ; 12,27]	5 [0,7 ; 35,5];	33,33 [-4,15 ; 70,82]; 0,172	0,172	0,1905
	White	535	182	34.02	536	144	26.87	1,27 [1,05 ; 1,52]	1,4 [1,08 ; 1,82];	7,15 [1,66 ; 12,65]; 0,012	0,012	
	No	347	119	34.29	379	107	28.23	1,21 [0,98 ; 1,51]	1,33 [0,97 ; 1,82];	6,06 [-0,68 ; 12,81]; 0,092	0,092	0,3374

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	68	34.34	169	39	23.08	1,49 [1,06 ; 2,08]	1,74 [1,1 ; 2,77];	11,27 [2,1 ; 20,44]; 0,021	0,021	
Region	Eastern Europe	492	166	33.74	495	131	26.46	1,27 [1,05 ; 1,54]	1,41 [1,08 ; 1,86];	7,28 [1,57 ; 12,98]; 0,015	0,015	0,7119
	USA and Western Europe	53	21	39.62	53	15	28.30	1,4 [0,81 ; 2,41]	1,66 [0,74 ; 3,75];	11,32 [-6,58 ; 29,22]; 0,305	0,305	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Nervous system disorders | Headache

6.2.32 Musculoskeletal and connective tissue disorders - Neck pain

Tabelle 393: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	8	2.45	302	9	2.98	0,82 [0,32 ; 2,11]	0,82 [0,31 ; 2,15];	-0,53 [-3,08 ; 2,02]; 0,807	0,807	0,3666
	>= 38 years	219	6	2.74	246	4	1.63	1,68 [0,48 ; 5,89]	1,7 [0,47 ; 6,12];	1,11 [-1,56 ; 3,79]; 0,527	0,527	
Disease Severity at baseline (EDSS)	<=3.5	419	12	2.86	415	9	2.17	1,32 [0,56 ; 3,1]	1,33 [0,55 ; 3,19];	0,7 [-1,43 ; 2,82]; 0,66	0,66	0,3276
	>3.5	126	2	1.59	133	4	3.01	0,53 [0,1 ; 2,83]	0,52 [0,09 ; 2,89];	-1,42 [-5,05 ; 2,21]; 0,685	0,685	
Gender	Female	345	12	3.48	356	9	2.53	1,38 [0,59 ; 3,22]	1,39 [0,58 ; 3,34];	0,95 [-1,58 ; 3,48]; 0,512	0,512	0,2606
	Male	200	2	1.00	192	4	2.08	0,48 [0,09 ; 2,59]	0,47 [0,09 ; 2,62];	-1,08 [-3,53 ; 1,36]; 0,441	0,441	
Number of baseline Gd-enhancing lesions	>=1	258	10	3.88	251	5	1.99	1,95 [0,67 ; 5,61]	1,98 [0,67 ; 5,89];	1,88 [-1,04 ; 4,81]; 0,295	0,295	0,0904
	0	286	4	1.40	293	8	2.73	0,51 [0,16 ; 1,68]	0,51 [0,15 ; 1,7];	-1,33 [-3,64 ; 0,98]; 0,383	0,383	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	4	1.78	202	6	2.97	0,6 [0,17 ; 2,09]	0,59 [0,16 ; 2,13];	-1,19 [-4,1 ; 1,72]; 0,527	0,527	0,4675
	>=3	84	2	2.38	98	2	2.04	1,17 [0,17 ; 8,1]	1,17 [0,16 ; 8,5];	0,34 [-3,96 ; 4,64]; 1	1	
	2	236	8	3.39	248	5	2.02	1,68 [0,56 ; 5,07]	1,71 [0,55 ; 5,29];	1,37 [-1,52 ; 4,27]; 0,408	0,408	
Race	Other	10	0	0.00	12	3	25.00	0,17 [0,01 ; 2,93]	0,13 [0,01 ; 2,84];	-22,38 [-49,45 ; 4,69]; 0,114	0,114	0,0309
	White	535	14	2.62	536	10	1.87	1,4 [0,63 ; 3,13]	1,41 [0,62 ; 3,21];	0,75 [-1,02 ; 2,52]; 0,419	0,419	
	No	347	10	2.88	379	7	1.85	1,56 [0,6 ; 4,05]	1,58 [0,59 ; 4,19];	1,03 [-1,19 ; 3,26]; 0,463	0,463	0,2033

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	4	2.02	169	6	3.55	0,57 [0,16 ; 1,98]	0,56 [0,16 ; 2,02];	-1,53 [-4,94 ; 1,88]; 0,523	0,523	
Region	Eastern Europe	492	12	2.44	495	7	1.41	1,72 [0,68 ; 4,34]	1,74 [0,68 ; 4,46];	1,02 [-0,69 ; 2,74]; 0,257	0,257	0,0577
	USA and Western Europe	53	2	3.77	53	6	11.32	0,33 [0,07 ; 1,58]	0,31 [0,06 ; 1,6];	-7,55 [-17,5 ; 2,41]; 0,27	0,27	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Musculoskeletal and connective tissue disorders | Neck pain

6.2.33 Cardiac disorders - Tachycardia

Tabelle 394: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	14	4.29	302	9	2.98	1,44 [0,63 ; 3,28]	1,46 [0,62 ; 3,43];	1,31 [-1,6 ; 4,23]; 0,404	0,404	0,5562
	>= 38 years	219	6	2.74	246	7	2.85	0,96 [0,33 ; 2,82]	0,96 [0,32 ; 2,91];	-0,11 [-3,1 ; 2,89]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	16	3.82	415	12	2.89	1,32 [0,63 ; 2,76]	1,33 [0,62 ; 2,85];	0,93 [-1,52 ; 3,37]; 0,565	0,565	0,7765
	>3.5	126	4	3.17	133	4	3.01	1,06 [0,27 ; 4,13]	1,06 [0,26 ; 4,32];	0,17 [-4,05 ; 4,39]; 1	1	
Gender	Female	345	9	2.61	356	12	3.37	0,77 [0,33 ; 1,81]	0,77 [0,32 ; 1,85];	-0,76 [-3,28 ; 1,76]; 0,66	0,66	0,0773
	Male	200	11	5.50	192	4	2.08	2,64 [0,86 ; 8,15]	2,74 [0,86 ; 8,74];	3,42 [-0,33 ; 7,17]; 0,113	0,113	
Number of baseline Gd-enhancing lesions	>=1	258	16	6.20	251	5	1.99	3,11 [1,16 ; 8,37]	3,25 [1,17 ; 9,02];	4,21 [0,8 ; 7,62]; 0,024	0,024	0,0029
	0	286	4	1.40	293	11	3.75	0,37 [0,12 ; 1,16]	0,36 [0,11 ; 1,16];	-2,36 [-4,92 ; 0,21]; 0,114	0,114	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	11	4.89	202	4	1.98	2,47 [0,8 ; 7,63]	2,54 [0,8 ; 8,12];	2,91 [-0,5 ; 6,32]; 0,12	0,12	0,2517
	>=3	84	2	2.38	98	4	4.08	0,58 [0,11 ; 3,11]	0,57 [0,1 ; 3,21];	-1,7 [-6,8 ; 3,4]; 0,688	0,688	
	2	236	7	2.97	248	8	3.23	0,92 [0,34 ; 2,5]	0,92 [0,33 ; 2,57];	-0,26 [-3,35 ; 2,83]; 1	1	
Race	Other	10	1	10.00	12	0	0.00	3,55 [0,16 ; 78,56]	3,95 [0,14 ; 108,09];	9,79 [-13,03 ; 32,61]; 0,478	0,478	0,2339
	White	535	19	3.55	536	16	2.99	1,19 [0,62 ; 2,29]	1,2 [0,61 ; 2,35];	0,57 [-1,56 ; 2,7]; 0,612	0,612	
	No	347	9	2.59	379	13	3.43	0,76 [0,33 ; 1,75]	0,75 [0,32 ; 1,78];	-0,84 [-3,32 ; 1,64]; 0,666	0,666	0,0507

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	11	5.56	169	3	1.78	3,13 [0,89 ; 11,03]	3,25 [0,89 ; 11,87];	3,78 [0,02 ; 7,54]; 0,098	0,098	
Region	Eastern Europe	492	16	3.25	495	14	2.83	1,15 [0,57 ; 2,33]	1,15 [0,56 ; 2,39];	0,42 [-1,72 ; 2,57]; 0,715	0,715	0,5337
	USA and Western Europe	53	4	7.55	53	2	3.77	2 [0,38 ; 10,46]	2,08 [0,36 ; 11,88];	3,77 [-5 ; 12,54]; 0,678	0,678	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Cardiac disorders | Tachycardia

6.2.34 Gastrointestinal disorders - Dyspepsia

Tabelle 395: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	17	5.21	302	10	3.31	1,57 [0,73 ; 3,39]	1,61 [0,72 ; 3,57];	1,9 [-1,24 ; 5,05]; 0,325	0,325	0,1778
	>= 38 years	219	6	2.74	246	10	4.07	0,67 [0,25 ; 1,82]	0,66 [0,24 ; 1,86];	-1,33 [-4,61 ; 1,96]; 0,459	0,459	
Disease Severity at baseline (EDSS)	<=3.5	419	19	4.53	415	17	4.10	1,11 [0,58 ; 2,1]	1,11 [0,57 ; 2,17];	0,44 [-2,32 ; 3,2]; 0,865	0,865	0,7714
	>3.5	126	4	3.17	133	3	2.26	1,41 [0,32 ; 6,16]	1,42 [0,31 ; 6,48];	0,92 [-3,05 ; 4,89]; 0,716	0,716	
Gender	Female	345	9	2.61	356	12	3.37	0,77 [0,33 ; 1,81]	0,77 [0,32 ; 1,85];	-0,76 [-3,28 ; 1,76]; 0,66	0,66	0,1984
	Male	200	14	7.00	192	8	4.17	1,68 [0,72 ; 3,91]	1,73 [0,71 ; 4,23];	2,83 [-1,69 ; 7,36]; 0,275	0,275	
Number of baseline Gd-enhancing lesions	>=1	258	16	6.20	251	8	3.19	1,95 [0,85 ; 4,47]	2,01 [0,84 ; 4,78];	3,01 [-0,64 ; 6,67]; 0,143	0,143	0,0553
	0	286	7	2.45	293	12	4.10	0,6 [0,24 ; 1,5]	0,59 [0,23 ; 1,51];	-1,65 [-4,54 ; 1,24]; 0,352	0,352	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	12	5.33	202	7	3.47	1,54 [0,62 ; 3,83]	1,57 [0,61 ; 4,07];	1,87 [-2 ; 5,74]; 0,482	0,482	0,478
	>=3	84	5	5.95	98	4	4.08	1,46 [0,4 ; 5,26]	1,49 [0,39 ; 5,73];	1,87 [-4,53 ; 8,27]; 0,735	0,735	
	2	236	6	2.54	248	9	3.63	0,7 [0,25 ; 1,94]	0,69 [0,24 ; 1,98];	-1,09 [-4,16 ; 1,99]; 0,603	0,603	
Race	Other	10	1	10.00	12	0	0.00	3,55 [0,16 ; 78,56]	3,95 [0,14 ; 108,09];	9,79 [-13,03 ; 32,61]; 0,478	0,478	0,2207
	White	535	22	4.11	536	20	3.73	1,1 [0,61 ; 2]	1,11 [0,6 ; 2,05];	0,38 [-1,94 ; 2,71]; 0,756	0,756	
	No	347	10	2.88	379	12	3.17	0,91 [0,4 ; 2,08]	0,91 [0,39 ; 2,13];	-0,28 [-2,78 ; 2,21]; 1	1	0,4823

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	13	6.57	169	8	4.73	1,39 [0,59 ; 3,27]	1,41 [0,57 ; 3,5];	1,83 [-2,87 ; 6,54]; 0,505	0,505	
Region	Eastern Europe	492	21	4.27	495	18	3.64	1,17 [0,63 ; 2,18]	1,18 [0,62 ; 2,25];	0,63 [-1,8 ; 3,06]; 0,628	0,628	0,8763
	USA and Western Europe	53	2	3.77	53	2	3.77	1 [0,15 ; 6,84]	1 [0,14 ; 7,37];	0 [-7,26 ; 7,26]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Gastrointestinal disorders | Dyspepsia

6.2.35 Infections and infestations - Nasopharyngitis

Tabelle 396: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	71	21.78	302	62	20.53	1,06 [0,78 ; 1,44]	1,08 [0,73 ; 1,58];	1,25 [-5,14 ; 7,64]; 0,769	0,769	0,5652
	>= 38 years	219	29	13.24	246	36	14.63	0,9 [0,57 ; 1,42]	0,89 [0,53 ; 1,51];	-1,39 [-7,69 ; 4,91]; 0,69	0,69	
Disease Severity at baseline (EDSS)	<=3.5	419	85	20.29	415	77	18.55	1,09 [0,83 ; 1,44]	1,12 [0,79 ; 1,57];	1,73 [-3,64 ; 7,1]; 0,541	0,541	0,2753
	>3.5	126	15	11.90	133	21	15.79	0,75 [0,41 ; 1,4]	0,72 [0,35 ; 1,47];	-3,88 [-12,27 ; 4,5]; 0,377	0,377	
Gender	Female	345	74	21.45	356	65	18.26	1,17 [0,87 ; 1,58]	1,22 [0,84 ; 1,77];	3,19 [-2,71 ; 9,1]; 0,299	0,299	0,1204
	Male	200	26	13.00	192	33	17.19	0,76 [0,47 ; 1,22]	0,72 [0,41 ; 1,26];	-4,19 [-11,27 ; 2,9]; 0,261	0,261	
Number of baseline Gd-enhancing lesions	>=1	258	53	20.54	251	54	21.51	0,95 [0,68 ; 1,34]	0,94 [0,62 ; 1,44];	-0,97 [-8,05 ; 6,11]; 0,828	0,828	0,6
	0	286	47	16.43	293	44	15.02	1,09 [0,75 ; 1,6]	1,11 [0,71 ; 1,74];	1,42 [-4,51 ; 7,35]; 0,65	0,65	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	44	19.56	202	42	20.79	0,94 [0,64 ; 1,37]	0,93 [0,58 ; 1,49];	-1,24 [-8,86 ; 6,39]; 0,809	0,809	0,4103
	>=3	84	14	16.67	98	10	10.20	1,63 [0,77 ; 3,48]	1,76 [0,74 ; 4,2];	6,46 [-3,51 ; 16,43]; 0,272	0,272	
	2	236	42	17.80	248	46	18.55	0,96 [0,66 ; 1,4]	0,95 [0,6 ; 1,51];	-0,75 [-7,62 ; 6,12]; 0,906	0,906	
Race	Other	10	1	10.00	12	6	50.00	0,2 [0,03 ; 1,4]	0,11 [0,01 ; 1,17];	-40 [-73,85 ; -6,15]; 0,074	0,074	0,0308
	White	535	99	18.50	536	92	17.16	1,08 [0,83 ; 1,39]	1,1 [0,8 ; 1,5];	1,34 [-3,24 ; 5,93]; 0,577	0,577	
	No	347	67	19.31	379	71	18.73	1,03 [0,76 ; 1,39]	1,04 [0,72 ; 1,5];	0,57 [-5,14 ; 6,29]; 0,85	0,85	0,969

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	33	16.67	169	27	15.98	1,04 [0,66 ; 1,66]	1,05 [0,6 ; 1,83];	0,69 [-6,89 ; 8,27]; 0,888	0,888	
Region	Eastern Europe	492	84	17.07	495	83	16.77	1,02 [0,77 ; 1,34]	1,02 [0,73 ; 1,43];	0,31 [-4,37 ; 4,98]; 0,932	0,932	0,8799
	USA and Western Europe	53	16	30.19	53	15	28.30	1,07 [0,59 ; 1,93]	1,1 [0,47 ; 2,53];	1,89 [-15,43 ; 19,2]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Nasopharyngitis

6.2.36 Infections and infestations - Urinary tract infection

Tabelle 397: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	10	3.07	302	10	3.31	0,93 [0,39 ; 2,19]	0,92 [0,38 ; 2,25];	-0,24 [-3 ; 2,51]; 1	1	0,6265
	>= 38 years	219	12	5.48	246	19	7.72	0,71 [0,35 ; 1,43]	0,69 [0,33 ; 1,46];	-2,24 [-6,74 ; 2,25]; 0,358	0,358	
Disease Severity at baseline (EDSS)	<=3.5	419	15	3.58	415	16	3.86	0,93 [0,47 ; 1,85]	0,93 [0,45 ; 1,9];	-0,28 [-2,84 ; 2,29]; 0,857	0,857	0,3771
	>3.5	126	7	5.56	133	13	9.77	0,57 [0,23 ; 1,38]	0,54 [0,21 ; 1,41];	-4,22 [-10,66 ; 2,22]; 0,248	0,248	
Gender	Female	345	20	5.80	356	24	6.74	0,86 [0,48 ; 1,53]	0,85 [0,46 ; 1,57];	-0,94 [-4,53 ; 2,64]; 0,643	0,643	0,349
	Male	200	2	1.00	192	5	2.60	0,38 [0,08 ; 1,96]	0,38 [0,07 ; 1,97];	-1,6 [-4,25 ; 1,04]; 0,276	0,276	
Number of baseline Gd-enhancing lesions	>=1	258	8	3.10	251	10	3.98	0,78 [0,31 ; 1,94]	0,77 [0,3 ; 1,99];	-0,88 [-4,1 ; 2,33]; 0,638	0,638	0,9495
	0	286	14	4.90	293	19	6.48	0,75 [0,39 ; 1,48]	0,74 [0,36 ; 1,51];	-1,59 [-5,36 ; 2,18]; 0,475	0,475	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	10	4.44	202	14	6.93	0,64 [0,29 ; 1,41]	0,62 [0,27 ; 1,44];	-2,49 [-6,9 ; 1,93]; 0,298	0,298	0,8617
	>=3	84	2	2.38	98	3	3.06	0,78 [0,13 ; 4,54]	0,77 [0,13 ; 4,74];	-0,68 [-5,4 ; 4,04]; 1	1	
	2	236	10	4.24	248	12	4.84	0,88 [0,39 ; 1,99]	0,87 [0,37 ; 2,05];	-0,6 [-4,31 ; 3,1]; 0,829	0,829	
Race	Other	10	1	10.00	12	1	8.33	1,2 [0,09 ; 16,84]	1,22 [0,07 ; 22,4];	1,67 [-22,63 ; 25,96]; 1	1	0,7418
	White	535	21	3.93	536	28	5.22	0,75 [0,43 ; 1,31]	0,74 [0,42 ; 1,32];	-1,3 [-3,8 ; 1,2]; 0,38	0,38	
	No	347	14	4.03	379	18	4.75	0,85 [0,43 ; 1,68]	0,84 [0,41 ; 1,72];	-0,71 [-3,69 ; 2,26]; 0,719	0,719	0,5792

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	8	4.04	169	11	6.51	0,62 [0,26 ; 1,51]	0,6 [0,24 ; 1,54];	-2,47 [-7,09 ; 2,15]; 0,347	0,347	
Region	Eastern Europe	492	15	3.05	495	21	4.24	0,72 [0,37 ; 1,38]	0,71 [0,36 ; 1,39];	-1,19 [-3,53 ; 1,14]; 0,396	0,396	0,7754
	USA and Western Europe	53	7	13.21	53	8	15.09	0,88 [0,34 ; 2,24]	0,86 [0,29 ; 2,56];	-1,89 [-15,15 ; 11,38]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Urinary tract infection

6.2.37 Investigations - Lipase increased

Tabelle 398: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	7	2.15	302	8	2.65	0,81 [0,3 ; 2,21]	0,81 [0,29 ; 2,25];	-0,5 [-2,9 ; 1,9]; 0,796	0,796	0,9235
	>= 38 years	219	4	1.83	246	6	2.44	0,75 [0,21 ; 2,62]	0,74 [0,21 ; 2,67];	-0,61 [-3,23 ; 2,01]; 0,755	0,755	
Disease Severity at baseline (EDSS)	<=3.5	419	8	1.91	415	12	2.89	0,66 [0,27 ; 1,6]	0,65 [0,26 ; 1,62];	-0,98 [-3,06 ; 1,1]; 0,376	0,376	0,3805
	>3.5	126	3	2.38	133	2	1.50	1,58 [0,27 ; 9,32]	1,6 [0,26 ; 9,72];	0,88 [-2,49 ; 4,25]; 0,677	0,677	
Gender	Female	345	5	1.45	356	7	1.97	0,74 [0,24 ; 2,3]	0,73 [0,23 ; 2,33];	-0,52 [-2,43 ; 1,4]; 0,773	0,773	0,8942
	Male	200	6	3.00	192	7	3.65	0,82 [0,28 ; 2,4]	0,82 [0,27 ; 2,48];	-0,65 [-4,2 ; 2,91]; 0,783	0,783	
Number of baseline Gd-enhancing lesions	>=1	258	6	2.33	251	2	0.80	2,92 [0,59 ; 14,32]	2,96 [0,59 ; 14,83];	1,53 [-0,61 ; 3,67]; 0,286	0,286	0,0329
	0	286	5	1.75	293	12	4.10	0,43 [0,15 ; 1,2]	0,42 [0,14 ; 1,2];	-2,35 [-5,08 ; 0,38]; 0,138	0,138	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	3	1.33	202	6	2.97	0,45 [0,11 ; 1,77]	0,44 [0,11 ; 1,79];	-1,64 [-4,42 ; 1,14]; 0,318	0,318	0,5223
	>=3	84	2	2.38	98	3	3.06	0,78 [0,13 ; 4,54]	0,77 [0,13 ; 4,74];	-0,68 [-5,4 ; 4,04]; 1	1	
	2	236	6	2.54	248	5	2.02	1,26 [0,39 ; 4,08]	1,27 [0,38 ; 4,21];	0,53 [-2,14 ; 3,19]; 0,767	0,767	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	11	2.06	536	14	2.61	0,79 [0,36 ; 1,72]	0,78 [0,35 ; 1,74];	-0,56 [-2,36 ; 1,25]; 0,687	0,687	
	No	347	6	1.73	379	9	2.37	0,73 [0,26 ; 2,02]	0,72 [0,25 ; 2,05];	-0,65 [-2,7 ; 1,41]; 0,609	0,609	0,8467

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	5	2.53	169	5	2.96	0,85 [0,25 ; 2,9]	0,85 [0,24 ; 2,99];	-0,43 [-3,8 ; 2,93]; 1	1	
Region	Eastern Europe	492	9	1.83	495	14	2.83	0,65 [0,28 ; 1,48]	0,64 [0,27 ; 1,49];	-1 [-2,88 ; 0,88]; 0,399	0,399	0,0596
	USA and Western Europe	53	2	3.77	53	0	0.00	5 [0,25 ; 101,73]	5,19 [0,24 ; 110,82];	3,7 [-2,46 ; 9,86]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Investigations | Lipase increased

6.2.38 Psychiatric disorders - Anxiety

Tabelle 399: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	19	5.83	302	11	3.64	1,6 [0,77 ; 3,31]	1,64 [0,77 ; 3,5];	2,19 [-1,12 ; 5,49]; 0,261	0,261	0,0469
	>= 38 years	219	5	2.28	246	12	4.88	0,47 [0,17 ; 1,31]	0,46 [0,16 ; 1,31];	-2,59 [-5,94 ; 0,75]; 0,215	0,215	
Disease Severity at baseline (EDSS)	<=3.5	419	22	5.25	415	16	3.86	1,36 [0,73 ; 2,56]	1,38 [0,72 ; 2,67];	1,4 [-1,43 ; 4,22]; 0,407	0,407	0,055
	>3.5	126	2	1.59	133	7	5.26	0,3 [0,06 ; 1,42]	0,29 [0,06 ; 1,42];	-3,68 [-8,05 ; 0,7]; 0,173	0,173	
Gender	Female	345	18	5.22	356	20	5.62	0,93 [0,5 ; 1,73]	0,92 [0,48 ; 1,78];	-0,4 [-3,75 ; 2,95]; 0,868	0,868	0,3344
	Male	200	6	3.00	192	3	1.56	1,92 [0,49 ; 7,57]	1,95 [0,48 ; 7,9];	1,44 [-1,51 ; 4,38]; 0,504	0,504	
Number of baseline Gd-enhancing lesions	>=1	258	18	6.98	251	11	4.38	1,59 [0,77 ; 3,3]	1,64 [0,76 ; 3,54];	2,59 [-1,42 ; 6,6]; 0,252	0,252	0,0595
	0	286	6	2.10	293	12	4.10	0,51 [0,19 ; 1,35]	0,5 [0,19 ; 1,36];	-2 [-4,81 ; 0,81]; 0,231	0,231	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	15	6.67	202	8	3.96	1,68 [0,73 ; 3,89]	1,73 [0,72 ; 4,18];	2,71 [-1,52 ; 6,93]; 0,284	0,284	0,0808
	>=3	84	5	5.95	98	4	4.08	1,46 [0,4 ; 5,26]	1,49 [0,39 ; 5,73];	1,87 [-4,53 ; 8,27]; 0,735	0,735	
	2	236	4	1.69	248	11	4.44	0,38 [0,12 ; 1,18]	0,37 [0,12 ; 1,18];	-2,74 [-5,79 ; 0,31]; 0,114	0,114	
Race	Other	10	1	10.00	12	0	0.00	3,55 [0,16 ; 78,56]	3,95 [0,14 ; 108,09];	9,79 [-13,03 ; 32,61]; 0,478	0,478	0,2051
	White	535	23	4.30	536	23	4.29	1 [0,57 ; 1,76]	1 [0,55 ; 1,81];	0,01 [-2,42 ; 2,44]; 1	1	
	No	347	11	3.17	379	15	3.96	0,8 [0,37 ; 1,72]	0,79 [0,36 ; 1,75];	-0,79 [-3,48 ; 1,9]; 0,69	0,69	0,3438

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	13	6.57	169	8	4.73	1,39 [0,59 ; 3,27]	1,41 [0,57 ; 3,5];	1,83 [-2,87 ; 6,54]; 0,505	0,505	
Region	Eastern Europe	492	19	3.86	495	20	4.04	0,96 [0,52 ; 1,77]	0,95 [0,5 ; 1,81];	-0,18 [-2,61 ; 2,25]; 1	1	0,4628
	USA and Western Europe	53	5	9.43	53	3	5.66	1,67 [0,42 ; 6,62]	1,74 [0,39 ; 7,67];	3,77 [-6,26 ; 13,81]; 0,716	0,716	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Psychiatric disorders | Anxiety

6.2.39 Skin and subcutaneous tissue disorders - Alopecia

Tabelle 400: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	15	4.60	302	49	16.23	0,28 [0,16 ; 0,49]	0,25 [0,14 ; 0,45];	-11,62 [-16,36 ; -6,88]; 0	0	0,1765
	>= 38 years	219	4	1.83	246	35	14.23	0,13 [0,05 ; 0,36]	0,11 [0,04 ; 0,32];	-12,4 [-17,11 ; -7,69]; 0	0	
Disease Severity at baseline (EDSS)	<=3.5	419	14	3.34	415	73	17.59	0,19 [0,11 ; 0,33]	0,16 [0,09 ; 0,29];	-14,25 [-18,3 ; -10,2]; 0	0	0,1128
	>3.5	126	5	3.97	133	11	8.27	0,48 [0,17 ; 1,34]	0,46 [0,15 ; 1,36];	-4,3 [-10,09 ; 1,49]; 0,198	0,198	
Gender	Female	345	14	4.06	356	72	20.22	0,2 [0,12 ; 0,35]	0,17 [0,09 ; 0,3];	-16,17 [-20,83 ; -11,5]; 0	0	0,1932
	Male	200	5	2.50	192	12	6.25	0,4 [0,14 ; 1,11]	0,38 [0,13 ; 1,11];	-3,75 [-7,8 ; 0,3]; 0,084	0,084	
Number of baseline Gd-enhancing lesions	>=1	258	9	3.49	251	38	15.14	0,23 [0,11 ; 0,47]	0,2 [0,1 ; 0,43];	-11,65 [-16,62 ; -6,68]; 0	0	0,9779
	0	286	10	3.50	293	45	15.36	0,23 [0,12 ; 0,44]	0,2 [0,1 ; 0,4];	-11,86 [-16,51 ; -7,22]; 0	0	
	NA	1	0	0.00	4	1	25.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	8	3.56	202	27	13.37	0,27 [0,12 ; 0,57]	0,24 [0,11 ; 0,54];	-9,81 [-15,09 ; -4,53]; 0	0	0,6212
	>=3	84	2	2.38	98	18	18.37	0,13 [0,03 ; 0,54]	0,11 [0,02 ; 0,48];	-15,99 [-24,32 ; -7,66]; 0,001	0,001	
	2	236	9	3.81	248	39	15.73	0,24 [0,12 ; 0,49]	0,21 [0,1 ; 0,45];	-11,91 [-17,06 ; -6,76]; 0	0	
Race	Other	10	0	0.00	12	1	8.33	0,39 [0,02 ; 8,73]	0,37 [0,01 ; 9,98];	-6,99 [-28,28 ; 14,29]; 0,493	0,493	0,5659
	White	535	19	3.55	536	83	15.49	0,23 [0,14 ; 0,37]	0,2 [0,12 ; 0,34];	-11,93 [-15,37 ; -8,49]; 0	0	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	No	347	11	3.17	379	58	15.30	0,21 [0,11 ; 0,39]	0,18 [0,09 ; 0,35];	-12,13 [-16,2 ; -8,07]; 0	0	0,6498
	Yes	198	8	4.04	169	26	15.38	0,26 [0,12 ; 0,56]	0,23 [0,1 ; 0,53];	-11,34 [-17,44 ; -5,25]; 0	0	
Region	Eastern Europe	492	19	3.86	495	75	15.15	0,25 [0,16 ; 0,42]	0,22 [0,13 ; 0,38];	-11,29 [-14,88 ; -7,7]; 0	0	0,0467
	USA and Western Europe	53	0	0.00	53	9	16.98	0,05 [0 ; 0,88]	0,04 [0 ; 0,77];	-16,67 [-27,14 ; -6,19]; 0,001	0,001	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Skin and subcutaneous tissue disorders | Alopecia

