Anhang 4-G: Ergänzende Unterlagen

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Anhang 4-G1: Beobachtungsdauer und Rücklaufquoten

Anhang 4-G1.1: Beobachtungsdauer

Table 1.1.1 Duration of observation time over 24 weeks
Treated Set

	Placebo		Nintedanib		Total	
Number of patients (N, %)	13	100.0	26	100.0	39	100.0
Observation time [months] over 24 weeks						
N	13		26		39	
Mean	5.25		5.24		5.24	
SD	0.92		1.01		0.97	
Min	2.2		1.9		1.9	
Median	5.51		5.51		5.51	
Max	5.6		6.6		6.6	

[1] Duration of observation time in months over 24 weeks is calculated as
(min(date of last blinded exposure including REP excluding open-label, death date, last contact date, snapshot date) - randomization date +1) / 30.5

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Anhang 4-G1.2: Rücklaufquoten

Table 1.2.1 Return rate by patient reported outcome parameter and visit over 24 weeks
Treated Set

	Placebo		Nintedanib		Total	
Number of patients (N, %)	13	100.0	26	100.0	39	100.0
Baseline						
N [1]	13	100.0	26	100.0	39	100.0
PedsQL Total Score	12	92.3	25	96.2	37	94.9
PedsQL Total Score - Parent	13	100.0	25	96.2	38	97.4
24 weeks						
N [1]	13	100.0	26	100.0	39	100.0
PedsQL Total Score	11	84.6	22	84.6	33	84.6
PedsQL Total Score - Parent	11	84.6	21	80.8	32	82.1

[1] N: Total number of patients who have not died.

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Anhang 4-G2: Weitere Ergebnisse zur Wirksamkeit aus der Studie InPedILD®

Anhang 4-G2.1: FVC

Table 2.1.1 Proportion of patients with absolute increase in FVC % predicted (>=5%) from baseline at week 24 overall and by subgroup
Treated Set

	Placebo			Nintedanib			Randomised Nintedanib vs. Placebo							
							Risk ratio [1]	95% confidence interval [1]		p-value [1]	Odds ratio [2]	95% confidence interval [2]		p-value [1][3]
	N	n	%	N	n	%		Lower	Upper			Lower	Upper	
Overall	12	0	0.0	23	5	21.7	NC	NC	NC	NC	NC	NC	NC	
Sex														
Male	4	0	0.0	9	2	22.2								
Female	8	0	0.0	14	3	21.4								
Age														
6-<12	3	0	0.0	7	3	42.9								
12-<18	9	0	0.0	16	2	12.5								
Region														
Europe	3	0	0.0	15	4	26.7								
Rest of World	9	0	0.0	8	1	12.5								
Corticosteroid at Baseline														
Yes	3	0	0.0	8	3	37.5								
No	9	0	0.0	15	2	13.3								

N represents the number of patients in the Treated Set with an available FVC value at baseline and at the respective visit based on observed data.
n represents the number of patients meeting the response criterion based on observed data.
[1] Based on a log-linked Poisson model with robust estimate of variance^.
[2] Based on a logistic regression model^ showing Wald confidence intervals.
[3] Interaction p-value from log-linked Poisson model with robust estimate of variance^.
^ All models contain continuous covariate baseline value and categorical covariate age-group. Subgroup and treatment by subgroup interaction term are additionally included for the subgroup analyses.
All model results are based on pooled results following multiple imputation procedure (m=100 imputations) as described in TSAP Section 6.6.2.3.
inf=infinity; NC=not calculabe because of errors/warnings in at least one of the 100 regression models.

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Table 2.1.2 Proportion of patients with absolute increase in FVC % predicted (>=10%) from baseline at week 24 overall and by subgroup
Treated Set

	Placebo			Nintedanib			Randomised Nintedanib vs. Placebo							
							Risk ratio	95% confidence interval [1]		p-value	Odds ratio	95% confidence interval [2]		p-value [1][3]
	N	n	%	N	n	%	[1]	Lower	Upper	[1]	[2]	Lower	Upper	
Overall	12	0	0.0	23	1	4.3	NC	NC	NC	NC	NC	NC	NC	
Sex														
Male	4	0	0.0	9	0	0.0								
Female	8	0	0.0	14	1	7.1								
Age														
6-<12	3	0	0.0	7	0	0.0								
12-<18	9	0	0.0	16	1	6.3								
Region														
Europe	3	0	0.0	15	0	0.0								
Rest of World	9	0	0.0	8	1	12.5								
Corticosteroid at Baseline														
Yes	3	0	0.0	8	1	12.5								
No	9	0	0.0	15	0	0.0								

N represents the number of patients in the Treated Set with an available FVC value at baseline and at the respective visit.
n represents the number of patients meeting the response criterion.
[1] Based on a log-linked Poisson model with robust estimate of variance^.
[2] Based on a logistic regression model^ showing Wald confidence intervals.
[3] Interaction p-value from log-linked Poisson model with robust estimate of variance^.
^ All models contain continuous covariate baseline value and categorical covariate age-group. Subgroup and treatment by subgroup interaction term are additionally included for the subgroup analyses.
All model results are based on pooled results following multiple imputation procedure (m=100 imputations) as described in TSAP Section 6.6.2.3.
inf=infinity; NC=not calculabe because of errors/warnings in at least one of the 100 regression models.

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Table 2.1.3 Adjusted mean (SE) of absolute change from baseline in FVC % predicted at week 24 by subgroup
Treated Set

Subgroup/ Category/ Treatment	N	Baseline [1] Mean	Baseline [1] SD	24 weeks [1] Mean	24 weeks [1] SD	Change from baseline to 24 weeks: Adjusted mean [2]	SE	95% confidence interval Lower	95% confidence interval Upper	Comparison vs. Randomised Placebo: Adjusted mean [2]	SE	95% confidence interval Lower	95% confidence interval Upper	p-value [3]
Sex														0.4696
Male														
Placebo	4	69.7115	9.3821	71.9383	11.1246	0.0614	3.0645	-6.2034	6.3262					
Nintedanib	9	49.6066	24.3810	48.4992	21.3323	-1.1386	2.1450	-5.5343	3.2572	-1.2000	3.7847	-8.9393	6.5394	
Female														
Placebo	8	62.3341	27.2004	61.2050	28.7767	-1.1172	2.2359	-5.7140	3.4796					
Nintedanib	14	61.4239	21.0712	62.1963	23.0489	1.1188	1.6527	-2.2666	4.5042	2.2360	2.7747	-3.4616	7.9336	
Age														0.1419
6-<12														
Placebo	3	72.8260	7.0073	72.9437	9.4219	-3.2867	3.5765	-10.5896	4.0162					
Nintedanib	7	55.4366	24.3179	57.6317	23.7528	3.4438	2.3818	-1.4387	8.3263	6.7305	4.3234	-2.1057	15.5668	
12-<18														
Placebo	9	62.1157	25.5733	62.0624	27.4573	-0.0851	2.1389	-4.4858	4.3155					
Nintedanib	16	57.3961	22.6944	56.4887	23.3567	-0.9790	1.5796	-4.2184	2.2603	-0.8939	2.6631	-6.3665	4.5787	
Region														0.0660
Europe														
Placebo	3	39.5810	13.6628	38.3003	13.7316	-4.6773	3.5216	-11.8639	2.5094					
Nintedanib	15	62.5525	21.0230	64.3229	21.3709	1.7784	1.5959	-1.4968	5.0537	6.4557	3.9104	-1.5245	14.4359	
Rest of World														
Placebo	9	73.1973	18.2766	73.6102	20.2879	0.9090	2.1376	-3.4823	5.3003					
Nintedanib	8	46.0134	22.9213	42.7996	19.8695	-2.9362	2.1879	-7.3844	1.5120	-3.8452	3.2144	-10.4046	2.7141	
Corticosteroid at Baseline														0.7146
Yes														
Placebo	3	64.9517	6.6442	66.8207	9.0311	-1.4595	3.6671	-8.9728	6.0538					
Nintedanib	8	50.7989	25.4079	51.8139	25.3852	1.1286	2.3501	-3.7072	5.9643	2.5881	4.3659	-6.3650	11.5411	
No														
Placebo	9	64.7404	26.2199	64.1034	28.0523	-0.7377	2.2204	-5.3227	3.8474					
Nintedanib	15	60.0002	21.2666	59.5153	21.9647	-0.0549	1.6731	-3.4971	3.3872	0.6828	2.7790	-5.0478	6.4134	

[1] Based on the number of patients having available data at baseline and at the respective visit.
[2] Based on Mixed Model for Repeated Measures (MMRM), with fixed categorical effect age-group and the fixed continuous effects of baseline value at each visit, (randomized) treatment-by-visit-by-subgroup interaction, and random effect for patient. [3] Interaction p-value.
Visit is treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
Adjusted mean is based on all analysed patients in the model (i.e. on patients with a baseline and at least one post-baseline measurement - not only on patients with a baseline and measurement at the respective visit).
For derivation of the MMRM available data from all visits up to week 52 is used.

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Table 2.1.4 Adjusted mean (SE) of absolute change from baseline in FVC z-score at week 24 by subgroup
Treated Set

Subgroup/ Category/ Treatment	N	Baseline [1] Mean	Baseline [1] SD	24 weeks [1] Mean	24 weeks [1] SD	Change from baseline to 24 weeks: Adjusted mean [2]	SE	95% confidence interval Lower	95% confidence interval Upper	Comparison vs. Randomised Placebo: Adjusted mean [2]	SE	95% confidence interval Lower	95% confidence interval Upper	p-value [3]
Sex														0.4481
Male														
Placebo	4	-2.640	0.821	-2.447	0.970	0.005	0.258	-0.522	0.532					
Nintedanib	9	-4.331	2.140	-4.447	1.889	-0.117	0.182	-0.489	0.255	-0.123	0.319	-0.774	0.529	
Female														
Placebo	8	-3.234	2.323	-3.322	2.457	-0.088	0.189	-0.476	0.300					
Nintedanib	14	-3.257	1.825	-3.188	1.988	0.094	0.140	-0.191	0.380	0.182	0.234	-0.299	0.662	
Age														0.1559
6-<12														
Placebo	3	-2.345	0.596	-2.334	0.802	-0.286	0.304	-0.905	0.334					
Nintedanib	7	-3.715	2.035	-3.553	2.001	0.257	0.202	-0.157	0.671	0.542	0.366	-0.206	1.291	
12-<18														
Placebo	9	-3.266	2.182	-3.262	2.343	0.002	0.182	-0.372	0.376					
Nintedanib	16	-3.661	2.023	-3.736	2.073	-0.080	0.134	-0.355	0.196	-0.082	0.226	-0.547	0.383	
Region														0.0732
Europe														
Placebo	3	-5.116	1.153	-5.208	1.157	-0.373	0.297	-0.980	0.233					
Nintedanib	15	-3.164	1.778	-3.023	1.818	0.142	0.135	-0.135	0.420	0.516	0.330	-0.158	1.190	
Rest of World														
Placebo	9	-2.342	1.611	-2.304	1.785	0.074	0.180	-0.295	0.443					
Nintedanib	8	-4.639	2.093	-4.913	1.842	-0.252	0.186	-0.629	0.126	-0.326	0.271	-0.878	0.226	
Corticosteroid at Baseline														0.6761
Yes														
Placebo	3	-3.046	0.583	-2.880	0.791	-0.120	0.309	-0.753	0.512					
Nintedanib	8	-4.242	2.265	-4.157	2.269	0.101	0.199	-0.308	0.510	0.221	0.368	-0.533	0.976	
No														
Placebo	9	-3.032	2.237	-3.080	2.392	-0.057	0.187	-0.443	0.329					
Nintedanib	15	-3.376	1.821	-3.427	1.886	-0.020	0.141	-0.310	0.270	0.037	0.234	-0.445	0.520	

[1] Based on the number of patients having available data at baseline and at the respective visit.
[2] Based on Mixed Model for Repeated Measures (MMRM), with fixed categorical effect age-group and the fixed continuous effects of baseline value at each visit, (randomized) treatment-by-visit-by-subgroup interaction, and random effect for patient. [3] Interaction p-value.
Visit is treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
Adjusted mean is based on all analysed patients in the model (i.e. on patients with a baseline and at least one post-baseline measurement - not only on patients with a baseline and measurement at the respective visit).
For derivation of the MMRM available data from all visits up to week 52 is used.

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Anhang 4-G2.2: SpO2

Table 2.3.1 Proportion of patients with increase (>4%) in SpO2 on room air at rest from baseline at week 24 overall and by subgroup
Treated Set

	Placebo			Nintedanib			Randomised Nintedanib vs. Placebo							
							Risk ratio [1]	95% confidence interval [1]		p-value [1]	Odds ratio [2]	95% confidence interval [2]		p-value [1][3]
	N	n	%	N	n	%		Lower	Upper			Lower	Upper	
Overall	2	0	0.0	7	1	14.3	NC	NC	NC	NC	NC	NC	NC	
Sex														
Male	0			3	0	0.0								
Female	2	0	0.0	4	1	25.0								
Age														
6-<12	0			1	0	0.0								
12-<18	2	0	0.0	6	1	16.7								
Region														
Europe	2	0	0.0	3	1	33.3								
Rest of World	0			4	0	0.0								
Corticosteroid at Baseline														
Yes	0			3	1	33.3								
No	2	0	0.0	4	0	0.0								

N represents the number of patients in the Treated Set with an available SpO2 value at baseline <96% and at the respective visit.
n represents the number of patients meeting the response criterion.
[1] Based on a log-linked Poisson model with robust estimate of variance^.
[2] Based on a logistic regression model^ showing Wald confidence intervals.
[3] Interaction p-value from log-linked Poisson model with robust estimate of variance^.
^ All models contain continuous covariate baseline value and categorical covariate age-group. Subgroup and treatment by subgroup interaction term are additionally included for the subgroup analyses.
All model results are based on pooled results following multiple imputation procedure (m=100 imputations) as described in TSAP Section 6.6.2.3.
inf=infinity; NC=not calculabe because of errors/warnings in at least one of the 100 regression models.

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Table 2.3.2 Adjusted mean (SE) of absolute change from baseline in SpO2 on room air at rest at week 24 by subgroup
Treated Set

Subgroup/ Category/ Treatment	N	Baseline Mean	Baseline [1] SD	24 weeks Mean	24 weeks [1] SD	Change from baseline to 24 weeks: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	Comparison vs. Randomised Placebo: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	p-value [3]
Sex														0.4987
Male														
Placebo	4	97.75	0.50	97.75	0.96	-2.09	1.78	-5.72	1.55					
Nintedanib	9	95.78	3.56	94.22	4.97	-1.00	1.25	-3.55	1.55	1.09	2.18	-3.35	5.53	
Female														
Placebo	8	96.50	5.01	94.25	7.03	-2.28	1.35	-5.05	0.49					
Nintedanib	15	96.93	2.66	97.73	2.89	0.69	0.97	-1.30	2.68	2.97	1.67	-0.44	6.38	
Age														0.9482
6-<12														
Placebo	3	98.33	1.53	98.67	1.53	-2.82	2.11	-7.12	1.48					
Nintedanib	8	97.63	2.92	97.38	2.77	-0.30	1.44	-3.24	2.64	2.52	2.54	-2.67	7.72	
12-<18														
Placebo	9	96.44	4.59	94.33	6.46	-2.10	1.34	-4.85	0.65					
Nintedanib	16	95.94	2.98	95.94	4.61	0.22	0.97	-1.77	2.21	2.33	1.65	-1.06	5.71	
Region														0.1044
Europe														
Placebo	3	93.00	7.55	91.33	8.62	-4.50	2.12	-8.83	-0.18					
Nintedanib	15	97.00	2.73	97.73	2.22	0.80	0.98	-1.22	2.81	5.30	2.36	0.48	10.11	
Rest of World														
Placebo	9	98.22	0.83	96.78	4.55	-1.25	1.30	-3.90	1.41					
Nintedanib	9	95.67	3.43	94.22	5.54	-1.15	1.20	-3.59	1.29	0.10	1.80	-3.57	3.77	
Corticosteroid at Baseline														0.9847
Yes														
Placebo	3	98.67	1.15	98.67	1.53	-2.57	2.07	-6.79	1.65					
Nintedanib	8	96.25	2.76	95.38	5.88	-0.25	1.33	-2.98	2.47	2.32	2.47	-2.72	7.35	
No														
Placebo	9	96.33	4.56	94.33	6.46	-2.02	1.31	-4.69	0.65					
Nintedanib	16	96.63	3.20	96.94	2.93	0.24	0.96	-1.72	2.20	2.26	1.62	-1.05	5.57	

[1] Based on the number of patients having available data at baseline and at the respective visit.
[2] Based on Mixed Model for Repeated Measures (MMRM), with fixed categorical effect age-group and the fixed continuous effects of baseline value at each visit, (randomized) treatment-by-visit-by-subgroup interaction, and random effect for patient. [3] Interaction p-value.
Visit is treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
Adjusted mean is based on all analysed patients in the model (i.e. on patients with a baseline and at least one post-baseline measurement - not only on patients with a baseline and measurement at the respective visit).
For derivation of the MMRM available data from all visits up to week 52 is used.