6.2.40 Infections and infestations - Sinusitis

Tabelle 401: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	15	4.60	302	14	4.64	0,99 [0,49 ; 2,02]	0,99 [0,47 ; 2,09];	-0,03 [-3,32 ; 3,25]; 1	1	0,5344
	>= 38 years	219	6	2.74	246	10	4.07	0,67 [0,25 ; 1,82]	0,66 [0,24 ; 1,86];	-1,33 [-4,61 ; 1,96]; 0,459	0,459	
Disease Severity at baseline (EDSS)	<=3.5	419	17	4.06	415	21	5.06	0,8 [0,43 ; 1,5]	0,79 [0,41 ; 1,53];	-1 [-3,83 ; 1,83]; 0,511	0,511	0,487
	>3.5	126	4	3.17	133	3	2.26	1,41 [0,32 ; 6,16]	1,42 [0,31 ; 6,48];	0,92 [-3,05 ; 4,89]; 0,716	0,716	
Gender	Female	345	16	4.64	356	13	3.65	1,27 [0,62 ; 2,6]	1,28 [0,61 ; 2,71];	0,99 [-1,97 ; 3,94]; 0,572	0,572	0,0884
	Male	200	5	2.50	192	11	5.73	0,44 [0,15 ; 1,23]	0,42 [0,14 ; 1,24];	-3,23 [-7,16 ; 0,71]; 0,129	0,129	
Number of baseline Gd-enhancing lesions	>=1	258	9	3.49	251	8	3.19	1,09 [0,43 ; 2,79]	1,1 [0,42 ; 2,89];	0,3 [-2,82 ; 3,42]; 1	1	0,5563
	0	286	12	4.20	293	16	5.46	0,77 [0,37 ; 1,6]	0,76 [0,35 ; 1,63];	-1,26 [-4,75 ; 2,22]; 0,563	0,563	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	11	4.89	202	6	2.97	1,65 [0,62 ; 4,37]	1,68 [0,61 ; 4,63];	1,92 [-1,74 ; 5,58]; 0,335	0,335	0,2517
	>=3	84	3	3.57	98	7	7.14	0,5 [0,13 ; 1,87]	0,48 [0,12 ; 1,92];	-3,57 [-10,03 ; 2,89]; 0,345	0,345	
	2	236	7	2.97	248	11	4.44	0,67 [0,26 ; 1,7]	0,66 [0,25 ; 1,73];	-1,47 [-4,82 ; 1,88]; 0,475	0,475	
Race	Other	10	1	10.00	12	0	0.00	3,55 [0,16 ; 78,56]	3,95 [0,14 ; 108,09];	9,79 [-13,03 ; 32,61]; 0,478	0,478	0,1779
	White	535	20	3.74	536	24	4.48	0,83 [0,47 ; 1,49]	0,83 [0,45 ; 1,52];	-0,74 [-3,12 ; 1,64]; 0,645	0,645	
	No	347	14	4.03	379	18	4.75	0,85 [0,43 ; 1,68]	0,84 [0,41 ; 1,72];	-0,71 [-3,69 ; 2,26]; 0,719	0,719	0,8049

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	7	3.54	169	6	3.55	1 [0,34 ; 2,91]	1 [0,33 ; 3,02];	-0,01 [-3,81 ; 3,78]; 1	1	
Region	Eastern Europe	492	16	3.25	495	20	4.04	0,8 [0,42 ; 1,53]	0,8 [0,41 ; 1,56];	-0,79 [-3,13 ; 1,55]; 0,611	0,611	0,5462
	USA and Western Europe	53	5	9.43	53	4	7.55	1,25 [0,36 ; 4,4]	1,28 [0,32 ; 5,04];	1,89 [-8,72 ; 12,49]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Sinusitis

6.2.41 Infections and infestations - Upper respiratory tract infection

Tabelle 402: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	24	7.36	302	21	6.95	1,06 [0,6 ; 1,86]	1,06 [0,58 ; 1,95];	0,41 [-3,62 ; 4,44]; 0,878	0,878	0,8922
	>= 38 years	219	17	7.76	246	17	6.91	1,12 [0,59 ; 2,15]	1,13 [0,56 ; 2,28];	0,85 [-3,9 ; 5,61]; 0,726	0,726	
Disease Severity at baseline (EDSS)	<=3.5	419	33	7.88	415	30	7.23	1,09 [0,68 ; 1,75]	1,1 [0,66 ; 1,83];	0,65 [-2,94 ; 4,23]; 0,794	0,794	0,9517
	>3.5	126	8	6.35	133	8	6.02	1,06 [0,41 ; 2,73]	1,06 [0,39 ; 2,91];	0,33 [-5,54 ; 6,2]; 1	1	
Gender	Female	345	29	8.41	356	25	7.02	1,2 [0,72 ; 2]	1,22 [0,7 ; 2,12];	1,38 [-2,57 ; 5,34]; 0,571	0,571	0,5184
	Male	200	12	6.00	192	13	6.77	0,89 [0,41 ; 1,89]	0,88 [0,39 ; 1,98];	-0,77 [-5,61 ; 4,07]; 0,837	0,837	
Number of baseline Gd-enhancing lesions	>=1	258	16	6.20	251	14	5.58	1,11 [0,55 ; 2,23]	1,12 [0,53 ; 2,34];	0,62 [-3,47 ; 4,71]; 0,852	0,852	0,931
	0	286	25	8.74	293	24	8.19	1,07 [0,62 ; 1,82]	1,07 [0,6 ; 1,93];	0,55 [-3,99 ; 5,09]; 0,882	0,882	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	18	8.00	202	14	6.93	1,15 [0,59 ; 2,26]	1,17 [0,57 ; 2,41];	1,07 [-3,91 ; 6,05]; 0,716	0,716	0,9678
	>=3	84	6	7.14	98	7	7.14	1 [0,35 ; 2,86]	1 [0,32 ; 3,1];	0 [-7,51 ; 7,51]; 1	1	
	2	236	17	7.20	248	17	6.85	1,05 [0,55 ; 2,01]	1,05 [0,53 ; 2,12];	0,35 [-4,21 ; 4,91]; 1	1	
Race	Other	10	2	20.00	12	2	16.67	1,2 [0,2 ; 7,05]	1,25 [0,14 ; 10,94];	3,33 [-29,21 ; 35,88]; 1	1	0,9051
	White	535	39	7.29	536	36	6.72	1,09 [0,7 ; 1,68]	1,09 [0,68 ; 1,75];	0,57 [-2,48 ; 3,63]; 0,721	0,721	
	No	347	21	6.05	379	30	7.92	0,76 [0,45 ; 1,31]	0,75 [0,42 ; 1,34];	-1,86 [-5,56 ; 1,84]; 0,384	0,384	0,0299

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	20	10.10	169	8	4.73	2,13 [0,96 ; 4,72]	2,26 [0,97 ; 5,28];	5,37 [0,09 ; 10,65]; 0,074	0,074	
Region	Eastern Europe	492	32	6.50	495	30	6.06	1,07 [0,66 ; 1,74]	1,08 [0,64 ; 1,8];	0,44 [-2,58 ; 3,47]; 0,794	0,794	0,9126
	USA and Western Europe	53	9	16.98	53	8	15.09	1,12 [0,47 ; 2,69]	1,15 [0,41 ; 3,25];	1,89 [-12,08 ; 15,85]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Upper respiratory tract infection

6.2.42 Respiratory, thoracic and mediastinal disorders - Dyspnoea

Tabelle 403: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	7	2.15	302	2	0.66	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>= 38 years	219	5	2.28	246	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	419	11	2.63	415	2	0.48	5,45 [1,21 ; 24,43]	5,57 [1,23 ; 25,27];	2,14 [0,47 ; 3,81]; 0,021	0,021	0,5628
	>3.5	126	1	0.79	133	0	0.00	3,17 [0,13 ; 76,99]	3,19 [0,13 ; 79,07];	0,81 [-1,34 ; 2,95]; 0,238	0,238	
Gender	Female	345	9	2.61	356	2	0.56	4,64 [1,01 ; 21,34]	4,74 [1,02 ; 22,1];	2,05 [0,19 ; 3,9]; 0,035	0,035	0,3211
	Male	200	3	1.50	192	0	0.00	6,72 [0,35 ; 129,27]	6,82 [0,35 ; 132,97];	1,48 [-0,46 ; 3,43]; 0,124	0,124	
Number of baseline Gd-enhancing lesions	>=1	258	7	2.71	251	1	0.40	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	286	5	1.75	293	1	0.34	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	7	3.11	202	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	1	1.19	98	1	1.02	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	4	1.69	248	1	0.40	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	1	10.00	12	0	0.00	3,55 [0,16 ; 78,56]	3,95 [0,14 ; 108,09];	9,79 [-13,03 ; 32,61]; 0,478	0,478	0,5269
	White	535	11	2.06	536	2	0.37	5,51 [1,23 ; 24,74]	5,6 [1,24 ; 25,41];	1,68 [0,37 ; 2,99]; 0,012	0,012	
	No	347	4	1.15	379	2	0.53	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	8	4.04	169	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Region	Eastern Europe	492	9	1.83	495	2	0.40	4,53 [0,98 ; 20,85]	4,59 [0,99 ; 21,37];	1,43 [0,12 ; 2,73]; 0,037	0,037	0,2994
	USA and Western Europe	53	3	5.66	53	0	0.00	7 [0,37 ; 132,29]	7,42 [0,37 ; 147,18];	5,56 [-1,49 ; 12,6]; 0,118	0,118	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Respiratory, thoracic and mediastinal disorders | Dyspnoea

6.2.43 Infections and infestations - Bronchitis

Tabelle 404: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	15	4.60	302	15	4.97	0,93 [0,46 ; 1,86]	0,92 [0,44 ; 1,92];	-0,37 [-3,71 ; 2,98]; 0,854	0,854	0,0291
	>= 38 years	219	9	4.11	246	2	0.81	5,05 [1,1 ; 23,14]	5,23 [1,12 ; 24,47];	3,3 [0,44 ; 6,16]; 0,029	0,029	
Disease Severity at baseline (EDSS)	<=3.5	419	20	4.77	415	16	3.86	1,24 [0,65 ; 2,36]	1,25 [0,64 ; 2,45];	0,92 [-1,84 ; 3,67]; 0,61	0,61	0,2505
	>3.5	126	4	3.17	133	1	0.75	4,22 [0,48 ; 37,27]	4,33 [0,48 ; 39,26];	2,42 [-0,97 ; 5,82]; 0,203	0,203	
Gender	Female	345	22	6.38	356	13	3.65	1,75 [0,89 ; 3,41]	1,8 [0,89 ; 3,63];	2,73 [-0,51 ; 5,96]; 0,119	0,119	0,1445
	Male	200	2	1.00	192	4	2.08	0,48 [0,09 ; 2,59]	0,47 [0,09 ; 2,62];	-1,08 [-3,53 ; 1,36]; 0,441	0,441	
Number of baseline Gd-enhancing lesions	>=1	258	11	4.26	251	8	3.19	1,34 [0,55 ; 3,27]	1,35 [0,53 ; 3,42];	1,08 [-2,21 ; 4,36]; 0,642	0,642	0,8711
	0	286	13	4.55	293	9	3.07	1,48 [0,64 ; 3,41]	1,5 [0,63 ; 3,57];	1,47 [-1,65 ; 4,59]; 0,391	0,391	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	11	4.89	202	5	2.48	1,98 [0,7 ; 5,59]	2,03 [0,69 ; 5,93];	2,41 [-1,13 ; 5,95]; 0,212	0,212	0,1452
	>=3	84	2	2.38	98	6	6.12	0,39 [0,08 ; 1,88]	0,37 [0,07 ; 1,9];	-3,74 [-9,5 ; 2,02]; 0,29	0,29	
	2	236	11	4.66	248	6	2.42	1,93 [0,72 ; 5,13]	1,97 [0,72 ; 5,42];	2,24 [-1,06 ; 5,54]; 0,22	0,22	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	24	4.49	536	17	3.17	1,41 [0,77 ; 2,6]	1,43 [0,76 ; 2,7];	1,31 [-0,98 ; 3,61]; 0,27	0,27	
	No	347	15	4.32	379	11	2.90	1,49 [0,69 ; 3,2]	1,51 [0,68 ; 3,34];	1,42 [-1,31 ; 4,15]; 0,324	0,324	0,8173

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	9	4.55	169	6	3.55	1,28 [0,47 ; 3,52]	1,29 [0,45 ; 3,71];	1 [-3,03 ; 5,02]; 0,793	0,793	
Region	Eastern Europe	492	22	4.47	495	14	2.83	1,58 [0,82 ; 3,05]	1,61 [0,81 ; 3,18];	1,64 [-0,7 ; 3,98]; 0,179	0,179	0,3608
	USA and Western Europe	53	2	3.77	53	3	5.66	0,67 [0,12 ; 3,83]	0,65 [0,1 ; 4,08];	-1,89 [-9,95 ; 6,18]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Bronchitis

6.2.44 Infections and infestations - Oral herpes

Tabelle 405: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	8	2.45	302	16	5.30	0,46 [0,2 ; 1,07]	0,45 [0,19 ; 1,07];	-2,84 [-5,88 ; 0,19]; 0,094	0,094	0,0024
	>= 38 years	219	9	4.11	246	2	0.81	5,05 [1,1 ; 23,14]	5,23 [1,12 ; 24,47];	3,3 [0,44 ; 6,16]; 0,029	0,029	
Disease Severity at baseline (EDSS)	<=3.5	419	16	3.82	415	13	3.13	1,22 [0,59 ; 2,5]	1,23 [0,58 ; 2,59];	0,69 [-1,8 ; 3,17]; 0,706	0,706	0,0821
	>3.5	126	1	0.79	133	5	3.76	0,21 [0,03 ; 1,78]	0,2 [0,02 ; 1,78];	-2,97 [-6,55 ; 0,62]; 0,214	0,214	
Gender	Female	345	16	4.64	356	15	4.21	1,1 [0,55 ; 2,19]	1,11 [0,54 ; 2,27];	0,42 [-2,62 ; 3,47]; 0,855	0,855	0,2723
	Male	200	1	0.50	192	3	1.56	0,32 [0,03 ; 3,05]	0,32 [0,03 ; 3,07];	-1,06 [-3,07 ; 0,95]; 0,363	0,363	
Number of baseline Gd-enhancing lesions	>=1	258	11	4.26	251	9	3.59	1,19 [0,5 ; 2,82]	1,2 [0,49 ; 2,94];	0,68 [-2,69 ; 4,05]; 0,821	0,821	0,4139
	0	286	6	2.10	293	9	3.07	0,68 [0,25 ; 1,89]	0,68 [0,24 ; 1,92];	-0,97 [-3,55 ; 1,61]; 0,603	0,603	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	8	3.56	202	9	4.46	0,8 [0,31 ; 2,03]	0,79 [0,3 ; 2,09];	-0,9 [-4,63 ; 2,84]; 0,805	0,805	0,0689
	>=3	84	3	3.57	98	0	0.00	8,15 [0,43 ; 155,61]	8,46 [0,43 ; 166,18];	3,61 [-0,84 ; 8,06]; 0,046	0,046	
	2	236	6	2.54	248	9	3.63	0,7 [0,25 ; 1,94]	0,69 [0,24 ; 1,98];	-1,09 [-4,16 ; 1,99]; 0,603	0,603	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	17	3.18	536	18	3.36	0,95 [0,49 ; 1,82]	0,94 [0,48 ; 1,85];	-0,18 [-2,31 ; 1,95]; 1	1	
	No	347	13	3.75	379	14	3.69	1,01 [0,48 ; 2,13]	1,01 [0,47 ; 2,19];	0,05 [-2,7 ; 2,81]; 1	1	0,8287

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	4	2.02	169	4	2.37	0,85 [0,22 ; 3,36]	0,85 [0,21 ; 3,45];	-0,35 [-3,36 ; 2,67]; 1	1	
Region	Eastern Europe	492	14	2.85	495	18	3.64	0,78 [0,39 ; 1,56]	0,78 [0,38 ; 1,58];	-0,79 [-3 ; 1,42]; 0,591	0,591	0,0299
	USA and Western Europe	53	3	5.66	53	0	0.00	7 [0,37 ; 132,29]	7,42 [0,37 ; 147,18];	5,56 [-1,49 ; 12,6]; 0,118	0,118	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Oral herpes

6.2.45 Psychiatric disorders - Depression

Tabelle 406: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	6	1.84	302	3	0.99	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>= 38 years	219	2	0.91	246	7	2.85	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	419	8	1.91	415	7	1.69	1,13 [0,41 ; 3,09]	1,13 [0,41 ; 3,16];	0,22 [-1,58 ; 2,03]; 1	1	0,0493
	>3.5	126	0	0.00	133	3	2.26	0,15 [0,01 ; 2,89]	0,15 [0,01 ; 2,88];	-2,22 [-5,13 ; 0,69]; 0,123	0,123	
Gender	Female	345	7	2.03	356	8	2.25	0,9 [0,33 ; 2,46]	0,9 [0,32 ; 2,51];	-0,22 [-2,36 ; 1,92]; 1	1	0,6276
	Male	200	1	0.50	192	2	1.04	0,48 [0,04 ; 5,25]	0,48 [0,04 ; 5,31];	-0,54 [-2,28 ; 1,2]; 0,616	0,616	
Number of baseline Gd-enhancing lesions	>=1	258	5	1.94	251	7	2.79	0,69 [0,22 ; 2,16]	0,69 [0,22 ; 2,2];	-0,85 [-3,49 ; 1,79]; 0,572	0,572	0,6948
	0	286	3	1.05	293	3	1.02	1,02 [0,21 ; 5,03]	1,02 [0,21 ; 5,12];	0,03 [-1,63 ; 1,68]; 1	1	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	3	1.33	202	7	3.47	0,38 [0,1 ; 1,47]	0,38 [0,1 ; 1,48];	-2,13 [-5,07 ; 0,8]; 0,202	0,202	0,2918
	>=3	84	0	0.00	98	0	0.00	1,16 [0,02 ; 58,07]	1,17 [0,02 ; 59,38];	0,08 [-2,06 ; 2,23]; 1	1	
	2	236	5	2.12	248	3	1.21	1,75 [0,42 ; 7,25]	1,77 [0,42 ; 7,48];	0,91 [-1,38 ; 3,2]; 0,495	0,495	
Race	Other	10	1	10.00	12	3	25.00	0,4 [0,05 ; 3,27]	0,33 [0,03 ; 3,84];	-15 [-45,76 ; 15,76]; 0,594	0,594	0,3995
	White	535	7	1.31	536	7	1.31	1 [0,35 ; 2,84]	1 [0,35 ; 2,88];	0 [-1,36 ; 1,36]; 1	1	
	No	347	6	1.73	379	6	1.58	1,09 [0,36 ; 3,35]	1,09 [0,35 ; 3,42];	0,15 [-1,71 ; 2,01]; 1	1	0,3538

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	2	1.01	169	4	2.37	0,43 [0,08 ; 2,3]	0,42 [0,08 ; 2,33];	-1,36 [-4,04 ; 1,33]; 0,42	0,42	
Region	Eastern Europe	492	5	1.02	495	7	1.41	0,72 [0,23 ; 2,25]	0,72 [0,23 ; 2,27];	-0,4 [-1,76 ; 0,97]; 0,773	0,773	0,7445
	USA and Western Europe	53	3	5.66	53	3	5.66	1 [0,21 ; 4,73]	1 [0,19 ; 5,19];	0 [-8,8 ; 8,8]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Psychiatric disorders | Depression

6.2.46 Nervous system disorders - Hypoaesthesia

Tabelle 407: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	7	2.15	302	9	2.98	0,72 [0,27 ; 1,91]	0,71 [0,26 ; 1,94];	-0,83 [-3,31 ; 1,65]; 0,615	0,615	0,0268
	>= 38 years	219	0	0.00	246	6	2.44	0,09 [0 ; 1,52]	0,08 [0 ; 1,5];	-2,4 [-4,5 ; -0,31]; 0,032	0,032	
Disease Severity at baseline (EDSS)	<=3.5	419	7	1.67	415	11	2.65	0,63 [0,25 ; 1,61]	0,62 [0,24 ; 1,63];	-0,98 [-2,95 ; 0,99]; 0,352	0,352	0,0682
	>3.5	126	0	0.00	133	4	3.01	0,12 [0,01 ; 2,16]	0,11 [0,01 ; 2,13];	-2,96 [-6,2 ; 0,27]; 0,123	0,123	
Gender	Female	345	5	1.45	356	10	2.81	0,52 [0,18 ; 1,49]	0,51 [0,17 ; 1,5];	-1,36 [-3,49 ; 0,77]; 0,297	0,297	0,7659
	Male	200	2	1.00	192	5	2.60	0,38 [0,08 ; 1,96]	0,38 [0,07 ; 1,97];	-1,6 [-4,25 ; 1,04]; 0,276	0,276	
Number of baseline Gd-enhancing lesions	>=1	258	5	1.94	251	6	2.39	0,81 [0,25 ; 2,62]	0,81 [0,24 ; 2,68];	-0,45 [-2,98 ; 2,08]; 0,769	0,769	0,2287
	0	286	2	0.70	293	8	2.73	0,26 [0,05 ; 1,2]	0,25 [0,05 ; 1,19];	-2,03 [-4,13 ; 0,07]; 0,107	0,107	
	NA	1	0	0.00	4	1	25.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	2	0.89	202	6	2.97	0,3 [0,06 ; 1,47]	0,29 [0,06 ; 1,47];	-2,08 [-4,72 ; 0,56]; 0,157	0,157	0,1817
	>=3	84	0	0.00	98	3	3.06	0,17 [0,01 ; 3,18]	0,16 [0,01 ; 3,17];	-2,95 [-6,93 ; 1,04]; 0,127	0,127	
	2	236	5	2.12	248	6	2.42	0,88 [0,27 ; 2,83]	0,87 [0,26 ; 2,9];	-0,3 [-2,95 ; 2,35]; 1	1	
Race	Other	10	0	0.00	12	2	16.67	0,24 [0,01 ; 4,42]	0,2 [0,01 ; 4,69];	-14,69 [-39,39 ; 10,02]; 0,481	0,481	0,2152
	White	535	7	1.31	536	13	2.43	0,54 [0,22 ; 1,34]	0,53 [0,21 ; 1,35];	-1,12 [-2,74 ; 0,5]; 0,259	0,259	
	No	347	5	1.44	379	7	1.85	0,78 [0,25 ; 2,44]	0,78 [0,24 ; 2,47];	-0,41 [-2,25 ; 1,44]; 0,775	0,775	0,1645

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	2	1.01	169	8	4.73	0,21 [0,05 ; 0,99]	0,21 [0,04 ; 0,98];	-3,72 [-7,22 ; -0,23]; 0,049	0,049	
Region	Eastern Europe	492	7	1.42	495	8	1.62	0,88 [0,32 ; 2,41]	0,88 [0,32 ; 2,44];	-0,19 [-1,72 ; 1,33]; 1	1	0,0072
	USA and Western Europe	53	0	0.00	53	7	13.21	0,07 [0 ; 1,14]	0,06 [0 ; 1,04];	-12,96 [-22,53 ; -3,39]; 0,006	0,006	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Nervous system disorders | Hypoaesthesia

6.2.47 Investigations - Lymphocyte count decreased

Tabelle 408: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	15	4.60	302	6	1.99	2,32 [0,91 ; 5,89]	2,38 [0,91 ; 6,21];	2,61 [-0,15 ; 5,38]; 0,078	0,078	0,534
	>= 38 years	219	5	2.28	246	4	1.63	1,4 [0,38 ; 5,16]	1,41 [0,37 ; 5,33];	0,66 [-1,87 ; 3,19]; 0,741	0,741	
Disease Severity at baseline (EDSS)	<=3.5	419	13	3.10	415	9	2.17	1,43 [0,62 ; 3,31]	1,44 [0,61 ; 3,42];	0,93 [-1,24 ; 3,11]; 0,518	0,518	0,101
	>3.5	126	7	5.56	133	1	0.75	7,39 [0,92 ; 59,21]	7,76 [0,94 ; 64,04];	4,8 [0,54 ; 9,06]; 0,032	0,032	
Gender	Female	345	10	2.90	356	5	1.40	2,06 [0,71 ; 5,98]	2,1 [0,71 ; 6,19];	1,49 [-0,66 ; 3,65]; 0,199	0,199	0,9365
	Male	200	10	5.00	192	5	2.60	1,92 [0,67 ; 5,51]	1,97 [0,66 ; 5,87];	2,4 [-1,37 ; 6,16]; 0,294	0,294	
Number of baseline Gd-enhancing lesions	>=1	258	8	3.10	251	3	1.20	2,59 [0,7 ; 9,67]	2,65 [0,69 ; 10,09];	1,91 [-0,6 ; 4,41]; 0,222	0,222	0,637
	0	286	12	4.20	293	7	2.39	1,76 [0,7 ; 4,4]	1,79 [0,69 ; 4,61];	1,81 [-1,1 ; 4,71]; 0,25	0,25	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	5	2.22	202	3	1.49	1,5 [0,36 ; 6,18]	1,51 [0,36 ; 6,39];	0,74 [-1,81 ; 3,29]; 0,727	0,727	0,8207
	>=3	84	5	5.95	98	2	2.04	2,92 [0,58 ; 14,65]	3,04 [0,57 ; 16,08];	3,91 [-1,87 ; 9,69]; 0,251	0,251	
	2	236	10	4.24	248	5	2.02	2,1 [0,73 ; 6,06]	2,15 [0,72 ; 6,39];	2,22 [-0,89 ; 5,33]; 0,194	0,194	
Race	Other	10	1	10.00	12	0	0.00	3,55 [0,16 ; 78,56]	3,95 [0,14 ; 108,09];	9,79 [-13,03 ; 32,61]; 0,478	0,478	0,3188
	White	535	19	3.55	536	10	1.87	1,9 [0,89 ; 4,06]	1,94 [0,89 ; 4,21];	1,69 [-0,26 ; 3,63]; 0,094	0,094	
	No	347	16	4.61	379	8	2.11	2,18 [0,95 ; 5,04]	2,24 [0,95 ; 5,31];	2,5 [-0,14 ; 5,14]; 0,064	0,064	0,7889

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	4	2.02	169	2	1.18	1,71 [0,32 ; 9,2]	1,72 [0,31 ; 9,52];	0,84 [-1,71 ; 3,39]; 0,691	0,691	
Region	Eastern Europe	492	19	3.86	495	8	1.62	2,39 [1,06 ; 5,41]	2,45 [1,06 ; 5,64];	2,25 [0,21 ; 4,28]; 0,033	0,033	0,2044
	USA and Western Europe	53	1	1.89	53	2	3.77	0,5 [0,05 ; 5,35]	0,49 [0,04 ; 5,58];	-1,89 [-8,19 ; 4,42]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Investigations | Lymphocyte count decreased

6.2.48 Investigations - White blood cell count decreased

Tabelle 409: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	5	1.53	302	12	3.97	0,39 [0,14 ; 1,08]	0,38 [0,13 ; 1,08];	-2,44 [-5,02 ; 0,14]; 0,083	0,083	0,9919
	>= 38 years	219	1	0.46	246	3	1.22	0,37 [0,04 ; 3,57]	0,37 [0,04 ; 3,6];	-0,76 [-2,4 ; 0,87]; 0,626	0,626	
Disease Severity at baseline (EDSS)	<=3.5	419	5	1.19	415	13	3.13	0,38 [0,14 ; 1,06]	0,37 [0,13 ; 1,06];	-1,94 [-3,91 ; 0,03]; 0,06	0,06	0,8033
	>3.5	126	1	0.79	133	2	1.50	0,53 [0,05 ; 5,75]	0,52 [0,05 ; 5,85];	-0,71 [-3,29 ; 1,87]; 1	1	
Gender	Female	345	3	0.87	356	9	2.53	0,34 [0,09 ; 1,26]	0,34 [0,09 ; 1,26];	-1,66 [-3,56 ; 0,24]; 0,143	0,143	0,7336
	Male	200	3	1.50	192	6	3.12	0,48 [0,12 ; 1,89]	0,47 [0,12 ; 1,91];	-1,62 [-4,61 ; 1,36]; 0,329	0,329	
Number of baseline Gd-enhancing lesions	>=1	258	4	1.55	251	9	3.59	0,43 [0,13 ; 1,39]	0,42 [0,13 ; 1,39];	-2,04 [-4,79 ; 0,71]; 0,169	0,169	0,8218
	0	286	2	0.70	293	6	2.05	0,34 [0,07 ; 1,68]	0,34 [0,07 ; 1,68];	-1,35 [-3,24 ; 0,54]; 0,286	0,286	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	1	0.44	202	8	3.96	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	4	4.76	98	3	3.06	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	1	0.42	248	4	1.61	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	6	1.12	536	15	2.80	0,4 [0,16 ; 1,03]	0,39 [0,15 ; 1,02];	-1,68 [-3,33 ; -0,02]; 0,075	0,075	
	No	347	4	1.15	379	8	2.11	0,55 [0,17 ; 1,8]	0,54 [0,16 ; 1,81];	-0,96 [-2,79 ; 0,87]; 0,389	0,389	0,4069

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	2	1.01	169	7	4.14	0,24 [0,05 ; 1,16]	0,24 [0,05 ; 1,15];	-3,13 [-6,44 ; 0,18]; 0,087	0,087	
Region	Eastern Europe	492	6	1.22	495	13	2.63	0,46 [0,18 ; 1,21]	0,46 [0,17 ; 1,21];	-1,41 [-3,12 ; 0,3]; 0,163	0,163	0,2287
	USA and Western Europe	53	0	0.00	53	2	3.77	0,2 [0,01 ; 4,07]	0,19 [0,01 ; 4,11];	-3,7 [-9,86 ; 2,46]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Investigations | White blood cell count decreased