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Table 2.3.3 Adjusted mean (SE) of absolute change from baseline in SpO2 on room air with exertion at week 24 by subgroup
Treated Set

Subgroup/ Category/ Treatment	N	Baseline Mean	Baseline SD [1]	24 weeks Mean	24 weeks SD [1]	Change from baseline to 24 weeks: Adjusted mean [2]	SE	95% confidence interval Lower	95% confidence interval Upper	Comparison vs. Randomised Placebo: Adjusted mean [2]	SE	95% confidence interval Lower	95% confidence interval Upper	p-value [3]
Sex														0.6030
Male														
Placebo	4	93.50	4.20	91.25	5.06	1.82	3.06	-4.51	8.16					
Nintedanib	7	85.86	4.67	87.71	6.99	-0.00	2.29	-4.74	4.74	-1.82	3.98	-10.06	6.41	
Female														
Placebo	6	85.17	12.40	90.33	8.80	3.39	2.39	-1.56	8.34					
Nintedanib	11	88.55	6.99	92.18	4.35	4.29	1.75	0.66	7.93	0.90	2.99	-5.28	7.09	
Age														0.4359
6-<12														
Placebo	3	96.00	2.00	95.67	5.13	5.18	3.60	-2.27	12.63					
Nintedanib	7	88.29	6.05	90.43	7.79	2.43	2.21	-2.13	7.00	-2.74	4.20	-11.44	5.95	
12-<18														
Placebo	7	85.29	11.10	88.57	7.16	1.55	2.24	-3.09	6.19					
Nintedanib	11	87.00	6.51	90.45	4.52	2.88	1.76	-0.77	6.53	1.33	2.83	-4.53	7.19	
Region														0.1408
Europe														
Placebo	2	84.00	0.00	79.50	0.71	-7.01	3.54	-14.34	0.32					
Nintedanib	14	86.57	6.27	89.36	5.89	1.67	1.37	-1.17	4.51	8.68	3.84	0.73	16.64	
Rest of World														
Placebo	8	89.63	11.58	93.50	4.66	5.18	1.74	1.57	8.78					
Nintedanib	4	90.75	5.32	94.25	3.77	6.04	2.64	0.57	11.50	0.86	3.12	-5.61	7.33	
Corticosteroid at Baseline														
Yes														
Placebo	3	93.00	3.61	94.00	7.94									
Nintedanib	5	91.20	4.49	92.60	5.59									
No														
Placebo	7	86.57	12.08	89.29	6.99									
Nintedanib	13	86.08	6.29	89.62	5.85									

[1] Based on the number of patients having available data at baseline and at the respective visit.
[2] Based on Mixed Model for Repeated Measures (MMRM), with fixed categorical effect age-group and the fixed continuous effects of baseline value at each visit, (randomized) treatment-by-visit-by-subgroup interaction, and random effect for patient. [3] Interaction p-value.
Visit is treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
Adjusted mean is based on all analysed patients in the model (i.e. on patients with a baseline and at least one post-baseline measurement - not only on patients with a baseline and measurement at the respective visit).
For derivation of the MMRM available data from all visits up to week 52 is used.

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Anhang 4-G2.3: 6-MWT

Table 2.4.1 Adjusted mean (SE) of absolute change from baseline in 6-min walk distance at week 24 by subgroup
Treated Set

Subgroup/ Category/ Treatment	N	Baseline [1] Mean	Baseline [1] SD	24 weeks [1] Mean	24 weeks [1] SD	Change from baseline to 24 weeks: Adjusted mean [2]	SE	95% confidence interval Lower	95% confidence interval Upper	Comparison vs. Randomised Placebo: Adjusted mean [2]	SE	95% confidence interval Lower	95% confidence interval Upper	p-value [3]
Sex														0.8228
Male														
Placebo	4	317.1	83.9	322.3	96.6	-14.6	39.3	-95.4	66.1					
Nintedanib	9	398.2	174.9	403.8	147.3	2.8	25.7	-50.1	55.8	17.5	47.2	-79.5	114.4	
Female														
Placebo	7	423.7	144.9	440.9	157.1	24.7	29.0	-35.0	84.5					
Nintedanib	12	398.6	97.1	425.5	83.2	28.6	22.1	-16.9	74.1	3.9	36.5	-71.1	78.9	
Age														0.2909
6-<12														
Placebo	3	444.0	48.5	500.9	60.2	69.4	43.6	-20.1	158.9					
Nintedanib	7	358.7	151.5	396.6	135.0	27.4	28.7	-31.4	86.3	-41.9	52.6	-149.9	66.0	
12-<18														
Placebo	8	362.8	149.7	359.1	151.5	-13.1	26.8	-68.0	41.9					
Nintedanib	14	418.3	122.2	426.0	103.3	13.3	20.2	-28.2	54.7	26.3	33.8	-43.0	95.7	
Region														0.9216
Europe														
Placebo	3	371.0	218.0	378.3	224.1	7.7	46.6	-88.1	103.4					
Nintedanib	14	435.7	144.9	444.4	119.5	13.7	22.5	-32.5	60.0	6.1	53.5	-103.8	115.9	
Rest of World														
Placebo	8	390.2	107.0	405.0	125.2	11.9	27.7	-45.1	68.9					
Nintedanib	7	323.9	53.6	359.8	74.3	25.2	33.1	-42.8	93.2	13.3	43.5	-76.1	102.8	
Corticosteroid at Baseline														0.8713
Yes														
Placebo	3	319.2	101.0	336.3	122.6	-4.5	45.3	-97.7	88.8					
Nintedanib	7	354.6	109.3	365.8	70.9	-2.9	29.7	-63.9	58.2	1.6	53.4	-108.2	111.4	
No														
Placebo	8	409.6	140.3	420.8	154.1	15.9	27.3	-40.4	72.1					
Nintedanib	14	420.4	140.5	441.4	122.6	27.8	20.8	-14.9	70.5	11.9	34.2	-58.4	82.3	

[1] Based on the number of patients having available data at baseline and at the respective visit.
[2] Based on Mixed Model for Repeated Measures (MMRM), with fixed categorical effect age-group and the fixed continuous effects of baseline value at each visit, (randomized) treatment-by-visit-by-subgroup interaction, and random effect for patient. [3] Interaction p-value.
Visit is treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
Adjusted mean is based on all analysed patients in the model (i.e. on patients with a baseline and at least one post-baseline measurement - not only on patients with a baseline and measurement at the respective visit).
For derivation of the MMRM available data from all visits up to week 52 is used.

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Anhang 4-G2.4: PedsQL™

Table 2.2.1 Proportion of patients with increase in PedsQL (parent report) total score (>=4.4 points) from baseline at week 24 overall and by subgroup - Treated Set

	Placebo			Nintedanib			Randomised Nintedanib vs. Placebo							
							Risk ratio	95% confidence interval [1]		p-value	Odds ratio	95% confidence interval [2]		p-value
	N	n	%	N	n	%	[1]	Lower	Upper	[1]	[2]	Lower	Upper	[1][3]
Overall	11	6	54.5	21	10	47.6	0.82	0.44	1.54	0.5387	0.58	0.10	3.49	
Sex														0.5216
Male	4	3	75.0	9	3	33.3	0.62	0.23	1.64	0.3330	0.32	0.02	4.94	
Female	7	3	42.9	12	7	58.3	0.96	0.40	2.30	0.9184	0.84	0.07	9.65	
Age														0.9112
6-<12	3	1	33.3	7	3	42.9	0.89	0.18	4.37	0.8888	0.57	0.02	17.72	
12-<18	8	5	62.5	14	7	50.0	0.81	0.41	1.59	0.5411	0.59	0.08	4.58	
Region														
Europe	3	2	66.7	14	5	35.7								
Rest of World	8	4	50.0	7	5	71.4								
Corticosteroid at Baseline														0.8046
Yes	3	1	33.3	7	3	42.9	0.99	0.21	4.55	0.9856	0.89	0.04	20.34	
No	8	5	62.5	14	7	50.0	0.80	0.41	1.56	0.5128	0.43	0.04	4.57	

N represents the number of patients in the Treated Set with an available PedsQL total score at baseline and at the respective visit.
n represents the number of patients meeting the response criterion.
[1] Based on a log-linked Poisson model with robust estimate of variance^.
[2] Based on a logistic regression model^ showing Wald confidence intervals.
[3] Interaction p-value from log-linked Poisson model with robust estimate of variance^.
^ All models contain continuous covariate baseline value and categorical covariate age-group. Subgroup and treatment by subgroup interaction term are additionally included for the subgroup analyses.
All model results are based on pooled results following multiple imputation procedure (m=100 imputations) as described in TSAP Section 6.6.2.3.
inf=infinity; NC=not calculabe because of errors/warnings in at least one of the 100 regression models.

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Table 2.2.2 Proportion of patients with increase in PedsQL (parent report) total score (>=15 points) from baseline at week 24 overall and by subgroup - Treated Set

	Placebo			Nintedanib			Randomised Nintedanib vs. Placebo							
							Risk ratio	95% confidence interval [1]		p-value	Odds ratio	95% confidence interval [2]		p-value [1][3]
	N	n	%	N	n	%	[1]	Lower	Upper	[1]	[2]	Lower	Upper	
Overall	11	0	0.0	21	5	23.8	NC	NC	NC	NC	NC	NC	NC	
Sex														
Male	4	0	0.0	9	2	22.2								
Female	7	0	0.0	12	3	25.0								
Age														
6-<12	3	0	0.0	7	3	42.9								
12-<18	8	0	0.0	14	2	14.3								
Region														
Europe	3	0	0.0	14	3	21.4								
Rest of World	8	0	0.0	7	2	28.6								
Corticosteroid at Baseline														
Yes	3	0	0.0	7	2	28.6								
No	8	0	0.0	14	3	21.4								

N represents the number of patients in the Treated Set with an available PedsQL total score at baseline and at the respective visit.
n represents the number of patients meeting the response criterion.
[1] Based on a log-linked Poisson model with robust estimate of variance^.
[2] Based on a logistic regression model^ showing Wald confidence intervals.
[3] Interaction p-value from log-linked Poisson model with robust estimate of variance^.
^ All models contain continuous covariate baseline value and categorical covariate age-group. Subgroup and treatment by subgroup interaction term are additionally included for the subgroup analyses.
All model results are based on pooled results following multiple imputation procedure (m=100 imputations) as described in TSAP Section 6.6.2.3.
inf=infinity; NC=not calculabe because of errors/warnings in at least one of the 100 regression models.

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Table 2.2.3 Proportion of patients with decrease in PedsQL (parent report) total score (>=4.4 points) from baseline at week 24 overall and by subgroup - Treated Set

	Placebo			Nintedanib			Randomised Nintedanib vs. Placebo						
							Risk ratio	95% confidence interval [1]		p-value	Odds ratio	95% confidence interval [2]		p-value [1][3]
	N	n	%	N	n	%	[1]	Lower	Upper	[1]	[2]	Lower	Upper	
Overall	11	1	9.1	21	4	19.0	2.51	0.29	21.40	0.4013	3.03	0.28	33.01	
Sex														
Male	4	1	25.0	9	2	22.2								
Female	7	0	0.0	12	2	16.7								
Age														
6-<12	3	0	0.0	7	1	14.3								
12-<18	8	1	12.5	14	3	21.4								
Region														
Europe	3	0	0.0	14	3	21.4								
Rest of World	8	1	12.5	7	1	14.3								
Corticosteroid at Baseline														
Yes	3	1	33.3	7	2	28.6								
No	8	0	0.0	14	2	14.3								

N represents the number of patients in the Treated Set with an available PedsQL total score at baseline and at the respective visit.
n represents the number of patients meeting the response criterion.
[1] Based on a log-linked Poisson model with robust estimate of variance^.
[2] Based on a logistic regression model^ showing Wald confidence intervals.
[3] Interaction p-value from log-linked Poisson model with robust estimate of variance^.
^ All models contain continuous covariate baseline value and categorical covariate age-group. Subgroup and treatment by subgroup interaction term are additionally included for the subgroup analyses.
All model results are based on pooled results following multiple imputation procedure (m=100 imputations) as described in TSAP Section 6.6.2.3.
inf=infinity; NC=not calculabe because of errors/warnings in at least one of the 100 regression models.

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Table 2.2.4 Proportion of patients with decrease in PedsQL (parent report) total score (>=15 points) from baseline at week 24 overall and by subgroup - Treated Set

	Placebo			Nintedanib			Randomised Nintedanib vs. Placebo							
							Risk ratio [1]	95% confidence interval [1]		p-value [1]	Odds ratio [2]	95% confidence interval [2]		p-value [1][3]
	N	n	%	N	n	%		Lower	Upper			Lower	Upper	
Overall	11	0	0.0	21	2	9.5	NC	NC	NC	NC	NC	NC	NC	
Sex														
Male	4	0	0.0	9	1	11.1								
Female	7	0	0.0	12	1	8.3								
Age														
6-<12	3	0	0.0	7	0	0.0								
12-<18	8	0	0.0	14	2	14.3								
Region														
Europe	3	0	0.0	14	2	14.3								
Rest of World	8	0	0.0	7	0	0.0								
Corticosteroid at Baseline														
Yes	3	0	0.0	7	0	0.0								
No	8	0	0.0	14	2	14.3								

N represents the number of patients in the Treated Set with an available PedsQL total score at baseline and at the respective visit.
n represents the number of patients meeting the response criterion.
[1] Based on a log-linked Poisson model with robust estimate of variance^.
[2] Based on a logistic regression model^ showing Wald confidence intervals.
[3] Interaction p-value from log-linked Poisson model with robust estimate of variance^.
^ All models contain continuous covariate baseline value and categorical covariate age-group. Subgroup and treatment by subgroup interaction term are additionally included for the subgroup analyses.
All model results are based on pooled results following multiple imputation procedure (m=100 imputations) as described in TSAP Section 6.6.2.3.
inf=infinity; NC=not calculabe because of errors/warnings in at least one of the 100 regression models.

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Table 2.2.5 Proportion of patients with increase in PedsQL (patient report) total score (>=4.4 points) from baseline at week 24 overall and by subgroup - Treated Set

	Placebo			Nintedanib			Randomised Nintedanib vs. Placebo							
							Risk ratio [1]	95% confidence interval [1]		p-value [1]	Odds ratio [2]	95% confidence interval [2]		p-value [1][3]
	N	n	%	N	n	%		Lower	Upper			Lower	Upper	
Overall	11	8	72.7	21	11	52.4	0.73	0.43	1.24	0.2374	0.32	0.05	2.00	
Sex														0.5297
Male	4	3	75.0	9	4	44.4	0.58	0.26	1.33	0.1992	0.22	0.01	3.60	
Female	7	5	71.4	12	7	58.3	0.82	0.41	1.62	0.5608	0.39	0.04	4.00	
Age														0.5194
6-<12	3	1	33.3	7	4	57.1	1.24	0.19	7.96	0.8239	0.99	0.03	35.14	
12-<18	8	7	87.5	14	7	50.0	0.65	0.37	1.14	0.1346	0.20	0.02	2.11	
Region														0.6902
Europe	3	2	66.7	14	7	50.0	0.88	0.31	2.51	0.8170	0.88	0.05	16.45	
Rest of World	8	6	75.0	7	4	57.1	0.68	0.34	1.35	0.2704	0.18	0.01	3.85	
Corticosteroid at Baseline														0.2312
Yes	3	3	100.0	7	4	57.1	0.46	0.21	1.02	0.0567	NC	NC	NC	
No	8	5	62.5	14	7	50.0	0.87	0.44	1.71	0.6847	NC	NC	NC	

N represents the number of patients in the Treated Set with an available PedsQL total score at baseline and at the respective visit.
n represents the number of patients meeting the response criterion.
[1] Based on a log-linked Poisson model with robust estimate of variance^.
[2] Based on a logistic regression model^ showing Wald confidence intervals.
[3] Interaction p-value from log-linked Poisson model with robust estimate of variance^.
^ All models contain continuous covariate baseline value and categorical covariate age-group. Subgroup and treatment by subgroup interaction term are additionally included for the subgroup analyses.
All model results are based on pooled results following multiple imputation procedure (m=100 imputations) as described in TSAP Section 6.6.2.3.
inf=infinity; NC=not calculabe because of errors/warnings in at least one of the 100 regression models.