6.2.49 General disorders and administration site conditions - Pyrexia

Tabelle 410: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	51	15.64	302	13	4.30	3,63 [2,02 ; 6,55]	4,12 [2,19 ; 7,75];	11,34 [6,78 ; 15,9]; 0	0	0,1382
	>= 38 years	219	24	10.96	246	14	5.69	1,93 [1,02 ; 3,63]	2,04 [1,03 ; 4,05];	5,27 [0,22 ; 10,32]; 0,043	0,043	
Disease Severity at baseline (EDSS)	<=3.5	419	63	15.04	415	20	4.82	3,12 [1,92 ; 5,06]	3,5 [2,07 ; 5,9];	10,22 [6,22 ; 14,21]; 0	0	0,2817
	>3.5	126	12	9.52	133	7	5.26	1,81 [0,74 ; 4,45]	1,89 [0,72 ; 4,98];	4,26 [-2,12 ; 10,64]; 0,236	0,236	
Gender	Female	345	56	16.23	356	20	5.62	2,89 [1,77 ; 4,71]	3,26 [1,91 ; 5,55];	10,61 [6,05 ; 15,18]; 0	0	0,764
	Male	200	19	9.50	192	7	3.65	2,61 [1,12 ; 6,06]	2,77 [1,14 ; 6,76];	5,85 [1 ; 10,71]; 0,025	0,025	
Number of baseline Gd-enhancing lesions	>=1	258	32	12.40	251	9	3.59	3,46 [1,69 ; 7,1]	3,81 [1,78 ; 8,15];	8,82 [4,18 ; 13,45]; 0	0	0,4788
	0	286	43	15.03	293	18	6.14	2,45 [1,45 ; 4,14]	2,7 [1,52 ; 4,81];	8,89 [3,92 ; 13,86]; 0,001	0,001	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	30	13.33	202	12	5.94	2,24 [1,18 ; 4,26]	2,44 [1,21 ; 4,9];	7,39 [1,88 ; 12,9]; 0,014	0,014	0,6681
	>=3	84	12	14.29	98	5	5.10	2,8 [1,03 ; 7,62]	3,1 [1,04 ; 9,2];	9,18 [0,52 ; 17,84]; 0,042	0,042	
	2	236	33	13.98	248	10	4.03	3,47 [1,75 ; 6,88]	3,87 [1,86 ; 8,04];	9,95 [4,89 ; 15,01]; 0	0	
Race	Other	10	1	10.00	12	1	8.33	1,2 [0,09 ; 16,84]	1,22 [0,07 ; 22,4];	1,67 [-22,63 ; 25,96]; 1	1	0,5341
	White	535	74	13.83	536	26	4.85	2,85 [1,85 ; 4,39]	3,15 [1,98 ; 5,01];	8,98 [5,54 ; 12,43]; 0	0	
	No	347	45	12.97	379	17	4.49	2,89 [1,69 ; 4,95]	3,17 [1,78 ; 5,66];	8,48 [4,38 ; 12,59]; 0	0	0,8182

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	30	15.15	169	10	5.92	2,56 [1,29 ; 5,08]	2,84 [1,34 ; 6];	9,23 [3,1 ; 15,37]; 0,007	0,007	
Region	Eastern Europe	492	66	13.41	495	23	4.65	2,89 [1,83 ; 4,56]	3,18 [1,94 ; 5,2];	8,77 [5,23 ; 12,3]; 0	0	0,73
	USA and Western Europe	53	9	16.98	53	4	7.55	2,25 [0,74 ; 6,86]	2,51 [0,72 ; 8,71];	9,43 [-2,93 ; 21,79]; 0,236	0,236	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - General disorders and administration site conditions | Pyrexia

6.2.50 Infections and infestations - Pneumonia

Tabelle 411: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	6	1.84	302	1	0.33	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>= 38 years	219	4	1.83	246	4	1.63	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	419	8	1.91	415	3	0.72	2,64 [0,71 ; 9,89]	2,67 [0,7 ; 10,15];	1,19 [-0,36 ; 2,73]; 0,224	0,224	0,4451
	>3.5	126	2	1.59	133	2	1.50	1,06 [0,15 ; 7,38]	1,06 [0,15 ; 7,62];	0,08 [-2,92 ; 3,09]; 1	1	
Gender	Female	345	9	2.61	356	5	1.40	1,86 [0,63 ; 5,49]	1,88 [0,62 ; 5,67];	1,2 [-0,88 ; 3,28]; 0,29	0,29	0,3732
	Male	200	1	0.50	192	0	0.00	2,88 [0,12 ; 70,28]	2,89 [0,12 ; 71,49];	0,49 [-0,9 ; 1,88]; 0,499	0,499	
Number of baseline Gd-enhancing lesions	>=1	258	6	2.33	251	2	0.80	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	286	4	1.40	293	3	1.02	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	6	2.67	202	2	0.99	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	3	3.57	98	2	2.04	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	1	0.42	248	1	0.40	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	10	1.87	536	5	0.93	2 [0,69 ; 5,82]	2,02 [0,69 ; 5,96];	0,94 [-0,47 ; 2,34]; 0,207	0,207	
	No	347	8	2.31	379	3	0.79	2,91 [0,78 ; 10,89]	2,96 [0,78 ; 11,24];	1,51 [-0,3 ; 3,33]; 0,129	0,129	0,3069

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	2	1.01	169	2	1.18	0,85 [0,12 ; 5,99]	0,85 [0,12 ; 6,11];	-0,17 [-2,32 ; 1,97]; 1	1	
Region	Eastern Europe	492	7	1.42	495	4	0.81	1,76 [0,52 ; 5,98]	1,77 [0,52 ; 6,09];	0,61 [-0,7 ; 1,93]; 0,384	0,384	0,6634
	USA and Western Europe	53	3	5.66	53	1	1.89	3 [0,32 ; 27,93]	3,12 [0,31 ; 31];	3,77 [-3,45 ; 10,99]; 0,618	0,618	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Pneumonia

6.2.51 Musculoskeletal and connective tissue disorders - Arthralgia

Tabelle 412: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	12	3.68	302	7	2.32	1,59 [0,63 ; 3,98]	1,61 [0,63 ; 4,15];	1,36 [-1,29 ; 4,02]; 0,359	0,359	0,3163
	>= 38 years	219	9	4.11	246	12	4.88	0,84 [0,36 ; 1,96]	0,84 [0,35 ; 2,02];	-0,77 [-4,53 ; 2,99]; 0,824	0,824	
Disease Severity at baseline (EDSS)	<=3.5	419	20	4.77	415	15	3.61	1,32 [0,69 ; 2,54]	1,34 [0,67 ; 2,65];	1,16 [-1,56 ; 3,88]; 0,49	0,49	0,1214
	>3.5	126	1	0.79	133	4	3.01	0,26 [0,03 ; 2,33]	0,26 [0,03 ; 2,34];	-2,21 [-5,5 ; 1,08]; 0,371	0,371	
Gender	Female	345	13	3.77	356	14	3.93	0,96 [0,46 ; 2,01]	0,96 [0,44 ; 2,07];	-0,16 [-3,01 ; 2,68]; 1	1	0,4826
	Male	200	8	4.00	192	5	2.60	1,54 [0,51 ; 4,61]	1,56 [0,5 ; 4,85];	1,4 [-2,13 ; 4,92]; 0,576	0,576	
Number of baseline Gd-enhancing lesions	>=1	258	14	5.43	251	7	2.79	1,95 [0,8 ; 4,74]	2 [0,79 ; 5,04];	2,64 [-0,8 ; 6,07]; 0,181	0,181	0,0637
	0	286	7	2.45	293	12	4.10	0,6 [0,24 ; 1,5]	0,59 [0,23 ; 1,51];	-1,65 [-4,54 ; 1,24]; 0,352	0,352	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	12	5.33	202	10	4.95	1,08 [0,48 ; 2,44]	1,08 [0,46 ; 2,56];	0,38 [-3,81 ; 4,57]; 1	1	0,2405
	>=3	84	0	0.00	98	2	2.04	0,23 [0,01 ; 4,79]	0,23 [0,01 ; 4,82];	-1,94 [-5,43 ; 1,55]; 0,5	0,5	
	2	236	9	3.81	248	7	2.82	1,35 [0,51 ; 3,57]	1,37 [0,5 ; 3,73];	0,99 [-2,21 ; 4,19]; 0,616	0,616	
Race	Other	10	1	10.00	12	2	16.67	0,6 [0,06 ; 5,69]	0,56 [0,04 ; 7,21];	-6,67 [-34,78 ; 21,45]; 1	1	0,566
	White	535	20	3.74	536	17	3.17	1,18 [0,62 ; 2,22]	1,19 [0,61 ; 2,29];	0,57 [-1,62 ; 2,75]; 0,621	0,621	
	No	347	13	3.75	379	10	2.64	1,42 [0,63 ; 3,2]	1,44 [0,62 ; 3,32];	1,11 [-1,46 ; 3,68]; 0,406	0,406	0,3194

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	8	4.04	169	9	5.33	0,76 [0,3 ; 1,92]	0,75 [0,28 ; 1,99];	-1,29 [-5,64 ; 3,07]; 0,623	0,623	
Region	Eastern Europe	492	12	2.44	495	13	2.63	0,93 [0,43 ; 2,02]	0,93 [0,42 ; 2,05];	-0,19 [-2,15 ; 1,77]; 1	1	0,4302
	USA and Western Europe	53	9	16.98	53	6	11.32	1,5 [0,57 ; 3,92]	1,6 [0,53 ; 4,87];	5,66 [-7,57 ; 18,89]; 0,579	0,579	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Musculoskeletal and connective tissue disorders | Arthralgia

6.2.52 Blood and lymphatic system disorders - Leukocytosis

Tabelle 413: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	5	1.53	302	9	2.98	0,51 [0,17 ; 1,52]	0,51 [0,17 ; 1,53];	-1,45 [-3,78 ; 0,89]; 0,282	0,282	0,3757
	>= 38 years	219	1	0.46	246	6	2.44	0,19 [0,02 ; 1,54]	0,18 [0,02 ; 1,54];	-1,98 [-4,11 ; 0,14]; 0,127	0,127	
Disease Severity at baseline (EDSS)	<=3.5	419	4	0.95	415	10	2.41	0,4 [0,13 ; 1,25]	0,39 [0,12 ; 1,25];	-1,45 [-3,2 ; 0,29]; 0,114	0,114	0,9568
	>3.5	126	2	1.59	133	5	3.76	0,42 [0,08 ; 2,14]	0,41 [0,08 ; 2,17];	-2,17 [-6,07 ; 1,73]; 0,448	0,448	
Gender	Female	345	4	1.16	356	10	2.81	0,41 [0,13 ; 1,3]	0,41 [0,13 ; 1,31];	-1,65 [-3,7 ; 0,41]; 0,176	0,176	0,9445
	Female	345	4	1.16	356	7	1.97	0,41 [0,13 ; 1,3]	0,41 [0,13 ; 1,31];	-1,65 [-3,7 ; 0,41]; 0,176	0,176	
	Female	345	2	0.58	356	10	2.81	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Female	345	2	0.58	356	7	1.97	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Male	200	2	1.00	192	5	2.60	0,38 [0,08 ; 1,96]	0,38 [0,07 ; 1,97];	-1,6 [-4,25 ; 1,04]; 0,276	0,276	
	Male	200	2	1.00	192	3	1.56	0,38 [0,08 ; 1,96]	0,38 [0,07 ; 1,97];	-1,6 [-4,25 ; 1,04]; 0,276	0,276	
	Male	200	3	1.50	192	5	2.60	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Male	200	3	1.50	192	3	1.56	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of baseline Gd-enhancing lesions	>=1	258	3	1.16	251	10	3.98	0,29 [0,08 ; 1,05]	0,28 [0,08 ; 1,04];	-2,82 [-5,57 ; -0,07]; 0,051	0,051	0,439
	0	286	3	1.05	293	5	1.71	0,61 [0,15 ; 2,55]	0,61 [0,14 ; 2,58];	-0,66 [-2,55 ; 1,24]; 0,725	0,725	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Number of relapses experienced in the 2 years prior to study start	<=1	225	1	0.44	202	9	4.46	0,1 [0,01 ; 0,78]	0,1 [0,01 ; 0,76];	-4,01 [-6,99 ; -1,04]; 0,008	0,008	0,1093
	>=3	84	2	2.38	98	2	2.04	1,17 [0,17 ; 8,1]	1,17 [0,16 ; 8,5];	0,34 [-3,96 ; 4,64]; 1	1	
	2	236	3	1.27	248	4	1.61	0,79 [0,18 ; 3,48]	0,79 [0,17 ; 3,55];	-0,34 [-2,46 ; 1,78]; 1	1	
Race	Other	10	0	0.00	12	1	8.33	0,39 [0,02 ; 8,73]	0,37 [0,01 ; 9,98];	-6,99 [-28,28 ; 14,29]; 0,493	0,493	0,4312
	White	535	6	1.12	536	14	2.61	0,43 [0,17 ; 1,11]	0,42 [0,16 ; 1,11];	-1,49 [-3,11 ; 0,13]; 0,112	0,112	
Received approved disease modifying MS drug prior to enrollment	No	347	1	0.29	379	7	1.85	0,16 [0,02 ; 1,26]	0,15 [0,02 ; 1,25];	-1,56 [-3,03 ; -0,09]; 0,071	0,071	0,2794
	Yes	198	5	2.53	169	8	4.73	0,53 [0,18 ; 1,6]	0,52 [0,17 ; 1,62];	-2,21 [-6,08 ; 1,67]; 0,273	0,273	
Region	Eastern Europe	492	6	1.22	495	14	2.83	0,43 [0,17 ; 1,11]	0,42 [0,16 ; 1,11];	-1,61 [-3,36 ; 0,14]; 0,112	0,112	0,4047
	USA and Western Europe	53	0	0.00	53	1	1.89	0,33 [0,01 ; 8]	0,33 [0,01 ; 8,21];	-1,85 [-6,93 ; 3,22]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Blood and lymphatic system disorders | Leukocytosis

6.2.53 Investigations - Weight decreased

Tabelle 414: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	3	0.92	302	6	1.99	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>= 38 years	219	2	0.91	246	4	1.63	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	419	4	0.95	415	7	1.69	0,57 [0,17 ; 1,92]	0,56 [0,16 ; 1,93];	-0,73 [-2,28 ; 0,82]; 0,382	0,382	0,7094
	>3.5	126	1	0.79	133	3	2.26	0,35 [0,04 ; 3,34]	0,35 [0,04 ; 3,38];	-1,46 [-4,42 ; 1,5]; 0,623	0,623	
Number of baseline Gd-enhancing lesions	>=1	258	1	0.39	251	6	2.39	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	286	4	1.40	293	3	1.02	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	1	0	0.00	4	1	25.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	2	0.89	202	4	1.98	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	0	0.00	98	5	5.10	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	3	1.27	248	1	0.40	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	0	0.00	12	1	8.33	0,39 [0,02 ; 8,73]	0,37 [0,01 ; 9,98];	-6,99 [-28,28 ; 14,29]; 0,493	0,493	0,3825
	White	535	5	0.93	536	9	1.68	0,56 [0,19 ; 1,65]	0,55 [0,18 ; 1,66];	-0,74 [-2,1 ; 0,61]; 0,421	0,421	
Received approved disease modifying MS drug prior to enrollment	No	347	5	1.44	379	5	1.32	1,09 [0,32 ; 3,74]	1,09 [0,31 ; 3,81];	0,12 [-1,58 ; 1,82]; 1	1	0,0131
	Yes	198	0	0.00	169	5	2.96	0,08 [0 ; 1,39]	0,08 [0 ; 1,37];	-2,98 [-5,73 ; -0,23]; 0,009	0,009	

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	492	4	0.81	495	9	1.82	0,45 [0,14 ; 1,44]	0,44 [0,14 ; 1,45];	-1,01 [-2,42 ; 0,41]; 0,264	0,264	0,6016
	USA and Western Europe	53	1	1.89	53	1	1.89	1 [0,06 ; 15,57]	1 [0,06 ; 16,42];	0 [-5,18 ; 5,18]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Investigations | Weight decreased

6.2.54 Psychiatric disorders - Insomnia

Tabelle 415: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	20	6.13	302	11	3.64	1,68 [0,82 ; 3,46]	1,73 [0,81 ; 3,67];	2,49 [-0,86 ; 5,85]; 0,197	0,197	0,3853
	>= 38 years	219	13	5.94	246	5	2.03	2,92 [1,06 ; 8,06]	3,04 [1,07 ; 8,68];	3,9 [0,31 ; 7,5]; 0,032	0,032	
Disease Severity at baseline (EDSS)	<=3.5	419	31	7.40	415	12	2.89	2,56 [1,33 ; 4,91]	2,68 [1,36 ; 5,3];	4,51 [1,53 ; 7,49]; 0,004	0,004	0,0711
	>3.5	126	2	1.59	133	4	3.01	0,53 [0,1 ; 2,83]	0,52 [0,09 ; 2,89];	-1,42 [-5,05 ; 2,21]; 0,685	0,685	
Gender	Female	345	22	6.38	356	7	1.97	3,24 [1,4 ; 7,49]	3,4 [1,43 ; 8,06];	4,41 [1,46 ; 7,36]; 0,004	0,004	0,0956
	Male	200	11	5.50	192	9	4.69	1,17 [0,5 ; 2,77]	1,18 [0,48 ; 2,92];	0,81 [-3,54 ; 5,16]; 0,82	0,82	
Number of baseline Gd-enhancing lesions	>=1	258	20	7.75	251	8	3.19	2,43 [1,09 ; 5,42]	2,55 [1,1 ; 5,91];	4,56 [0,64 ; 8,49]; 0,031	0,031	0,5141
	0	286	13	4.55	293	8	2.73	1,66 [0,7 ; 3,96]	1,7 [0,69 ; 4,16];	1,82 [-1,24 ; 4,87]; 0,272	0,272	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	15	6.67	202	2	0.99	6,73 [1,56 ; 29,08]	7,14 [1,61 ; 31,63];	5,68 [2,14 ; 9,21]; 0,002	0,002	0,0626
	>=3	84	3	3.57	98	1	1.02	3,5 [0,37 ; 33,02]	3,59 [0,37 ; 35,21];	2,55 [-1,89 ; 6,99]; 0,336	0,336	
	2	236	15	6.36	248	13	5.24	1,21 [0,59 ; 2,49]	1,23 [0,57 ; 2,64];	1,11 [-3,06 ; 5,28]; 0,698	0,698	
Race	Other	10	2	20.00	12	0	0.00	5,91 [0,32 ; 110,47]	7,35 [0,31 ; 173,13];	18,88 [-8 ; 45,76]; 0,195	0,195	0,1529
	White	535	31	5.79	536	16	2.99	1,94 [1,07 ; 3,51]	2 [1,08 ; 3,7];	2,81 [0,36 ; 5,26]; 0,026	0,026	
	No	347	22	6.34	379	11	2.90	2,18 [1,08 ; 4,44]	2,26 [1,08 ; 4,74];	3,44 [0,37 ; 6,51]; 0,032	0,032	0,8108

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	11	5.56	169	5	2.96	1,88 [0,67 ; 5,3]	1,93 [0,66 ; 5,67];	2,6 [-1,49 ; 6,68]; 0,307	0,307	
Region	Eastern Europe	492	23	4.67	495	16	3.23	1,45 [0,77 ; 2,7]	1,47 [0,77 ; 2,81];	1,44 [-0,99 ; 3,87]; 0,257	0,257	0,0017
	USA and Western Europe	53	10	18.87	53	0	0.00	21 [1,26 ; 349,45]	25,83 [1,47 ; 453,3];	18,52 [7,66 ; 29,38]; 0,001	0,001	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Psychiatric disorders | Insomnia

6.2.55 Respiratory, thoracic and mediastinal disorders - Cough

Tabelle 416: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	13	3.99	302	8	2.65	1,51 [0,63 ; 3,58]	1,53 [0,62 ; 3,74];	1,34 [-1,45 ; 4,13]; 0,383	0,383	0,0863
	>= 38 years	219	11	5.02	246	2	0.81	6,18 [1,38 ; 27,57]	6,45 [1,41 ; 29,44];	4,21 [1,11 ; 7,31]; 0,009	0,009	
Disease Severity at baseline (EDSS)	<=3.5	419	21	5.01	415	10	2.41	2,08 [0,99 ; 4,36]	2,14 [0,99 ; 4,6];	2,6 [0,04 ; 5,16]; 0,066	0,066	0,1293
	>3.5	126	3	2.38	133	0	0.00	7,39 [0,39 ; 141,57]	7,57 [0,39 ; 147,98];	2,38 [-0,65 ; 5,41]; 0,056	0,056	
Gender	Female	345	20	5.80	356	8	2.25	2,58 [1,15 ; 5,78]	2,68 [1,16 ; 6,16];	3,55 [0,64 ; 6,46]; 0,02	0,02	0,7424
	Female	345	20	5.80	356	3	0.84	2,58 [1,15 ; 5,78]	2,68 [1,16 ; 6,16];	3,55 [0,64 ; 6,46]; 0,02	0,02	
	Female	345	4	1.16	356	8	2.25	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Female	345	4	1.16	356	3	0.84	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Male	200	4	2.00	192	2	1.04	1,92 [0,36 ; 10,36]	1,94 [0,35 ; 10,71];	0,96 [-1,46 ; 3,37]; 0,685	0,685	
	Male	200	4	2.00	192	1	0.52	1,92 [0,36 ; 10,36]	1,94 [0,35 ; 10,71];	0,96 [-1,46 ; 3,37]; 0,685	0,685	
	Male	200	8	4.00	192	2	1.04	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Male	200	8	4.00	192	1	0.52	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of baseline Gd-enhancing lesions	>=1	258	12	4.65	251	5	1.99	2,33 [0,83 ; 6,53]	2,4 [0,83 ; 6,91];	2,66 [-0,44 ; 5,76]; 0,137	0,137	0,9479
	0	286	12	4.20	293	5	1.71	2,46 [0,88 ; 6,89]	2,52 [0,88 ; 7,25];	2,49 [-0,27 ; 5,25]; 0,088	0,088	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Number of relapses experienced in the 2 years prior to study start	<=1	225	17	7.56	202	3	1.49	5,09 [1,51 ; 17,1]	5,42 [1,56 ; 18,78];	6,07 [2,24 ; 9,91]; 0,003	0,003	0,1302
	>=3	84	2	2.38	98	2	2.04	1,17 [0,17 ; 8,1]	1,17 [0,16 ; 8,5];	0,34 [-3,96 ; 4,64]; 1	1	
	2	236	5	2.12	248	5	2.02	1,05 [0,31 ; 3,58]	1,05 [0,3 ; 3,68];	0,1 [-2,43 ; 2,64]; 1	1	
Race	Other	10	1	10.00	12	0	0.00	3,55 [0,16 ; 78,56]	3,95 [0,14 ; 108,09];	9,79 [-13,03 ; 32,61]; 0,478	0,478	0,3555
	White	535	23	4.30	536	10	1.87	2,3 [1,11 ; 4,79]	2,36 [1,11 ; 5,01];	2,43 [0,37 ; 4,5]; 0,022	0,022	
Received approved disease modifying MS drug prior to enrollment	No	347	15	4.32	379	8	2.11	2,05 [0,88 ; 4,77]	2,1 [0,88 ; 5];	2,21 [-0,37 ; 4,8]; 0,095	0,095	0,4649
	Yes	198	9	4.55	169	2	1.18	3,84 [0,84 ; 17,53]	3,98 [0,85 ; 18,66];	3,36 [0,03 ; 6,69]; 0,071	0,071	
Region	Eastern Europe	492	20	4.07	495	9	1.82	2,24 [1,03 ; 4,86]	2,29 [1,03 ; 5,08];	2,25 [0,14 ; 4,35]; 0,039	0,039	0,5933
	USA and Western Europe	53	4	7.55	53	1	1.89	4 [0,46 ; 34,61]	4,24 [0,46 ; 39,31];	5,66 [-2,34 ; 13,66]; 0,363	0,363	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Respiratory, thoracic and mediastinal disorders | Cough

6.2.56 Skin and subcutaneous tissue disorders - Erythema

Tabelle 417: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	6	1.84	302	1	0.33	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>= 38 years	219	6	2.74	246	3	1.22	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	419	11	2.63	415	2	0.48	5,45 [1,21 ; 24,43]	5,57 [1,23 ; 25,27];	2,14 [0,47 ; 3,81]; 0,021	0,021	0,0888
	>3.5	126	1	0.79	133	2	1.50	0,53 [0,05 ; 5,75]	0,52 [0,05 ; 5,85];	-0,71 [-3,29 ; 1,87]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	258	10	3.88	251	2	0.80	4,86 [1,08 ; 21,98]	5,02 [1,09 ; 23,15];	3,08 [0,48 ; 5,68]; 0,037	0,037	0,2086
	0	286	2	0.70	293	2	0.68	1,02 [0,15 ; 7,22]	1,02 [0,14 ; 7,32];	0,02 [-1,33 ; 1,37]; 1	1	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	7	3.11	202	2	0.99	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	0	0.00	98	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	5	2.12	248	2	0.81	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	12	2.24	536	4	0.75	3,01 [0,98 ; 9,26]	3,05 [0,98 ; 9,52];	1,5 [0,05 ; 2,95]; 0,047	0,047	
Received approved disease modifying MS drug prior to enrollment	No	347	6	1.73	379	4	1.06	1,64 [0,47 ; 5,76]	1,65 [0,46 ; 5,9];	0,67 [-1,04 ; 2,39]; 0,532	0,532	0,0491
	Yes	198	6	3.03	169	0	0.00	11,11 [0,63 ; 195,7]	11,45 [0,64 ; 204,7];	2,97 [0,37 ; 5,57]; 0,033	0,033	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Region	Eastern Europe	492	11	2.24	495	3	0.61	3,69 [1,04 ; 13,14]	3,75 [1,04 ; 13,53];	1,63 [0,16 ; 3,1]; 0,033	0,033	0,4076
	USA and Western Europe	53	1	1.89	53	1	1.89	1 [0,06 ; 15,57]	1 [0,06 ; 16,42];	0 [-5,18 ; 5,18]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Skin and subcutaneous tissue disorders | Erythema

6.2.57 General disorders and administration site conditions - Chills

Tabelle 418: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	33	10.12	302	1	0.33	30,57 [4,21 ; 222,14]	33,9 [4,61 ; 249,48];	9,79 [6,45 ; 13,13]; 0	0	0,0517
	>= 38 years	219	10	4.57	246	3	1.22	3,74 [1,04 ; 13,43]	3,88 [1,05 ; 14,27];	3,35 [0,26 ; 6,43]; 0,045	0,045	
Disease Severity at baseline (EDSS)	<=3.5	419	37	8.83	415	2	0.48	18,32 [4,45 ; 75,53]	20 [4,79 ; 83,55];	8,35 [5,55 ; 11,15]; 0	0	0,1121
	>3.5	126	6	4.76	133	2	1.50	3,17 [0,65 ; 15,4]	3,28 [0,65 ; 16,54];	3,26 [-1 ; 7,51]; 0,163	0,163	
Gender	Female	345	17	4.93	356	3	0.84	5,85 [1,73 ; 19,77]	6,1 [1,77 ; 21];	4,08 [1,61 ; 6,56]; 0,001	0,001	0,1658
	Male	200	26	13.00	192	1	0.52	24,96 [3,42 ; 182,13]	28,54 [3,83 ; 212,54];	12,48 [7,71 ; 17,25]; 0	0	
Number of baseline Gd-enhancing lesions	>=1	258	23	8.91	251	4	1.59	5,59 [1,96 ; 15,95]	6,04 [2,06 ; 17,74];	7,32 [3,51 ; 11,13]; 0	0	0,0281
	0	286	20	6.99	293	0	0.00	42 [2,55 ; 691,15]	45,15 [2,72 ; 750,23];	6,97 [3,96 ; 9,99]; 0	0	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	12	5.33	202	2	0.99	5,39 [1,22 ; 23,78]	5,63 [1,25 ; 25,49];	4,34 [1,11 ; 7,58]; 0,013	0,013	0,3555
	>=3	84	6	7.14	98	0	0.00	15,14 [0,87 ; 264,87]	16,31 [0,91 ; 294];	7,14 [1,32 ; 12,96]; 0,009	0,009	
	2	236	25	10.59	248	2	0.81	13,14 [3,15 ; 54,85]	14,57 [3,41 ; 62,25];	9,79 [5,71 ; 13,87]; 0	0	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9997
	White	535	43	8.04	536	4	0.75	10,77 [3,89 ; 29,79]	11,62 [4,14 ; 32,62];	7,29 [4,87 ; 9,71]; 0	0	
	No	347	27	7.78	379	2	0.53	14,74 [3,53 ; 61,55]	15,9 [3,75 ; 67,4];	7,25 [4,34 ; 10,16]; 0	0	0,4682

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	16	8.08	169	2	1.18	6,83 [1,59 ; 29,27]	7,34 [1,66 ; 32,41];	6,9 [2,77 ; 11,03]; 0,003	0,003	
Region	Eastern Europe	492	38	7.72	495	3	0.61	12,74 [3,96 ; 41,01]	13,73 [4,21 ; 44,78];	7,12 [4,66 ; 9,57]; 0	0	0,489
	USA and Western Europe	53	5	9.43	53	1	1.89	5 [0,6 ; 41,37]	5,42 [0,61 ; 48,04];	7,55 [-1,13 ; 16,23]; 0,205	0,205	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - General disorders and administration site conditions | Chills

6.2.58 Gastrointestinal disorders - Constipation

Tabelle 419: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	16	4.91	302	11	3.64	1,35 [0,64 ; 2,86]	1,37 [0,62 ; 2,99];	1,27 [-1,89 ; 4,42]; 0,556	0,556	0,2265
	>= 38 years	219	7	3.20	246	12	4.88	0,66 [0,26 ; 1,63]	0,64 [0,25 ; 1,67];	-1,68 [-5,24 ; 1,88]; 0,483	0,483	
Disease Severity at baseline (EDSS)	<=3.5	419	19	4.53	415	18	4.34	1,05 [0,56 ; 1,96]	1,05 [0,54 ; 2,03];	0,2 [-2,6 ; 2,99]; 1	1	0,7704
	>3.5	126	4	3.17	133	5	3.76	0,84 [0,23 ; 3,07]	0,84 [0,22 ; 3,2];	-0,58 [-5,04 ; 3,87]; 1	1	
Gender	Female	345	16	4.64	356	14	3.93	1,18 [0,58 ; 2,38]	1,19 [0,57 ; 2,47];	0,71 [-2,3 ; 3,71]; 0,711	0,711	0,452
	Male	200	7	3.50	192	9	4.69	0,75 [0,28 ; 1,97]	0,74 [0,27 ; 2,02];	-1,19 [-5,12 ; 2,74]; 0,616	0,616	
Number of baseline Gd-enhancing lesions	>=1	258	13	5.04	251	11	4.38	1,15 [0,52 ; 2,52]	1,16 [0,51 ; 2,63];	0,66 [-3,02 ; 4,34]; 0,835	0,835	0,6071
	0	286	10	3.50	293	12	4.10	0,85 [0,37 ; 1,94]	0,85 [0,36 ; 2];	-0,6 [-3,71 ; 2,51]; 0,829	0,829	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	10	4.44	202	8	3.96	1,12 [0,45 ; 2,79]	1,13 [0,44 ; 2,92];	0,48 [-3,32 ; 4,29]; 1	1	0,25
	>=3	84	1	1.19	98	5	5.10	0,23 [0,03 ; 1,96]	0,22 [0,03 ; 1,96];	-3,91 [-8,85 ; 1,02]; 0,219	0,219	
	2	236	12	5.08	248	10	4.03	1,26 [0,56 ; 2,86]	1,27 [0,54 ; 3,01];	1,05 [-2,67 ; 4,77]; 0,665	0,665	
Race	Other	10	1	10.00	12	0	0.00	3,55 [0,16 ; 78,56]	3,95 [0,14 ; 108,09];	9,79 [-13,03 ; 32,61]; 0,478	0,478	0,1983
	White	535	22	4.11	536	23	4.29	0,96 [0,54 ; 1,7]	0,96 [0,53 ; 1,74];	-0,18 [-2,58 ; 2,22]; 1	1	
	No	347	16	4.61	379	12	3.17	1,46 [0,7 ; 3,03]	1,48 [0,69 ; 3,17];	1,44 [-1,38 ; 4,27]; 0,34	0,34	0,0975