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Table 2.2.6 Proportion of patients with increasee in PedsQL (patient report) total score (>=15 points) from baseline at week 24 overall and by subgroup - Treated Set

	Placebo			Nintedanib			Randomised Nintedanib vs. Placebo						
							Risk ratio [1]	95% confidence interval [1]		p-value [1]	Odds ratio [2]	95% confidence interval [2]		p-value [1][3]
	N	n	%	N	n	%		Lower	Upper			Lower	Upper	
Overall	11	1	9.1	21	4	19.0	1.56	0.19	12.66	0.6756	1.80	0.13	24.06	
Sex														
Male	4	1	25.0	9	0	0.0								
Female	7	0	0.0	12	4	33.3								
Age														
6-<12	3	0	0.0	7	2	28.6								
12-<18	8	1	12.5	14	2	14.3								
Region														
Europe	3	0	0.0	14	3	21.4								
Rest of World	8	1	12.5	7	1	14.3								
Corticosteroid at Baseline														
Yes	3	0	0.0	7	2	28.6								
No	8	1	12.5	14	2	14.3								

N represents the number of patients in the Treated Set with an available PedsQL total score at baseline and at the respective visit.
n represents the number of patients meeting the response criterion.
[1] Based on a log-linked Poisson model with robust estimate of variance^.
[2] Based on a logistic regression model^ showing Wald confidence intervals.
[3] Interaction p-value from log-linked Poisson model with robust estimate of variance^.
^ All models contain continuous covariate baseline value and categorical covariate age-group. Subgroup and treatment by subgroup interaction term are additionally included for the subgroup analyses.
All model results are based on pooled results following multiple imputation procedure (m=100 imputations) as described in TSAP Section 6.6.2.3.
inf=infinity; NC=not calculabe because of errors/warnings in at least one of the 100 regression models.

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Table 2.2.7 Proportion of patients with decrease in PedsQL (patient report) total score (>=4.4 points) from baseline at week 24 overall and by subgroup - Treated Set

	Placebo			Nintedanib			Randomised Nintedanib vs. Placebo							
							Risk ratio	95% confidence interval [1]		p-value	Odds ratio	95% confidence interval [2]		p-value [1][3]
	N	n	%	N	n	%	[1]	Lower	Upper	[1]	[2]	Lower	Upper	
Overall	11	2	18.2	21	2	9.5	0.83	0.15	4.53	0.8322	0.69	0.05	10.10	
Sex														
Male	4	1	25.0	9	1	11.1								
Female	7	1	14.3	12	1	8.3								
Age														
6-<12	3	2	66.7	7	1	14.3								
12-<18	8	0	0.0	14	1	7.1								
Region														
Europe	3	0	0.0	14	2	14.3								
Rest of World	8	2	25.0	7	0	0.0								
Corticosteroid at Baseline														
Yes	3	0	0.0	7	0	0.0								
No	8	2	25.0	14	2	14.3								

N represents the number of patients in the Treated Set with an available PedsQL total score at baseline and at the respective visit.
n represents the number of patients meeting the response criterion.
[1] Based on a log-linked Poisson model with robust estimate of variance^.
[2] Based on a logistic regression model^ showing Wald confidence intervals.
[3] Interaction p-value from log-linked Poisson model with robust estimate of variance^.
^ All models contain continuous covariate baseline value and categorical covariate age-group. Subgroup and treatment by subgroup interaction term are additionally included for the subgroup analyses.
All model results are based on pooled results following multiple imputation procedure (m=100 imputations) as described in TSAP Section 6.6.2.3.
inf=infinity; NC=not calculabe because of errors/warnings in at least one of the 100 regression models.

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Table 2.2.8 Proportion of patients with decrease in PedsQL (patient report) total score (>=15 points) from baseline at week 24 overall and by subgroup - Treated Set

	Placebo			Nintedanib			Randomised Nintedanib vs. Placebo							
							Risk ratio	95% confidence interval [1]		p-value	Odds ratio	95% confidence interval [2]		p-value [1][3]
	N	n	%	N	n	%	[1]	Lower	Upper	[1]	[2]	Lower	Upper	
Overall	11	1	9.1	21	0	0.0	NC	NC	NC	NC	NC	NC	NC	
Sex														
Male	4	1	25.0	9	0	0.0								
Female	7	0	0.0	12	0	0.0								
Age														
6-<12	3	1	33.3	7	0	0.0								
12-<18	8	0	0.0	14	0	0.0								
Region														
Europe	3	0	0.0	14	0	0.0								
Rest of World	8	1	12.5	7	0	0.0								
Corticosteroid at Baseline														
Yes	3	0	0.0	7	0	0.0								
No	8	1	12.5	14	0	0.0								

N represents the number of patients in the Treated Set with an available PedsQL total score at baseline and at the respective visit.
n represents the number of patients meeting the response criterion.
[1] Based on a log-linked Poisson model with robust estimate of variance^.
[2] Based on a logistic regression model^ showing Wald confidence intervals.
[3] Interaction p-value from log-linked Poisson model with robust estimate of variance^.
^ All models contain continuous covariate baseline value and categorical covariate age-group. Subgroup and treatment by subgroup interaction term are additionally included for the subgroup analyses.
All model results are based on pooled results following multiple imputation procedure (m=100 imputations) as described in TSAP Section 6.6.2.3.
inf=infinity; NC=not calculabe because of errors/warnings in at least one of the 100 regression models.

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Table 2.2.9 Adjusted mean (SE) of absolute change from baseline in PedsQL (parent report) at week 24 by subgroup
Treated Set

Subgroup/ Category/ Treatment	N	Baseline [1] Mean	Baseline [1] SD	24 weeks [1] Mean	24 weeks [1] SD	Change from baseline to 24 weeks: Adjusted mean [2]	SE	95% confidence interval Lower	95% confidence interval Upper	Comparison vs. Randomised Placebo: Adjusted mean [2]	SE	95% confidence interval Lower	95% confidence interval Upper	p-value [3]
Sex														0.7609
Male														
Placebo	4	51.087	6.582	54.620	5.978	-0.292	5.705	-12.019	11.434					
Nintedanib	9	58.333	12.676	61.232	13.434	1.166	3.730	-6.500	8.831	1.458	6.753	-12.422	15.338	
Female														
Placebo	7	77.484	19.114	81.832	16.361	9.709	4.579	0.298	19.120					
Nintedanib	12	61.322	19.213	69.928	16.803	8.374	3.189	1.820	14.928	-1.335	5.642	-12.931	10.261	
Age														0.5957
6-<12														
Placebo	3	76.449	20.804	77.536	18.521	4.519	6.875	-9.588	18.625					
Nintedanib	7	49.068	8.217	60.714	11.459	8.403	4.668	-1.175	17.981	3.885	8.677	-13.920	21.689	
12-<18														
Placebo	8	64.674	20.451	69.837	19.939	5.724	4.071	-2.629	14.078					
Nintedanib	14	65.528	16.922	68.944	17.174	4.186	3.096	-2.168	10.539	-1.539	5.091	-11.985	8.908	
Region														0.5494
Europe														
Placebo	3	64.130	23.540	69.928	16.710	7.450	6.916	-6.764	21.664					
Nintedanib	14	63.432	18.805	68.090	16.939	4.144	3.302	-2.642	10.930	-3.306	7.887	-19.514	12.901	
Rest of World														
Placebo	8	69.293	20.457	72.690	20.782	4.765	4.262	-3.993	13.524					
Nintedanib	7	53.261	7.210	62.422	13.281	8.251	5.018	-2.060	18.561	3.485	6.944	-10.783	17.754	
Corticosteroid at Baseline														0.5382
Yes														
Placebo	3	68.116	23.872	68.478	25.071	1.823	6.773	-12.098	15.744					
Nintedanib	7	51.087	8.182	60.404	15.125	6.089	4.637	-3.442	15.620	4.266	8.323	-12.841	21.372	
No														
Placebo	8	67.799	20.549	73.234	18.095	6.991	4.180	-1.601	15.582					
Nintedanib	14	64.519	17.864	69.099	15.721	5.196	3.128	-1.232	11.625	-1.794	5.184	-12.449	8.860	

[1] Based on the number of patients having available data at baseline and at the respective visit.
[2] Based on Mixed Model for Repeated Measures (MMRM), with fixed categorical effect age-group and the fixed continuous effects of baseline value at each visit, (randomized) treatment-by-visit-by-subgroup interaction, and random effect for patient. [3] Interaction p-value.
Visit is treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
Adjusted mean is based on all analysed patients in the model (i.e. on patients with a baseline and at least one post-baseline measurement - not only on patients with a baseline and measurement at the respective visit).
For derivation of the MMRM available data from all visits up to week 52 is used.

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Table 2.2.10 Adjusted mean (SE) of absolute change from baseline in PedsQL (patient report) at week 24 by subgroup
Treated Set

Subgroup/ Category/ Treatment	N	Baseline [1] Mean	Baseline [1] SD	24 weeks [1] Mean	24 weeks [1] SD	Change from baseline to 24 weeks: Adjusted mean [2]	SE	95% confidence interval: Lower	Upper	Comparison vs. Randomised Placebo: Adjusted mean [2]	SE	95% confidence interval: Lower	Upper	p-value [3]
Sex														0.9324
Male														
Placebo	4	70.109	11.924	72.554	12.964	2.131	4.394	-6.901	11.162					
Nintedanib	9	67.271	15.849	70.993	15.760	3.709	2.975	-2.406	9.824	1.578	5.323	-9.362	12.519	
Female														
Placebo	7	75.776	13.873	81.988	13.041	7.536	3.385	0.579	14.493					
Nintedanib	12	68.931	13.178	78.080	13.440	8.532	2.548	3.294	13.770	0.996	4.261	-7.763	9.754	
Age														0.2069
6-<12														
Placebo	3	87.319	6.988	80.797	19.332	-4.256	5.628	-15.803	7.292					
Nintedanib	7	57.609	13.416	64.596	12.069	5.339	3.768	-2.391	13.070	9.595	7.408	-5.605	24.795	
12-<18														
Placebo	8	68.614	10.704	77.717	11.850	8.905	3.099	2.547	15.263					
Nintedanib	14	73.525	11.341	80.265	13.046	7.189	2.388	2.289	12.089	-1.716	3.940	-9.799	6.368	
Region														0.3770
Europe														
Placebo	3	65.942	13.763	72.464	14.677	2.928	5.424	-8.220	14.077					
Nintedanib	14	68.711	16.491	75.452	16.895	7.880	2.528	2.684	13.076	4.952	6.146	-7.680	17.585	
Rest of World														
Placebo	8	76.630	12.159	80.842	12.913	6.500	3.326	-0.336	13.336					
Nintedanib	7	67.236	8.047	74.224	9.260	3.745	3.697	-3.855	11.344	-2.756	5.168	-13.379	7.868	
Corticosteroid at Baseline														0.8317
Yes														
Placebo	3	75.362	19.332	81.884	17.572	7.857	5.304	-3.046	18.760					
Nintedanib	7	60.248	12.423	69.410	14.426	7.665	3.681	0.100	15.231	-0.191	6.583	-13.723	13.340	
No														
Placebo	8	73.098	11.367	77.310	12.467	4.522	3.246	-2.151	11.194					
Nintedanib	14	72.205	13.419	77.859	14.279	5.981	2.449	0.948	11.015	1.460	4.039	-6.842	9.762	

[1] Based on the number of patients having available data at baseline and at the respective visit.
[2] Based on Mixed Model for Repeated Measures (MMRM), with fixed categorical effect age-group and the fixed continuous effects of baseline value at each visit, (randomized) treatment-by-visit-by-subgroup interaction, and random effect for patient. [3] Interaction p-value.
Visit is treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
Adjusted mean is based on all analysed patients in the model (i.e. on patients with a baseline and at least one post-baseline measurement - not only on patients with a baseline and measurement at the respective visit).
For derivation of the MMRM available data from all visits up to week 52 is used.

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Anhang 4-G3: PT für die Definition präspezifizierter Safety Topics in der Studie InPedILD®

Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Blood	Bleeding	CNS bleeding	Group of MedDRA PTs	Acute haemorrhagic leukoencephalitis
				Basal ganglia haematoma
				Basal ganglia haemorrhage
				Basilar artery perforation
				Brain contusion
				Brain stem haematoma
				Brain stem haemorrhage
				Brain stem microhaemorrhage
				Carotid aneurysm rupture
				Carotid artery perforation
				Central nervous system haemorrhage
				Cephalhaematoma
				Cerebellar haematoma
				Cerebellar haemorrhage
				Cerebellar microhaemorrhage
				Cerebral aneurysm perforation
				Cerebral aneurysm ruptured syphilitic
				Cerebral arteriovenous malformation haemorrhagic
				Cerebral artery perforation
				Cerebral cyst haemorrhage
				Cerebral haematoma
				Cerebral haemorrhage
				Cerebral haemorrhage foetal
				Cerebral haemorrhage neonatal
				Cerebral microhaemorrhage
				Encephalitis haemorrhagic
				Epidural haemorrhage
				Extra-axial haemorrhage
				Extradural haematoma
				Extradural haematoma evacuation
				Haemorrhage intracranial
				Haemorrhagic cerebellar infarction
				Haemorrhagic cerebral infarction
				Haemorrhagic stroke
				Haemorrhagic transformation stroke
				Intracerebral haematoma evacuation
				Intracranial haematoma
				Intracranial haemorrhage neonatal
				Intracranial tumour haemorrhage
				Intraventricular haemorrhage
				Intraventricular haemorrhage neonatal
				Meningorrhagia
				Periventricular haemorrhage neonatal

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Blood	Bleeding	CNS bleeding	Group of MedDRA PTs	Pituitary apoplexy
				Pituitary haemorrhage
				Putamen haemorrhage
				Ruptured cerebral aneurysm
				Spinal cord haematoma
				Spinal cord haemorrhage
				Spinal epidural haematoma
				Spinal epidural haemorrhage
				Spinal subarachnoid haemorrhage
				Spinal subdural haematoma
				Spinal subdural haemorrhage
				Subarachnoid haematoma
				Subarachnoid haemorrhage
				Subarachnoid haemorrhage neonatal
				Subdural haematoma
				Subdural haematoma evacuation
				Subdural haemorrhage
				Subdural haemorrhage neonatal
				Thalamus haemorrhage
				Traumatic intracranial haematoma
				Traumatic intracranial haemorrhage
				Vertebral artery perforation
		GI bleeding - lower	Group of MedDRA PTs	Acute haemorrhagic ulcerative colitis
				Anal fissure haemorrhage
				Anal haemorrhage
				Anal ulcer haemorrhage
				Anorectal varices haemorrhage
				Colonic haematoma
				Diarrhoea haemorrhagic
				Diverticulitis intestinal haemorrhagic
				Diverticulum intestinal haemorrhagic
				Enterocolitis haemorrhagic
				Haematochezia
				Haemorrhoidal haemorrhage
				Intra-abdominal haematoma
				Intra-abdominal haemorrhage
				Large intestinal haemorrhage
				Large intestinal ulcer haemorrhage
				Lower gastrointestinal haemorrhage
				Melaena
				Melaena neonatal
				Proctitis haemorrhagic
				Rectal haemorrhage