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	7	3.54	169	11	6.51	0,54 [0,22 ; 1,37]	0,53 [0,2 ; 1,39];	-2,97 [-7,5 ; 1,55]; 0,229	0,229	
Region	Eastern Europe	492	19	3.86	495	22	4.44	0,87 [0,48 ; 1,58]	0,86 [0,46 ; 1,62];	-0,58 [-3,07 ; 1,91]; 0,75	0,75	0,1356
	USA and Western Europe	53	4	7.55	53	1	1.89	4 [0,46 ; 34,61]	4,24 [0,46 ; 39,31];	5,66 [-2,34 ; 13,66]; 0,363	0,363	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Gastrointestinal disorders | Constipation

6.2.59 Gastrointestinal disorders - Vomiting

Tabelle 420: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	9	2.76	302	11	3.64	0,76 [0,32 ; 1,8]	0,75 [0,31 ; 1,84];	-0,88 [-3,64 ; 1,88]; 0,651	0,651	0,1847
	>= 38 years	219	1	0.46	246	6	2.44	0,19 [0,02 ; 1,54]	0,18 [0,02 ; 1,54];	-1,98 [-4,11 ; 0,14]; 0,127	0,127	
Disease Severity at baseline (EDSS)	<=3.5	419	8	1.91	415	15	3.61	0,53 [0,23 ; 1,23]	0,52 [0,22 ; 1,24];	-1,71 [-3,93 ; 0,52]; 0,144	0,144	0,5208
	>3.5	126	2	1.59	133	2	1.50	1,06 [0,15 ; 7,38]	1,06 [0,15 ; 7,62];	0,08 [-2,92 ; 3,09]; 1	1	
Gender	Female	345	8	2.32	356	14	3.93	0,59 [0,25 ; 1,39]	0,58 [0,24 ; 1,4];	-1,61 [-4,18 ; 0,96]; 0,28	0,28	0,9278
	Male	200	2	1.00	192	3	1.56	0,64 [0,11 ; 3,79]	0,64 [0,11 ; 3,85];	-0,56 [-2,79 ; 1,67]; 0,68	0,68	
Number of baseline Gd-enhancing lesions	>=1	258	8	3.10	251	11	4.38	0,71 [0,29 ; 1,73]	0,7 [0,28 ; 1,77];	-1,28 [-4,58 ; 2,02]; 0,49	0,49	0,429
	0	286	2	0.70	293	6	2.05	0,34 [0,07 ; 1,68]	0,34 [0,07 ; 1,68];	-1,35 [-3,24 ; 0,54]; 0,286	0,286	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	5	2.22	202	7	3.47	0,64 [0,21 ; 1,99]	0,63 [0,2 ; 2,03];	-1,24 [-4,42 ; 1,93]; 0,561	0,561	0,6477
	>=3	84	2	2.38	98	2	2.04	1,17 [0,17 ; 8,1]	1,17 [0,16 ; 8,5];	0,34 [-3,96 ; 4,64]; 1	1	
	2	236	3	1.27	248	8	3.23	0,39 [0,11 ; 1,47]	0,39 [0,1 ; 1,47];	-1,95 [-4,58 ; 0,67]; 0,223	0,223	
Race	Other	10	1	10.00	12	1	8.33	1,2 [0,09 ; 16,84]	1,22 [0,07 ; 22,4];	1,67 [-22,63 ; 25,96]; 1	1	0,6123
	White	535	9	1.68	536	16	2.99	0,56 [0,25 ; 1,26]	0,56 [0,24 ; 1,27];	-1,3 [-3,11 ; 0,5]; 0,224	0,224	
	No	347	7	2.02	379	13	3.43	0,59 [0,24 ; 1,46]	0,58 [0,23 ; 1,47];	-1,41 [-3,77 ; 0,94]; 0,266	0,266	0,9204

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	3	1.52	169	4	2.37	0,64 [0,15 ; 2,82]	0,63 [0,14 ; 2,88];	-0,85 [-3,71 ; 2]; 0,708	0,708	
Region	Eastern Europe	492	8	1.63	495	12	2.42	0,67 [0,28 ; 1,63]	0,67 [0,27 ; 1,64];	-0,8 [-2,55 ; 0,96]; 0,499	0,499	0,5525
	USA and Western Europe	53	2	3.77	53	5	9.43	0,4 [0,08 ; 1,97]	0,38 [0,07 ; 2,03];	-5,66 [-15,05 ; 3,73]; 0,437	0,437	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Gastrointestinal disorders | Vomiting

6.2.60 Injury, poisoning and procedural complications - Infusion related reaction

Tabelle 421: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	18	5.52	302	2	0.66	8,34 [1,95 ; 35,63]	8,77 [2,02 ; 38,11];	4,86 [2,22 ; 7,5]; 0	0	0,9644
	>= 38 years	219	8	3.65	246	1	0.41	8,99 [1,13 ; 71,28]	9,29 [1,15 ; 74,88];	3,25 [0,64 ; 5,86]; 0,015	0,015	
Disease Severity at baseline (EDSS)	<=3.5	419	23	5.49	415	2	0.48	11,39 [2,7 ; 48]	11,99 [2,81 ; 51,21];	5,01 [2,73 ; 7,29]; 0	0	0,3672
	>3.5	126	3	2.38	133	1	0.75	3,17 [0,33 ; 30,04]	3,22 [0,33 ; 31,36];	1,63 [-1,41 ; 4,67]; 0,359	0,359	
Gender	Female	345	18	5.22	356	2	0.56	9,29 [2,17 ; 39,72]	9,74 [2,24 ; 42,32];	4,66 [2,18 ; 7,13]; 0	0	0,8777
	Male	200	8	4.00	192	1	0.52	7,68 [0,97 ; 60,83]	7,96 [0,99 ; 64,24];	3,48 [0,58 ; 6,38]; 0,037	0,037	
Number of baseline Gd-enhancing lesions	>=1	258	13	5.04	251	1	0.40	12,65 [1,67 ; 95,96]	13,27 [1,72 ; 102,18];	4,64 [1,86 ; 7,42]; 0,002	0,002	0,6068
	0	286	13	4.55	293	2	0.68	6,66 [1,52 ; 29,25]	6,93 [1,55 ; 30,98];	3,86 [1,27 ; 6,45]; 0,003	0,003	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	17	7.56	202	1	0.50	15,26 [2,05 ; 113,66]	16,43 [2,17 ; 124,59];	7,06 [3,47 ; 10,65]; 0	0	0,3888
	>=3	84	2	2.38	98	0	0.00	5,82 [0,28 ; 119,63]	5,97 [0,28 ; 126,11];	2,44 [-1,42 ; 6,29]; 0,212	0,212	
	2	236	7	2.97	248	2	0.81	3,68 [0,77 ; 17,53]	3,76 [0,77 ; 18,29];	2,16 [-0,27 ; 4,59]; 0,099	0,099	
Race	Other	10	1	10.00	12	0	0.00	3,55 [0,16 ; 78,56]	3,95 [0,14 ; 108,09];	9,79 [-13,03 ; 32,61]; 0,478	0,478	0,5998
	White	535	25	4.67	536	3	0.56	8,35 [2,54 ; 27,49]	8,71 [2,61 ; 29,02];	4,11 [2,22 ; 6,01]; 0	0	
	No	347	15	4.32	379	2	0.53	8,19 [1,89 ; 35,56]	8,52 [1,93 ; 37,52];	3,8 [1,53 ; 6,06]; 0,001	0,001	0,9079

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	11	5.56	169	1	0.59	9,39 [1,22 ; 71,98]	9,88 [1,26 ; 77,36];	4,96 [1,57 ; 8,36]; 0,007	0,007	
Region	Eastern Europe	492	21	4.27	495	3	0.61	7,04 [2,11 ; 23,46]	7,31 [2,17 ; 24,68];	3,66 [1,75 ; 5,57]; 0	0	0,2633
	USA and Western Europe	53	5	9.43	53	0	0.00	11 [0,62 ; 194,08]	12,13 [0,65 ; 225,21];	9,26 [0,8 ; 17,72]; 0,027	0,027	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Injury, poisoning and procedural complications | Infusion related reaction

6.2.61 Nervous system disorders - Dizziness

Tabelle 422: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	19	5.83	302	7	2.32	2,51 [1,07 ; 5,9]	2,61 [1,08 ; 6,3];	3,51 [0,45 ; 6,57]; 0,029	0,029	0,0243
	>= 38 years	219	5	2.28	246	10	4.07	0,56 [0,19 ; 1,62]	0,55 [0,19 ; 1,64];	-1,78 [-4,94 ; 1,38]; 0,306	0,306	
Disease Severity at baseline (EDSS)	<=3.5	419	24	5.73	415	11	2.65	2,16 [1,07 ; 4,35]	2,23 [1,08 ; 4,62];	3,08 [0,37 ; 5,79]; 0,037	0,037	0,0006
	>3.5	126	0	0.00	133	6	4.51	0,08 [0 ; 1,43]	0,08 [0 ; 1,39];	-4,46 [-8,25 ; -0,66]; 0,03	0,03	
Gender	Female	345	18	5.22	356	10	2.81	1,86 [0,87 ; 3,97]	1,9 [0,87 ; 4,19];	2,41 [-0,5 ; 5,32]; 0,124	0,124	0,2209
	Male	200	6	3.00	192	7	3.65	0,82 [0,28 ; 2,4]	0,82 [0,27 ; 2,48];	-0,65 [-4,2 ; 2,91]; 0,783	0,783	
Number of baseline Gd-enhancing lesions	>=1	258	16	6.20	251	11	4.38	1,42 [0,67 ; 2,99]	1,44 [0,66 ; 3,17];	1,82 [-2,06 ; 5,7]; 0,431	0,431	
	0	286	8	2.80	293	6	2.05	1,37 [0,48 ; 3,89]	1,38 [0,47 ; 4,02];	0,75 [-1,76 ; 3,26]; 0,599	0,599	0,945
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	11	4.89	202	8	3.96	1,23 [0,51 ; 3,01]	1,25 [0,49 ; 3,16];	0,93 [-2,97 ; 4,82]; 0,815	0,815	
	>=3	84	2	2.38	98	0	0.00	5,82 [0,28 ; 119,63]	5,97 [0,28 ; 126,11];	2,44 [-1,42 ; 6,29]; 0,212	0,212	0,2814
	2	236	11	4.66	248	9	3.63	1,28 [0,54 ; 3,04]	1,3 [0,53 ; 3,19];	1,03 [-2,52 ; 4,59]; 0,651	0,651	
Race	Other	10	2	20.00	12	0	0.00	5,91 [0,32 ; 110,47]	7,35 [0,31 ; 173,13];	18,88 [-8 ; 45,76]; 0,195	0,195	0,0976
	White	535	22	4.11	536	17	3.17	1,3 [0,7 ; 2,41]	1,31 [0,69 ; 2,49];	0,94 [-1,3 ; 3,18]; 0,421	0,421	
	No	347	16	4.61	379	13	3.43	1,34 [0,66 ; 2,75]	1,36 [0,64 ; 2,87];	1,18 [-1,69 ; 4,05]; 0,452	0,452	0,7364

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	8	4.04	169	4	2.37	1,71 [0,52 ; 5,57]	1,74 [0,51 ; 5,87];	1,67 [-1,9 ; 5,25]; 0,558	0,558	
Region	Eastern Europe	492	18	3.66	495	12	2.42	1,51 [0,73 ; 3,1]	1,53 [0,73 ; 3,21];	1,23 [-0,91 ; 3,38]; 0,272	0,272	0,7665
	USA and Western Europe	53	6	11.32	53	5	9.43	1,2 [0,39 ; 3,69]	1,23 [0,35 ; 4,29];	1,89 [-9,72 ; 13,49]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Nervous system disorders | Dizziness

6.2.62 Gastrointestinal disorders - Abdominal pain

Tabelle 423: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	31	9.51	302	13	4.30	2,21 [1,18 ; 4,14]	2,34 [1,2 ; 4,55];	5,2 [1,28 ; 9,13]; 0,012	0,012	0,6
	>= 38 years	219	12	5.48	246	8	3.25	1,68 [0,7 ; 4,05]	1,72 [0,69 ; 4,3];	2,23 [-1,51 ; 5,97]; 0,26	0,26	
Disease Severity at baseline (EDSS)	<=3.5	419	32	7.64	415	18	4.34	1,76 [1 ; 3,09]	1,82 [1,01 ; 3,3];	3,3 [0,09 ; 6,51]; 0,057	0,057	0,2405
	>3.5	126	11	8.73	133	3	2.26	3,87 [1,11 ; 13,55]	4,14 [1,13 ; 15,22];	6,47 [0,94 ; 12,01]; 0,027	0,027	
Gender	Female	345	32	9.28	356	16	4.49	2,06 [1,15 ; 3,69]	2,17 [1,17 ; 4,04];	4,78 [1,04 ; 8,52]; 0,016	0,016	0,9976
	Male	200	11	5.50	192	5	2.60	2,11 [0,75 ; 5,97]	2,18 [0,74 ; 6,39];	2,9 [-0,98 ; 6,78]; 0,202	0,202	
Number of baseline Gd-enhancing lesions	>=1	258	25	9.69	251	5	1.99	4,86 [1,89 ; 12,51]	5,28 [1,99 ; 14,02];	7,7 [3,7 ; 11,7]; 0	0	0,0091
	0	286	18	6.29	293	16	5.46	1,15 [0,6 ; 2,22]	1,16 [0,58 ; 2,33];	0,83 [-3 ; 4,67]; 0,726	0,726	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	13	5.78	202	9	4.46	1,3 [0,57 ; 2,97]	1,31 [0,55 ; 3,14];	1,32 [-2,85 ; 5,49]; 0,662	0,662	0,2451
	>=3	84	11	13.10	98	3	3.06	4,28 [1,23 ; 14,83]	4,77 [1,28 ; 17,73];	10,03 [2,05 ; 18,01]; 0,013	0,013	
	2	236	19	8.05	248	9	3.63	2,22 [1,02 ; 4,8]	2,33 [1,03 ; 5,25];	4,42 [0,24 ; 8,6]; 0,05	0,05	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	43	8.04	536	21	3.92	2,05 [1,23 ; 3,41]	2,14 [1,25 ; 3,66];	4,12 [1,29 ; 6,95]; 0,005	0,005	
	No	347	26	7.49	379	15	3.96	1,89 [1,02 ; 3,51]	1,97 [1,02 ; 3,78];	3,54 [0,14 ; 6,93]; 0,052	0,052	0,656

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	17	8.59	169	6	3.55	2,42 [0,98 ; 5,99]	2,55 [0,98 ; 6,63];	5,04 [0,24 ; 9,83]; 0,053	0,053	
Region	Eastern Europe	492	40	8.13	495	19	3.84	2,12 [1,24 ; 3,6]	2,22 [1,27 ; 3,89];	4,29 [1,34 ; 7,24]; 0,005	0,005	0,7074
	USA and Western Europe	53	3	5.66	53	2	3.77	1,5 [0,26 ; 8,62]	1,53 [0,25 ; 9,55];	1,89 [-6,18 ; 9,95]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Gastrointestinal disorders | Abdominal pain

6.2.63 Gastrointestinal disorders - Diarrhoea

Tabelle 424: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	26	7.98	302	32	10.60	0,75 [0,46 ; 1,23]	0,73 [0,42 ; 1,26];	-2,62 [-7,17 ; 1,93]; 0,272	0,272	0,9332
	>= 38 years	219	18	8.22	246	26	10.57	0,78 [0,44 ; 1,38]	0,76 [0,4 ; 1,42];	-2,35 [-7,64 ; 2,94]; 0,43	0,43	
Disease Severity at baseline (EDSS)	<=3.5	419	34	8.11	415	43	10.36	0,78 [0,51 ; 1,2]	0,76 [0,48 ; 1,22];	-2,25 [-6,18 ; 1,68]; 0,283	0,283	0,8081
	>3.5	126	10	7.94	133	15	11.28	0,7 [0,33 ; 1,51]	0,68 [0,29 ; 1,57];	-3,34 [-10,5 ; 3,81]; 0,405	0,405	
Gender	Female	345	32	9.28	356	40	11.24	0,83 [0,53 ; 1,28]	0,81 [0,49 ; 1,32];	-1,96 [-6,45 ; 2,53]; 0,456	0,456	0,558
	Male	200	12	6.00	192	18	9.38	0,64 [0,32 ; 1,29]	0,62 [0,29 ; 1,32];	-3,38 [-8,65 ; 1,9]; 0,255	0,255	
Number of baseline Gd-enhancing lesions	>=1	258	27	10.47	251	29	11.55	0,91 [0,55 ; 1,49]	0,89 [0,51 ; 1,56];	-1,09 [-6,53 ; 4,35]; 0,777	0,777	0,344
	0	286	17	5.94	293	28	9.56	0,62 [0,35 ; 1,11]	0,6 [0,32 ; 1,12];	-3,61 [-7,95 ; 0,73]; 0,121	0,121	
	NA	1	0	0.00	4	1	25.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	17	7.56	202	21	10.40	0,73 [0,39 ; 1,34]	0,7 [0,36 ; 1,38];	-2,84 [-8,28 ; 2,6]; 0,313	0,313	0,9814
	>=3	84	6	7.14	98	9	9.18	0,78 [0,29 ; 2,1]	0,76 [0,26 ; 2,23];	-2,04 [-9,98 ; 5,9]; 0,788	0,788	
	2	236	21	8.90	248	28	11.29	0,79 [0,46 ; 1,35]	0,77 [0,42 ; 1,39];	-2,39 [-7,75 ; 2,97]; 0,452	0,452	
Race	Other	10	1	10.00	12	0	0.00	3,55 [0,16 ; 78,56]	3,95 [0,14 ; 108,09];	9,79 [-13,03 ; 32,61]; 0,478	0,478	0,1573
	White	535	43	8.04	536	58	10.82	0,74 [0,51 ; 1,08]	0,72 [0,48 ; 1,09];	-2,78 [-6,28 ; 0,71]; 0,143	0,143	
	No	347	24	6.92	379	39	10.29	0,67 [0,41 ; 1,09]	0,65 [0,38 ; 1,1];	-3,37 [-7,43 ; 0,69]; 0,115	0,115	0,4681

Subgruppenanalysen zu Unerwünschten Ereignissen nach MedDRA SOC und PT

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	20	10.10	169	19	11.24	0,9 [0,5 ; 1,63]	0,89 [0,46 ; 1,72];	-1,14 [-7,49 ; 5,21]; 0,737	0,737	
Region	Eastern Europe	492	39	7.93	495	52	10.51	0,75 [0,51 ; 1,12]	0,73 [0,47 ; 1,13];	-2,58 [-6,18 ; 1,03]; 0,187	0,187	0,875
	USA and Western Europe	53	5	9.43	53	6	11.32	0,83 [0,27 ; 2,56]	0,82 [0,23 ; 2,86];	-1,89 [-13,49 ; 9,72]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Gastrointestinal disorders | Diarrhoea

6.2.64 Skin and subcutaneous tissue disorders - Pruritus

Tabelle 425: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	4	1.23	302	2	0.66	1,85 [0,34 ; 10,04]	1,86 [0,34 ; 10,25];	0,56 [-0,94 ; 2,07]; 0,687	0,687	0,9345
	>= 38 years	219	6	2.74	246	4	1.63	1,68 [0,48 ; 5,89]	1,7 [0,47 ; 6,12];	1,11 [-1,56 ; 3,79]; 0,527	0,527	
Disease Severity at baseline (EDSS)	<=3.5	419	8	1.91	415	4	0.96	1,98 [0,6 ; 6,53]	2 [0,6 ; 6,69];	0,95 [-0,67 ; 2,56]; 0,384	0,384	0,5893
	>3.5	126	2	1.59	133	2	1.50	1,06 [0,15 ; 7,38]	1,06 [0,15 ; 7,62];	0,08 [-2,92 ; 3,09]; 1	1	
Gender	Female	345	9	2.61	356	5	1.40	1,86 [0,63 ; 5,49]	1,88 [0,62 ; 5,67];	1,2 [-0,88 ; 3,28]; 0,29	0,29	0,6611
	Male	200	1	0.50	192	1	0.52	0,96 [0,06 ; 15,24]	0,96 [0,06 ; 15,45];	-0,02 [-1,43 ; 1,39]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	258	5	1.94	251	4	1.59	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	286	5	1.75	293	2	0.68	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	5	2.22	202	2	0.99	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	2	2.38	98	3	3.06	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	3	1.27	248	1	0.40	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	1	10.00	12	0	0.00	3,55 [0,16 ; 78,56]	3,95 [0,14 ; 108,09];	9,79 [-13,03 ; 32,61]; 0,478	0,478	0,2792
	White	535	9	1.68	536	6	1.12	1,5 [0,54 ; 4,19]	1,51 [0,53 ; 4,28];	0,56 [-0,84 ; 1,97]; 0,451	0,451	
	No	347	7	2.02	379	4	1.06	1,91 [0,56 ; 6,47]	1,93 [0,56 ; 6,65];	0,96 [-0,84 ; 2,76]; 0,368	0,368	0,7165

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	3	1.52	169	2	1.18	1,28 [0,22 ; 7,57]	1,28 [0,21 ; 7,78];	0,33 [-2,02 ; 2,69]; 1	1	
Region	Eastern Europe	492	8	1.63	495	6	1.21	1,34 [0,47 ; 3,84]	1,35 [0,46 ; 3,91];	0,41 [-1,06 ; 1,89]; 0,604	0,604	0,1505
	USA and Western Europe	53	2	3.77	53	0	0.00	5 [0,25 ; 101,73]	5,19 [0,24 ; 110,82];	3,7 [-2,46 ; 9,86]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Skin and subcutaneous tissue disorders | Pruritus

6.2.65 Infections and infestations - Gastroenteritis

Tabelle 426: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	4	1.23	302	9	2.98	0,41 [0,13 ; 1,32]	0,4 [0,12 ; 1,33];	-1,75 [-4,01 ; 0,51]; 0,162	0,162	0,2849
	>= 38 years	219	0	0.00	246	2	0.81	0,22 [0,01 ; 4,65]	0,22 [0,01 ; 4,67];	-0,78 [-2,18 ; 0,61]; 0,5	0,5	
Disease Severity at baseline (EDSS)	<=3.5	419	4	0.95	415	10	2.41	0,4 [0,13 ; 1,25]	0,39 [0,12 ; 1,25];	-1,45 [-3,2 ; 0,29]; 0,114	0,114	0,4357
	>3.5	126	0	0.00	133	1	0.75	0,35 [0,01 ; 8,55]	0,35 [0,01 ; 8,65];	-0,73 [-2,81 ; 1,36]; 0,499	0,499	
Gender	Female	345	3	0.87	356	9	2.53	0,34 [0,09 ; 1,26]	0,34 [0,09 ; 1,26];	-1,66 [-3,56 ; 0,24]; 0,143	0,143	0,8076
	Male	200	1	0.50	192	2	1.04	0,48 [0,04 ; 5,25]	0,48 [0,04 ; 5,31];	-0,54 [-2,28 ; 1,2]; 0,616	0,616	
Number of baseline Gd-enhancing lesions	>=1	258	2	0.78	251	5	1.99	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	286	2	0.70	293	6	2.05	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	2	0.89	202	5	2.48	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	0	0.00	98	1	1.02	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	2	0.85	248	5	2.02	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	1	10.00	12	0	0.00	3,55 [0,16 ; 78,56]	3,95 [0,14 ; 108,09];	9,79 [-13,03 ; 32,61]; 0,478	0,478	0,0741
	White	535	3	0.56	536	11	2.05	0,27 [0,08 ; 0,97]	0,27 [0,07 ; 0,97];	-1,49 [-2,85 ; -0,13]; 0,056	0,056	
	No	347	3	0.86	379	7	1.85	0,47 [0,12 ; 1,8]	0,46 [0,12 ; 1,81];	-0,98 [-2,65 ; 0,69]; 0,345	0,345	0,5347

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	1	0.51	169	4	2.37	0,21 [0,02 ; 1,89]	0,21 [0,02 ; 1,89];	-1,86 [-4,36 ; 0,63]; 0,185	0,185	
Region	Eastern Europe	492	3	0.61	495	10	2.02	0,3 [0,08 ; 1,09]	0,3 [0,08 ; 1,09];	-1,41 [-2,83 ; 0,01]; 0,09	0,09	0,4471
	USA and Western Europe	53	1	1.89	53	1	1.89	1 [0,06 ; 15,57]	1 [0,06 ; 16,42];	0 [-5,18 ; 5,18]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Gastroenteritis

6.2.66 General disorders and administration site conditions - Chest pain

Tabelle 427: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	6	1.84	302	0	0.00	12,05 [0,68 ; 212,92]	12,27 [0,69 ; 218,74];	1,82 [0,24 ; 3,4]; 0,031	0,031	0,021
	>= 38 years	219	5	2.28	246	5	2.03	1,12 [0,33 ; 3,83]	1,13 [0,32 ; 3,94];	0,25 [-2,4 ; 2,9]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	10	2.39	415	5	1.20	1,98 [0,68 ; 5,75]	2 [0,68 ; 5,92];	1,18 [-0,62 ; 2,98]; 0,297	0,297	0,3666
	>3.5	126	1	0.79	133	0	0.00	3,17 [0,13 ; 76,99]	3,19 [0,13 ; 79,07];	0,81 [-1,34 ; 2,95]; 0,238	0,238	
Gender	Female	345	10	2.90	356	4	1.12	2,58 [0,82 ; 8,15]	2,63 [0,82 ; 8,46];	1,77 [-0,31 ; 3,86]; 0,11	0,11	0,5175
	Male	200	1	0.50	192	1	0.52	0,96 [0,06 ; 15,24]	0,96 [0,06 ; 15,45];	-0,02 [-1,43 ; 1,39]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	258	4	1.55	251	2	0.80	1,95 [0,36 ; 10,53]	1,96 [0,36 ; 10,8];	0,75 [-1,11 ; 2,62]; 0,686	0,686	0,849
	0	286	7	2.45	293	3	1.02	2,39 [0,62 ; 9,15]	2,43 [0,62 ; 9,47];	1,42 [-0,71 ; 3,55]; 0,217	0,217	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	4	1.78	202	3	1.49	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	4	4.76	98	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	3	1.27	248	2	0.81	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	11	2.06	536	5	0.93	2,2 [0,77 ; 6,3]	2,23 [0,77 ; 6,46];	1,12 [-0,33 ; 2,58]; 0,14	0,14	
	No	347	5	1.44	379	4	1.06	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	6	3.03	169	1	0.59	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Region	Eastern Europe	492	10	2.03	495	2	0.40	5,03 [1,11 ; 22,84]	5,11 [1,11 ; 23,46];	1,63 [0,26 ; 2,99]; 0,021	0,021	0,0311
	USA and Western Europe	53	1	1.89	53	3	5.66	0,33 [0,04 ; 3,1]	0,32 [0,03 ; 3,18];	-3,77 [-10,99 ; 3,45]; 0,618	0,618	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - General disorders and administration site conditions | Chest pain

6.2.67 Blood and lymphatic system disorders - Leukopenia

Tabelle 428: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	7	2.15	302	15	4.97	0,43 [0,18 ; 1,05]	0,42 [0,17 ; 1,04];	-2,82 [-5,73 ; 0,09]; 0,08	0,08	0,2479
	>= 38 years	219	4	1.83	246	4	1.63	1,12 [0,28 ; 4,44]	1,13 [0,28 ; 4,56];	0,2 [-2,18 ; 2,58]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	9	2.15	415	18	4.34	0,5 [0,23 ; 1,09]	0,48 [0,21 ; 1,09];	-2,19 [-4,59 ; 0,21]; 0,081	0,081	0,2374
	>3.5	126	2	1.59	133	1	0.75	2,11 [0,19 ; 22,99]	2,13 [0,19 ; 23,77];	0,84 [-1,79 ; 3,47]; 0,614	0,614	
Gender	Female	345	7	2.03	356	14	3.93	0,52 [0,21 ; 1,26]	0,51 [0,2 ; 1,27];	-1,9 [-4,41 ; 0,6]; 0,184	0,184	0,619
	Male	200	4	2.00	192	5	2.60	0,77 [0,21 ; 2,82]	0,76 [0,2 ; 2,89];	-0,6 [-3,58 ; 2,37]; 0,747	0,747	
Number of baseline Gd-enhancing lesions	>=1	258	3	1.16	251	8	3.19	0,36 [0,1 ; 1,36]	0,36 [0,09 ; 1,36];	-2,02 [-4,56 ; 0,51]; 0,137	0,137	0,3144
	0	286	8	2.80	293	10	3.41	0,82 [0,33 ; 2,05]	0,81 [0,32 ; 2,09];	-0,62 [-3,44 ; 2,21]; 0,812	0,812	
	NA	1	0	0.00	4	1	25.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	5	2.22	202	4	1.98	1,12 [0,31 ; 4,12]	1,12 [0,3 ; 4,25];	0,24 [-2,48 ; 2,96]; 1	1	0,3788
	>=3	84	2	2.38	98	8	8.16	0,29 [0,06 ; 1,34]	0,27 [0,06 ; 1,33];	-5,78 [-12,11 ; 0,54]; 0,11	0,11	
	2	236	4	1.69	248	7	2.82	0,6 [0,18 ; 2,02]	0,59 [0,17 ; 2,05];	-1,13 [-3,77 ; 1,51]; 0,546	0,546	
Race	Other	10	0	0.00	12	1	8.33	0,39 [0,02 ; 8,73]	0,37 [0,01 ; 9,98];	-6,99 [-28,28 ; 14,29]; 0,493	0,493	0,3607
	White	535	11	2.06	536	18	3.36	0,61 [0,29 ; 1,28]	0,6 [0,28 ; 1,29];	-1,3 [-3,24 ; 0,64]; 0,258	0,258	
	No	347	9	2.59	379	8	2.11	1,23 [0,48 ; 3,15]	1,23 [0,47 ; 3,24];	0,48 [-1,73 ; 2,69]; 0,807	0,807	0,0111