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Blood	Bleeding	GI bleeding - lower	Group of MedDRA PTs	Rectal ulcer haemorrhage
		GI bleeding - nonspecific	Group of MedDRA PTs	Anastomotic haemorrhage Anastomotic ulcer haemorrhage Bloody peritoneal effluent Cullen's sign Gastrointestinal anastomotic haemorrhage Gastrointestinal vascular malformation haemorrhagic Grey Turner's sign Haemorrhagic ascites Haemorrhagic hepatic cyst Hepatic haematoma Hepatic haemorrhage Intestinal haematoma Intestinal haemorrhage Intestinal varices haemorrhage Mesenteric haematoma Mesenteric haemorrhage Mucosal haemorrhage Neonatal gastrointestinal haemorrhage Peritoneal haematoma
		GI bleeding - oral	Group of MedDRA PTs	Angina bullosa haemorrhagica Gingival bleeding Mouth haemorrhage Oral blood blister Oral contusion Oral mucosa haematoma Oral purpura Pharyngeal contusion Pharyngeal haematoma Pharyngeal haemorrhage Stomatitis haemorrhagic Tongue haematoma Tongue haemorrhage Tonsillar haemorrhage Tooth pulp haemorrhage Tooth socket haemorrhage
		GI bleeding - upper	Group of MedDRA PTs	Chronic gastrointestinal bleeding Duodenal ulcer haemorrhage Duodenitis haemorrhagic Gastric haemorrhage

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Blood	Bleeding	GI bleeding - upper	Group of MedDRA PTs	Gastric ulcer haemorrhage Gastric ulcer haemorrhage, obstructive Gastric varices haemorrhage Gastritis alcoholic haemorrhagic Gastritis haemorrhagic Gastroduodenal haemorrhage Gastrointestinal haemorrhage Gastrointestinal polyp haemorrhage Gastrointestinal ulcer haemorrhage Haematemesis Haemorrhagic erosive gastritis Haemorrhagic gastroenteritis Haemorrhagic necrotic pancreatitis Mallory-Weiss syndrome Oesophageal haemorrhage Oesophageal intramural haematoma Oesophageal ulcer haemorrhage Oesophageal varices haemorrhage Oesophagitis haemorrhagic Pancreatic haemorrhage Pancreatitis haemorrhagic Peptic ulcer haemorrhage Small intestinal haemorrhage Small intestinal ulcer haemorrhage Ulcer haemorrhage Upper gastrointestinal haemorrhage
		Other bleeding	Group of MedDRA PTs	Abnormal withdrawal bleeding Adrenal haematoma Adrenal haemorrhage Aneurysm ruptured Anticoagulant-related nephropathy Antiplatelet reversal therapy Aortic aneurysm rupture Aortic dissection rupture Aortic intramural haematoma Aortic perforation Aortic rupture Aponeurosis contusion Arterial haemorrhage Arterial intramural haematoma Arterial perforation Arterial rupture Arteriovenous fistula site haematoma

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Blood	Bleeding	Other bleeding	Group of MedDRA PTs	Arteriovenous fistula site haemorrhage Arteriovenous graft site haematoma Arteriovenous graft site haemorrhage Astringent therapy Atrial rupture Auricular haematoma Blood loss anaemia Bloody discharge Bone contusion Bone marrow haemorrhage Breast haemorrhage Bursal haematoma Cardiac contusion Catheter site bruise Catheter site haematoma Catheter site haemorrhage Choroidal haematoma Choroidal haemorrhage Ciliary body haemorrhage Conjunctival haemorrhage Corneal bleeding Deep dissecting haematoma Disseminated intravascular coagulation Ear haemorrhage Exsanguination Extravasation blood Eye contusion Eye haematoma Eye haemorrhage Femoral artery perforation Femoral vein perforation Foetal-maternal haemorrhage Fothergill sign positive Gallbladder haematoma Graft haemorrhage Haemangioma rupture Haemarthrosis Haematocoele Haematoma Haematoma evacuation Haematoma infection Haematoma muscle Haematotympanum Haemobilia

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Blood	Bleeding	Other bleeding	Group of MedDRA PTs	Haemoperitoneum
				Haemophilic arthropathy
				Haemophilic pseudotumour
				Haemorrhage
				Haemorrhage coronary artery
				Haemorrhage foetal
				Haemorrhage in pregnancy
				Haemorrhage neonatal
				Haemorrhagic adrenal infarction
				Haemorrhagic arteriovenous malformation
				Haemorrhagic breast cyst
				Haemorrhagic cyst
				Haemorrhagic diathesis
				Haemorrhagic disease of newborn
				Haemorrhagic disorder
				Haemorrhagic infarction
				Haemorrhagic occlusive retinal vasculitis
				Haemorrhagic thyroid cyst
				Haemorrhagic tumour necrosis
				Haemorrhagic vasculitis
				Haemostasis
				Hepatic artery haemorrhage
				Hepatic haemangioma rupture
				Hereditary haemorrhagic telangiectasia
				Hyperfibrinolysis
				Hypergammaglobulinaemic purpura of Waldenstrom
				Hyphaema
				Iliac artery perforation
				Iliac artery rupture
				Iliac vein perforation
				Immune thrombocytopenia
				Induced abortion haemorrhage
				Inferior vena cava perforation
				Internal haemorrhage
				Intraocular haematoma
				Intratumoural haematoma
				Iris haemorrhage
				Joint microhaemorrhage
				Jugular vein haemorrhage
				Lacrimal haemorrhage
				Liver contusion
				Lower limb artery perforation

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Blood	Bleeding	Other bleeding	Group of MedDRA PTs	Lymph node haemorrhage
				Mediastinal haematoma
				Mediastinal haemorrhage
				Myocardial haemorrhage
				Myocardial rupture
				Nipple exudate bloody
				Ocular retrobulbar haemorrhage
				Omental haemorrhage
				Optic disc haemorrhage
				Optic nerve sheath haemorrhage
				Orbital haematoma
				Orbital haemorrhage
				Osteorrhagia
				Pancreatic pseudocyst haemorrhage
				Papillary muscle haemorrhage
				Parathyroid haemorrhage
				Parotid gland haemorrhage
				Pericardial haemorrhage
				Periorbital haematoma
				Periorbital haemorrhage
				Periosteal haematoma
				Peripheral artery aneurysm rupture
				Peripheral artery haematoma
				Peripheral exudative haemorrhagic chorioretinopathy
				Placenta praevia haemorrhage
				Procedural haemorrhage
				Puncture site bruise
				Puncture site haematoma
				Radiation associated haemorrhage
				Retinal aneurysm rupture
				Retinal haemorrhage
				Retinopathy haemorrhagic
				Retroperitoneal haematoma
				Retroperitoneal haemorrhage
				Scleral haematoma
				Scleral haemorrhage
				Shock haemorrhagic
				Soft tissue haemorrhage
				Spleen contusion
				Splenic artery perforation
				Splenic haematoma
				Splenic haemorrhage
				Splenic varices haemorrhage

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Blood	Bleeding	Other bleeding	Group of MedDRA PTs	Spontaneous haematoma Spontaneous haemorrhage Stoma site haemorrhage Subcapsular hepatic haematoma Subcapsular splenic haematoma Subclavian artery perforation Subclavian vein perforation Subendocardial haemorrhage Subgaleal haematoma Subgaleal haemorrhage Subretinal haematoma Superior vena cava perforation Thyroid haemorrhage Tumour haemorrhage Umbilical cord haemorrhage Vascular anastomotic haemorrhage Vascular rupture Vein rupture Venous haemorrhage Venous perforation Ventricle rupture Vitreous haematoma Vitreous haemorrhage Withdrawal bleed
		Respiratory bleeding	Group of MedDRA PTs	Bronchial haemorrhage Bronchial varices haemorrhage Epistaxis Haemoptysis Haemothorax Laryngeal haematoma Laryngeal haemorrhage Nasal septum haematoma Paranasal sinus haematoma Paranasal sinus haemorrhage Pulmonary alveolar haemorrhage Pulmonary contusion Pulmonary haematoma Pulmonary haemorrhage Pulmonary haemorrhage neonatal Respiratory tract haemorrhage Respiratory tract haemorrhage neonatal Thoracic haemorrhage Tracheal haemorrhage

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
MedDRA version: 25.0

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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Blood	Bleeding	Respiratory bleeding	Group of MedDRA PTs	Traumatic haemothorax
		Skin bleeding	Group of MedDRA PTs	Abdominal wall haematoma Abdominal wall haemorrhage Achenbach syndrome Administration site bruise Administration site haematoma Administration site haemorrhage Application site bruise Application site haematoma Application site haemorrhage Application site purpura Bleeding varicose vein Blood blister Breast haematoma Bullous haemorrhagic dermatosis Chest wall haematoma Chronic pigmented purpura Contusion Ecchymosis Eyelid bleeding Eyelid contusion Eyelid haematoma Haemorrhage subcutaneous Haemorrhage subepidermal Haemorrhagic urticaria Henoch-Schonlein purpura Implant site bruising Implant site haematoma Implant site haemorrhage Incision site haematoma Incision site haemorrhage Increased tendency to bruise Infusion site bruising Infusion site haematoma Infusion site haemorrhage Injection site bruising Injection site haematoma Injection site haemorrhage Instillation site bruise Instillation site haematoma Instillation site haemorrhage Lip haematoma Lip haemorrhage

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Blood	Bleeding	Skin bleeding	Group of MedDRA PTs	Medical device site bruise Medical device site haematoma Medical device site haemorrhage Mucocutaneous haemorrhage Muscle contusion Muscle haemorrhage Naevus haemorrhage Nail bed bleeding Palpable purpura Petechiae Post procedural contusion Post procedural haematoma Post procedural haematuria Post procedural haemorrhage Post transfusion purpura Post-traumatic punctate intraepidermal haemorrhage Puncture site haemorrhage Purpura Purpura fulminans Purpura neonatal Purpura non-thrombocytopenic Purpura senile Skin haemorrhage Skin neoplasm bleeding Skin ulcer haemorrhage Splinter haemorrhages Subcutaneous haematoma Thrombocytopenic purpura Thrombotic thrombocytopenic purpura Traumatic haematoma Traumatic haemorrhage Umbilical haematoma Umbilical haemorrhage Vaccination site bruising Vaccination site haematoma Vaccination site haemorrhage Varicose vein ruptured Vascular access site bruising Vascular access site haematoma Vascular access site haemorrhage Vascular access site rupture Vascular graft haemorrhage Vascular pseudoaneurysm ruptured

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Blood	Bleeding	Skin bleeding	Group of MedDRA PTs	Vascular purpura
				Vessel puncture site bruise
				Vessel puncture site haematoma
				Vessel puncture site haemorrhage
				Wound haematoma
				Wound haemorrhage
		Urogenital bleeding	Group of MedDRA PTs	Abnormal uterine bleeding
				Bladder tamponade
				Blood urine
				Blood urine present
				Broad ligament haematoma
				Cervix haematoma uterine
				Cervix haemorrhage uterine
				Coital bleeding
				Cystitis haemorrhagic
				Genital contusion
				Genital haemorrhage
				Haematosalpinx
				Haematospermia
				Haematuria
				Haematuria traumatic
				Haemorrhage urinary tract
				Haemorrhagic ovarian cyst
				Heavy menstrual bleeding
				Intermenstrual bleeding
				Intrapartum haemorrhage
				Kidney contusion
				Menometrorrhagia
				Nephritis haemorrhagic
				Ovarian haematoma
				Ovarian haemorrhage
				Pelvic haematoma
				Pelvic haematoma obstetric
				Pelvic haemorrhage
				Penile contusion
				Penile haematoma
				Penile haemorrhage
				Perineal haematoma
				Peripartum haemorrhage
				Polymenorrhagia
				Post abortion haemorrhage
				Postmenopausal haemorrhage
				Postpartum haemorrhage

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
MedDRA version: 25.0

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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Blood	Bleeding	Urogenital bleeding	Group of MedDRA PTs	Premature separation of placenta Prostatic haemorrhage Renal artery perforation Renal cyst haemorrhage Renal haematoma Renal haemorrhage Retroplacental haematoma Scrotal haematocoele Scrotal haematoma Scrotal haemorrhage Spermatic cord haemorrhage Subcapsular renal haematoma Subchorionic haematoma Subchorionic haemorrhage Testicular haemorrhage Third stage postpartum haemorrhage Ureteric haemorrhage Urethral haemorrhage Urinary bladder haematoma Urinary bladder haemorrhage Urinary occult blood Urinary occult blood positive Urogenital haemorrhage Uterine haematoma Uterine haemorrhage Vaginal haematoma Vaginal haemorrhage Vulval haematoma Vulval haematoma evacuation Vulval haemorrhage
	Haematopoietic thrombocytopenia		SMQ - broad	Acquired amegakaryocytic thrombocytopenia Megakaryocytes abnormal Megakaryocytes decreased Platelet count abnormal Platelet count decreased Platelet disorder Platelet maturation arrest Platelet production decreased Platelet toxicity Plateletcrit abnormal Plateletcrit decreased

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
MedDRA version: 25.0

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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Blood	Haematopoietic thrombocytopenia		SMQ - broad	Thrombocytopenia
				Thrombocytopenia neonatal
	Neutropenia		SMQ - narrow	Agranulocytosis
				Aplastic anaemia
				Autoimmune aplastic anaemia
				B-lymphocyte count decreased
				Band neutrophil count decreased
				Band neutrophil percentage decreased
				Basophil count decreased
				Basophilopenia
				Bone marrow failure
				CD19 lymphocytes decreased
				Cyclic neutropenia
				Cytopenia
				Eosinopenia
				Eosinophil count decreased
				Febrile bone marrow aplasia
				Febrile neutropenia
				Granulocyte count decreased
				Granulocyte percentage decreased
				Granulocytes maturation arrest
				Granulocytopenia
				Idiopathic neutropenia
				Immune-mediated cytopenia
				Leukopenia
				Lymphocyte count decreased
				Lymphopenia
				Metamyelocyte count decreased
				Monoblast count decreased
				Monocyte count decreased
				Monocytopenia
				Myeloblast count decreased
				Myelocyte count decreased
				Myelosuppression
				Neutropenia
				Neutropenic colitis
				Neutropenic infection
				Neutropenic sepsis
				Neutrophil count decreased
				Pancytopenia
				Panmyelopathy

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Blood	Neutropenia		SMQ - narrow	Promyelocyte count decreased Pure white cell aplasia Radiation leukopenia T-lymphocyte count decreased White blood cell count decreased
	Thrombocytopenia		Group of MedDRA PTs	Immune thrombocytopenia Platelet count decreased Thrombocytopenia
Cardiovascular	Arterial thromboembolism		SMQ - narrow	Acute aortic syndrome Acute coronary syndrome Acute myocardial infarction Amaurosis Amaurosis fugax Aneurysm thrombosis Angioplasty Aortic bypass Aortic embolus Aortic surgery Aortic thrombosis Aortogram abnormal Arterectomy Arterectomy with graft replacement Arterial angioplasty Arterial bypass operation Arterial graft Arterial occlusive disease Arterial revascularisation Arterial stent insertion Arterial therapeutic procedure Arterial thrombosis Arteriogram abnormal Arteriogram carotid abnormal Arteriotomy Atherectomy Atherosclerotic plaque rupture Atrial appendage closure Atrial appendage resection Basal ganglia infarction Basilar artery occlusion

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
MedDRA version: 25.0

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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	Arterial thromboembolism		SMQ - narrow	Basilar artery thrombosis
				Blindness transient
				Brachiocephalic artery occlusion
				Capsular warning syndrome
				Carotid angioplasty
				Carotid arterial embolus
				Carotid artery bypass
				Carotid artery occlusion
				Carotid artery stent insertion
				Carotid artery thrombosis
				Carotid endarterectomy
				Cerebellar artery occlusion
				Cerebellar artery thrombosis
				Cerebral artery embolism
				Cerebral artery occlusion
				Cerebral artery stent insertion
				Cerebral artery thrombosis
				Cerebral hypoperfusion
				Cerebrovascular insufficiency
				Cerebrovascular stenosis
				Coeliac artery occlusion
				Coronary angioplasty
				Coronary arterial stent insertion
				Coronary artery bypass
				Coronary artery embolism
				Coronary artery occlusion
				Coronary artery reocclusion
				Coronary artery surgery
				Coronary artery thrombosis
				Coronary endarterectomy
				Coronary revascularisation
				Coronary vascular graft occlusion
				Embolia cutis medicamentosa
				Embolism arterial
				Endarterectomy
				Femoral artery embolism
				Hepatic artery embolism
				Hepatic artery occlusion
				Hepatic artery thrombosis
				Hypothenar hammer syndrome
				Iliac artery embolism
				Iliac artery occlusion
				Internal capsule infarction
				Intra-aortic balloon placement

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
MedDRA version: 25.0

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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	Arterial thromboembolism		SMQ - narrow	Intraoperative cerebral artery occlusion
				Ischaemic cerebral infarction
				Ischaemic stroke
				Lacunar infarction
				Left atrial appendage closure implant
				Leriche syndrome
				Mesenteric arterial occlusion
				Mesenteric arteriosclerosis
				Mesenteric artery embolism
				Mesenteric artery stenosis
				Mesenteric artery stent insertion
				Mesenteric artery thrombosis
				Metabolic stroke
				Myocardial infarction
				Myocardial necrosis
				Ophthalmic artery occlusion
				Ophthalmic artery thrombosis
				Papillary muscle infarction
				Penile artery occlusion
				Percutaneous coronary intervention
				Peripheral arterial occlusive disease
				Peripheral arterial reocclusion
				Peripheral artery angioplasty
				Peripheral artery bypass
				Peripheral artery occlusion
				Peripheral artery stent insertion
				Peripheral artery surgery
				Peripheral artery thrombosis
				Peripheral embolism
				Peripheral endarterectomy
				Popliteal artery entrapment syndrome
				Post procedural myocardial infarction
				Postinfarction angina
				Precerebral artery embolism
				Precerebral artery occlusion
				Precerebral artery thrombosis
				Profundaplasty
				Pseudo-occlusion of internal carotid artery
				Pulmonary artery occlusion
				Pulmonary artery therapeutic procedure
				Pulmonary artery thrombosis
				Pulmonary endarterectomy

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
MedDRA version: 25.0

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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	Arterial thromboembolism		SMQ - narrow	Pulmonary tumour thrombotic microangiopathy Renal artery angioplasty Renal artery occlusion Renal artery thrombosis Renal embolism Renal-limited thrombotic microangiopathy Retinal artery embolism Retinal artery occlusion Retinal artery thrombosis Segmental arterial mediolysis Silent myocardial infarction Spinal artery embolism Spinal artery thrombosis Splenic artery thrombosis Splenic embolism Stress cardiomyopathy Subclavian artery embolism Subclavian artery occlusion Subclavian artery thrombosis Thromboembolectomy Thrombotic microangiopathy Thrombotic thrombocytopenic purpura Transient ischaemic attack Truncus coeliacus thrombosis Vascular pseudoaneurysm thrombosis Vertebral artery occlusion Vertebral artery thrombosis Visual acuity reduced transiently
	Cardiac failure		SMQ - narrow	Acute left ventricular failure Acute pulmonary oedema Acute right ventricular failure Cardiac asthma Cardiac failure Cardiac failure acute Cardiac failure chronic Cardiac failure congestive Cardiac failure high output Cardiogenic shock Cardiohepatic syndrome Cardiopulmonary failure Cardiorenal syndrome

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	Cardiac failure		SMQ - narrow	Chronic left ventricular failure Chronic right ventricular failure Congestive hepatopathy Cor pulmonale Cor pulmonale acute Cor pulmonale chronic Ejection fraction decreased Hepatojugular reflux Left ventricular failure Low cardiac output syndrome Neonatal cardiac failure Obstructive shock Pulmonary oedema Pulmonary oedema neonatal Radiation associated cardiac failure Right ventricular ejection fraction decreased Right ventricular failure Ventricular failure
	DVT		Single MedDRA PT	Deep vein thrombosis
	Hypertension		SMQ - narrow	Accelerated hypertension Blood pressure ambulatory increased Blood pressure diastolic increased Blood pressure inadequately controlled Blood pressure increased Blood pressure management Blood pressure orthostatic increased Blood pressure systolic increased Catecholamine crisis Dialysis induced hypertension Diastolic hypertension Eclampsia Endocrine hypertension Essential hypertension Gestational hypertension HELLP syndrome Hyperaldosteronism Hypertension Hypertension neonatal Hypertensive angiopathy

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	Hypertension		SMQ - narrow	Hypertensive cardiomegaly Hypertensive cardiomyopathy Hypertensive cerebrovascular disease Hypertensive crisis Hypertensive emergency Hypertensive encephalopathy Hypertensive end-organ damage Hypertensive heart disease Hypertensive nephropathy Hypertensive urgency Labile hypertension Malignant hypertension Malignant hypertensive heart disease Malignant renal hypertension Maternal hypertension affecting foetus Mean arterial pressure increased Metabolic syndrome Neurogenic hypertension Orthostatic hypertension Page kidney Postoperative hypertension Pre-eclampsia Prehypertension Procedural hypertension Renal hypertension Renal sympathetic nerve ablation Renovascular hypertension Retinopathy hypertensive Secondary aldosteronism Secondary hypertension Superimposed pre-eclampsia Supine hypertension Systolic hypertension Withdrawal hypertension
	MACE	Any fatal or non-fatal events in SMQ Myocardial infarction (broad)	SMQ - broad	Acute cardiac event Acute coronary syndrome Acute myocardial infarction Angina unstable Blood creatine phosphokinase MB abnormal

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	MACE	Any fatal or non-fatal events in SMQ Myocardial infarction (broad)	SMQ - broad	Blood creatine phosphokinase MB increased
				Blood creatine phosphokinase abnormal
				Blood creatine phosphokinase increased
				Cardiac ventricular scarring
				Coronary artery embolism
				Coronary artery occlusion
				Coronary artery reocclusion
				Coronary artery thrombosis
				Coronary bypass thrombosis
				Coronary vascular graft occlusion
				ECG electrically inactive area
				ECG signs of myocardial infarction
				Electrocardiogram Q wave abnormal
				Electrocardiogram ST segment abnormal
				Electrocardiogram ST segment elevation
				Electrocardiogram ST-T segment elevation
				Electrocardiogram U wave inversion
				Infarction
				Kounis syndrome
				Myocardial infarction
				Myocardial necrosis
				Myocardial necrosis marker increased
				Myocardial reperfusion injury
				Myocardial stunning
				Papillary muscle infarction
				Periprocedural myocardial infarction
				Post procedural myocardial infarction
				Postinfarction angina
				Scan myocardial perfusion abnormal
				Silent myocardial infarction
				Troponin I increased
				Troponin T increased
				Troponin increased
				Vascular graft occlusion
				Vascular stent occlusion
				Vascular stent thrombosis
		Any fatal or non-fatal stroke events	Group of MedDRA PTs	Amaurosis fugax
				Amyloid related imaging abnormalities

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	MACE	Any fatal or non-fatal stroke events	Group of MedDRA PTs	Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits Amyloid related imaging abnormality-oedema/effusion Basal ganglia haematoma Basal ganglia haemorrhage Basal ganglia stroke Basilar artery occlusion Basilar artery perforation Basilar artery thrombosis Brachiocephalic artery occlusion Brain stem embolism Brain stem haematoma Brain stem haemorrhage Brain stem infarction Brain stem ischaemia Brain stem stroke Brain stem thrombosis Brain stent insertion Carotid aneurysm rupture Carotid arterial embolus Carotid artery occlusion Carotid artery perforation Carotid artery thrombosis Central nervous system haemorrhage Cerebellar artery occlusion Cerebellar artery thrombosis Cerebellar embolism Cerebellar haematoma Cerebellar haemorrhage Cerebellar infarction Cerebellar ischaemia Cerebellar stroke Cerebral aneurysm perforation Cerebral arteriovenous malformation haemorrhagic Cerebral artery embolism Cerebral artery occlusion Cerebral artery perforation Cerebral artery restenosis Cerebral artery thrombosis Cerebral haematoma Cerebral haemorrhage

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	MACE	Any fatal or non-fatal stroke events	Group of MedDRA PTs	Cerebral haemorrhage foetal
				Cerebral haemorrhage neonatal
				Cerebral infarction
				Cerebral infarction foetal
				Cerebral ischaemia
				Cerebral microembolism
				Cerebral microinfarction
				Cerebral thrombosis
				Cerebral vascular occlusion
				Cerebrovascular accident
				Delayed ischaemic neurological deficit
				Embolic cerebellar infarction
				Embolic cerebral infarction
				Embolic stroke
				Haemorrhage intracranial
				Haemorrhagic cerebellar infarction
				Haemorrhagic cerebral infarction
				Haemorrhagic stroke
				Haemorrhagic transformation stroke
				Internal capsule infarction
				Intracranial haematoma
				Intracranial haemorrhage neonatal
				Intracranial tumour haemorrhage
				Intraoperative cerebral artery occlusion
				Intraventricular haemorrhage
				Intraventricular haemorrhage neonatal
				Ischaemic cerebral infarction
				Ischaemic stroke
				Lacunar infarction
				Lacunar stroke
				Lateral medullary syndrome
				Metabolic stroke
				Perfusion brain scan abnormal
				Perinatal stroke
				Periventricular haemorrhage neonatal
				Pituitary apoplexy
				Pituitary haemorrhage
				Pituitary infarction
				Post procedural stroke
				Precerebral artery aneurysm
				Precerebral artery dissection
				Precerebral artery occlusion
				Precerebral artery thrombosis

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	MACE	Any fatal or non-fatal stroke events	Group of MedDRA PTs	Pseudo-occlusion of internal carotid artery Pseudostroke Putamen haemorrhage Reversible ischaemic neurological deficit Ruptured cerebral aneurysm Septic cerebral embolism Spinal stroke Stroke in evolution Subarachnoid haematoma Subarachnoid haemorrhage Subarachnoid haemorrhage neonatal Subdural haemorrhage neonatal Thalamic infarction Thalamus haemorrhage Thrombotic cerebral infarction Thrombotic stroke Transient ischaemic attack Vertebral artery occlusion Vertebral artery perforation Vertebral artery thrombosis Vertebrobasilar stroke
		Fatal events in SOC Cardiac disorders	Group of MedDRA PTs	Abnormal precordial movement Accelerated idioventricular rhythm Accessory cardiac pathway Acquired cardiac septal defect Acquired coronary artery fistula Acquired left ventricle outflow tract obstruction Acquired right ventricle outflow obstruction Acute cardiac event Acute coronary syndrome Acute left ventricular failure Acute myocardial infarction Acute right ventricular failure Adams-Stokes syndrome Agonal rhythm Angina pectoris Angina unstable Anginal equivalent

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	MACE	Fatal events in SOC Cardiac disorders	Group of MedDRA PTs	Anomalous atrioventricular excitation
				Aortic valve calcification
				Aortic valve disease
				Aortic valve disease mixed
				Aortic valve incompetence
				Aortic valve prolapse
				Aortic valve sclerosis
				Aortic valve stenosis
				Aortic valve thickening
				Arrhythmia
				Arrhythmia neonatal
				Arrhythmia supraventricular
				Arrhythmic storm
				Arteriosclerosis coronary artery
				Arteriospasm coronary
				Arteritis coronary
				Athletic heart syndrome
				Atrial conduction time prolongation
				Atrial enlargement
				Atrial escape rhythm
				Atrial fibrillation
				Atrial flutter
				Atrial hypertrophy
				Atrial parasystole
				Atrial rupture
				Atrial septal defect acquired
				Atrial standstill
				Atrial tachycardia
				Atrial thrombosis
				Atrioventricular block
				Atrioventricular block complete
				Atrioventricular block first degree
				Atrioventricular block second degree
				Atrioventricular conduction time shortened
				Atrioventricular dissociation
				Atrioventricular node dysfunction
				Autoimmune myocarditis
				Autoimmune pericarditis
				BRASH syndrome
				Baseline foetal heart rate variability disorder
				Bezold-Jarisch reflex

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	MACE	Fatal events in SOC Cardiac disorders	Group of MedDRA PTs	Bifascicular block
				Bradyarrhythmia
				Bradycardia
				Bradycardia foetal
				Bradycardia neonatal
				Bundle branch block
				Bundle branch block bilateral
				Bundle branch block left
				Bundle branch block right
				Carcinoid heart disease
				Cardiac amyloidosis
				Cardiac aneurysm
				Cardiac arrest
				Cardiac arrest neonatal
				Cardiac asthma
				Cardiac contractility decreased
				Cardiac discomfort
				Cardiac disorder
				Cardiac dysfunction
				Cardiac failure
				Cardiac failure acute
				Cardiac failure chronic
				Cardiac failure congestive
				Cardiac failure high output
				Cardiac fibrillation
				Cardiac flutter
				Cardiac granuloma
				Cardiac hypertrophy
				Cardiac iron overload
				Cardiac perforation
				Cardiac perfusion defect
				Cardiac polyp
				Cardiac pseudoaneurysm
				Cardiac sarcoidosis
				Cardiac septal hypertrophy
				Cardiac steatosis
				Cardiac tamponade
				Cardiac valve discolouration
				Cardiac valve disease
				Cardiac valve sclerosis
				Cardiac valve thickening
				Cardiac ventricular disorder
				Cardiac ventricular scarring

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	MACE	Fatal events in SOC Cardiac disorders	Group of MedDRA PTs	Cardiac ventricular thrombosis
				Cardio-respiratory arrest
				Cardio-respiratory arrest neonatal
				Cardio-respiratory distress
				Cardiogenic shock
				Cardiohepatic syndrome
				Cardiomegaly
				Cardiomyopathy
				Cardiomyopathy acute
				Cardiomyopathy alcoholic
				Cardiomyopathy neonatal
				Cardiopulmonary failure
				Cardiorenal syndrome
				Cardiotoxicity
				Cardiovascular deconditioning
				Cardiovascular disorder
				Cardiovascular insufficiency
				Cardiovascular symptom
				Carditis
				Central bradycardia
				Cerebrocardiac syndrome
				Chordae tendinae rupture
				Chronic coronary syndrome
				Chronic left ventricular failure
				Chronic myocarditis
				Chronic right ventricular failure
				Chronotropic incompetence
				Conduction disorder
				Congestive cardiomyopathy
				Cor pulmonale
				Cor pulmonale acute
				Cor pulmonale chronic
				Coronary artery aneurysm
				Coronary artery compression
				Coronary artery dilatation
				Coronary artery disease
				Coronary artery dissection
				Coronary artery embolism
				Coronary artery insufficiency
				Coronary artery occlusion
				Coronary artery perforation
				Coronary artery stenosis
				Coronary artery thrombosis

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	MACE	Fatal events in SOC Cardiac disorders	Group of MedDRA PTs	Coronary no-reflow phenomenon
				Coronary ostial stenosis
				Coronary sinus dilatation
				Coronary steal syndrome
				Coronary vein stenosis
				Defect conduction intraventricular
				Degenerative aortic valve disease
				Degenerative mitral valve disease
				Degenerative multivalvular disease
				Degenerative tricuspid valve disease
				Diabetic cardiomyopathy
				Diabetic complication cardiovascular
				Diabetic coronary microangiopathy
				Diastolic dysfunction
				Dilatation atrial
				Dilatation ventricular
				Dressler’s syndrome
				Early repolarisation syndrome
				Endocardial disease
				Endocardial fibrosis
				Endocardial varices
				Endocarditis fibroplastica
				Endocarditis noninfective
				Endocarditis rheumatic
				Eosinophilic myocarditis
				Eustachian valve hypertrophy
				Extrasystoles
				Fascicular block
				Fat embolism syndrome
				Foetal arrhythmia
				Foetal cardiac arrest
				Foetal heart rate acceleration abnormality
				Foetal heart rate deceleration abnormality
				Foetal heart rate disorder
				Foetal tachyarrhythmia
				Frederick’s syndrome
				Gastrocardiac syndrome
				Giant cell myocarditis
				Grey syndrome neonatal
				Haemorrhage coronary artery
				Heart alternation