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	2	1.01	169	11	6.51	0,16 [0,03 ; 0,69]	0,15 [0,03 ; 0,67];	-5,5 [-9,47 ; -1,53]; 0,008	0,008	
Region	Eastern Europe	492	11	2.24	495	18	3.64	0,61 [0,29 ; 1,29]	0,61 [0,28 ; 1,3];	-1,4 [-3,5 ; 0,7]; 0,258	0,258	0,3334
	USA and Western Europe	53	0	0.00	53	1	1.89	0,33 [0,01 ; 8]	0,33 [0,01 ; 8,21];	-1,85 [-6,93 ; 3,22]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Blood and lymphatic system disorders | Leukopenia

6.2.68 Blood and lymphatic system disorders - Neutropenia

Tabelle 429: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	6	1.84	302	15	4.97	0,37 [0,15 ; 0,94]	0,36 [0,14 ; 0,94];	-3,13 [-5,98 ; -0,27]; 0,043	0,043	0,8276
	>= 38 years	219	2	0.91	246	5	2.03	0,45 [0,09 ; 2,29]	0,44 [0,09 ; 2,31];	-1,12 [-3,29 ; 1,05]; 0,455	0,455	
Disease Severity at baseline (EDSS)	<=3.5	419	7	1.67	415	16	3.86	0,43 [0,18 ; 1,04]	0,42 [0,17 ; 1,04];	-2,18 [-4,41 ; 0,04]; 0,059	0,059	0,6732
	>3.5	126	1	0.79	133	4	3.01	0,26 [0,03 ; 2,33]	0,26 [0,03 ; 2,34];	-2,21 [-5,5 ; 1,08]; 0,371	0,371	
Gender	Female	345	4	1.16	356	14	3.93	0,29 [0,1 ; 0,89]	0,29 [0,09 ; 0,88];	-2,77 [-5,09 ; -0,46]; 0,029	0,029	0,3615
	Male	200	4	2.00	192	6	3.12	0,64 [0,18 ; 2,23]	0,63 [0,18 ; 2,28];	-1,12 [-4,26 ; 2,01]; 0,536	0,536	
Number of baseline Gd-enhancing lesions	>=1	258	2	0.78	251	12	4.78	0,16 [0,04 ; 0,72]	0,16 [0,03 ; 0,7];	-4,01 [-6,85 ; -1,16]; 0,006	0,006	0,0742
	0	286	6	2.10	293	8	2.73	0,77 [0,27 ; 2,19]	0,76 [0,26 ; 2,23];	-0,63 [-3,13 ; 1,87]; 0,788	0,788	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	3	1.33	202	6	2.97	0,45 [0,11 ; 1,77]	0,44 [0,11 ; 1,79];	-1,64 [-4,42 ; 1,14]; 0,318	0,318	0,8257
	>=3	84	2	2.38	98	8	8.16	0,29 [0,06 ; 1,34]	0,27 [0,06 ; 1,33];	-5,78 [-12,11 ; 0,54]; 0,11	0,11	
	2	236	3	1.27	248	6	2.42	0,53 [0,13 ; 2,08]	0,52 [0,13 ; 2,1];	-1,15 [-3,54 ; 1,24]; 0,505	0,505	
Race	Other	10	0	0.00	12	1	8.33	0,39 [0,02 ; 8,73]	0,37 [0,01 ; 9,98];	-6,99 [-28,28 ; 14,29]; 0,493	0,493	0,4341
	White	535	8	1.50	536	19	3.54	0,42 [0,19 ; 0,96]	0,41 [0,18 ; 0,95];	-2,05 [-3,92 ; -0,18]; 0,049	0,049	
	No	347	4	1.15	379	14	3.69	0,31 [0,1 ; 0,94]	0,3 [0,1 ; 0,93];	-2,54 [-4,75 ; -0,34]; 0,032	0,032	0,4813

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	4	2.02	169	6	3.55	0,57 [0,16 ; 1,98]	0,56 [0,16 ; 2,02];	-1,53 [-4,94 ; 1,88]; 0,523	0,523	
Region	Eastern Europe	492	8	1.63	495	19	3.84	0,42 [0,19 ; 0,96]	0,41 [0,18 ; 0,96];	-2,21 [-4,24 ; -0,18]; 0,049	0,049	0,4077
	USA and Western Europe	53	0	0.00	53	1	1.89	0,33 [0,01 ; 8]	0,33 [0,01 ; 8,21];	-1,85 [-6,93 ; 3,22]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Blood and lymphatic system disorders | Neutropenia

6.2.69 Respiratory, thoracic and mediastinal disorders - Oropharyngeal pain

Tabelle 430: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	21	6.44	302	12	3.97	1,62 [0,81 ; 3,24]	1,66 [0,8 ; 3,44];	2,47 [-0,99 ; 5,93]; 0,21	0,21	0,9765
	>= 38 years	219	10	4.57	246	7	2.85	1,6 [0,62 ; 4,14]	1,63 [0,61 ; 4,37];	1,72 [-1,74 ; 5,18]; 0,336	0,336	
Disease Severity at baseline (EDSS)	<=3.5	419	25	5.97	415	15	3.61	1,65 [0,88 ; 3,09]	1,69 [0,88 ; 3,26];	2,35 [-0,54 ; 5,24]; 0,144	0,144	0,948
	>3.5	126	6	4.76	133	4	3.01	1,58 [0,46 ; 5,48]	1,61 [0,44 ; 5,85];	1,75 [-2,96 ; 6,47]; 0,531	0,531	
Gender	Female	345	24	6.96	356	17	4.78	1,46 [0,8 ; 2,66]	1,49 [0,79 ; 2,83];	2,18 [-1,3 ; 5,66]; 0,26	0,26	0,3133
	Male	200	7	3.50	192	2	1.04	3,36 [0,71 ; 15,97]	3,45 [0,71 ; 16,8];	2,46 [-0,47 ; 5,38]; 0,175	0,175	
Number of baseline Gd-enhancing lesions	>=1	258	17	6.59	251	5	1.99	3,31 [1,24 ; 8,83]	3,47 [1,26 ; 9,56];	4,6 [1,11 ; 8,08]; 0,015	0,015	0,051
	0	286	14	4.90	293	14	4.78	1,02 [0,5 ; 2,11]	1,03 [0,48 ; 2,19];	0,12 [-3,38 ; 3,61]; 1	1	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	14	6.22	202	5	2.48	2,51 [0,92 ; 6,86]	2,61 [0,92 ; 7,39];	3,75 [-0,07 ; 7,56]; 0,098	0,098	0,342
	>=3	84	6	7.14	98	3	3.06	2,33 [0,6 ; 9,05]	2,44 [0,59 ; 10,06];	4,08 [-2,4 ; 10,56]; 0,306	0,306	
	2	236	11	4.66	248	11	4.44	1,05 [0,46 ; 2,38]	1,05 [0,45 ; 2,48];	0,23 [-3,49 ; 3,94]; 1	1	
Race	Other	10	0	0.00	12	2	16.67	0,24 [0,01 ; 4,42]	0,2 [0,01 ; 4,69];	-14,69 [-39,39 ; 10,02]; 0,481	0,481	0,0516
	White	535	31	5.79	536	17	3.17	1,83 [1,02 ; 3,26]	1,88 [1,03 ; 3,44];	2,62 [0,15 ; 5,1]; 0,04	0,04	
	No	347	16	4.61	379	13	3.43	1,34 [0,66 ; 2,75]	1,36 [0,64 ; 2,87];	1,18 [-1,69 ; 4,05]; 0,452	0,452	0,4258

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	15	7.58	169	6	3.55	2,13 [0,85 ; 5,38]	2,23 [0,84 ; 5,87];	4,03 [-0,6 ; 8,65]; 0,117	0,117	
Region	Eastern Europe	492	26	5.28	495	16	3.23	1,63 [0,89 ; 3,01]	1,67 [0,88 ; 3,15];	2,05 [-0,46 ; 4,57]; 0,117	0,117	0,9626
	USA and Western Europe	53	5	9.43	53	3	5.66	1,67 [0,42 ; 6,62]	1,74 [0,39 ; 7,67];	3,77 [-6,26 ; 13,81]; 0,716	0,716	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Respiratory, thoracic and mediastinal disorders | Oropharyngeal pain

6.2.70 Skin and subcutaneous tissue disorders - Rash

Tabelle 431: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	3	0.92	302	7	2.32	0,4 [0,1 ; 1,52]	0,39 [0,1 ; 1,53];	-1,4 [-3,39 ; 0,59]; 0,208	0,208	0,3898
	>= 38 years	219	4	1.83	246	5	2.03	0,9 [0,24 ; 3,3]	0,9 [0,24 ; 3,38];	-0,21 [-2,71 ; 2,29]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	5	1.19	415	8	1.93	0,62 [0,2 ; 1,88]	0,61 [0,2 ; 1,89];	-0,73 [-2,42 ; 0,95]; 0,418	0,418	0,8731
	>3.5	126	2	1.59	133	4	3.01	0,53 [0,1 ; 2,83]	0,52 [0,09 ; 2,89];	-1,42 [-5,05 ; 2,21]; 0,685	0,685	
Gender	Female	345	6	1.74	356	8	2.25	0,77 [0,27 ; 2,21]	0,77 [0,26 ; 2,24];	-0,51 [-2,58 ; 1,56]; 0,789	0,789	0,3136
	Female	345	6	1.74	356	0	0.00	0,77 [0,27 ; 2,21]	0,77 [0,26 ; 2,24];	-0,51 [-2,58 ; 1,56]; 0,789	0,789	
	Female	345	6	1.74	356	8	2.25	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Female	345	6	1.74	356	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Male	200	1	0.50	192	4	2.08	0,24 [0,03 ; 2,13]	0,24 [0,03 ; 2,13];	-1,58 [-3,83 ; 0,66]; 0,207	0,207	
	Male	200	1	0.50	192	1	0.52	0,24 [0,03 ; 2,13]	0,24 [0,03 ; 2,13];	-1,58 [-3,83 ; 0,66]; 0,207	0,207	
	Male	200	5	2.50	192	4	2.08	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	Male	200	5	2.50	192	1	0.52	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of baseline Gd-enhancing lesions	>=1	258	3	1.16	251	3	1.20	0,97 [0,2 ; 4,77]	0,97 [0,19 ; 4,86];	-0,03 [-1,91 ; 1,84]; 1	1	0,4464
	0	286	4	1.40	293	9	3.07	0,46 [0,14 ; 1,46]	0,45 [0,14 ; 1,47];	-1,67 [-4,07 ; 0,73]; 0,262	0,262	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Number of relapses experienced in the 2 years prior to study start	<=1	225	2	0.89	202	4	1.98	0,45 [0,08 ; 2,42]	0,44 [0,08 ; 2,45];	-1,09 [-3,37 ; 1,19]; 0,428	0,428	0,5815
	>=3	84	0	0.00	98	1	1.02	0,39 [0,02 ; 9,41]	0,38 [0,02 ; 9,57];	-0,93 [-3,83 ; 1,98]; 0,501	0,501	
	2	236	5	2.12	248	7	2.82	0,75 [0,24 ; 2,33]	0,75 [0,23 ; 2,38];	-0,7 [-3,47 ; 2,06]; 0,772	0,772	
Race	Other	10	0	0.00	12	2	16.67	0,24 [0,01 ; 4,42]	0,2 [0,01 ; 4,69];	-14,69 [-39,39 ; 10,02]; 0,481	0,481	0,1719
	White	535	7	1.31	536	10	1.87	0,7 [0,27 ; 1,83]	0,7 [0,26 ; 1,85];	-0,56 [-2,05 ; 0,94]; 0,626	0,626	
Received approved disease modifying MS drug prior to enrollment	No	347	4	1.15	379	6	1.58	0,73 [0,21 ; 2,56]	0,72 [0,2 ; 2,59];	-0,43 [-2,12 ; 1,26]; 0,755	0,755	0,5674
	Yes	198	3	1.52	169	6	3.55	0,43 [0,11 ; 1,68]	0,42 [0,1 ; 1,7];	-2,04 [-5,3 ; 1,23]; 0,312	0,312	
Region	Eastern Europe	492	4	0.81	495	8	1.62	0,5 [0,15 ; 1,66]	0,5 [0,15 ; 1,67];	-0,8 [-2,17 ; 0,56]; 0,385	0,385	0,6992
	USA and Western Europe	53	3	5.66	53	4	7.55	0,75 [0,18 ; 3,19]	0,74 [0,16 ; 3,46];	-1,89 [-11,34 ; 7,56]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Skin and subcutaneous tissue disorders | Rash

6.2.71 Infections and infestations - Respiratory tract infection

Tabelle 432: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	28	8.59	302	24	7.95	1,08 [0,64 ; 1,82]	1,09 [0,62 ; 1,92];	0,64 [-3,67 ; 4,95]; 0,885	0,885	0,936
	>= 38 years	219	14	6.39	246	14	5.69	1,12 [0,55 ; 2,3]	1,13 [0,53 ; 2,43];	0,7 [-3,64 ; 5,05]; 0,846	0,846	
Disease Severity at baseline (EDSS)	<=3.5	419	35	8.35	415	30	7.23	1,16 [0,72 ; 1,85]	1,17 [0,7 ; 1,94];	1,12 [-2,51 ; 4,76]; 0,606	0,606	0,6839
	>3.5	126	7	5.56	133	8	6.02	0,92 [0,35 ; 2,47]	0,92 [0,32 ; 2,61];	-0,46 [-6,14 ; 5,23]; 1	1	
Gender	Female	345	31	8.99	356	25	7.02	1,28 [0,77 ; 2,12]	1,31 [0,75 ; 2,26];	1,96 [-2,06 ; 5,98]; 0,403	0,403	0,3337
	Male	200	11	5.50	192	13	6.77	0,81 [0,37 ; 1,77]	0,8 [0,35 ; 1,84];	-1,27 [-6,03 ; 3,48]; 0,676	0,676	
Number of baseline Gd-enhancing lesions	>=1	258	31	12.02	251	17	6.77	1,77 [1,01 ; 3,12]	1,88 [1,01 ; 3,49];	5,24 [0,2 ; 10,28]; 0,049	0,049	0,0078
	0	286	11	3.85	293	21	7.17	0,54 [0,26 ; 1,09]	0,52 [0,25 ; 1,1];	-3,32 [-7,02 ; 0,38]; 0,101	0,101	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	17	7.56	202	12	5.94	1,27 [0,62 ; 2,6]	1,29 [0,6 ; 2,78];	1,61 [-3,13 ; 6,36]; 0,567	0,567	0,6004
	>=3	84	9	10.71	98	7	7.14	1,5 [0,58 ; 3,85]	1,56 [0,55 ; 4,39];	3,57 [-4,78 ; 11,92]; 0,44	0,44	
	2	236	16	6.78	248	19	7.66	0,88 [0,47 ; 1,68]	0,88 [0,44 ; 1,75];	-0,88 [-5,49 ; 3,73]; 0,729	0,729	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	42	7.85	536	38	7.09	1,11 [0,73 ; 1,69]	1,12 [0,71 ; 1,76];	0,76 [-2,39 ; 3,91]; 0,644	0,644	
	No	347	22	6.34	379	24	6.33	1 [0,57 ; 1,75]	1 [0,55 ; 1,82];	0,01 [-3,54 ; 3,56]; 1	1	0,6478

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	20	10.10	169	14	8.28	1,22 [0,64 ; 2,34]	1,24 [0,61 ; 2,55];	1,82 [-4,09 ; 7,72]; 0,592	0,592	
Region	Eastern Europe	492	41	8.33	495	36	7.27	1,15 [0,75 ; 1,76]	1,16 [0,73 ; 1,85];	1,06 [-2,29 ; 4,41]; 0,555	0,555	0,4826
	USA and Western Europe	53	1	1.89	53	2	3.77	0,5 [0,05 ; 5,35]	0,49 [0,04 ; 5,58];	-1,89 [-8,19 ; 4,42]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Respiratory tract infection

6.2.72 Vascular disorders - Hypertension

Tabelle 433: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	13	3.99	302	13	4.30	0,93 [0,44 ; 1,97]	0,92 [0,42 ; 2,02];	-0,32 [-3,44 ; 2,81]; 0,844	0,844	0,1298
	>= 38 years	219	8	3.65	246	22	8.94	0,41 [0,19 ; 0,9]	0,39 [0,17 ; 0,89];	-5,29 [-9,64 ; -0,94]; 0,023	0,023	
Disease Severity at baseline (EDSS)	<=3.5	419	17	4.06	415	27	6.51	0,62 [0,35 ; 1,13]	0,61 [0,33 ; 1,13];	-2,45 [-5,48 ; 0,58]; 0,123	0,123	0,8067
	>3.5	126	4	3.17	133	8	6.02	0,53 [0,16 ; 1,71]	0,51 [0,15 ; 1,75];	-2,84 [-7,91 ; 2,23]; 0,378	0,378	
Gender	Female	345	15	4.35	356	23	6.46	0,67 [0,36 ; 1,27]	0,66 [0,34 ; 1,28];	-2,11 [-5,45 ; 1,23]; 0,245	0,245	0,5664
	Male	200	6	3.00	192	12	6.25	0,48 [0,18 ; 1,25]	0,46 [0,17 ; 1,26];	-3,25 [-7,41 ; 0,91]; 0,15	0,15	
Number of baseline Gd-enhancing lesions	>=1	258	9	3.49	251	16	6.37	0,55 [0,25 ; 1,22]	0,53 [0,23 ; 1,22];	-2,89 [-6,65 ; 0,88]; 0,153	0,153	0,7604
	0	286	12	4.20	293	19	6.48	0,65 [0,32 ; 1,31]	0,63 [0,3 ; 1,33];	-2,29 [-5,94 ; 1,36]; 0,269	0,269	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	9	4.00	202	14	6.93	0,58 [0,26 ; 1,3]	0,56 [0,24 ; 1,32];	-2,93 [-7,27 ; 1,41]; 0,202	0,202	0,5639
	>=3	84	4	4.76	98	4	4.08	1,17 [0,3 ; 4,52]	1,18 [0,28 ; 4,85];	0,68 [-5,33 ; 6,69]; 1	1	
	2	236	8	3.39	248	17	6.85	0,49 [0,22 ; 1,12]	0,48 [0,2 ; 1,13];	-3,47 [-7,37 ; 0,44]; 0,101	0,101	
Race	Other	10	0	0.00	12	1	8.33	0,39 [0,02 ; 8,73]	0,37 [0,01 ; 9,98];	-6,99 [-28,28 ; 14,29]; 0,493	0,493	0,3588
	White	535	21	3.93	536	34	6.34	0,62 [0,36 ; 1,05]	0,6 [0,35 ; 1,05];	-2,42 [-5,06 ; 0,22]; 0,096	0,096	
	No	347	8	2.31	379	24	6.33	0,36 [0,17 ; 0,8]	0,35 [0,15 ; 0,79];	-4,03 [-6,94 ; -1,11]; 0,01	0,01	0,0685

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	13	6.57	169	11	6.51	1,01 [0,46 ; 2,19]	1,01 [0,44 ; 2,32];	0,06 [-5,02 ; 5,13]; 1	1	
Region	Eastern Europe	492	21	4.27	495	32	6.46	0,66 [0,39 ; 1,13]	0,65 [0,37 ; 1,14];	-2,2 [-5 ; 0,61]; 0,157	0,157	0,0854
	USA and Western Europe	53	0	0.00	53	3	5.66	0,14 [0,01 ; 2,7]	0,13 [0,01 ; 2,68];	-5,56 [-12,6 ; 1,49]; 0,118	0,118	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Vascular disorders | Hypertension

6.2.73 General disorders and administration site conditions - Asthenia

Tabelle 434: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	18	5.52	302	18	5.96	0,93 [0,49 ; 1,75]	0,92 [0,47 ; 1,81];	-0,44 [-4,08 ; 3,2]; 0,865	0,865	0,8246
	>= 38 years	219	8	3.65	246	11	4.47	0,82 [0,33 ; 1,99]	0,81 [0,32 ; 2,05];	-0,82 [-4,4 ; 2,77]; 0,815	0,815	
Disease Severity at baseline (EDSS)	<=3.5	419	22	5.25	415	20	4.82	1,09 [0,6 ; 1,97]	1,09 [0,59 ; 2,04];	0,43 [-2,54 ; 3,4]; 0,874	0,874	0,1889
	>3.5	126	4	3.17	133	9	6.77	0,47 [0,15 ; 1,49]	0,45 [0,14 ; 1,51];	-3,59 [-8,85 ; 1,66]; 0,257	0,257	
Gender	Female	345	17	4.93	356	17	4.78	1,03 [0,54 ; 1,99]	1,03 [0,52 ; 2,06];	0,15 [-3,03 ; 3,33]; 1	1	0,5066
	Male	200	9	4.50	192	12	6.25	0,72 [0,31 ; 1,67]	0,71 [0,29 ; 1,72];	-1,75 [-6,22 ; 2,72]; 0,505	0,505	
Number of baseline Gd-enhancing lesions	>=1	258	11	4.26	251	14	5.58	0,76 [0,35 ; 1,65]	0,75 [0,34 ; 1,69];	-1,31 [-5,07 ; 2,45]; 0,543	0,543	0,5804
	0	286	15	5.24	293	15	5.12	1,02 [0,51 ; 2,06]	1,03 [0,49 ; 2,14];	0,13 [-3,49 ; 3,74]; 1	1	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	13	5.78	202	7	3.47	1,67 [0,68 ; 4,1]	1,71 [0,67 ; 4,37];	2,31 [-1,64 ; 6,27]; 0,359	0,359	0,2057
	>=3	84	2	2.38	98	5	5.10	0,47 [0,09 ; 2,34]	0,45 [0,09 ; 2,4];	-2,72 [-8,16 ; 2,72]; 0,454	0,454	
	2	236	11	4.66	248	17	6.85	0,68 [0,33 ; 1,42]	0,66 [0,3 ; 1,45];	-2,19 [-6,33 ; 1,94]; 0,335	0,335	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	26	4.86	536	29	5.41	0,9 [0,54 ; 1,5]	0,89 [0,52 ; 1,54];	-0,55 [-3,19 ; 2,09]; 0,782	0,782	
	No	347	14	4.03	379	19	5.01	0,8 [0,41 ; 1,58]	0,8 [0,39 ; 1,61];	-0,98 [-4 ; 2,04]; 0,595	0,595	0,6567

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	12	6.06	169	10	5.92	1,02 [0,45 ; 2,31]	1,03 [0,43 ; 2,44];	0,14 [-4,72 ; 5,01]; 1	1	
Region	Eastern Europe	492	25	5.08	495	28	5.66	0,9 [0,53 ; 1,52]	0,89 [0,51 ; 1,55];	-0,58 [-3,39 ; 2,24]; 0,778	0,778	0,938
	USA and Western Europe	53	1	1.89	53	1	1.89	1 [0,06 ; 15,57]	1 [0,06 ; 16,42];	0 [-5,18 ; 5,18]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - General disorders and administration site conditions | Asthenia

6.2.74 Blood and lymphatic system disorders - Lymphopenia

Tabelle 435: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	23	7.06	302	2	0.66	10,65 [2,53 ; 44,8]	11,39 [2,66 ; 48,72];	6,39 [3,47 ; 9,32]; 0	0	0,5978
	>= 38 years	219	11	5.02	246	2	0.81	6,18 [1,38 ; 27,57]	6,45 [1,41 ; 29,44];	4,21 [1,11 ; 7,31]; 0,009	0,009	
Disease Severity at baseline (EDSS)	<=3.5	419	28	6.68	415	2	0.48	13,87 [3,32 ; 57,83]	14,79 [3,5 ; 62,49];	6,2 [3,72 ; 8,68]; 0	0	0,1824
	>3.5	126	6	4.76	133	2	1.50	3,17 [0,65 ; 15,4]	3,28 [0,65 ; 16,54];	3,26 [-1 ; 7,51]; 0,163	0,163	
Gender	Female	345	22	6.38	356	2	0.56	11,35 [2,69 ; 47,9]	12,06 [2,81 ; 51,67];	5,82 [3,12 ; 8,51]; 0	0	0,5233
	Male	200	12	6.00	192	2	1.04	5,76 [1,31 ; 25,4]	6,06 [1,34 ; 27,46];	4,96 [1,37 ; 8,55]; 0,012	0,012	
Number of baseline Gd-enhancing lesions	>=1	258	14	5.43	251	3	1.20	4,54 [1,32 ; 15,61]	4,74 [1,35 ; 16,71];	4,23 [1,16 ; 7,3]; 0,011	0,011	
	0	286	20	6.99	293	1	0.34	20,49 [2,77 ; 151,66]	21,95 [2,93 ; 164,71];	6,65 [3,62 ; 9,68]; 0	0	0,1731
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	14	6.22	202	1	0.50	12,57 [1,67 ; 94,73]	13,34 [1,74 ; 102,35];	5,73 [2,43 ; 9,03]; 0,001	0,001	
	>=3	84	7	8.33	98	0	0.00	17,47 [1,01 ; 301,42]	19,06 [1,07 ; 338,99];	8,32 [2,13 ; 14,51]; 0,002	0,002	0,2414
	2	236	13	5.51	248	3	1.21	4,55 [1,31 ; 15,78]	4,76 [1,34 ; 16,93];	4,3 [1,09 ; 7,51]; 0,01	0,01	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9997
	White	535	34	6.36	536	4	0.75	8,52 [3,04 ; 23,83]	9,03 [3,18 ; 25,62];	5,61 [3,42 ; 7,8]; 0	0	
	No	347	13	3.75	379	1	0.26	14,2 [1,87 ; 107,97]	14,71 [1,91 ; 113,07];	3,48 [1,42 ; 5,55]; 0,001	0,001	0,4863

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	21	10.61	169	3	1.78	5,97 [1,81 ; 19,68]	6,56 [1,92 ; 22,42];	8,83 [4,1 ; 13,56]; 0,001	0,001	
Region	Eastern Europe	492	33	6.71	495	4	0.81	8,3 [2,96 ; 23,25]	8,83 [3,1 ; 25,1];	5,9 [3,55 ; 8,25]; 0	0	0,6427
	USA and Western Europe	53	1	1.89	53	0	0.00	3 [0,12 ; 72,02]	3,06 [0,12 ; 76,76];	1,85 [-3,22 ; 6,93]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Blood and lymphatic system disorders | Lymphopenia

6.2.75 Infections and infestations - Respiratory tract infection viral

Tabelle 436: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	33	10.12	302	21	6.95	1,46 [0,86 ; 2,46]	1,51 [0,85 ; 2,67];	3,17 [-1,18 ; 7,52]; 0,2	0,2	0,4696
	>= 38 years	219	9	4.11	246	10	4.07	1,01 [0,42 ; 2,44]	1,01 [0,4 ; 2,54];	0,04 [-3,56 ; 3,65]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	35	8.35	415	25	6.02	1,39 [0,85 ; 2,27]	1,42 [0,84 ; 2,42];	2,33 [-1,17 ; 5,83]; 0,228	0,228	0,8338
	>3.5	126	7	5.56	133	6	4.51	1,23 [0,43 ; 3,56]	1,25 [0,41 ; 3,81];	1,04 [-4,29 ; 6,38]; 0,78	0,78	
Gender	Female	345	26	7.54	356	21	5.90	1,28 [0,73 ; 2,23]	1,3 [0,72 ; 2,36];	1,64 [-2,07 ; 5,35]; 0,451	0,451	0,7023
	Male	200	16	8.00	192	10	5.21	1,54 [0,71 ; 3,3]	1,58 [0,7 ; 3,58];	2,79 [-2,11 ; 7,69]; 0,313	0,313	
Number of baseline Gd-enhancing lesions	>=1	258	17	6.59	251	16	6.37	1,03 [0,53 ; 2]	1,04 [0,51 ; 2,1];	0,21 [-4,06 ; 4,49]; 1	1	0,2743
	0	286	25	8.74	293	15	5.12	1,71 [0,92 ; 3,17]	1,78 [0,92 ; 3,44];	3,62 [-0,51 ; 7,75]; 0,101	0,101	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	17	7.56	202	9	4.46	1,7 [0,77 ; 3,72]	1,75 [0,76 ; 4,02];	3,1 [-1,37 ; 7,57]; 0,225	0,225	0,3502
	>=3	84	8	9.52	98	4	4.08	2,33 [0,73 ; 7,48]	2,47 [0,72 ; 8,53];	5,44 [-1,96 ; 12,84]; 0,23	0,23	
	2	236	17	7.20	248	18	7.26	0,99 [0,52 ; 1,88]	0,99 [0,5 ; 1,97];	-0,05 [-4,67 ; 4,56]; 1	1	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	42	7.85	536	31	5.78	1,36 [0,87 ; 2,13]	1,39 [0,86 ; 2,24];	2,07 [-0,95 ; 5,08]; 0,185	0,185	
	No	347	13	3.75	379	13	3.43	1,09 [0,51 ; 2,32]	1,1 [0,5 ; 2,4];	0,32 [-2,39 ; 3,03]; 0,844	0,844	0,5938

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	29	14.65	169	18	10.65	1,38 [0,79 ; 2,39]	1,44 [0,77 ; 2,7];	4 [-2,78 ; 10,77]; 0,276	0,276	
Region	Eastern Europe	492	42	8.54	495	31	6.26	1,36 [0,87 ; 2,13]	1,4 [0,86 ; 2,26];	2,27 [-0,99 ; 5,54]; 0,183	0,183	0,9999
	USA and Western Europe	53	0	0.00	53	0	0.00	1 [0,02 ; 49,49]	1 [0,02 ; 51,33];	0 [-3,61 ; 3,61]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Respiratory tract infection viral

6.2.76 General disorders and administration site conditions - Hyperthermia

Tabelle 437: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	25	7.67	302	2	0.66	11,58 [2,77 ; 48,47]	12,46 [2,92 ; 53,07];	7,01 [3,98 ; 10,04]; 0	0	0,036
	>= 38 years	219	6	2.74	246	4	1.63	1,68 [0,48 ; 5,89]	1,7 [0,47 ; 6,12];	1,11 [-1,56 ; 3,79]; 0,527	0,527	
Disease Severity at baseline (EDSS)	<=3.5	419	22	5.25	415	3	0.72	7,26 [2,19 ; 24,08]	7,61 [2,26 ; 25,63];	4,53 [2,24 ; 6,81]; 0	0	0,3715
	>3.5	126	9	7.14	133	3	2.26	3,17 [0,88 ; 11,43]	3,33 [0,88 ; 12,61];	4,89 [-0,27 ; 10,04]; 0,078	0,078	
Gender	Female	345	22	6.38	356	5	1.40	4,54 [1,74 ; 11,85]	4,78 [1,79 ; 12,77];	4,97 [2,12 ; 7,83]; 0,001	0,001	0,5706
	Male	200	9	4.50	192	1	0.52	8,64 [1,11 ; 67,55]	9 [1,13 ; 71,73];	3,98 [0,93 ; 7,03]; 0,02	0,02	
Number of baseline Gd-enhancing lesions	>=1	258	17	6.59	251	4	1.59	4,13 [1,41 ; 12,12]	4,36 [1,44 ; 13,13];	5 [1,59 ; 8,4]; 0,006	0,006	
	0	286	14	4.90	293	2	0.68	7,17 [1,64 ; 31,27]	7,49 [1,69 ; 33,26];	4,21 [1,54 ; 6,88]; 0,002	0,002	0,56
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	8	3.56	202	2	0.99	3,59 [0,77 ; 16,71]	3,69 [0,77 ; 17,57];	2,57 [-0,21 ; 5,34]; 0,11	0,11	
	>=3	84	13	15.48	98	1	1.02	15,17 [2,03 ; 113,53]	17,76 [2,27 ; 138,91];	14,46 [6,47 ; 22,44]; 0	0	0,3158
	2	236	10	4.24	248	3	1.21	3,5 [0,98 ; 12,57]	3,61 [0,98 ; 13,3];	3,03 [0,12 ; 5,94]; 0,049	0,049	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9998
	White	535	31	5.79	536	6	1.12	5,18 [2,18 ; 12,31]	5,43 [2,25 ; 13,13];	4,67 [2,5 ; 6,85]; 0	0	
	No	347	17	4.90	379	4	1.06	4,64 [1,58 ; 13,66]	4,83 [1,61 ; 14,5];	3,84 [1,35 ; 6,34]; 0,003	0,003	0,7701

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	14	7.07	169	2	1.18	5,97 [1,38 ; 25,92]	6,35 [1,42 ; 28,37];	5,89 [1,96 ; 9,81]; 0,008	0,008	
Region	Eastern Europe	492	31	6.30	495	6	1.21	5,2 [2,19 ; 12,35]	5,48 [2,27 ; 13,26];	5,09 [2,74 ; 7,44]; 0	0	0,9998
	USA and Western Europe	53	0	0.00	53	0	0.00	1 [0,02 ; 49,49]	1 [0,02 ; 51,33];	0 [-3,61 ; 3,61]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - General disorders and administration site conditions | Hyperthermia

6.2.77 General disorders and administration site conditions - Influenza like illness

Tabelle 438: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	28	8.59	302	5	1.66	5,19 [2,03 ; 13,26]	5,58 [2,13 ; 14,65];	6,93 [3,57 ; 10,3]; 0	0	0,1721
	>= 38 years	219	11	5.02	246	6	2.44	2,06 [0,77 ; 5,48]	2,12 [0,77 ; 5,82];	2,58 [-0,89 ; 6,06]; 0,148	0,148	
Disease Severity at baseline (EDSS)	<=3.5	419	32	7.64	415	6	1.45	5,28 [2,23 ; 12,5]	5,64 [2,33 ; 13,63];	6,19 [3,4 ; 8,98]; 0	0	0,0809
	>3.5	126	7	5.56	133	5	3.76	1,48 [0,48 ; 4,54]	1,51 [0,47 ; 4,87];	1,8 [-3,35 ; 6,94]; 0,563	0,563	
Gender	Female	345	27	7.83	356	11	3.09	2,53 [1,28 ; 5,03]	2,66 [1,3 ; 5,46];	4,74 [1,38 ; 8,09]; 0,007	0,007	0,0105
	Male	200	12	6.00	192	0	0.00	24 [1,43 ; 402,64]	25,53 [1,5 ; 434,28];	5,96 [2,55 ; 9,37]; 0	0	
Number of baseline Gd-enhancing lesions	>=1	258	18	6.98	251	5	1.99	3,5 [1,32 ; 9,29]	3,69 [1,35 ; 10,1];	4,98 [1,43 ; 8,54]; 0,009	0,009	0,9692
	0	286	21	7.34	293	6	2.05	3,59 [1,47 ; 8,75]	3,79 [1,51 ; 9,54];	5,29 [1,86 ; 8,73]; 0,003	0,003	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	14	6.22	202	4	1.98	3,14 [1,05 ; 9,39]	3,28 [1,06 ; 10,15];	4,24 [0,55 ; 7,94]; 0,032	0,032	0,9074
	>=3	84	8	9.52	98	2	2.04	4,67 [1,02 ; 21,38]	5,05 [1,04 ; 24,49];	7,48 [0,61 ; 14,36]; 0,046	0,046	
	2	236	17	7.20	248	5	2.02	3,57 [1,34 ; 9,53]	3,77 [1,37 ; 10,4];	5,19 [1,45 ; 8,92]; 0,008	0,008	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9998
	White	535	39	7.29	536	11	2.05	3,55 [1,84 ; 6,86]	3,75 [1,9 ; 7,41];	5,24 [2,73 ; 7,75]; 0	0	
	No	347	26	7.49	379	7	1.85	4,06 [1,78 ; 9,23]	4,3 [1,84 ; 10,05];	5,65 [2,56 ; 8,73]; 0	0	0,5893

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	13	6.57	169	4	2.37	2,77 [0,92 ; 8,35]	2,9 [0,93 ; 9,06];	4,2 [0,06 ; 8,34]; 0,079	0,079	
Region	Eastern Europe	492	39	7.93	495	11	2.22	3,57 [1,85 ; 6,88]	3,79 [1,92 ; 7,49];	5,7 [2,99 ; 8,42]; 0	0	0,9998
	USA and Western Europe	53	0	0.00	53	0	0.00	1 [0,02 ; 49,49]	1 [0,02 ; 51,33];	0 [-3,61 ; 3,61]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - General disorders and administration site conditions | Influenza like illness

6.2.78 Investigations - Alanine aminotransferase increased

Tabelle 439: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	12	3.68	302	16	5.30	0,69 [0,33 ; 1,44]	0,68 [0,32 ; 1,47];	-1,62 [-4,87 ; 1,63]; 0,341	0,341	0,4539
	>= 38 years	219	7	3.20	246	7	2.85	1,12 [0,4 ; 3,15]	1,13 [0,39 ; 3,27];	0,35 [-2,77 ; 3,47]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	16	3.82	415	18	4.34	0,88 [0,46 ; 1,7]	0,88 [0,44 ; 1,74];	-0,52 [-3,2 ; 2,17]; 0,729	0,729	0,6777
	>3.5	126	3	2.38	133	5	3.76	0,63 [0,15 ; 2,6]	0,62 [0,15 ; 2,67];	-1,38 [-5,57 ; 2,81]; 0,723	0,723	
Gender	Female	345	9	2.61	356	11	3.09	0,84 [0,35 ; 2,01]	0,84 [0,34 ; 2,05];	-0,48 [-2,94 ; 1,98]; 0,822	0,822	0,9219
	Male	200	10	5.00	192	12	6.25	0,8 [0,35 ; 1,81]	0,79 [0,33 ; 1,87];	-1,25 [-5,82 ; 3,32]; 0,664	0,664	
Number of baseline Gd-enhancing lesions	>=1	258	13	5.04	251	12	4.78	1,05 [0,49 ; 2,27]	1,06 [0,47 ; 2,36];	0,26 [-3,5 ; 4,01]; 1	1	0,3156
	0	286	6	2.10	293	11	3.75	0,56 [0,21 ; 1,49]	0,55 [0,2 ; 1,51];	-1,66 [-4,39 ; 1,08]; 0,326	0,326	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	9	4.00	202	6	2.97	1,35 [0,49 ; 3,72]	1,36 [0,48 ; 3,89];	1,03 [-2,44 ; 4,5]; 0,609	0,609	0,5024
	>=3	84	4	4.76	98	8	8.16	0,58 [0,18 ; 1,87]	0,56 [0,16 ; 1,94];	-3,4 [-10,48 ; 3,68]; 0,389	0,389	
	2	236	6	2.54	248	9	3.63	0,7 [0,25 ; 1,94]	0,69 [0,24 ; 1,98];	-1,09 [-4,16 ; 1,99]; 0,603	0,603	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	19	3.55	536	23	4.29	0,83 [0,46 ; 1,5]	0,82 [0,44 ; 1,53];	-0,74 [-3,06 ; 1,58]; 0,637	0,637	
	No	347	13	3.75	379	14	3.69	1,01 [0,48 ; 2,13]	1,01 [0,47 ; 2,19];	0,05 [-2,7 ; 2,81]; 1	1	0,363

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	6	3.03	169	9	5.33	0,57 [0,21 ; 1,57]	0,56 [0,19 ; 1,59];	-2,3 [-6,44 ; 1,85]; 0,3	0,3	
Region	Eastern Europe	492	17	3.46	495	22	4.44	0,78 [0,42 ; 1,45]	0,77 [0,4 ; 1,47];	-0,99 [-3,42 ; 1,44]; 0,514	0,514	0,4334
	USA and Western Europe	53	2	3.77	53	1	1.89	2 [0,19 ; 21,4]	2,04 [0,18 ; 23,19];	1,89 [-4,42 ; 8,19]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Investigations | Alanine aminotransferase increased

6.2.79 Investigations - Body temperature increased

Tabelle 440: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	16	4.91	302	4	1.32	3,71 [1,25 ; 10,96]	3,85 [1,27 ; 11,63];	3,58 [0,91 ; 6,26]; 0,012	0,012	0,849
	>= 38 years	219	8	3.65	246	2	0.81	4,49 [0,96 ; 20,93]	4,63 [0,97 ; 22,02];	2,84 [0,11 ; 5,57]; 0,052	0,052	
Disease Severity at baseline (EDSS)	<=3.5	419	18	4.30	415	4	0.96	4,46 [1,52 ; 13,06]	4,61 [1,55 ; 13,75];	3,33 [1,18 ; 5,49]; 0,004	0,004	0,7339
	>3.5	126	6	4.76	133	2	1.50	3,17 [0,65 ; 15,4]	3,28 [0,65 ; 16,54];	3,26 [-1 ; 7,51]; 0,163	0,163	
Gender	Female	345	16	4.64	356	3	0.84	5,5 [1,62 ; 18,72]	5,72 [1,65 ; 19,82];	3,79 [1,38 ; 6,21]; 0,002	0,002	0,4054
	Male	200	8	4.00	192	3	1.56	2,56 [0,69 ; 9,51]	2,62 [0,69 ; 10,05];	2,44 [-0,8 ; 5,67]; 0,221	0,221	
Number of baseline Gd-enhancing lesions	>=1	258	7	2.71	251	4	1.59	1,7 [0,5 ; 5,74]	1,72 [0,5 ; 5,96];	1,12 [-1,4 ; 3,64]; 0,545	0,545	0,0777
	0	286	17	5.94	293	2	0.68	8,71 [2,03 ; 37,35]	9,2 [2,1 ; 40,17];	5,26 [2,36 ; 8,16]; 0	0	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	8	3.56	202	1	0.50	7,18 [0,91 ; 56,93]	7,41 [0,92 ; 59,77];	3,06 [0,45 ; 5,67]; 0,04	0,04	0,7707
	>=3	84	4	4.76	98	1	1.02	4,67 [0,53 ; 40,95]	4,85 [0,53 ; 44,26];	3,74 [-1,23 ; 8,71]; 0,183	0,183	
	2	236	12	5.08	248	4	1.61	3,15 [1,03 ; 9,64]	3,27 [1,04 ; 10,28];	3,47 [0,26 ; 6,68]; 0,041	0,041	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9998
	White	535	24	4.49	536	6	1.12	4,01 [1,65 ; 9,73]	4,15 [1,68 ; 10,23];	3,37 [1,4 ; 5,33]; 0,001	0,001	
	No	347	12	3.46	379	3	0.79	4,37 [1,24 ; 15,35]	4,49 [1,26 ; 16,05];	2,67 [0,55 ; 4,79]; 0,016	0,016	0,8038

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	12	6.06	169	3	1.78	3,41 [0,98 ; 11,9]	3,57 [0,99 ; 12,87];	4,29 [0,41 ; 8,16]; 0,061	0,061	
Region	Eastern Europe	492	22	4.47	495	6	1.21	3,69 [1,51 ; 9,02]	3,81 [1,53 ; 9,49];	3,26 [1,19 ; 5,32]; 0,002	0,002	0,3375
	USA and Western Europe	53	2	3.77	53	0	0.00	5 [0,25 ; 101,73]	5,19 [0,24 ; 110,82];	3,7 [-2,46 ; 9,86]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Investigations | Body temperature increased

6.2.80 Investigations - Aspartate aminotransferase increased

Tabelle 441: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	13	3.99	302	6	1.99	2,01 [0,77 ; 5,21]	2,05 [0,77 ; 5,46];	2 [-0,64 ; 4,64]; 0,167	0,167	0,3717
	>= 38 years	219	8	3.65	246	2	0.81	4,49 [0,96 ; 20,93]	4,63 [0,97 ; 22,02];	2,84 [0,11 ; 5,57]; 0,052	0,052	
Disease Severity at baseline (EDSS)	<=3.5	419	15	3.58	415	8	1.93	1,86 [0,8 ; 4,33]	1,89 [0,79 ; 4,5];	1,65 [-0,56 ; 3,87]; 0,204	0,204	0,0301
	>3.5	126	6	4.76	133	0	0.00	13,72 [0,78 ; 241]	14,4 [0,8 ; 258,36];	4,74 [0,78 ; 8,71]; 0,012	0,012	
Gender	Female	345	13	3.77	356	5	1.40	2,68 [0,97 ; 7,45]	2,75 [0,97 ; 7,79];	2,36 [0,01 ; 4,72]; 0,057	0,057	0,9576
	Male	200	8	4.00	192	3	1.56	2,56 [0,69 ; 9,51]	2,62 [0,69 ; 10,05];	2,44 [-0,8 ; 5,67]; 0,221	0,221	
Number of baseline Gd-enhancing lesions	>=1	258	12	4.65	251	4	1.59	2,92 [0,95 ; 8,93]	3,01 [0,96 ; 9,47];	3,06 [0,06 ; 6,06]; 0,073	0,073	0,7673
	0	286	9	3.15	293	4	1.37	2,31 [0,72 ; 7,4]	2,35 [0,71 ; 7,71];	1,78 [-0,64 ; 4,2]; 0,17	0,17	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	7	3.11	202	1	0.50	6,28 [0,78 ; 50,64]	6,45 [0,79 ; 52,92];	2,62 [0,15 ; 5,08]; 0,071	0,071	0,4683
	>=3	84	8	9.52	98	3	3.06	3,11 [0,85 ; 11,35]	3,33 [0,85 ; 13];	6,46 [-0,68 ; 13,61]; 0,116	0,116	
	2	236	6	2.54	248	4	1.61	1,58 [0,45 ; 5,52]	1,59 [0,44 ; 5,71];	0,93 [-1,62 ; 3,48]; 0,536	0,536	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	21	3.93	536	8	1.49	2,63 [1,18 ; 5,88]	2,7 [1,18 ; 6,14];	2,43 [0,49 ; 4,37]; 0,015	0,015	
	No	347	13	3.75	379	5	1.32	2,84 [1,02 ; 7,88]	2,91 [1,03 ; 8,25];	2,43 [0,12 ; 4,73]; 0,053	0,053	0,7981

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	8	4.04	169	3	1.78	2,28 [0,61 ; 8,44]	2,33 [0,61 ; 8,93];	2,27 [-1,12 ; 5,65]; 0,236	0,236	
Region	Eastern Europe	492	20	4.07	495	7	1.41	2,87 [1,23 ; 6,74]	2,95 [1,24 ; 7,05];	2,65 [0,62 ; 4,68]; 0,011	0,011	0,4761
	USA and Western Europe	53	1	1.89	53	1	1.89	1 [0,06 ; 15,57]	1 [0,06 ; 16,42];	0 [-5,18 ; 5,18]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Investigations | Aspartate aminotransferase increased

6.2.81 Gastrointestinal disorders - Toothache

Tabelle 442: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	20	6.13	302	14	4.64	1,32 [0,68 ; 2,57]	1,34 [0,67 ; 2,71];	1,5 [-2,02 ; 5,02]; 0,482	0,482	0,1688
	>= 38 years	219	3	1.37	246	7	2.85	0,48 [0,13 ; 1,84]	0,47 [0,12 ; 1,86];	-1,48 [-4,06 ; 1,11]; 0,347	0,347	
Disease Severity at baseline (EDSS)	<=3.5	419	21	5.01	415	18	4.34	1,16 [0,62 ; 2,14]	1,16 [0,61 ; 2,22];	0,67 [-2,19 ; 3,54]; 0,743	0,743	0,5989
	>3.5	126	2	1.59	133	3	2.26	0,7 [0,12 ; 4,14]	0,7 [0,11 ; 4,25];	-0,67 [-4 ; 2,67]; 1	1	
Gender	Female	345	12	3.48	356	17	4.78	0,73 [0,35 ; 1,5]	0,72 [0,34 ; 1,53];	-1,3 [-4,24 ; 1,64]; 0,45	0,45	0,049
	Male	200	11	5.50	192	4	2.08	2,64 [0,86 ; 8,15]	2,74 [0,86 ; 8,74];	3,42 [-0,33 ; 7,17]; 0,113	0,113	
Number of baseline Gd-enhancing lesions	>=1	258	9	3.49	251	11	4.38	0,8 [0,34 ; 1,89]	0,79 [0,32 ; 1,94];	-0,89 [-4,27 ; 2,49]; 0,653	0,653	0,323
	0	286	14	4.90	293	10	3.41	1,43 [0,65 ; 3,18]	1,46 [0,64 ; 3,34];	1,48 [-1,77 ; 4,73]; 0,41	0,41	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	9	4.00	202	10	4.95	0,81 [0,34 ; 1,95]	0,8 [0,32 ; 2,01];	-0,95 [-4,89 ; 2,99]; 0,647	0,647	0,5179
	>=3	84	4	4.76	98	2	2.04	2,33 [0,44 ; 12,42]	2,4 [0,43 ; 13,44];	2,72 [-2,62 ; 8,07]; 0,417	0,417	
	2	236	10	4.24	248	9	3.63	1,17 [0,48 ; 2,82]	1,18 [0,47 ; 2,94];	0,61 [-2,86 ; 4,08]; 0,817	0,817	
Race	Other	10	0	0.00	12	1	8.33	0,39 [0,02 ; 8,73]	0,37 [0,01 ; 9,98];	-6,99 [-28,28 ; 14,29]; 0,493	0,493	0,2421
	White	535	23	4.30	536	20	3.73	1,15 [0,64 ; 2,07]	1,16 [0,63 ; 2,14];	0,57 [-1,78 ; 2,92]; 0,645	0,645	
	No	347	13	3.75	379	17	4.49	0,84 [0,41 ; 1,69]	0,83 [0,4 ; 1,73];	-0,74 [-3,63 ; 2,15]; 0,71	0,71	0,1577

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	10	5.05	169	4	2.37	2,13 [0,68 ; 6,68]	2,19 [0,68 ; 7,13];	2,68 [-1,13 ; 6,5]; 0,274	0,274	
Region	Eastern Europe	492	21	4.27	495	20	4.04	1,06 [0,58 ; 1,92]	1,06 [0,57 ; 1,98];	0,23 [-2,26 ; 2,72]; 0,875	0,875	0,6002
	USA and Western Europe	53	2	3.77	53	1	1.89	2 [0,19 ; 21,4]	2,04 [0,18 ; 23,19];	1,89 [-4,42 ; 8,19]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Gastrointestinal disorders | Toothache

6.2.82 Infections and infestations - Acute sinusitis

Tabelle 443: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	11	3.37	302	5	1.66	2,04 [0,72 ; 5,8]	2,07 [0,71 ; 6,04];	1,72 [-0,71 ; 4,15]; 0,21	0,21	0,3136
	>= 38 years	219	1	0.46	246	2	0.81	0,56 [0,05 ; 6,15]	0,56 [0,05 ; 6,21];	-0,36 [-1,79 ; 1,08]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	11	2.63	415	6	1.45	1,82 [0,68 ; 4,86]	1,84 [0,67 ; 5,02];	1,18 [-0,73 ; 3,09]; 0,327	0,327	0,7146
	>3.5	126	1	0.79	133	1	0.75	1,06 [0,07 ; 16,7]	1,06 [0,07 ; 17,07];	0,04 [-2,09 ; 2,18]; 1	1	
Gender	Female	345	12	3.48	356	6	1.69	2,06 [0,78 ; 5,44]	2,1 [0,78 ; 5,67];	1,79 [-0,56 ; 4,14]; 0,156	0,156	0,1371
	Male	200	0	0.00	192	1	0.52	0,32 [0,01 ; 7,81]	0,32 [0,01 ; 7,86];	-0,53 [-1,95 ; 0,89]; 0,242	0,242	
Number of baseline Gd-enhancing lesions	>=1	258	4	1.55	251	3	1.20	1,3 [0,29 ; 5,74]	1,3 [0,29 ; 5,88];	0,36 [-1,66 ; 2,38]; 1	1	0,6356
	0	286	8	2.80	293	4	1.37	2,05 [0,62 ; 6,73]	2,08 [0,62 ; 6,98];	1,43 [-0,9 ; 3,76]; 0,257	0,257	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	6	2.67	202	2	0.99	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	2	2.38	98	4	4.08	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	4	1.69	248	1	0.40	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	12	2.24	536	7	1.31	1,72 [0,68 ; 4,33]	1,73 [0,68 ; 4,44];	0,94 [-0,64 ; 2,52]; 0,259	0,259	
	No	347	8	2.31	379	3	0.79	2,91 [0,78 ; 10,89]	2,96 [0,78 ; 11,24];	1,51 [-0,3 ; 3,33]; 0,129	0,129	0,2014

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	4	2.02	169	4	2.37	0,85 [0,22 ; 3,36]	0,85 [0,21 ; 3,45];	-0,35 [-3,36 ; 2,67]; 1	1	
Region	Eastern Europe	492	12	2.44	495	7	1.41	1,72 [0,68 ; 4,34]	1,74 [0,68 ; 4,46];	1,02 [-0,69 ; 2,74]; 0,257	0,257	0,9999
	USA and Western Europe	53	0	0.00	53	0	0.00	1 [0,02 ; 49,49]	1 [0,02 ; 51,33];	0 [-3,61 ; 3,61]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Acute sinusitis

6.2.83 Infections and infestations - Pharyngitis

Tabelle 444: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	22	6.75	302	9	2.98	2,26 [1,06 ; 4,84]	2,36 [1,07 ; 5,2];	3,77 [0,44 ; 7,1]; 0,041	0,041	0,5147
	>= 38 years	219	10	4.57	246	3	1.22	3,74 [1,04 ; 13,43]	3,88 [1,05 ; 14,27];	3,35 [0,26 ; 6,43]; 0,045	0,045	
Disease Severity at baseline (EDSS)	<=3.5	419	24	5.73	415	12	2.89	1,98 [1 ; 3,91]	2,04 [1,01 ; 4,14];	2,84 [0,09 ; 5,58]; 0,06	0,06	0,0137
	>3.5	126	8	6.35	133	0	0.00	17,94 [1,05 ; 307,56]	19,15 [1,09 ; 335,38];	6,32 [1,85 ; 10,79]; 0,003	0,003	
Gender	Female	345	26	7.54	356	11	3.09	2,44 [1,22 ; 4,86]	2,56 [1,24 ; 5,26];	4,45 [1,13 ; 7,76]; 0,011	0,011	0,4318
	Male	200	6	3.00	192	1	0.52	5,76 [0,7 ; 47,4]	5,91 [0,7 ; 49,53];	2,48 [-0,09 ; 5,05]; 0,122	0,122	
Number of baseline Gd-enhancing lesions	>=1	258	16	6.20	251	5	1.99	3,11 [1,16 ; 8,37]	3,25 [1,17 ; 9,02];	4,21 [0,8 ; 7,62]; 0,024	0,024	0,6699
	0	286	16	5.59	293	7	2.39	2,34 [0,98 ; 5,61]	2,42 [0,98 ; 5,98];	3,21 [0,02 ; 6,39]; 0,056	0,056	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	13	5.78	202	5	2.48	2,33 [0,85 ; 6,43]	2,42 [0,85 ; 6,9];	3,3 [-0,42 ; 7,03]; 0,098	0,098	0,929
	>=3	84	7	8.33	98	3	3.06	2,72 [0,73 ; 10,2]	2,88 [0,72 ; 11,51];	5,27 [-1,55 ; 12,1]; 0,191	0,191	
	2	236	12	5.08	248	4	1.61	3,15 [1,03 ; 9,64]	3,27 [1,04 ; 10,28];	3,47 [0,26 ; 6,68]; 0,041	0,041	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	32	5.98	536	12	2.24	2,67 [1,39 ; 5,13]	2,78 [1,41 ; 5,45];	3,74 [1,37 ; 6,11]; 0,002	0,002	
	No	347	18	5.19	379	8	2.11	2,46 [1,08 ; 5,58]	2,54 [1,09 ; 5,91];	3,08 [0,33 ; 5,82]; 0,029	0,029	0,7666

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	14	7.07	169	4	2.37	2,99 [1 ; 8,9]	3,14 [1,01 ; 9,72];	4,7 [0,46 ; 8,95]; 0,051	0,051	
Region	Eastern Europe	492	31	6.30	495	12	2.42	2,6 [1,35 ; 5]	2,71 [1,37 ; 5,33];	3,88 [1,34 ; 6,42]; 0,003	0,003	0,4282
	USA and Western Europe	53	1	1.89	53	0	0.00	3 [0,12 ; 72,02]	3,06 [0,12 ; 76,76];	1,85 [-3,22 ; 6,93]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Pharyngitis

6.2.84 Blood and lymphatic system disorders - Anaemia

Tabelle 445: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	11	3.37	302	10	3.31	1,02 [0,44 ; 2,37]	1,02 [0,43 ; 2,44];	0,06 [-2,75 ; 2,88]; 1	1	0,3826
	>= 38 years	219	5	2.28	246	10	4.07	0,56 [0,19 ; 1,62]	0,55 [0,19 ; 1,64];	-1,78 [-4,94 ; 1,38]; 0,306	0,306	
Disease Severity at baseline (EDSS)	<=3.5	419	11	2.63	415	13	3.13	0,84 [0,38 ; 1,85]	0,83 [0,37 ; 1,88];	-0,51 [-2,78 ; 1,76]; 0,684	0,684	0,8755
	>3.5	126	5	3.97	133	7	5.26	0,75 [0,25 ; 2,31]	0,74 [0,23 ; 2,41];	-1,29 [-6,4 ; 3,81]; 0,77	0,77	
Gender	Female	345	16	4.64	356	20	5.62	0,83 [0,44 ; 1,57]	0,82 [0,42 ; 1,6];	-0,98 [-4,24 ; 2,28]; 0,61	0,61	1
	Male	200	0	0.00	192	0	0.00	0,96 [0,02 ; 48,15]	0,96 [0,02 ; 48,63];	-0,01 [-1 ; 0,98]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	258	9	3.49	251	7	2.79	1,25 [0,47 ; 3,31]	1,26 [0,46 ; 3,44];	0,7 [-2,33 ; 3,73]; 0,801	0,801	0,2215
	0	286	7	2.45	293	13	4.44	0,55 [0,22 ; 1,36]	0,54 [0,21 ; 1,37];	-1,99 [-4,95 ; 0,97]; 0,255	0,255	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	6	2.67	202	8	3.96	0,67 [0,24 ; 1,91]	0,66 [0,23 ; 1,95];	-1,29 [-4,71 ; 2,12]; 0,588	0,588	0,9028
	>=3	84	4	4.76	98	5	5.10	0,93 [0,26 ; 3,36]	0,93 [0,24 ; 3,58];	-0,34 [-6,64 ; 5,96]; 1	1	
	2	236	6	2.54	248	7	2.82	0,9 [0,31 ; 2,64]	0,9 [0,3 ; 2,71];	-0,28 [-3,16 ; 2,6]; 1	1	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	16	2.99	536	20	3.73	0,8 [0,42 ; 1,53]	0,8 [0,41 ; 1,55];	-0,74 [-2,9 ; 1,42]; 0,612	0,612	
	No	347	9	2.59	379	14	3.69	0,7 [0,31 ; 1,6]	0,69 [0,3 ; 1,62];	-1,1 [-3,63 ; 1,43]; 0,526	0,526	0,6123

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	7	3.54	169	6	3.55	1 [0,34 ; 2,91]	1 [0,33 ; 3,02];	-0,01 [-3,81 ; 3,78]; 1	1	
Region	Eastern Europe	492	16	3.25	495	19	3.84	0,85 [0,44 ; 1,63]	0,84 [0,43 ; 1,66];	-0,59 [-2,89 ; 1,72]; 0,731	0,731	0,2719
	USA and Western Europe	53	0	0.00	53	1	1.89	0,33 [0,01 ; 8]	0,33 [0,01 ; 8,21];	-1,85 [-6,93 ; 3,22]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Blood and lymphatic system disorders | Anaemia