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	MACE	Fatal events in SOC Cardiac disorders	Group of MedDRA PTs	Heart valve calcification
				Heart valve incompetence
				Heart valve stenosis
				Hepatojugular reflux
				Holiday heart syndrome
				Hyperdynamic left ventricle
				Hyperkinetic heart syndrome
				Hypersensitivity myocarditis
				Hypertensive cardiomegaly
				Hypertensive cardiomyopathy
				Hypertensive heart disease
				Immune-mediated myocarditis
				Interventricular septum rupture
				Intracardiac mass
				Intracardiac thrombus
				Intrapericardial thrombosis
				Ischaemic cardiomyopathy
				Ischaemic mitral regurgitation
				Junctional ectopic tachycardia
				Kounis syndrome
				Kyphoscoliotic heart disease
				Lambl's excrescences
				Left atrial dilatation
				Left atrial enlargement
				Left atrial hypertrophy
				Left ventricular diastolic collapse
				Left ventricular dilatation
				Left ventricular dysfunction
				Left ventricular enlargement
				Left ventricular failure
				Left ventricular heave
				Left ventricular hypertrophy
				Lenegre's disease
				Long QT syndrome
				Low cardiac output syndrome
				Lupus endocarditis
				Lupus myocarditis
				Mahler sign
				Malignant hypertensive heart disease
				Metabolic cardiomyopathy
				Microvascular coronary artery disease
				Mitral perforation
				Mitral valve calcification

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	MACE	Fatal events in SOC Cardiac disorders	Group of MedDRA PTs	Mitral valve disease
				Mitral valve disease mixed
				Mitral valve incompetence
				Mitral valve prolapse
				Mitral valve sclerosis
				Mitral valve stenosis
				Mitral valve thickening
				Myocardial calcification
				Myocardial depression
				Myocardial fibrosis
				Myocardial haemorrhage
				Myocardial hypoperfusion
				Myocardial hypoxia
				Myocardial infarction
				Myocardial injury
				Myocardial ischaemia
				Myocardial necrosis
				Myocardial oedema
				Myocardial reperfusion injury
				Myocardial rupture
				Myocardial stunning
				Myocarditis
				Myocarditis post infection
				Myopericarditis
				Myxomatous mitral valve degeneration
				Negative cardiac inotropic effect
				Neonatal bradyarrhythmia
				Neonatal cardiac failure
				Neonatal sinus bradycardia
				Neonatal sinus tachycardia
				Neonatal tachyarrhythmia
				Neonatal tachycardia
				Nodal arrhythmia
				Nodal rhythm
				Non-obstructive cardiomyopathy
				Nonreassuring foetal heart rate pattern
				Obesity cardiomyopathy
				Oculocardiac reflex
				Pacing induced cardiomyopathy
				Palpitations
				Papillary muscle disorder
				Papillary muscle haemorrhage
				Papillary muscle infarction

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	MACE	Fatal events in SOC Cardiac disorders	Group of MedDRA PTs	Papillary muscle rupture
				Parasystole
				Paroxysmal arrhythmia
				Paroxysmal atrioventricular block
				Pericardial calcification
				Pericardial cyst
				Pericardial disease
				Pericardial effusion
				Pericardial fibrosis
				Pericardial haemorrhage
				Pericardial mass
				Pericardial rub
				Pericarditis
				Pericarditis adhesive
				Pericarditis constrictive
				Pericarditis lupus
				Pericarditis rheumatic
				Pericarditis uraemic
				Pleuropericarditis
				Pneumopericardium
				Positive cardiac inotropic effect
				Postinfarction angina
				Postural orthostatic tachycardia syndrome
				Prinzmetal angina
				Pulmonary valve calcification
				Pulmonary valve disease
				Pulmonary valve incompetence
				Pulmonary valve sclerosis
				Pulmonary valve stenosis
				Pulmonary valve thickening
				Pulseless electrical activity
				Rebound tachycardia
				Reperfusion arrhythmia
				Restrictive cardiomyopathy
				Rheumatic heart disease
				Rhythm idioventricular
				Right atrial dilatation
				Right atrial enlargement
				Right atrial hypertrophy
				Right ventricular diastolic collapse
				Right ventricular dilatation
				Right ventricular dysfunction

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	MACE	Fatal events in SOC Cardiac disorders	Group of MedDRA PTs	Right ventricular enlargement
				Right ventricular failure
				Right ventricular heave
				Right ventricular hypertension
				Right ventricular hypertrophy
				Shoshin beriberi
				Sigmoid-shaped ventricular septum
				Silent myocardial infarction
				Sinoatrial block
				Sinus arrest
				Sinus arrhythmia
				Sinus bradycardia
				Sinus node dysfunction
				Sinus tachycardia
				Sinusoidal foetal heart rate pattern
				Stress cardiomyopathy
				Subclavian coronary steal syndrome
				Subendocardial haemorrhage
				Subendocardial ischaemia
				Subvalvular aortic stenosis
				Supravalvular aortic stenosis
				Supraventricular extrasystoles
				Supraventricular tachyarrhythmia
				Supraventricular tachycardia
				Systolic anterior motion of mitral valve
				Systolic dysfunction
				Tachyarrhythmia
				Tachycardia
				Tachycardia foetal
				Tachycardia induced cardiomyopathy
				Tachycardia paroxysmal
				Thyrotoxic cardiomyopathy
				Torsade de pointes
				Toxic cardiomyopathy
				Tricuspid valve calcification
				Tricuspid valve disease
				Tricuspid valve disease mixed
				Tricuspid valve incompetence
				Tricuspid valve prolapse
				Tricuspid valve sclerosis
				Tricuspid valve stenosis
				Tricuspid valve thickening
				Trifascicular block

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	MACE	Fatal events in SOC Cardiac disorders	Group of MedDRA PTs	Ventricle rupture
				Ventricular arrhythmia
				Ventricular asystole
				Ventricular compliance decreased
				Ventricular dysfunction
				Ventricular dyskinesia
				Ventricular dyssynchrony
				Ventricular enlargement
				Ventricular extrasystoles
				Ventricular failure
				Ventricular fibrillation
				Ventricular flutter
				Ventricular hyperkinesia
				Ventricular hypertrophy
				Ventricular hypokinesia
				Ventricular parasystole
				Ventricular pre-excitation
				Ventricular remodelling
				Ventricular septal defect acquired
				Ventricular tachyarrhythmia
				Ventricular tachycardia
				Wandering pacemaker
				Wellens' syndrome
				Withdrawal arrhythmia
				Wolff-Parkinson-White syndrome
		Fatal events in SOC Vascular disorders	Group of MedDRA PTs	Accelerated hypertension
				Achenbach syndrome
				Acute aortic syndrome
				Adventitial cystic disease
				Air embolism
				Aneurysm
				Aneurysm arteriovenous
				Aneurysm ruptured
				Aneurysm thrombosis
				Angiodysplasia
				Angiopathy
				Angiosclerosis
				Aortic aneurysm
				Aortic aneurysm rupture
				Aortic arteriosclerosis
				Aortic dilatation

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	MACE	Fatal events in SOC Vascular disorders	Group of MedDRA PTs	Aortic disorder
				Aortic dissection
				Aortic dissection rupture
				Aortic elongation
				Aortic embolus
				Aortic intramural haematoma
				Aortic necrosis
				Aortic occlusion
				Aortic perforation
				Aortic rupture
				Aortic stenosis
				Aortic thrombosis
				Aortic wall hypertrophy
				Aortitis
				Aorto-atrial fistula
				Arterial disorder
				Arterial dolichoectasia
				Arterial fibrosis
				Arterial haemorrhage
				Arterial insufficiency
				Arterial intramural haematoma
				Arterial occlusive disease
				Arterial perforation
				Arterial rupture
				Arterial spasm
				Arterial stenosis
				Arterial stiffness
				Arterial thrombosis
				Arterial wall hypertrophy
				Arterioenteric fistula
				Arteriosclerosis
				Arteriosclerosis Moenckeberg-type
				Arteriovenous fistula
				Arteritis
				Artery dissection
				Atheroembolism
				Atherosclerotic plaque rupture
				Axillary vein thrombosis
				Behcet's syndrome
				Bleeding varicose vein
				Blood pressure fluctuation
				Blood pressure inadequately controlled
				Bloody discharge

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	MACE	Fatal events in SOC Vascular disorders	Group of MedDRA PTs	Blue toe syndrome
				Brachial artery entrapment syndrome
				Brachiocephalic arteriosclerosis
				Brachiocephalic artery occlusion
				Brachiocephalic artery stenosis
				Brachiocephalic vein occlusion
				Brachiocephalic vein stenosis
				Brachiocephalic vein thrombosis
				Buttock claudication
				CT hypotension complex
				Calcium embolism
				Capillary disorder
				Capillary fragility
				Capillary leak syndrome
				Carotidynia
				Catecholamine crisis
				Circulatory collapse
				Circulatory failure neonatal
				Claudication of jaw muscles
				Coeliac artery occlusion
				Collateral circulation
				Cryoglobulinaemia
				Cyanosis
				Deep vein thrombosis
				Dependent rubor
				Diabetic arteritis
				Diabetic macroangiopathy
				Diabetic microangiopathy
				Diabetic vascular disorder
				Dialysis hypotension
				Dialysis induced hypertension
				Diastolic hypertension
				Diastolic hypotension
				Diffuse vasculitis
				Distributive shock
				Dry gangrene
				Elephantiasis nostras verrucosa
				Embolism
				Embolism arterial
				Embolism venous
				Endocrine hypertension
				Endothelial dysfunction
				Erythrocyanosis

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	MACE	Fatal events in SOC Vascular disorders	Group of MedDRA PTs	Erythromelalgia
				Essential hypertension
				Exsanguination
				Extravasation blood
				Extremity necrosis
				Extrinsic iliac vein compression
				False lumen dilatation of aortic dissection
				Femoral artery aneurysm
				Femoral artery dissection
				Femoral artery embolism
				Femoral artery perforation
				Femoral vein perforation
				Fibromuscular dysplasia
				Flushing
				Foreign body embolism
				Giant cell arteritis
				Granulomatosis with polyangiitis
				Haematocoele
				Haematoma
				Haemodynamic instability
				Haemodynamic rebound
				Haemorrhage
				Haemorrhage neonatal
				Haemorrhagic infarction
				Haemorrhagic vasculitis
				Hot flush
				Hyperaemia
				Hypertension
				Hypertension neonatal
				Hypertensive angiopathy
				Hypertensive crisis
				Hypertensive emergency
				Hypertensive end-organ damage
				Hypertensive urgency
				Hypoperfusion
				Hypotension
				Hypotensive crisis
				Hypothenar hammer syndrome
				Hypovolaemic shock
				Iliac artery arteriosclerosis
				Iliac artery disease
				Iliac artery dissection

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	MACE	Fatal events in SOC Vascular disorders	Group of MedDRA PTs	Iliac artery embolism
				Iliac artery occlusion
				Iliac artery perforation
				Iliac artery restenosis
				Iliac artery rupture
				Iliac artery stenosis
				Iliac vein occlusion
				Iliac vein perforation
				Iliac vein stenosis
				Infarction
				Inferior vena cava dilatation
				Inferior vena cava perforation
				Inferior vena cava stenosis
				Inferior vena cava syndrome
				Inferior vena caval occlusion
				Intermittent claudication
				Internal haemorrhage
				Intravascular gas
				Ischaemia
				Ischaemic limb pain
				Jugular vein distension
				Jugular vein embolism
				Jugular vein haemorrhage
				Jugular vein occlusion
				Jugular vein thrombosis
				Kawasaki's disease
				Labile blood pressure
				Labile hypertension
				Leriche syndrome
				Lower limb artery perforation
				Lupus vasculitis
				Lymphangiectasia
				Lymphangiopathy
				Lymphatic fistula
				Lymphocele
				Lymphoedema
				Lymphorrhoea
				Lymphostasis
				MAGIC syndrome
				Macroangiopathy
				Malignant hypertension
				Maternal hypertension affecting foetus
				May-Thurner syndrome

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	MACE	Fatal events in SOC Vascular disorders	Group of MedDRA PTs	Microangiopathy
				Microembolism
				Microscopic polyangiitis
				Necrosis ischaemic
				Necrosis of artery
				Neonatal hypotension
				Neovascularisation
				Neurogenic hypertension
				Neurogenic shock
				Nitritoid reaction
				Non-dipping
				Obstructive shock
				Orthostatic hypertension
				Orthostatic hypotension
				Paget-Schroetter syndrome
				Pallor
				Paradoxical embolism
				Paradoxical pressor response
				Paraneoplastic erythromelalgia
				Paraneoplastic thrombosis
				Pelvic venous thrombosis
				Penetrating aortic ulcer
				Penetrating atherosclerotic ulcer
				Perforation of great vessels
				Peripheral arterial occlusive disease
				Peripheral artery aneurysm
				Peripheral artery aneurysm rupture
				Peripheral artery dissection
				Peripheral artery haematoma
				Peripheral artery occlusion
				Peripheral artery stenosis
				Peripheral artery thrombosis
				Peripheral circulatory failure
				Peripheral coldness
				Peripheral embolism
				Peripheral ischaemia
				Peripheral vascular disorder
				Peripheral vein occlusion
				Peripheral vein stenosis
				Peripheral vein thrombosis
				Peripheral vein thrombus extension
				Peripheral venous disease
				Periphlebitis

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	MACE	Fatal events in SOC Vascular disorders	Group of MedDRA PTs	Phlebitis
				Phlebitis deep
				Phlebitis superficial
				Phlebolith
				Phlebosclerosis
				Plethoric face
				Polyarteritis nodosa
				Poor peripheral circulation
				Poor venous access
				Popliteal artery entrapment syndrome
				Positive vessel remodelling
				Post thrombotic syndrome
				Postpartum thrombosis
				Postpartum venous thrombosis
				Prehypertension
				Pseudovasculitis
				Raynaud's phenomenon
				Renovascular hypertension
				Reperfusion injury
				Rheumatoid vasculitis
				Secondary hypertension
				Segmental arterial mediolysis
				Shock
				Shock haemorrhagic
				Shock symptom
				Spider vein
				Spontaneous amputation
				Steal syndrome
				Subclavian arteriosclerosis
				Subclavian artery aneurysm
				Subclavian artery dissection
				Subclavian artery embolism
				Subclavian artery occlusion
				Subclavian artery perforation
				Subclavian artery stenosis
				Subclavian artery thrombosis
				Subclavian steal syndrome
				Subclavian vein occlusion
				Subclavian vein perforation
				Subclavian vein stenosis
				Subclavian vein thrombosis
				Subgaleal haematoma
				Subgaleal haemorrhage

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	MACE	Fatal events in SOC Vascular disorders	Group of MedDRA PTs	Superficial vein prominence
				Superficial vein thrombosis
				Superior vena cava dilatation
				Superior vena cava occlusion
				Superior vena cava perforation
				Superior vena cava stenosis
				Superior vena cava syndrome
				Supine hypertension
				Supra-aortic trunk sclerosis
				Supra-aortic trunk stenosis
				Susac's syndrome
				Systolic hypertension
				Takayasu's arteritis
				Thromboangiitis obliterans
				Thrombophlebitis
				Thrombophlebitis migrans
				Thrombophlebitis neonatal
				Thrombosed varicose vein
				Thrombosis
				Tyramine reaction
				Varicophlebitis
				Varicose ulceration
				Varicose vein
				Varicose vein ruptured
				Vascular calcification
				Vascular compression
				Vascular dissection
				Vascular fragility
				Vascular hyalinosis
				Vascular insufficiency
				Vascular occlusion
				Vascular pain
				Vascular rupture
				Vascular shunt
				Vascular stenosis
				Vascular wall discolouration
				Vascular wall hypertrophy
				Vasculitis
				Vasculitis necrotising
				Vasoconstriction
				Vasodilatation
				Vasospasm
				Vein collapse

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	MACE	Fatal events in SOC Vascular disorders	Group of MedDRA PTs	Vein discolouration
				Vein disorder
				Vein dissection
				Vein rupture
				Vein wall hypertrophy
				Vena cava embolism
				Vena cava thrombosis
				Venoocclusive disease
				Venous aneurysm
				Venous haemorrhage
				Venous hypertension
				Venous occlusion
				Venous perforation
				Venous recanalisation
				Venous stenosis
				Venous thrombosis
				Venous thrombosis in pregnancy
				Venous thrombosis limb
				Venous thrombosis neonatal
				Venous valve ruptured
				Vessel perforation
				Visceral congestion
				White coat hypertension
				Withdrawal hypertension
		PTs Cardiac death, Sudden death, Sudden cardiac death	Group of MedDRA PTs	Cardiac death
				Sudden cardiac death
				Sudden death
	Myocardial infarction		SMQ - narrow	Acute cardiac event
				Acute coronary syndrome
				Acute myocardial infarction
				Angina unstable
				Blood creatine phosphokinase MB abnormal
				Blood creatine phosphokinase MB increased
				Coronary artery embolism
				Coronary artery occlusion
				Coronary artery reocclusion
				Coronary artery thrombosis