6.2.85 Infections and infestations - Rhinitis

Tabelle 446: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	20	6.13	302	14	4.64	1,32 [0,68 ; 2,57]	1,34 [0,67 ; 2,71];	1,5 [-2,02 ; 5,02]; 0,482	0,482	0,2956
	>= 38 years	219	4	1.83	246	7	2.85	0,64 [0,19 ; 2,16]	0,64 [0,18 ; 2,2];	-1,02 [-3,75 ; 1,71]; 0,552	0,552	
Disease Severity at baseline (EDSS)	<=3.5	419	19	4.53	415	18	4.34	1,05 [0,56 ; 1,96]	1,05 [0,54 ; 2,03];	0,2 [-2,6 ; 2,99]; 1	1	0,5054
	>3.5	126	5	3.97	133	3	2.26	1,76 [0,43 ; 7,21]	1,79 [0,42 ; 7,65];	1,71 [-2,53 ; 5,95]; 0,491	0,491	
Gender	Female	345	10	2.90	356	16	4.49	0,64 [0,3 ; 1,4]	0,63 [0,28 ; 1,42];	-1,6 [-4,38 ; 1,19]; 0,319	0,319	0,021
	Male	200	14	7.00	192	5	2.60	2,69 [0,99 ; 7,32]	2,82 [0,99 ; 7,97];	4,4 [0,2 ; 8,59]; 0,058	0,058	
Number of baseline Gd-enhancing lesions	>=1	258	12	4.65	251	11	4.38	1,06 [0,48 ; 2,36]	1,06 [0,46 ; 2,46];	0,27 [-3,34 ; 3,88]; 1	1	0,803
	0	286	12	4.20	293	10	3.41	1,23 [0,54 ; 2,8]	1,24 [0,53 ; 2,92];	0,78 [-2,34 ; 3,9]; 0,668	0,668	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	3	1.33	202	12	5.94	0,22 [0,06 ; 0,78]	0,21 [0,06 ; 0,77];	-4,61 [-8,2 ; -1,02]; 0,015	0,015	0,0009
	>=3	84	3	3.57	98	3	3.06	1,17 [0,24 ; 5,63]	1,17 [0,23 ; 5,97];	0,51 [-4,72 ; 5,74]; 1	1	
	2	236	18	7.63	248	6	2.42	3,15 [1,27 ; 7,81]	3,33 [1,3 ; 8,54];	5,21 [1,32 ; 9,1]; 0,011	0,011	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	24	4.49	536	21	3.92	1,14 [0,65 ; 2,03]	1,15 [0,63 ; 2,1];	0,57 [-1,83 ; 2,97]; 0,652	0,652	
	No	347	17	4.90	379	16	4.22	1,16 [0,6 ; 2,26]	1,17 [0,58 ; 2,35];	0,68 [-2,36 ; 3,72]; 0,723	0,723	0,9676

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	7	3.54	169	5	2.96	1,19 [0,39 ; 3,7]	1,2 [0,37 ; 3,86];	0,58 [-3,05 ; 4,2]; 1	1	
Region	Eastern Europe	492	24	4.88	495	21	4.24	1,15 [0,65 ; 2,04]	1,16 [0,64 ; 2,11];	0,64 [-1,97 ; 3,24]; 0,65	0,65	1
	USA and Western Europe	53	0	0.00	53	0	0.00	1 [0,02 ; 49,49]	1 [0,02 ; 51,33];	0 [-3,61 ; 3,61]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Rhinitis

6.2.86 Infections and infestations - Vaginal infection

Tabelle 447: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	7	2.15	302	7	2.32	0,93 [0,33 ; 2,61]	0,92 [0,32 ; 2,67];	-0,17 [-2,48 ; 2,14]; 1	1	0,3059
	>= 38 years	219	6	2.74	246	3	1.22	2,25 [0,57 ; 8,88]	2,28 [0,56 ; 9,23];	1,52 [-1,04 ; 4,08]; 0,317	0,317	
Disease Severity at baseline (EDSS)	<=3.5	419	6	1.43	415	8	1.93	0,74 [0,26 ; 2,12]	0,74 [0,25 ; 2,15];	-0,5 [-2,24 ; 1,25]; 0,603	0,603	0,0741
	>3.5	126	7	5.56	133	2	1.50	3,69 [0,78 ; 17,45]	3,85 [0,78 ; 18,91];	4,05 [-0,45 ; 8,55]; 0,095	0,095	
Gender	Female	345	13	3.77	356	10	2.81	1,34 [0,6 ; 3,02]	1,35 [0,59 ; 3,13];	0,96 [-1,68 ; 3,6]; 0,529	0,529	1
	Male	200	0	0.00	192	0	0.00	0,96 [0,02 ; 48,15]	0,96 [0,02 ; 48,63];	-0,01 [-1 ; 0,98]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	258	6	2.33	251	4	1.59	1,46 [0,42 ; 5,11]	1,47 [0,41 ; 5,27];	0,73 [-1,67 ; 3,14]; 0,752	0,752	0,8133
	0	286	7	2.45	293	6	2.05	1,2 [0,41 ; 3,51]	1,2 [0,4 ; 3,62];	0,4 [-2,02 ; 2,82]; 0,786	0,786	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	3	1.33	202	5	2.48	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	3	3.57	98	3	3.06	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	7	2.97	248	2	0.81	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	13	2.43	536	10	1.87	1,3 [0,58 ; 2,94]	1,31 [0,57 ; 3,01];	0,56 [-1,17 ; 2,3]; 0,537	0,537	
	No	347	9	2.59	379	8	2.11	1,23 [0,48 ; 3,15]	1,23 [0,47 ; 3,24];	0,48 [-1,73 ; 2,69]; 0,807	0,807	0,7377

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	4	2.02	169	2	1.18	1,71 [0,32 ; 9,2]	1,72 [0,31 ; 9,52];	0,84 [-1,71 ; 3,39]; 0,691	0,691	
Region	Eastern Europe	492	12	2.44	495	10	2.02	1,21 [0,53 ; 2,77]	1,21 [0,52 ; 2,83];	0,42 [-1,42 ; 2,26]; 0,673	0,673	0,2783
	USA and Western Europe	53	1	1.89	53	0	0.00	3 [0,12 ; 72,02]	3,06 [0,12 ; 76,76];	1,85 [-3,22 ; 6,93]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Vaginal infection

6.2.87 Infections and infestations - Conjunctivitis

Tabelle 448: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	9	2.76	302	6	1.99	1,39 [0,5 ; 3,86]	1,4 [0,49 ; 3,98];	0,77 [-1,6 ; 3,15]; 0,607	0,607	0,0197
	>= 38 years	219	0	0.00	246	4	1.63	0,12 [0,01 ; 2,3]	0,12 [0,01 ; 2,29];	-1,59 [-3,38 ; 0,19]; 0,126	0,126	
Disease Severity at baseline (EDSS)	<=3.5	419	9	2.15	415	10	2.41	0,89 [0,37 ; 2,17]	0,89 [0,36 ; 2,21];	-0,26 [-2,29 ; 1,76]; 0,821	0,821	1
	>3.5	126	0	0.00	133	0	0.00	1,06 [0,02 ; 52,78]	1,06 [0,02 ; 53,59];	0,02 [-1,48 ; 1,52]; 1	1	
Gender	Female	345	7	2.03	356	5	1.40	1,44 [0,46 ; 4,51]	1,45 [0,46 ; 4,63];	0,62 [-1,3 ; 2,55]; 0,572	0,572	0,1752
	Male	200	2	1.00	192	5	2.60	0,38 [0,08 ; 1,96]	0,38 [0,07 ; 1,97];	-1,6 [-4,25 ; 1,04]; 0,276	0,276	
Number of baseline Gd-enhancing lesions	>=1	258	4	1.55	251	5	1.99	0,78 [0,21 ; 2,87]	0,77 [0,21 ; 2,92];	-0,44 [-2,74 ; 1,85]; 0,749	0,749	0,7633
	0	286	5	1.75	293	5	1.71	1,02 [0,3 ; 3,5]	1,02 [0,29 ; 3,58];	0,04 [-2,08 ; 2,16]; 1	1	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	3	1.33	202	3	1.49	0,9 [0,18 ; 4,4]	0,9 [0,18 ; 4,49];	-0,15 [-2,39 ; 2,09]; 1	1	0,1499
	>=3	84	2	2.38	98	0	0.00	5,82 [0,28 ; 119,63]	5,97 [0,28 ; 126,11];	2,44 [-1,42 ; 6,29]; 0,212	0,212	
	2	236	4	1.69	248	7	2.82	0,6 [0,18 ; 2,02]	0,59 [0,17 ; 2,05];	-1,13 [-3,77 ; 1,51]; 0,546	0,546	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	9	1.68	536	10	1.87	0,9 [0,37 ; 2,2]	0,9 [0,36 ; 2,23];	-0,18 [-1,76 ; 1,4]; 1	1	
	No	347	5	1.44	379	7	1.85	0,78 [0,25 ; 2,44]	0,78 [0,24 ; 2,47];	-0,41 [-2,25 ; 1,44]; 0,775	0,775	0,6912

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	4	2.02	169	3	1.78	1,14 [0,26 ; 5,01]	1,14 [0,25 ; 5,17];	0,25 [-2,55 ; 3,04]; 1	1	
Region	Eastern Europe	492	9	1.83	495	8	1.62	1,13 [0,44 ; 2,91]	1,13 [0,43 ; 2,96];	0,21 [-1,41 ; 1,84]; 0,812	0,812	0,0926
	USA and Western Europe	53	0	0.00	53	2	3.77	0,2 [0,01 ; 4,07]	0,19 [0,01 ; 4,11];	-3,7 [-9,86 ; 2,46]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Conjunctivitis

6.2.88 Immune system disorders - Hypersensitivity

Tabelle 449: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	8	2.45	302	1	0.33	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>= 38 years	219	5	2.28	246	4	1.63	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	419	11	2.63	415	3	0.72	3,63 [1,02 ; 12,92]	3,7 [1,03 ; 13,37];	1,9 [0,17 ; 3,64]; 0,055	0,055	0,2981
	>3.5	126	2	1.59	133	2	1.50	1,06 [0,15 ; 7,38]	1,06 [0,15 ; 7,62];	0,08 [-2,92 ; 3,09]; 1	1	
Gender	Female	345	9	2.61	356	5	1.40	1,86 [0,63 ; 5,49]	1,88 [0,62 ; 5,67];	1,2 [-0,88 ; 3,28]; 0,29	0,29	0,0907
	Male	200	4	2.00	192	0	0.00	8,64 [0,47 ; 159,44]	8,82 [0,47 ; 164,87];	1,98 [-0,19 ; 4,15]; 0,123	0,123	
Number of baseline Gd-enhancing lesions	>=1	258	6	2.33	251	1	0.40	5,84 [0,71 ; 48,14]	5,95 [0,71 ; 49,8];	1,93 [-0,07 ; 3,92]; 0,123	0,123	0,3135
	0	286	7	2.45	293	4	1.37	1,79 [0,53 ; 6,06]	1,81 [0,52 ; 6,26];	1,08 [-1,15 ; 3,31]; 0,378	0,378	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	5	2.22	202	3	1.49	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	1	1.19	98	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	7	2.97	248	2	0.81	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	0	0.00	12	2	16.67	0,24 [0,01 ; 4,42]	0,2 [0,01 ; 4,69];	-14,69 [-39,39 ; 10,02]; 0,481	0,481	0,0192
	White	535	13	2.43	536	3	0.56	4,34 [1,24 ; 15,15]	4,42 [1,25 ; 15,62];	1,87 [0,42 ; 3,32]; 0,012	0,012	
	No	347	8	2.31	379	1	0.26	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	5	2.53	169	4	2.37	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Region	Eastern Europe	492	13	2.64	495	3	0.61	4,36 [1,25 ; 15,2]	4,45 [1,26 ; 15,72];	2,04 [0,46 ; 3,61]; 0,012	0,012	0,0149
	USA and Western Europe	53	0	0.00	53	2	3.77	0,2 [0,01 ; 4,07]	0,19 [0,01 ; 4,11];	-3,7 [-9,86 ; 2,46]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Immune system disorders | Hypersensitivity

6.2.89 Infections and infestations - Cystitis

Tabelle 450: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	19	5.83	302	14	4.64	1,26 [0,64 ; 2,46]	1,27 [0,63 ; 2,59];	1,19 [-2,28 ; 4,67]; 0,592	0,592	0,859
	>= 38 years	219	6	2.74	246	6	2.44	1,12 [0,37 ; 3,43]	1,13 [0,36 ; 3,55];	0,3 [-2,6 ; 3,2]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	20	4.77	415	14	3.37	1,41 [0,72 ; 2,76]	1,44 [0,72 ; 2,88];	1,4 [-1,28 ; 4,08]; 0,382	0,382	0,4862
	>3.5	126	5	3.97	133	6	4.51	0,88 [0,28 ; 2,81]	0,87 [0,26 ; 2,94];	-0,54 [-5,45 ; 4,36]; 1	1	
Gender	Female	345	23	6.67	356	20	5.62	1,19 [0,66 ; 2,12]	1,2 [0,65 ; 2,23];	1,05 [-2,51 ; 4,61]; 0,638	0,638	0,1306
	Male	200	2	1.00	192	0	0.00	4,8 [0,23 ; 99,36]	4,85 [0,23 ; 101,65];	0,98 [-0,71 ; 2,68]; 0,499	0,499	
Number of baseline Gd-enhancing lesions	>=1	258	15	5.81	251	9	3.59	1,62 [0,72 ; 3,64]	1,66 [0,71 ; 3,87];	2,23 [-1,44 ; 5,89]; 0,297	0,297	0,3466
	0	286	10	3.50	293	11	3.75	0,93 [0,4 ; 2,16]	0,93 [0,39 ; 2,22];	-0,26 [-3,3 ; 2,79]; 1	1	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	7	3.11	202	8	3.96	0,79 [0,29 ; 2,13]	0,78 [0,28 ; 2,19];	-0,85 [-4,37 ; 2,67]; 0,794	0,794	0,2678
	>=3	84	4	4.76	98	1	1.02	4,67 [0,53 ; 40,95]	4,85 [0,53 ; 44,26];	3,74 [-1,23 ; 8,71]; 0,183	0,183	
	2	236	14	5.93	248	11	4.44	1,34 [0,62 ; 2,89]	1,36 [0,6 ; 3,06];	1,5 [-2,46 ; 5,45]; 0,54	0,54	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	25	4.67	536	20	3.73	1,25 [0,7 ; 2,23]	1,26 [0,69 ; 2,31];	0,94 [-1,46 ; 3,34]; 0,451	0,451	
	No	347	10	2.88	379	13	3.43	0,84 [0,37 ; 1,89]	0,84 [0,36 ; 1,93];	-0,55 [-3,09 ; 1,99]; 0,833	0,833	0,1907

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	15	7.58	169	7	4.14	1,83 [0,76 ; 4,38]	1,9 [0,75 ; 4,77];	3,43 [-1,32 ; 8,19]; 0,191	0,191	
Region	Eastern Europe	492	25	5.08	495	20	4.04	1,26 [0,71 ; 2,23]	1,27 [0,7 ; 2,32];	1,04 [-1,56 ; 3,64]; 0,45	0,45	1
	USA and Western Europe	53	0	0.00	53	0	0.00	1 [0,02 ; 49,49]	1 [0,02 ; 51,33];	0 [-3,61 ; 3,61]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Cystitis

6.2.90 Renal and urinary disorders - Leukocyturia

Tabelle 451: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	6	1.84	302	4	1.32	1,39 [0,4 ; 4,88]	1,4 [0,39 ; 5];	0,52 [-1,43 ; 2,46]; 0,754	0,754	0,9899
	>= 38 years	219	5	2.28	246	4	1.63	1,4 [0,38 ; 5,16]	1,41 [0,37 ; 5,33];	0,66 [-1,87 ; 3,19]; 0,741	0,741	
Disease Severity at baseline (EDSS)	<=3.5	419	8	1.91	415	4	0.96	1,98 [0,6 ; 6,53]	2 [0,6 ; 6,69];	0,95 [-0,67 ; 2,56]; 0,384	0,384	0,3405
	>3.5	126	3	2.38	133	4	3.01	0,79 [0,18 ; 3,47]	0,79 [0,17 ; 3,59];	-0,63 [-4,57 ; 3,31]; 1	1	
Gender	Female	345	10	2.90	356	6	1.69	1,72 [0,63 ; 4,68]	1,74 [0,63 ; 4,84];	1,21 [-1,01 ; 3,43]; 0,32	0,32	0,3167
	Male	200	1	0.50	192	2	1.04	0,48 [0,04 ; 5,25]	0,48 [0,04 ; 5,31];	-0,54 [-2,28 ; 1,2]; 0,616	0,616	
Number of baseline Gd-enhancing lesions	>=1	258	5	1.94	251	5	1.99	0,97 [0,29 ; 3,32]	0,97 [0,28 ; 3,4];	-0,05 [-2,47 ; 2,36]; 1	1	0,4248
	0	286	6	2.10	293	3	1.02	2,05 [0,52 ; 8,11]	2,07 [0,51 ; 8,36];	1,07 [-0,95 ; 3,1]; 0,335	0,335	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	1	0.44	202	3	1.49	0,3 [0,03 ; 2,85]	0,3 [0,03 ; 2,87];	-1,04 [-2,92 ; 0,84]; 0,348	0,348	0,0538
	>=3	84	3	3.57	98	0	0.00	8,15 [0,43 ; 155,61]	8,46 [0,43 ; 166,18];	3,61 [-0,84 ; 8,06]; 0,046	0,046	
	2	236	7	2.97	248	5	2.02	1,47 [0,47 ; 4,57]	1,49 [0,46 ; 4,75];	0,95 [-1,83 ; 3,73]; 0,568	0,568	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	11	2.06	536	8	1.49	1,38 [0,56 ; 3,4]	1,39 [0,55 ; 3,47];	0,56 [-1,02 ; 2,14]; 0,499	0,499	
	No	347	5	1.44	379	3	0.79	1,82 [0,44 ; 7,56]	1,83 [0,43 ; 7,72];	0,65 [-0,89 ; 2,19]; 0,489	0,489	0,5421

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	6	3.03	169	5	2.96	1,02 [0,32 ; 3,3]	1,03 [0,31 ; 3,42];	0,07 [-3,42 ; 3,57]; 1	1	
Region	Eastern Europe	492	11	2.24	495	8	1.62	1,38 [0,56 ; 3,41]	1,39 [0,56 ; 3,49];	0,62 [-1,1 ; 2,33]; 0,498	0,498	1
	USA and Western Europe	53	0	0.00	53	0	0.00	1 [0,02 ; 49,49]	1 [0,02 ; 51,33];	0 [-3,61 ; 3,61]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Renal and urinary disorders | Leukocyturia

6.2.91 Gastrointestinal disorders - Chronic gastritis

Tabelle 452: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	2	0.61	302	5	1.66	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>= 38 years	219	2	0.91	246	5	2.03	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Disease Severity at baseline (EDSS)	<=3.5	419	2	0.48	415	5	1.20	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>3.5	126	2	1.59	133	5	3.76	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Gender	Female	345	4	1.16	356	6	1.69	0,69 [0,2 ; 2,42]	0,68 [0,19 ; 2,45];	-0,53 [-2,28 ; 1,22]; 0,752	0,752	0,0623
	Male	200	0	0.00	192	4	2.08	0,11 [0,01 ; 1,97]	0,1 [0,01 ; 1,95];	-2,08 [-4,32 ; 0,15]; 0,057	0,057	
Number of baseline Gd-enhancing lesions	>=1	258	2	0.78	251	3	1.20	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	0	286	2	0.70	293	7	2.39	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	1	0.44	202	1	0.50	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	1	1.19	98	6	6.12	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	2	0.85	248	3	1.21	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	4	0.75	536	10	1.87	0,4 [0,13 ; 1,27]	0,4 [0,12 ; 1,27];	-1,12 [-2,48 ; 0,24]; 0,177	0,177	
	No	347	2	0.58	379	5	1.32	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	2	1.01	169	5	2.96	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Region	Eastern Europe	492	4	0.81	495	10	2.02	0,4 [0,13 ; 1,27]	0,4 [0,12 ; 1,28];	-1,21 [-2,68 ; 0,26]; 0,176	0,176	0,9999
	USA and Western Europe	53	0	0.00	53	0	0.00	1 [0,02 ; 49,49]	1 [0,02 ; 51,33];	0 [-3,61 ; 3,61]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Gastrointestinal disorders | Chronic gastritis

6.2.92 Infections and infestations - Tonsillitis

Tabelle 453: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	8	2.45	302	10	3.31	0,74 [0,3 ; 1,85]	0,73 [0,29 ; 1,89];	-0,86 [-3,48 ; 1,77]; 0,634	0,634	0,7769
	>= 38 years	219	1	0.46	246	1	0.41	1,12 [0,07 ; 17,85]	1,12 [0,07 ; 18,08];	0,05 [-1,15 ; 1,25]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	7	1.67	415	9	2.17	0,77 [0,29 ; 2,05]	0,77 [0,28 ; 2,08];	-0,5 [-2,36 ; 1,36]; 0,624	0,624	0,7764
	>3.5	126	2	1.59	133	2	1.50	1,06 [0,15 ; 7,38]	1,06 [0,15 ; 7,62];	0,08 [-2,92 ; 3,09]; 1	1	
Gender	Female	345	8	2.32	356	9	2.53	0,92 [0,36 ; 2,35]	0,92 [0,35 ; 2,4];	-0,21 [-2,49 ; 2,07]; 1	1	0,6155
	Male	200	1	0.50	192	2	1.04	0,48 [0,04 ; 5,25]	0,48 [0,04 ; 5,31];	-0,54 [-2,28 ; 1,2]; 0,616	0,616	
Number of baseline Gd-enhancing lesions	>=1	258	5	1.94	251	8	3.19	0,61 [0,2 ; 1,83]	0,6 [0,19 ; 1,86];	-1,25 [-4 ; 1,5]; 0,412	0,412	0,3864
	0	286	4	1.40	293	3	1.02	1,37 [0,31 ; 6,05]	1,37 [0,3 ; 6,18];	0,37 [-1,41 ; 2,16]; 0,722	0,722	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	2	0.89	202	3	1.49	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	5	5.95	98	4	4.08	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	2	0.85	248	4	1.61	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	9	1.68	536	11	2.05	0,82 [0,34 ; 1,96]	0,82 [0,34 ; 1,99];	-0,37 [-1,99 ; 1,25]; 0,822	0,822	
	No	347	5	1.44	379	9	2.37	0,61 [0,21 ; 1,79]	0,6 [0,2 ; 1,81];	-0,93 [-2,91 ; 1,05]; 0,426	0,426	0,2987

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	4	2.02	169	2	1.18	1,71 [0,32 ; 9,2]	1,72 [0,31 ; 9,52];	0,84 [-1,71 ; 3,39]; 0,691	0,691	
Region	Eastern Europe	492	9	1.83	495	10	2.02	0,91 [0,37 ; 2,21]	0,9 [0,36 ; 2,24];	-0,19 [-1,91 ; 1,52]; 1	1	0,2634
	USA and Western Europe	53	0	0.00	53	1	1.89	0,33 [0,01 ; 8]	0,33 [0,01 ; 8,21];	-1,85 [-6,93 ; 3,22]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Infections and infestations | Tonsillitis

6.2.93 Respiratory, thoracic and mediastinal disorders - Rhinitis allergic

Tabelle 454: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	9	2.76	302	6	1.99	1,39 [0,5 ; 3,86]	1,4 [0,49 ; 3,98];	0,77 [-1,6 ; 3,15]; 0,607	0,607	0,0926
	>= 38 years	219	1	0.46	246	5	2.03	0,22 [0,03 ; 1,91]	0,22 [0,03 ; 1,91];	-1,58 [-3,55 ; 0,4]; 0,22	0,22	
Disease Severity at baseline (EDSS)	<=3.5	419	9	2.15	415	9	2.17	0,99 [0,4 ; 2,47]	0,99 [0,39 ; 2,52];	-0,02 [-1,99 ; 1,95]; 1	1	0,6224
	>3.5	126	1	0.79	133	2	1.50	0,53 [0,05 ; 5,75]	0,52 [0,05 ; 5,85];	-0,71 [-3,29 ; 1,87]; 1	1	
Gender	Female	345	8	2.32	356	10	2.81	0,83 [0,33 ; 2,07]	0,82 [0,32 ; 2,11];	-0,49 [-2,83 ; 1,85]; 0,813	0,813	0,5064
	Male	200	2	1.00	192	1	0.52	1,92 [0,18 ; 21]	1,93 [0,17 ; 21,45];	0,48 [-1,23 ; 2,19]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	258	4	1.55	251	8	3.19	0,49 [0,15 ; 1,6]	0,48 [0,14 ; 1,61];	-1,64 [-4,28 ; 1,01]; 0,255	0,255	0,1094
	0	286	6	2.10	293	3	1.02	2,05 [0,52 ; 8,11]	2,07 [0,51 ; 8,36];	1,07 [-0,95 ; 3,1]; 0,335	0,335	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	3	1.33	202	6	2.97	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	>=3	84	2	2.38	98	3	3.06	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	2	236	5	2.12	248	2	0.81	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	1
	White	535	10	1.87	536	11	2.05	0,91 [0,39 ; 2,13]	0,91 [0,38 ; 2,16];	-0,18 [-1,84 ; 1,48]; 1	1	
	No	347	5	1.44	379	9	2.37	0,61 [0,21 ; 1,79]	0,6 [0,2 ; 1,81];	-0,93 [-2,91 ; 1,05]; 0,426	0,426	0,1896

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	5	2.53	169	2	1.18	2,13 [0,42 ; 10,86]	2,16 [0,41 ; 11,3];	1,34 [-1,38 ; 4,07]; 0,459	0,459	
Region	Eastern Europe	492	10	2.03	495	11	2.22	0,91 [0,39 ; 2,13]	0,91 [0,38 ; 2,17];	-0,19 [-1,99 ; 1,61]; 1	1	1
	USA and Western Europe	53	0	0.00	53	0	0.00	1 [0,02 ; 49,49]	1 [0,02 ; 51,33];	0 [-3,61 ; 3,61]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Respiratory, thoracic and mediastinal disorders | Rhinitis allergic

6.2.94 Cardiac disorders - Sinus tachycardia

Tabelle 455: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	13	3.99	302	8	2.65	1,51 [0,63 ; 3,58]	1,53 [0,62 ; 3,74];	1,34 [-1,45 ; 4,13]; 0,383	0,383	0,0654
	>= 38 years	219	12	5.48	246	2	0.81	6,74 [1,53 ; 29,78]	7,07 [1,56 ; 31,96];	4,67 [1,45 ; 7,88]; 0,005	0,005	
Disease Severity at baseline (EDSS)	<=3.5	419	18	4.30	415	6	1.45	2,97 [1,19 ; 7,41]	3,06 [1,2 ; 7,79];	2,85 [0,59 ; 5,11]; 0,021	0,021	0,551
	>3.5	126	7	5.56	133	4	3.01	1,85 [0,55 ; 6,16]	1,9 [0,54 ; 6,64];	2,55 [-2,39 ; 7,49]; 0,366	0,366	
Gender	Female	345	18	5.22	356	4	1.12	4,64 [1,59 ; 13,58]	4,84 [1,62 ; 14,46];	4,09 [1,5 ; 6,68]; 0,002	0,002	0,0614
	Male	200	7	3.50	192	6	3.12	1,12 [0,38 ; 3,27]	1,12 [0,37 ; 3,41];	0,38 [-3,17 ; 3,92]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	258	15	5.81	251	4	1.59	3,65 [1,23 ; 10,84]	3,81 [1,25 ; 11,65];	4,22 [0,97 ; 7,47]; 0,017	0,017	0,3034
	0	286	10	3.50	293	6	2.05	1,71 [0,63 ; 4,64]	1,73 [0,62 ; 4,83];	1,45 [-1,23 ; 4,12]; 0,32	0,32	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	13	5.78	202	3	1.49	3,89 [1,12 ; 13,46]	4,07 [1,14 ; 14,49];	4,29 [0,82 ; 7,77]; 0,022	0,022	0,585
	>=3	84	6	7.14	98	3	3.06	2,33 [0,6 ; 9,05]	2,44 [0,59 ; 10,06];	4,08 [-2,4 ; 10,56]; 0,306	0,306	
	2	236	6	2.54	248	4	1.61	1,58 [0,45 ; 5,52]	1,59 [0,44 ; 5,71];	0,93 [-1,62 ; 3,48]; 0,536	0,536	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	25	4.67	536	10	1.87	2,5 [1,21 ; 5,16]	2,58 [1,23 ; 5,42];	2,81 [0,68 ; 4,93]; 0,01	0,01	
	No	347	16	4.61	379	8	2.11	2,18 [0,95 ; 5,04]	2,24 [0,95 ; 5,31];	2,5 [-0,14 ; 5,14]; 0,064	0,064	0,5134

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	9	4.55	169	2	1.18	3,84 [0,84 ; 17,53]	3,98 [0,85 ; 18,66];	3,36 [0,03 ; 6,69]; 0,071	0,071	
Region	Eastern Europe	492	24	4.88	495	10	2.02	2,41 [1,17 ; 5]	2,49 [1,18 ; 5,26];	2,86 [0,59 ; 5,13]; 0,015	0,015	0,4124
	USA and Western Europe	53	1	1.89	53	0	0.00	3 [0,12 ; 72,02]	3,06 [0,12 ; 76,76];	1,85 [-3,22 ; 6,93]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Cardiac disorders | Sinus tachycardia

6.2.95 Blood and lymphatic system disorders - Neutrophilia

Tabelle 456: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	6	1.84	302	8	2.65	0,69 [0,24 ; 1,98]	0,69 [0,24 ; 2,01];	-0,81 [-3,13 ; 1,52]; 0,593	0,593	0,4434
	>= 38 years	219	1	0.46	246	4	1.63	0,28 [0,03 ; 2,49]	0,28 [0,03 ; 2,5];	-1,17 [-2,98 ; 0,65]; 0,377	0,377	
Disease Severity at baseline (EDSS)	<=3.5	419	5	1.19	415	8	1.93	0,62 [0,2 ; 1,88]	0,61 [0,2 ; 1,89];	-0,73 [-2,42 ; 0,95]; 0,418	0,418	0,8731
	>3.5	126	2	1.59	133	4	3.01	0,53 [0,1 ; 2,83]	0,52 [0,09 ; 2,89];	-1,42 [-5,05 ; 2,21]; 0,685	0,685	
Gender	Female	345	5	1.45	356	8	2.25	0,64 [0,21 ; 1,95]	0,64 [0,21 ; 1,97];	-0,8 [-2,79 ; 1,19]; 0,578	0,578	0,7739
	Male	200	2	1.00	192	4	2.08	0,48 [0,09 ; 2,59]	0,47 [0,09 ; 2,62];	-1,08 [-3,53 ; 1,36]; 0,441	0,441	
Number of baseline Gd-enhancing lesions	>=1	258	3	1.16	251	9	3.59	0,32 [0,09 ; 1,18]	0,32 [0,08 ; 1,18];	-2,42 [-5,07 ; 0,22]; 0,085	0,085	0,1423
	0	286	4	1.40	293	3	1.02	1,37 [0,31 ; 6,05]	1,37 [0,3 ; 6,18];	0,37 [-1,41 ; 2,16]; 0,722	0,722	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	1	0.44	202	9	4.46	0,1 [0,01 ; 0,78]	0,1 [0,01 ; 0,76];	-4,01 [-6,99 ; -1,04]; 0,008	0,008	0,0131
	>=3	84	3	3.57	98	1	1.02	3,5 [0,37 ; 33,02]	3,59 [0,37 ; 35,21];	2,55 [-1,89 ; 6,99]; 0,336	0,336	
	2	236	3	1.27	248	2	0.81	1,58 [0,27 ; 9,35]	1,58 [0,26 ; 9,56];	0,46 [-1,35 ; 2,28]; 0,679	0,679	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	7	1.31	536	12	2.24	0,58 [0,23 ; 1,47]	0,58 [0,23 ; 1,48];	-0,93 [-2,51 ; 0,65]; 0,355	0,355	
	No	347	2	0.58	379	5	1.32	0,44 [0,09 ; 2,24]	0,43 [0,08 ; 2,25];	-0,74 [-2,14 ; 0,65]; 0,454	0,454	0,7509