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	Myocardial infarction		SMQ - narrow	Coronary bypass thrombosis Coronary vascular graft occlusion Kounis syndrome Myocardial infarction Myocardial necrosis Myocardial reperfusion injury Myocardial stunning Papillary muscle infarction Periprocedural myocardial infarction Post procedural myocardial infarction Postinfarction angina Silent myocardial infarction Troponin I increased Troponin T increased Troponin increased
	Pulmonary embolism		Single MedDRA PT	Pulmonary embolism
	QT prolongation		SMQ - narrow	Electrocardiogram QT interval abnormal Electrocardiogram QT prolonged Long QT syndrome Long QT syndrome congenital Torsade de pointes Ventricular tachycardia
	Stroke haemorrhagic		SMQ - narrow	Basal ganglia haematoma Basal ganglia haemorrhage Basal ganglia stroke Basilar artery perforation Brain stem haematoma Brain stem haemorrhage Brain stem microhaemorrhage Brain stem stroke Carotid aneurysm rupture Carotid artery perforation Central nervous system haemorrhage Cerebellar haematoma Cerebellar haemorrhage Cerebellar microhaemorrhage Cerebellar stroke Cerebral aneurysm perforation

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	Stroke haemorrhagic		SMQ - narrow	Cerebral aneurysm ruptured syphilitic Cerebral arteriovenous malformation haemorrhagic Cerebral artery perforation Cerebral cyst haemorrhage Cerebral haematoma Cerebral haemorrhage Cerebral haemorrhage foetal Cerebral haemorrhage neonatal Cerebral microhaemorrhage Cerebrovascular accident Cerebrovascular disorder Epidural haemorrhage Extra-axial haemorrhage Extradural haematoma Extradural haematoma evacuation Extraischaemic cerebral haematoma Foville syndrome Haemorrhage intracranial Haemorrhagic cerebellar infarction Haemorrhagic cerebral infarction Haemorrhagic stroke Haemorrhagic transformation stroke Intracerebral haematoma evacuation Intracranial haematoma Intracranial haemorrhage neonatal Intracranial tumour haemorrhage Intraventricular haemorrhage Intraventricular haemorrhage neonatal Meningorrhagia Perinatal stroke Periventricular haemorrhage neonatal Pituitary apoplexy Pituitary haemorrhage Putamen haemorrhage Ruptured cerebral aneurysm Spinal cord haematoma Spinal cord haemorrhage Spinal epidural haematoma Spinal epidural haemorrhage Spinal stroke Spinal subarachnoid haemorrhage Spinal subdural haematoma Spinal subdural haemorrhage

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	Stroke haemorrhagic		SMQ - narrow	Stroke in evolution
				Subarachnoid haematoma
				Subarachnoid haemorrhage
				Subarachnoid haemorrhage neonatal
				Subdural haematoma
				Subdural haematoma evacuation
				Subdural haemorrhage
				Subdural haemorrhage neonatal
				Thalamus haemorrhage
				Vertebral artery perforation
				Vertebrobasilar stroke
	Stroke ischaemic		SMQ - narrow	Amaurosis fugax
				Basal ganglia infarction
				Basal ganglia stroke
				Basilar artery occlusion
				Basilar artery stenosis
				Basilar artery thrombosis
				Benedikt's syndrome
				Brachiocephalic arteriosclerosis
				Brachiocephalic artery occlusion
				Brachiocephalic artery stenosis
				Brain hypoxia
				Brain stem embolism
				Brain stem infarction
				Brain stem ischaemia
				Brain stem stroke
				Brain stem thrombosis
				Brain stent insertion
				CADASIL
				CARASIL syndrome
				Capsular warning syndrome
				Carotid angioplasty
				Carotid arterial embolus
				Carotid arteriosclerosis
				Carotid artery bypass
				Carotid artery disease
				Carotid artery insufficiency
				Carotid artery occlusion
				Carotid artery restenosis
				Carotid artery stenosis
				Carotid artery stent insertion
				Carotid artery stent removal

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	Stroke ischaemic		SMQ - narrow	Carotid artery thrombosis
				Carotid endarterectomy
				Carotid revascularisation
				Cerebellar artery occlusion
				Cerebellar artery thrombosis
				Cerebellar atherosclerosis
				Cerebellar embolism
				Cerebellar infarction
				Cerebellar ischaemia
				Cerebellar stroke
				Cerebral arteriosclerosis
				Cerebral artery embolism
				Cerebral artery occlusion
				Cerebral artery restenosis
				Cerebral artery stenosis
				Cerebral artery stent insertion
				Cerebral artery thrombosis
				Cerebral gas embolism
				Cerebral infarction
				Cerebral infarction foetal
				Cerebral ischaemia
				Cerebral microembolism
				Cerebral microinfarction
				Cerebral revascularisation
				Cerebral septic infarct
				Cerebral small vessel ischaemic disease
				Cerebral thrombosis
				Cerebral vascular occlusion
				Cerebral vasoconstriction
				Cerebral venous thrombosis
				Cerebrovascular accident
				Cerebrovascular disorder
				Cerebrovascular insufficiency
				Cerebrovascular stenosis
				Claude’s syndrome
				Delayed ischaemic neurological deficit
				Embolic cerebellar infarction
				Embolic cerebral infarction
				Embolic stroke
				Foville syndrome
				Hypoxic-ischaemic encephalopathy
				Inner ear infarction
				Internal capsule infarction
				Ischaemic cerebral infarction

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	Stroke ischaemic		SMQ - narrow	Ischaemic stroke Lacunar infarction Lacunar stroke Lateral medullary syndrome Migrainous infarction Millard-Gubler syndrome Moyamoya disease Perinatal stroke Post cardiac arrest syndrome Post procedural stroke Precerebral arteriosclerosis Precerebral artery embolism Precerebral artery occlusion Precerebral artery thrombosis Pseudo-occlusion of internal carotid artery Reversible cerebral vasoconstriction syndrome Reversible ischaemic neurological deficit Spinal artery embolism Spinal artery thrombosis Spinal cord infarction Spinal cord ischaemia Spinal stroke Stroke in evolution Subclavian steal syndrome Thalamic infarction Thrombotic cerebral infarction Thrombotic stroke Transient ischaemic attack Vascular encephalopathy Vascular stent occlusion Vascular stent stenosis Vertebral artery arteriosclerosis Vertebral artery occlusion Vertebral artery stenosis Vertebral artery thrombosis Vertebrobasilar insufficiency Vertebrobasilar stroke Weber’s syndrome

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	Stroke ischaemic and haemorrhagic		SMQ - narrow	Amaurosis fugax
				Basal ganglia haematoma
				Basal ganglia haemorrhage
				Basal ganglia infarction
				Basal ganglia stroke
				Basilar artery occlusion
				Basilar artery perforation
				Basilar artery stenosis
				Basilar artery thrombosis
				Benedikt's syndrome
				Brachiocephalic arteriosclerosis
				Brachiocephalic artery occlusion
				Brachiocephalic artery stenosis
				Brain hypoxia
				Brain stem embolism
				Brain stem haematoma
				Brain stem haemorrhage
				Brain stem infarction
				Brain stem ischaemia
				Brain stem microhaemorrhage
				Brain stem stroke
				Brain stem thrombosis
				Brain stent insertion
				CADASIL
				CARASIL syndrome
				Capsular warning syndrome
				Carotid aneurysm rupture
				Carotid angioplasty
				Carotid arterial embolus
				Carotid arteriosclerosis
				Carotid artery bypass
				Carotid artery disease
				Carotid artery insufficiency
				Carotid artery occlusion
				Carotid artery perforation
				Carotid artery restenosis
				Carotid artery stenosis
				Carotid artery stent insertion
				Carotid artery stent removal
				Carotid artery thrombosis
				Carotid endarterectomy
				Carotid revascularisation
				Central nervous system haemorrhage

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	Stroke ischaemic and haemorrhagic		SMQ - narrow	Cerebellar artery occlusion
				Cerebellar artery thrombosis
				Cerebellar atherosclerosis
				Cerebellar embolism
				Cerebellar haematoma
				Cerebellar haemorrhage
				Cerebellar infarction
				Cerebellar ischaemia
				Cerebellar microhaemorrhage
				Cerebellar stroke
				Cerebral aneurysm perforation
				Cerebral aneurysm ruptured syphilitic
				Cerebral arteriosclerosis
				Cerebral arteriovenous malformation haemorrhagic
				Cerebral artery embolism
				Cerebral artery occlusion
				Cerebral artery perforation
				Cerebral artery restenosis
				Cerebral artery stenosis
				Cerebral artery stent insertion
				Cerebral artery thrombosis
				Cerebral cyst haemorrhage
				Cerebral gas embolism
				Cerebral haematoma
				Cerebral haemorrhage
				Cerebral haemorrhage foetal
				Cerebral haemorrhage neonatal
				Cerebral infarction
				Cerebral infarction foetal
				Cerebral ischaemia
				Cerebral microembolism
				Cerebral microhaemorrhage
				Cerebral microinfarction
				Cerebral revascularisation
				Cerebral septic infarct
				Cerebral small vessel ischaemic disease
				Cerebral thrombosis
				Cerebral vascular occlusion
				Cerebral vasoconstriction
				Cerebral venous thrombosis
				Cerebrovascular accident
				Cerebrovascular disorder

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	Stroke ischaemic and haemorrhagic		SMQ - narrow	Cerebrovascular insufficiency
				Cerebrovascular stenosis
				Claude's syndrome
				Delayed ischaemic neurological deficit
				Embolic cerebellar infarction
				Embolic cerebral infarction
				Embolic stroke
				Epidural haemorrhage
				Extra-axial haemorrhage
				Extradural haematoma
				Extradural haematoma evacuation
				Extraischaemic cerebral haematoma
				Foville syndrome
				Haemorrhage intracranial
				Haemorrhagic cerebellar infarction
				Haemorrhagic cerebral infarction
				Haemorrhagic stroke
				Haemorrhagic transformation stroke
				Hypoxic-ischaemic encephalopathy
				Inner ear infarction
				Internal capsule infarction
				Intracerebral haematoma evacuation
				Intracranial haematoma
				Intracranial haemorrhage neonatal
				Intracranial tumour haemorrhage
				Intraventricular haemorrhage
				Intraventricular haemorrhage neonatal
				Ischaemic cerebral infarction
				Ischaemic stroke
				Lacunar infarction
				Lacunar stroke
				Lateral medullary syndrome
				Meningorrhagia
				Migrainous infarction
				Millard-Gubler syndrome
				Moyamoya disease
				Perinatal stroke
				Periventricular haemorrhage neonatal
				Pituitary apoplexy
				Pituitary haemorrhage
				Post cardiac arrest syndrome
				Post procedural stroke
				Precerebral arteriosclerosis

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	Stroke ischaemic and haemorrhagic		SMQ - narrow	Precerebral artery embolism
				Precerebral artery occlusion
				Precerebral artery thrombosis
				Pseudo-occlusion of internal carotid artery
				Putamen haemorrhage
				Reversible cerebral vasoconstriction syndrome
				Reversible ischaemic neurological deficit
				Ruptured cerebral aneurysm
				Spinal artery embolism
				Spinal artery thrombosis
				Spinal cord haematoma
				Spinal cord haemorrhage
				Spinal cord infarction
				Spinal cord ischaemia
				Spinal epidural haematoma
				Spinal epidural haemorrhage
				Spinal stroke
				Spinal subarachnoid haemorrhage
				Spinal subdural haematoma
				Spinal subdural haemorrhage
				Stroke in evolution
				Subarachnoid haematoma
				Subarachnoid haemorrhage
				Subarachnoid haemorrhage neonatal
				Subclavian steal syndrome
				Subdural haematoma
				Subdural haematoma evacuation
				Subdural haemorrhage
				Subdural haemorrhage neonatal
				Thalamic infarction
				Thalamus haemorrhage
				Thrombotic cerebral infarction
				Thrombotic stroke
				Transient ischaemic attack
				Vascular encephalopathy
				Vascular stent occlusion
				Vascular stent stenosis
				Vertebral artery arteriosclerosis
				Vertebral artery occlusion
				Vertebral artery perforation

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	Stroke ischaemic and haemorrhagic		SMQ - narrow	Vertebral artery stenosis
				Vertebral artery thrombosis
				Vertebrobasilar insufficiency
				Vertebrobasilar stroke
				Weber's syndrome
	Venous thromboembolism		SMQ - narrow	Aseptic cavernous sinus thrombosis
				Axillary vein thrombosis
				Brachiocephalic vein occlusion
				Brachiocephalic vein thrombosis
				Budd-Chiari syndrome
				Catheterisation venous
				Cavernous sinus thrombosis
				Central venous catheterisation
				Cerebral venous sinus thrombosis
				Cerebral venous thrombosis
				Compression garment application
				Deep vein thrombosis
				Deep vein thrombosis postoperative
				Embolism venous
				Hepatic vein embolism
				Hepatic vein occlusion
				Hepatic vein thrombosis
				Homans' sign positive
				Iliac vein occlusion
				Inferior vena cava syndrome
				Inferior vena caval occlusion
				Jugular vein embolism
				Jugular vein occlusion
				Jugular vein thrombosis
				Mahler sign
				May-Thurner syndrome
				Mesenteric vein thrombosis
				Mesenteric venous occlusion
				Obstetrical pulmonary embolism
				Obstructive shock
				Ophthalmic vein thrombosis
				Ovarian vein thrombosis
				Paget-Schroetter syndrome
				Pelvic venous thrombosis
				Penile vein thrombosis
				Peripheral vein occlusion

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	Venous thromboembolism		SMQ - narrow	Peripheral vein thrombosis
				Peripheral vein thrombus extension
				Phlebectomy
				Portal vein cavernous transformation
				Portal vein embolism
				Portal vein occlusion
				Portal vein thrombosis
				Portosplenomesenteric venous thrombosis
				Post procedural pulmonary embolism
				Post thrombotic syndrome
				Postoperative thrombosis
				Postpartum venous thrombosis
				Pulmonary embolism
				Pulmonary infarction
				Pulmonary microemboli
				Pulmonary thrombosis
				Pulmonary vein occlusion
				Pulmonary veno-occlusive disease
				Pulmonary venous thrombosis
				Renal vein embolism
				Renal vein occlusion
				Renal vein thrombosis
				Retinal vein occlusion
				Retinal vein thrombosis
				SI QIII TIII pattern
				Sigmoid sinus thrombosis
				Splenic vein occlusion
				Splenic vein thrombosis
				Subclavian vein occlusion
				Subclavian vein thrombosis
				Superficial vein thrombosis
				Superior sagittal sinus thrombosis
				Superior vena cava occlusion
				Superior vena cava syndrome
				Thrombophlebitis
				Thrombophlebitis migrans
				Thrombophlebitis neonatal
				Thrombosed varicose vein
				Thrombosis corpora cavernosa
				Transverse sinus thrombosis
				Vena cava embolism
				Vena cava filter insertion
				Vena cava filter removal
				Vena cava thrombosis

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cardiovascular	Venous thromboembolism		SMQ - narrow	Venogram abnormal Venoocclusive disease Venoocclusive liver disease Venous angioplasty Venous occlusion Venous operation Venous recanalisation Venous repair Venous stent insertion Venous thrombosis Venous thrombosis in pregnancy Venous thrombosis limb Venous thrombosis neonatal Visceral venous thrombosis
Cutaneous	Pruritus		Single MedDRA PT	Pruritus
	Rash		BIcMQ - narrow	Acute generalised exanthematous pustulosis Administration site erythema Administration site joint erythema Administration site rash Anal erythema Anal rash Application site dermatitis Application site erythema Application site joint erythema Application site rash Butterfly rash Catheter site erythema Catheter site rash Dermatitis Dermatitis acneiform Dermatitis allergic Dermatitis bullous Dermatitis exfoliative Dermatitis exfoliative generalised Drug eruption Drug reaction with eosinophilia and systemic symptoms Ear canal erythema