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	5	2.53	169	7	4.14	0,61 [0,2 ; 1,89]	0,6 [0,19 ; 1,92];	-1,62 [-5,33 ; 2,1]; 0,398	0,398	
Region	Eastern Europe	492	7	1.42	495	12	2.42	0,59 [0,23 ; 1,48]	0,58 [0,23 ; 1,49];	-1 [-2,71 ; 0,71]; 0,355	0,355	0,9999
	USA and Western Europe	53	0	0.00	53	0	0.00	1 [0,02 ; 49,49]	1 [0,02 ; 51,33];	0 [-3,61 ; 3,61]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Blood and lymphatic system disorders | Neutrophilia

6.2.96 Respiratory, thoracic and mediastinal disorders - Throat irritation

Tabelle 457: Non-severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	11	3.37	302	0	0.00	21,31 [1,26 ; 360,1]	22,05 [1,29 ; 375,86];	3,35 [1,3 ; 5,4]; 0	0	0,1603
	>= 38 years	219	5	2.28	246	1	0.41	5,62 [0,66 ; 47,7]	5,72 [0,66 ; 49,38];	1,88 [-0,26 ; 4,01]; 0,104	0,104	
Disease Severity at baseline (EDSS)	<=3.5	419	14	3.34	415	0	0.00	28,72 [1,72 ; 479,94]	29,72 [1,77 ; 499,78];	3,33 [1,55 ; 5,11]; 0	0	0,0541
	>3.5	126	2	1.59	133	1	0.75	2,11 [0,19 ; 22,99]	2,13 [0,19 ; 23,77];	0,84 [-1,79 ; 3,47]; 0,614	0,614	
Gender	Female	345	12	3.48	356	1	0.28	12,38 [1,62 ; 94,72]	12,79 [1,65 ; 98,92];	3,2 [1,19 ; 5,21]; 0,001	0,001	0,4725
	Male	200	4	2.00	192	0	0.00	8,64 [0,47 ; 159,44]	8,82 [0,47 ; 164,87];	1,98 [-0,19 ; 4,15]; 0,123	0,123	
Number of baseline Gd-enhancing lesions	>=1	258	10	3.88	251	0	0.00	20,43 [1,2 ; 346,84]	21,25 [1,24 ; 364,66];	3,86 [1,39 ; 6,32]; 0,002	0,002	
	0	286	6	2.10	293	1	0.34	6,15 [0,74 ; 50,74]	6,26 [0,75 ; 52,3];	1,76 [-0,03 ; 3,55]; 0,066	0,066	0,1768
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	8	3.56	202	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
	>=3	84	6	7.14	98	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	NA
	2	236	2	0.85	248	1	0.40	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9998
	White	535	16	2.99	536	1	0.19	16,03 [2,13 ; 120,44]	16,49 [2,18 ; 124,82];	2,8 [1,32 ; 4,29]; 0	0	
	No	347	9	2.59	379	1	0.26	9,83 [1,25 ; 77,19]	10,07 [1,27 ; 79,86];	2,33 [0,58 ; 4,08]; 0,009	0,009	0,3369

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	7	3.54	169	0	0.00	12,81 [0,74 ; 222,72]	13,28 [0,75 ; 234,2];	3,47 [0,71 ; 6,24]; 0,009	0,009	
Region	Eastern Europe	492	13	2.64	495	1	0.20	13,08 [1,72 ; 99,6]	13,41 [1,75 ; 102,89];	2,44 [0,97 ; 3,91]; 0,001	0,001	0,522
	USA and Western Europe	53	3	5.66	53	0	0.00	7 [0,37 ; 132,29]	7,42 [0,37 ; 147,18];	5,56 [-1,49 ; 12,6]; 0,118	0,118	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Non-severe TEAE - Respiratory, thoracic and mediastinal disorders | Throat irritation

6.3 Severe TEAE

6.3.1 Infections and infestations - any

Tabelle 458: Severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	15	4.60	302	5	1.66	2,78 [1,02 ; 7,55]	2,86 [1,03 ; 7,98];	2,95 [0,25 ; 5,64]; 0,041	0,041	0,1583
	>= 38 years	219	5	2.28	246	6	2.44	0,94 [0,29 ; 3,02]	0,93 [0,28 ; 3,11];	-0,16 [-2,92 ; 2,61]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	16	3.82	415	7	1.69	2,26 [0,94 ; 5,45]	2,31 [0,94 ; 5,68];	2,13 [-0,08 ; 4,35]; 0,089	0,089	0,3583
	>3.5	126	4	3.17	133	4	3.01	1,06 [0,27 ; 4,13]	1,06 [0,26 ; 4,32];	0,17 [-4,05 ; 4,39]; 1	1	
Gender	Female	345	16	4.64	356	8	2.25	2,06 [0,89 ; 4,76]	2,12 [0,89 ; 5,01];	2,39 [-0,31 ; 5,09]; 0,097	0,097	0,5773
	Male	200	4	2.00	192	3	1.56	1,28 [0,29 ; 5,64]	1,29 [0,28 ; 5,82];	0,44 [-2,18 ; 3,05]; 1	1	
Number of baseline Gd-enhancing lesions	>=1	258	11	4.26	251	4	1.59	2,68 [0,86 ; 8,29]	2,75 [0,86 ; 8,75];	2,67 [-0,24 ; 5,58]; 0,114	0,114	0,3454
	0	286	9	3.15	293	7	2.39	1,32 [0,5 ; 3,49]	1,33 [0,49 ; 3,61];	0,76 [-1,92 ; 3,43]; 0,62	0,62	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	7	3.11	202	2	0.99	3,14 [0,66 ; 14,95]	3,21 [0,66 ; 15,64];	2,12 [-0,53 ; 4,77]; 0,181	0,181	0,4657
	>=3	84	3	3.57	98	4	4.08	0,88 [0,2 ; 3,8]	0,87 [0,19 ; 4];	-0,51 [-6,09 ; 5,07]; 1	1	
	2	236	10	4.24	248	5	2.02	2,1 [0,73 ; 6,06]	2,15 [0,72 ; 6,39];	2,22 [-0,89 ; 5,33]; 0,194	0,194	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	20	3.74	536	11	2.05	1,82 [0,88 ; 3,76]	1,85 [0,88 ; 3,91];	1,69 [-0,32 ; 3,69]; 0,105	0,105	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	No	347	13	3.75	379	6	1.58	2,37 [0,91 ; 6,16]	2,42 [0,91 ; 6,44];	2,16 [-0,2 ; 4,52]; 0,101	0,101	0,3689
	Yes	198	7	3.54	169	5	2.96	1,19 [0,39 ; 3,7]	1,2 [0,37 ; 3,86];	0,58 [-3,05 ; 4,2]; 1	1	
Region	Eastern Europe	492	19	3.86	495	11	2.22	1,74 [0,84 ; 3,61]	1,77 [0,83 ; 3,75];	1,64 [-0,5 ; 3,78]; 0,142	0,142	0,3464
	USA and Western Europe	53	1	1.89	53	0	0.00	3 [0,12 ; 72,02]	3,06 [0,12 ; 76,76];	1,85 [-3,22 ; 6,93]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Severe TEAE - Infections and infestations | any

6.3.2 Investigations - any

Tabelle 459: Severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	30	9.20	302	16	5.30	1,74 [0,97 ; 3,12]	1,81 [0,97 ; 3,4];	3,9 [-0,12 ; 7,93]; 0,067	0,067	0,2993
	>= 38 years	219	25	11.42	246	10	4.07	2,81 [1,38 ; 5,71]	3,04 [1,43 ; 6,49];	7,35 [2,47 ; 12,23]; 0,004	0,004	
Disease Severity at baseline (EDSS)	<=3.5	419	44	10.50	415	20	4.82	2,18 [1,31 ; 3,63]	2,32 [1,34 ; 4,01];	5,68 [2,1 ; 9,27]; 0,003	0,003	0,8206
	>3.5	126	11	8.73	133	6	4.51	1,94 [0,74 ; 5,08]	2,02 [0,73 ; 5,65];	4,22 [-1,84 ; 10,28]; 0,212	0,212	
Gender	Female	345	32	9.28	356	16	4.49	2,06 [1,15 ; 3,69]	2,17 [1,17 ; 4,04];	4,78 [1,04 ; 8,52]; 0,016	0,016	0,8662
	Male	200	23	11.50	192	10	5.21	2,21 [1,08 ; 4,52]	2,36 [1,09 ; 5,11];	6,29 [0,87 ; 11,72]; 0,029	0,029	
Number of baseline Gd-enhancing lesions	>=1	258	28	10.85	251	15	5.98	1,82 [0,99 ; 3,32]	1,92 [1 ; 3,68];	4,88 [0,08 ; 9,67]; 0,056	0,056	0,5009
	0	286	27	9.44	293	11	3.75	2,51 [1,27 ; 4,97]	2,67 [1,3 ; 5,5];	5,69 [1,66 ; 9,71]; 0,007	0,007	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	18	8.00	202	6	2.97	2,69 [1,09 ; 6,65]	2,84 [1,1 ; 7,3];	5,03 [0,78 ; 9,28]; 0,034	0,034	0,8579
	>=3	84	13	15.48	98	7	7.14	2,17 [0,91 ; 5,18]	2,38 [0,9 ; 6,28];	8,33 [-0,93 ; 17,6]; 0,096	0,096	
	2	236	24	10.17	248	13	5.24	1,94 [1,01 ; 3,72]	2,05 [1,02 ; 4,12];	4,93 [0,18 ; 9,68]; 0,059	0,059	
Race	Other	10	0	0.00	12	1	8.33	0,39 [0,02 ; 8,73]	0,37 [0,01 ; 9,98];	-6,99 [-28,28 ; 14,29]; 0,493	0,493	0,1407
	White	535	55	10.28	536	25	4.66	2,2 [1,4 ; 3,48]	2,34 [1,44 ; 3,82];	5,62 [2,48 ; 8,75]; 0	0	
	No	347	37	10.66	379	16	4.22	2,53 [1,43 ; 4,46]	2,71 [1,48 ; 4,96];	6,44 [2,61 ; 10,27]; 0,001	0,001	0,3023

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	18	9.09	169	10	5.92	1,54 [0,73 ; 3,24]	1,59 [0,71 ; 3,55];	3,17 [-2,18 ; 8,53]; 0,325	0,325	
Region	Eastern Europe	492	53	10.77	495	23	4.65	2,32 [1,44 ; 3,72]	2,48 [1,49 ; 4,11];	6,13 [2,82 ; 9,43]; 0	0	0,165
	USA and Western Europe	53	2	3.77	53	3	5.66	0,67 [0,12 ; 3,83]	0,65 [0,1 ; 4,08];	-1,89 [-9,95 ; 6,18]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Severe TEAE - Investigations | any

6.3.3 Blood and lymphatic system disorders - any

Tabelle 460: Severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	24	7.36	302	5	1.66	4,45 [1,72 ; 11,51]	4,72 [1,78 ; 12,54];	5,71 [2,53 ; 8,89]; 0,001	0,001	0,0787
	>= 38 years	219	10	4.57	246	8	3.25	1,4 [0,56 ; 3,49]	1,42 [0,55 ; 3,67];	1,31 [-2,23 ; 4,86]; 0,481	0,481	
Disease Severity at baseline (EDSS)	<=3.5	419	31	7.40	415	9	2.17	3,41 [1,64 ; 7,08]	3,6 [1,69 ; 7,67];	5,23 [2,36 ; 8,1]; 0,001	0,001	0,0772
	>3.5	126	3	2.38	133	4	3.01	0,79 [0,18 ; 3,47]	0,79 [0,17 ; 3,59];	-0,63 [-4,57 ; 3,31]; 1	1	
Gender	Female	345	22	6.38	356	13	3.65	1,75 [0,89 ; 3,41]	1,8 [0,89 ; 3,63];	2,73 [-0,51 ; 5,96]; 0,119	0,119	0,003
	Male	200	12	6.00	192	0	0.00	24 [1,43 ; 402,64]	25,53 [1,5 ; 434,28];	5,96 [2,55 ; 9,37]; 0	0	
Number of baseline Gd-enhancing lesions	>=1	258	17	6.59	251	4	1.59	4,13 [1,41 ; 12,12]	4,36 [1,44 ; 13,13];	5 [1,59 ; 8,4]; 0,006	0,006	0,256
	0	286	17	5.94	293	9	3.07	1,94 [0,88 ; 4,27]	1,99 [0,87 ; 4,55];	2,87 [-0,51 ; 6,25]; 0,11	0,11	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	16	7.11	202	5	2.48	2,87 [1,07 ; 7,7]	3,02 [1,08 ; 8,39];	4,64 [0,65 ; 8,62]; 0,041	0,041	0,7753
	>=3	84	6	7.14	98	4	4.08	1,75 [0,51 ; 5,99]	1,81 [0,49 ; 6,63];	3,06 [-3,7 ; 9,82]; 0,517	0,517	
	2	236	12	5.08	248	4	1.61	3,15 [1,03 ; 9,64]	3,27 [1,04 ; 10,28];	3,47 [0,26 ; 6,68]; 0,041	0,041	
Race	Other	10	0	0.00	12	1	8.33	0,39 [0,02 ; 8,73]	0,37 [0,01 ; 9,98];	-6,99 [-28,28 ; 14,29]; 0,493	0,493	0,1168
	White	535	34	6.36	536	12	2.24	2,84 [1,49 ; 5,42]	2,96 [1,52 ; 5,79];	4,12 [1,7 ; 6,53]; 0,001	0,001	
	No	347	17	4.90	379	8	2.11	2,32 [1,01 ; 5,31]	2,39 [1,02 ; 5,61];	2,79 [0,1 ; 5,48]; 0,043	0,043	0,7065

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	17	8.59	169	5	2.96	2,9 [1,09 ; 7,7]	3,08 [1,11 ; 8,54];	5,63 [0,96 ; 10,29]; 0,027	0,027	
Region	Eastern Europe	492	31	6.30	495	12	2.42	2,6 [1,35 ; 5]	2,71 [1,37 ; 5,33];	3,88 [1,34 ; 6,42]; 0,003	0,003	0,9065
	USA and Western Europe	53	3	5.66	53	1	1.89	3 [0,32 ; 27,93]	3,12 [0,31 ; 31];	3,77 [-3,45 ; 10,99]; 0,618	0,618	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Severe TEAE - Blood and lymphatic system disorders | any

6.3.4 Investigations - Lymphocyte count decreased

Tabelle 461: Severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	17	5.21	302	0	0	32,43 [1,96 ; 536,95]	34,21 [2,05 ; 571,38];	5,19 [2,7 ; 7,67]; 0	0	1
	>= 38 years	219	13	5.94	246	0	0	30,31 [1,81 ; 506,95]	32,23 [1,9 ; 545,45];	5,93 [2,71 ; 9,15]; 0	0	
Disease Severity at baseline (EDSS)	<=3.5	419	22	5.25	415	0	0	44,57 [2,71 ; 732,34]	47,04 [2,84 ; 778,02];	5,24 [3,06 ; 7,42]; 0	0	1
	>3.5	126	8	6.35	133	0	0	17,94 [1,05 ; 307,56]	19,15 [1,09 ; 335,38];	6,32 [1,85 ; 10,79]; 0,003	0,003	
Gender	Female	345	21	6.09	356	0	0	44,37 [2,7 ; 729,56]	47,24 [2,85 ; 783];	6,07 [3,5 ; 8,65]; 0	0	1
	Male	200	9	4.50	192	0	0	18,24 [1,07 ; 311,3]	19,1 [1,1 ; 330,46];	4,47 [1,45 ; 7,49]; 0,002	0,002	
Number of baseline Gd-enhancing lesions	>=1	258	12	4.65	251	0	0	24,32 [1,45 ; 408,65]	25,51 [1,5 ; 433,16];	4,63 [1,96 ; 7,3]; 0	0	0,9999
	0	286	18	6.29	293	0	0	37,9 [2,29 ; 625,98]	40,45 [2,43 ; 674,41];	6,28 [3,4 ; 9,16]; 0	0	
	NA	1	0	0.00	4	0	0	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	9	4.00	202	0	0	17,07 [1 ; 291,37]	17,77 [1,03 ; 307,31];	3,96 [1,25 ; 6,66]; 0,002	0,002	1
	>=3	84	9	10.71	98	0	0	22,13 [1,31 ; 374,62]	24,79 [1,42 ; 432,65];	10,67 [3,83 ; 17,51]; 0	0	
	2	236	12	5.08	248	0	0	26,27 [1,56 ; 441,14]	27,67 [1,63 ; 470,08];	5,07 [2,17 ; 7,97]; 0	0	
Race	Other	10	0	0.00	12	0	0	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9993
	White	535	30	5.61	536	0	0	61,11 [3,75 ; 996,86]	64,74 [3,95 ; 1061,53];	5,6 [3,62 ; 7,58]; 0	0	
	No	347	23	6.63	379	0	0	51,32 [3,13 ; 841,75]	54,97 [3,33 ; 908,48];	6,62 [3,96 ; 9,28]; 0	0	0,9999

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	7	3.54	169	0	0	12,81 [0,74 ; 222,72]	13,28 [0,75 ; 234,2];	3,47 [0,71 ; 6,24]; 0,009	0,009	
Region	Eastern Europe	492	30	6.10	495	0	0	61,37 [3,76 ; 1000,84]	65,35 [3,98 ; 1071,81];	6,09 [3,94 ; 8,23]; 0	0	0,9998
	USA and Western Europe	53	0	0.00	53	0	0	1 [0,02 ; 49,49]	1 [0,02 ; 51,33];	0 [-3,61 ; 3,61]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Severe TEAE - Investigations | Lymphocyte count decreased

6.3.5 Blood and lymphatic system disorders - Neutropenia

Tabelle 462: Severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	9	2.76	302	3	0.99	2,78 [0,76 ; 10,17]	2,83 [0,76 ; 10,55];	1,77 [-0,33 ; 3,87]; 0,146	0,146	0,2317
	>= 38 years	219	2	0.91	246	3	1.22	0,75 [0,13 ; 4,44]	0,75 [0,12 ; 4,51];	-0,31 [-2,17 ; 1,56]; 1	1	
Disease Severity at baseline (EDSS)	<=3.5	419	10	2.39	415	6	1.45	1,65 [0,61 ; 4,5]	1,67 [0,6 ; 4,63];	0,94 [-0,92 ; 2,8]; 0,45	0,45	0,3307
	>3.5	126	1	0.79	133	0	0.00	3,17 [0,13 ; 76,99]	3,19 [0,13 ; 79,07];	0,81 [-1,34 ; 2,95]; 0,238	0,238	
Gender	Female	345	8	2.32	356	6	1.69	1,38 [0,48 ; 3,92]	1,38 [0,48 ; 4,03];	0,63 [-1,44 ; 2,71]; 0,599	0,599	0,094
	Male	200	3	1.50	192	0	0.00	6,72 [0,35 ; 129,27]	6,82 [0,35 ; 132,97];	1,48 [-0,46 ; 3,43]; 0,124	0,124	
Number of baseline Gd-enhancing lesions	>=1	258	4	1.55	251	2	0.80	1,95 [0,36 ; 10,53]	1,96 [0,36 ; 10,8];	0,75 [-1,11 ; 2,62]; 0,686	0,686	0,9418
	0	286	7	2.45	293	4	1.37	1,79 [0,53 ; 6,06]	1,81 [0,52 ; 6,26];	1,08 [-1,15 ; 3,31]; 0,378	0,378	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	7	3.11	202	3	1.49	2,09 [0,55 ; 7,99]	2,13 [0,54 ; 8,35];	1,63 [-1,19 ; 4,44]; 0,345	0,345	0,5394
	>=3	84	1	1.19	98	2	2.04	0,58 [0,05 ; 6,32]	0,58 [0,05 ; 6,49];	-0,85 [-4,49 ; 2,79]; 1	1	
	2	236	3	1.27	248	1	0.40	3,15 [0,33 ; 30,09]	3,18 [0,33 ; 30,79];	0,87 [-0,76 ; 2,5]; 0,361	0,361	
Race	Other	10	0	0.00	12	1	8.33	0,39 [0,02 ; 8,73]	0,37 [0,01 ; 9,98];	-6,99 [-28,28 ; 14,29]; 0,493	0,493	0,1551
	White	535	11	2.06	536	5	0.93	2,2 [0,77 ; 6,3]	2,23 [0,77 ; 6,46];	1,12 [-0,33 ; 2,58]; 0,14	0,14	
	No	347	6	1.73	379	4	1.06	1,64 [0,47 ; 5,76]	1,65 [0,46 ; 5,9];	0,67 [-1,04 ; 2,39]; 0,532	0,532	0,7979

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	5	2.53	169	2	1.18	2,13 [0,42 ; 10,86]	2,16 [0,41 ; 11,3];	1,34 [-1,38 ; 4,07]; 0,459	0,459	
Region	Eastern Europe	492	9	1.83	495	5	1.01	1,81 [0,61 ; 5,37]	1,83 [0,61 ; 5,49];	0,82 [-0,66 ; 2,3]; 0,297	0,297	0,9351
	USA and Western Europe	53	2	3.77	53	1	1.89	2 [0,19 ; 21,4]	2,04 [0,18 ; 23,19];	1,89 [-4,42 ; 8,19]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Severe TEAE - Blood and lymphatic system disorders | Neutropenia

6.3.6 Blood and lymphatic system disorders - Lymphopenia

Tabelle 463: Severe TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	15	4.60	302	1	0.33	13,9 [1,85 ; 104,56]	14,52 [1,91 ; 110,59];	4,27 [1,91 ; 6,63]; 0,001	0,001	0,3126
	>= 38 years	219	7	3.20	246	2	0.81	3,93 [0,83 ; 18,73]	4,03 [0,83 ; 19,6];	2,38 [-0,2 ; 4,97]; 0,091	0,091	
Disease Severity at baseline (EDSS)	<=3.5	419	20	4.77	415	1	0.24	19,81 [2,67 ; 146,92]	20,75 [2,77 ; 155,35];	4,53 [2,44 ; 6,63]; 0	0	0,0309
	>3.5	126	2	1.59	133	2	1.50	1,06 [0,15 ; 7,38]	1,06 [0,15 ; 7,62];	0,08 [-2,92 ; 3,09]; 1	1	
Gender	Female	345	13	3.77	356	3	0.84	4,47 [1,29 ; 15,55]	4,61 [1,3 ; 16,31];	2,93 [0,7 ; 5,15]; 0,011	0,011	0,0962
	Male	200	9	4.50	192	0	0.00	18,24 [1,07 ; 311,3]	19,1 [1,1 ; 330,46];	4,47 [1,45 ; 7,49]; 0,002	0,002	
Number of baseline Gd-enhancing lesions	>=1	258	13	5.04	251	1	0.40	12,65 [1,67 ; 95,96]	13,27 [1,72 ; 102,18];	4,64 [1,86 ; 7,42]; 0,002	0,002	0,4149
	0	286	9	3.15	293	2	0.68	4,61 [1 ; 21,15]	4,73 [1,01 ; 22,07];	2,46 [0,23 ; 4,7]; 0,035	0,035	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	9	4.00	202	0	0.00	17,07 [1 ; 291,37]	17,77 [1,03 ; 307,31];	3,96 [1,25 ; 6,66]; 0,002	0,002	0,2708
	>=3	84	3	3.57	98	1	1.02	3,5 [0,37 ; 33,02]	3,59 [0,37 ; 35,21];	2,55 [-1,89 ; 6,99]; 0,336	0,336	
	2	236	10	4.24	248	2	0.81	5,25 [1,16 ; 23,73]	5,44 [1,18 ; 25,11];	3,43 [0,63 ; 6,23]; 0,018	0,018	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9997
	White	535	22	4.11	536	3	0.56	7,35 [2,21 ; 24,4]	7,62 [2,27 ; 25,61];	3,55 [1,76 ; 5,35]; 0	0	
	No	347	11	3.17	379	2	0.53	6,01 [1,34 ; 26,91]	6,17 [1,36 ; 28,04];	2,64 [0,66 ; 4,62]; 0,01	0,01	0,7131

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	Yes	198	11	5.56	169	1	0.59	9,39 [1,22 ; 71,98]	9,88 [1,26 ; 77,36];	4,96 [1,57 ; 8,36]; 0,007	0,007	
Region	Eastern Europe	492	22	4.47	495	3	0.61	7,38 [2,22 ; 24,49]	7,68 [2,28 ; 25,82];	3,87 [1,92 ; 5,82]; 0	0	0,9998
	USA and Western Europe	53	0	0.00	53	0	0.00	1 [0,02 ; 49,49]	1 [0,02 ; 51,33];	0 [-3,61 ; 3,61]; 1	1	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Severe TEAE - Blood and lymphatic system disorders | Lymphopenia

6.4 Serious TEAE

6.4.1 Infections and infestations - any

Tabelle 464: Serious TEAE by SOC/PT: Subgroup analysis - (Safety Set) (ULTIMATE 1+2)

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Age	< 38 years	326	22	6.75	302	7	2.32	2,91 [1,26 ; 6,72]	3,05 [1,28 ; 7,25];	4,43 [1,22 ; 7,64]; 0,012	0,012	0,0212
	>= 38 years	219	5	2.28	246	9	3.66	0,62 [0,21 ; 1,83]	0,62 [0,2 ; 1,86];	-1,38 [-4,44 ; 1,69]; 0,428	0,428	
Disease Severity at baseline (EDSS)	<=3.5	419	21	5.01	415	10	2.41	2,08 [0,99 ; 4,36]	2,14 [0,99 ; 4,6];	2,6 [0,04 ; 5,16]; 0,066	0,066	0,3213
	>3.5	126	6	4.76	133	6	4.51	1,06 [0,35 ; 3,19]	1,06 [0,33 ; 3,37];	0,25 [-4,87 ; 5,38]; 1	1	
Gender	Female	345	20	5.80	356	12	3.37	1,72 [0,85 ; 3,46]	1,76 [0,85 ; 3,67];	2,43 [-0,67 ; 5,52]; 0,148	0,148	0,9629
	Male	200	7	3.50	192	4	2.08	1,68 [0,5 ; 5,65]	1,7 [0,49 ; 5,92];	1,42 [-1,83 ; 4,67]; 0,544	0,544	
Number of baseline Gd-enhancing lesions	>=1	258	15	5.81	251	6	2.39	2,43 [0,96 ; 6,17]	2,52 [0,96 ; 6,6];	3,42 [0 ; 6,85]; 0,073	0,073	0,2754
	0	286	12	4.20	293	10	3.41	1,23 [0,54 ; 2,8]	1,24 [0,53 ; 2,92];	0,78 [-2,34 ; 3,9]; 0,668	0,668	
	NA	1	0	0.00	4	0	0.00	NA [NA ; NA]	NA [NA ; NA];	NA [NA ; NA]; NA	NA	
Number of relapses experienced in the 2 years prior to study start	<=1	225	10	4.44	202	6	2.97	1,5 [0,55 ; 4,04]	1,52 [0,54 ; 4,26];	1,47 [-2,09 ; 5,04]; 0,457	0,457	0,9381
	>=3	84	6	7.14	98	4	4.08	1,75 [0,51 ; 5,99]	1,81 [0,49 ; 6,63];	3,06 [-3,7 ; 9,82]; 0,517	0,517	
	2	236	11	4.66	248	6	2.42	1,93 [0,72 ; 5,13]	1,97 [0,72 ; 5,42];	2,24 [-1,06 ; 5,54]; 0,22	0,22	
Race	Other	10	0	0.00	12	0	0.00	1,18 [0,03 ; 54,81]	1,19 [0,02 ; 65,32];	0,7 [-15,45 ; 16,85]; 1	1	0,9999
	White	535	27	5.05	536	16	2.99	1,69 [0,92 ; 3,1]	1,73 [0,92 ; 3,24];	2,06 [-0,29 ; 4,41]; 0,089	0,089	

Subgroup	Level	UBLITUXIMAB/ORAL PLACEBO			TERIFLUNOMIDE/IV PLACEBO			UBLITUXIMAB/ORAL PLACEBO vs. TERIFLUNOMIDE/IV PLACEBO				
		N	Events	Proportion (%)	N	Events	Proportion (%)	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	interaction p-value
Received approved disease modifying MS drug prior to enrollment	No	347	16	4.61	379	10	2.64	1,75 [0,8 ; 3,8]	1,78 [0,8 ; 3,99];	1,97 [-0,76 ; 4,71]; 0,166	0,166	0,8682
	Yes	198	11	5.56	169	6	3.55	1,56 [0,59 ; 4,14]	1,6 [0,58 ; 4,42];	2,01 [-2,23 ; 6,24]; 0,458	0,458	
Region	Eastern Europe	492	26	5.28	495	16	3.23	1,63 [0,89 ; 3,01]	1,67 [0,88 ; 3,15];	2,05 [-0,46 ; 4,57]; 0,117	0,117	0,3341
	USA and Western Europe	53	1	1.89	53	0	0.00	3 [0,12 ; 72,02]	3,06 [0,12 ; 76,76];	1,85 [-3,22 ; 6,93]; 0,495	0,495	

RR: Risk Ratio, OR: Odds Ratio, RD: Risk Difference;
CI: Confidence interval;
N: Number of patients; NA: not available/not reached/not estimable;
p-value: fisher test;
interaction p-value: LR test between m0 = Evt ~ Treat + SG and m1 = Evt ~ Treat + SG + Treat*SG;
mo and m1 are logit models

Serious TEAE - Infections and infestations | any