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cutaneous	Rash		BIcMQ - narrow	Erythema Erythema ab igne Erythema annulare Erythema dyschromicum perstans Erythema elevatum diutinum Erythema marginatum Erythema multiforme Erythema nodosum Erythema of eyelid Exfoliative rash Eyelid rash Follicular eczema Generalised bullous fixed drug eruption Genital erythema Genital rash Heliotrope rash Implant site erythema Implant site rash Incision site erythema Incision site rash Infusion site erythema Infusion site joint erythema Infusion site rash Injection site erythema Injection site joint erythema Injection site rash Instillation site erythema Instillation site rash Medical device site erythema Medical device site joint erythema Medical device site rash Mucocutaneous rash Necrolytic migratory erythema Nodular rash Palmar erythema Penile rash Periarticular thenar erythema with onycholysis Perineal erythema Perineal rash Perioral dermatitis Periorbital irritation Plantar erythema Post procedural erythema

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cutaneous	Rash		BIcMQ - narrow	Puncture site erythema Rash Rash erythematous Rash follicular Rash macular Rash maculo-papular Rash maculovesicular Rash morbilliform Rash neonatal Rash papular Rash papulosquamous Rash pruritic Rash pustular Rash rubelliform Rash scarlatiniform Rash vesicular Reticular erythematous mucinosis Scrotal dermatitis Scrotal erythema Skin toxicity Stoma site erythema Stoma site rash Symmetrical drug-related intertriginous and flexural exanthema Umbilical erythema Urticarial dermatitis Vaccination site erythema Vaccination site joint erythema Vaccination site rash Vascular access site erythema Vascular access site rash Vasculitic rash Vessel puncture site erythema Vessel puncture site rash Vulvovaginal erythema Vulvovaginal exfoliation Vulvovaginal rash
	Severe skin reactions		SMQ - narrow	Acute generalised exanthematous pustulosis Bullous haemorrhagic dermatosis Cutaneous vasculitis Dermatitis bullous

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Cutaneous	Severe skin reactions		SMQ - narrow	Dermatitis exfoliative Dermatitis exfoliative generalised Drug reaction with eosinophilia and systemic symptoms Epidermal necrosis Erythema multiforme Erythrodermic atopic dermatitis Exfoliative rash Generalised bullous fixed drug eruption Oculomucocutaneous syndrome SJS-TEN overlap Severe cutaneous adverse reaction Skin necrosis Stevens-Johnson syndrome Target skin lesion Toxic epidermal necrolysis Toxic skin eruption
Gastrointestinal	Abdominal pain		MedDRA HLT	Abdominal migraine Abdominal pain Abdominal pain lower Abdominal pain upper Abdominal rebound tenderness Abdominal rigidity Abdominal tenderness Gastrointestinal pain Infantile colic Oesophageal pain
	Dental disorders		Group of MedDRA PTs	Acquired enamel hypoplasia Alveolar bone resorption Alveolar osteitis Anodontia Apical granuloma Basal cell naevus syndrome Cemento osseous dysplasia Dental abfraction Dental alveolar anomaly Dental attrition Dental caries Dental cyst

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Gastrointestinal	Dental disorders		Group of MedDRA PTs	Dental discomfort
				Dental dysaesthesia
				Dental gangrene
				Dental leakage
				Dental necrosis
				Dental paraesthesia
				Dental plaque
				Dental pulp disorder
				Dental root perforation
				Dentofacial anomaly
				Dentofacial functional disorder
				Diastema
				Embedded tooth
				Enamel anomaly
				Fluorosis dental
				Hyperaesthesia teeth
				Hypercementosis
				Hypoaesthesia teeth
				Hypodontia
				Loose tooth
				Malocclusion
				Malpositioned teeth
				Necrotising ulcerative periodontitis
				Odontogenic cyst
				Odontoma
				Papillon-Lefevre syndrome
				Pathological tooth fracture
				Peri-implantitis
				Pericoronitis
				Periodontal congenital anomaly
				Periodontal destruction
				Periodontal disease
				Periodontal inflammation
				Periodontitis
				Poor dental condition
				Pulpitis dental
				Pulpless tooth
				Radiation related tooth disorder
				Retained deciduous tooth
				Root canal infection
				Supernumerary teeth
				Teeth brittle
				Teething
				Tooth abscess

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Gastrointestinal	Dental disorders		Group of MedDRA PTs	Tooth ankylosis
				Tooth avulsion
				Tooth delamination
				Tooth demineralisation
				Tooth deposit
				Tooth development disorder
				Tooth discolouration
				Tooth discolouration congenital
				Tooth dislocation
				Tooth disorder
				Tooth erosion
				Tooth fracture
				Tooth hypoplasia
				Tooth impacted
				Tooth infection
				Tooth injury
				Tooth loss
				Tooth malformation
				Tooth malformation hereditary
				Tooth pulp haemorrhage
				Tooth resorption
				Tooth socket haemorrhage
				Toothache
				Traumatic occlusion
				Traumatic tooth displacement
				X-ray dental abnormal
	Diarrhoea		Single MedDRA PT	Diarrhoea
	Gastrointestinal perforation		SMQ - narrow	Abdominal abscess
				Abdominal hernia perforation
				Abdominal wall abscess
				Abscess intestinal
				Acquired tracheo-oesophageal fistula
				Anal abscess
				Anal fistula
				Anal fistula infection
				Anal fistula repair
				Anastomotic ulcer perforation
				Anovulvar fistula
				Aorto-oesophageal fistula

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Gastrointestinal	Gastrointestinal perforation		SMQ - narrow	Aortoenteric fistula
				Appendiceal abscess
				Appendicitis perforated
				Arterioenteric fistula
				Atrio-oesophageal fistula
				Chemical peritonitis
				Colo-urethral fistula
				Colon fistula repair
				Colonic abscess
				Colonic fistula
				Diverticular fistula
				Diverticular perforation
				Diverticulitis intestinal perforated
				Douglas' abscess
				Duodenal perforation
				Duodenal rupture
				Duodenal ulcer perforation
				Duodenal ulcer perforation, obstructive
				Duodenal ulcer repair
				Enterocolonic fistula
				Enterocutaneous fistula
				Enterovesical fistula
				Fistula of small intestine
				Focal peritonitis
				Gastric fistula
				Gastric fistula repair
				Gastric perforation
				Gastric ulcer perforation
				Gastric ulcer perforation, obstructive
				Gastrointestinal anastomotic leak
				Gastrointestinal fistula
				Gastrointestinal fistula repair
				Gastrointestinal perforation
				Gastrointestinal ulcer perforation
				Gastropleural fistula
				Gastrosplenic fistula
				Ileal perforation
				Ileal ulcer perforation
				Incisional hernia perforation
				Inguinal hernia perforation
				Intestinal fistula
				Intestinal fistula infection
				Intestinal fistula repair

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Gastrointestinal	Gastrointestinal perforation		SMQ - narrow	Intestinal perforation
				Intestinal ulcer perforation
				Jejunal perforation
				Jejunal ulcer perforation
				Large intestinal ulcer perforation
				Large intestine perforation
				Lower gastrointestinal perforation
				Mesenteric abscess
				Neonatal intestinal perforation
				Oesophageal abscess
				Oesophageal fistula
				Oesophageal fistula repair
				Oesophageal perforation
				Oesophageal rupture
				Oesophageal ulcer perforation
				Oesophageal-pulmonary fistula
				Oesophagobronchial fistula
				Oesophagomediastinal fistula
				Oesophagopleural fistula
				Pancreatic fistula
				Pancreatic fistula repair
				Peptic ulcer perforation
				Peptic ulcer perforation, obstructive
				Peptic ulcer repair
				Perforated ulcer
				Perineal abscess
				Perirectal abscess
				Peritoneal abscess
				Peritoneocutaneous fistula
				Peritonitis
				Peritonitis bacterial
				Pneumoperitoneum
				Pneumoretroperitoneum
				Procedural intestinal perforation
				Rectal abscess
				Rectal fistula repair
				Rectal perforation
				Rectoprostatic fistula
				Rectourethral fistula
				Retroperitoneal abscess
				Small intestinal perforation
				Small intestinal ulcer perforation
				Spontaneous bacterial peritonitis

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Gastrointestinal	Gastrointestinal perforation		SMQ - narrow	Umbilical hernia perforation
				Upper gastrointestinal perforation
	Nausea		Single MedDRA PT	Nausea
	Pancreatitis		SMQ - narrow	Cullen's sign Grey Turner's sign Haemorrhagic necrotic pancreatitis Immune-mediated pancreatitis Ischaemic pancreatitis Oedematous pancreatitis Pancreatic abscess Pancreatic cyst drainage Pancreatic haemorrhage Pancreatic phlegmon Pancreatic pseudoaneurysm Pancreatic pseudocyst Pancreatic pseudocyst drainage Pancreatic pseudocyst haemorrhage Pancreatic pseudocyst rupture Pancreatitis Pancreatitis acute Pancreatitis haemorrhagic Pancreatitis necrotising Pancreatitis relapsing Pancreatorenal syndrome Subacute pancreatitis Walled-off pancreatic necrosis
	Tooth developmental disorders		MedDRA HLT	Acquired enamel hypoplasia
				Basal cell naevus syndrome Dentofacial anomaly Embedded tooth Hypodontia Odontogenic cyst Odontoma Supernumerary teeth Tooth ankylosis Tooth development disorder

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Gastrointestinal	Tooth developmental disorders		MedDRA HLT	Tooth hypoplasia
				Tooth impacted
				Tooth malformation
				Tooth malformation hereditary
	Vomiting		Single MedDRA PT	Vomiting
Hepatobiliary	Drug-induced liver injury (DILI)		Single MedDRA PT	Drug-induced liver injury
	Hepatic disorders combined	Cholestasis and jaundice of hepatic origin (SMQ narrow)	SMQ - narrow	Bilirubin excretion disorder
				Cholaemia
				Cholestasis
				Cholestatic liver injury
				Cholestatic pruritus
				Drug-induced liver injury
				Hepatitis cholestatic
				Hyperbilirubinaemia
				Icterus index increased
				Jaundice
				Jaundice cholestatic
				Jaundice hepatocellular
				Mixed liver injury
				Ocular icterus
				Parenteral nutrition associated liver disease
		Drug related hepatic disorders - comprehensive search (SMQ narrow)	SMQ - narrow	AST/ALT ratio abnormal
				Acquired antithrombin III deficiency
				Acquired factor IX deficiency
				Acquired factor V deficiency
				Acquired factor VIII deficiency
				Acquired factor XI deficiency
				Acquired hepatocerebral degeneration

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Hepatobiliary	Hepatic disorders combined	Drug related hepatic disorders - comprehensive search (SMQ narrow)	SMQ - narrow	Acquired protein S deficiency
				Acute graft versus host disease in liver
				Acute hepatic failure
				Acute on chronic liver failure
				Acute yellow liver atrophy
				Alanine aminotransferase abnormal
				Alanine aminotransferase increased
				Allergic hepatitis
				Alloimmune hepatitis
				Ammonia abnormal
				Ammonia increased
				Anti factor X activity abnormal
				Anti factor X activity decreased
				Anti factor X activity increased
				Anti-liver cytosol antibody type 1 positive
				Antithrombin III decreased
				Ascites
				Aspartate aminotransferase abnormal
				Aspartate aminotransferase increased
				Asterixis
				Autoimmune hepatitis
				Bacterascites
				Benign hepatic neoplasm
				Benign hepatobiliary neoplasm
				Bile output abnormal
				Bile output decreased
				Biliary ascites
				Biliary cirrhosis
				Biliary fibrosis
				Bilirubin conjugated abnormal
				Bilirubin conjugated increased
				Bilirubin excretion disorder
				Bilirubin urine present
				Biopsy liver abnormal
				Blood bilirubin abnormal
				Blood bilirubin increased
				Blood bilirubin unconjugated increased
				Blood fibrinogen abnormal
				Blood fibrinogen decreased
				Blood thrombin abnormal

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Hepatobiliary	Hepatic disorders combined	Drug related hepatic disorders - comprehensive search (SMQ narrow)	SMQ - narrow	Blood thrombin decreased
				Blood thromboplastin abnormal
				Blood thromboplastin decreased
				Bromosulphthalein test abnormal
				Cardiohepatic syndrome
				Child-Pugh-Turcotte score abnormal
				Child-Pugh-Turcotte score increased
				Cholaemia
				Cholangiosarcoma
				Cholestasis
				Cholestatic liver injury
				Cholestatic pruritus
				Chronic graft versus host disease in liver
				Chronic hepatic failure
				Chronic hepatitis
				Coagulation factor IX level abnormal
				Coagulation factor IX level decreased
				Coagulation factor V level abnormal
				Coagulation factor V level decreased
				Coagulation factor VII level abnormal
				Coagulation factor VII level decreased
				Coagulation factor X level abnormal
				Coagulation factor X level decreased
				Coagulation factor decreased
				Coma hepatic
				Computerised tomogram liver abnormal
				Congestive hepatopathy
				Cryptogenic cirrhosis
				Diabetic hepatopathy
				Drug-induced liver injury
				Duodenal varices
				Flood syndrome
				Focal nodular hyperplasia
				Foetor hepaticus
				Galactose elimination capacity test abnormal
				Galactose elimination capacity test decreased
				Gallbladder varices
				Gamma-glutamyltransferase abnormal

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Hepatobiliary	Hepatic disorders combined	Drug related hepatic disorders - comprehensive search (SMQ narrow)	SMQ - narrow	Gamma-glutamyltransferase increased
				Gastric variceal injection
				Gastric variceal ligation
				Gastric varices
				Gastric varices haemorrhage
				Gastrooesophageal variceal haemorrhage prophylaxis
				Graft versus host disease in liver
				Guanase increased
				Haemangioma of liver
				Haemorrhagic hepatic cyst
				Hepaplastin abnormal
				Hepaplastin decreased
				Hepatectomy
				Hepatic adenoma
				Hepatic angiosarcoma
				Hepatic artery flow decreased
				Hepatic atrophy
				Hepatic calcification
				Hepatic cancer
				Hepatic cancer metastatic
				Hepatic cancer recurrent
				Hepatic cancer stage I
				Hepatic cancer stage II
				Hepatic cancer stage III
				Hepatic cancer stage IV
				Hepatic cirrhosis
				Hepatic cyst
				Hepatic cyst ruptured
				Hepatic cytolysis
				Hepatic encephalopathy
				Hepatic encephalopathy prophylaxis
				Hepatic enzyme abnormal
				Hepatic enzyme decreased
				Hepatic enzyme increased
				Hepatic failure
				Hepatic fibrosis
				Hepatic function abnormal
				Hepatic haemangioma rupture
				Hepatic hamartoma
				Hepatic hydrothorax

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Hepatobiliary	Hepatic disorders combined	Drug related hepatic disorders - comprehensive search (SMQ narrow)	SMQ - narrow	Hepatic hypertrophy
				Hepatic hypoperfusion
				Hepatic infiltration eosinophilic
				Hepatic lesion
				Hepatic lipoma
				Hepatic mass
				Hepatic necrosis
				Hepatic neoplasm
				Hepatic neuroendocrine tumour
				Hepatic pain
				Hepatic sarcoma
				Hepatic sequestration
				Hepatic steato-fibrosis
				Hepatic steatosis
				Hepatic vascular resistance increased
				Hepatic venous pressure gradient abnormal
				Hepatic venous pressure gradient increased
				Hepatitis
				Hepatitis acute
				Hepatitis cholestatic
				Hepatitis chronic active
				Hepatitis chronic persistent
				Hepatitis fulminant
				Hepatitis toxic
				Hepatobiliary cancer
				Hepatobiliary cancer in situ
				Hepatobiliary cyst
				Hepatobiliary disease
				Hepatobiliary neoplasm
				Hepatobiliary scan abnormal
				Hepatoblastoma
				Hepatoblastoma recurrent
				Hepatocellular carcinoma
				Hepatocellular foamy cell syndrome
				Hepatocellular injury
				Hepatomegaly
				Hepatopulmonary syndrome
				Hepatorenal failure
				Hepatorenal syndrome

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Hepatobiliary	Hepatic disorders combined	Drug related hepatic disorders - comprehensive search (SMQ narrow)	SMQ - narrow	Hepatosplenomegaly
				Hepatotoxicity
				Hyperammonaemia
				Hyperbilirubinaemia
				Hypercholia
				Hyperfibrinolysis
				Hypertransaminasaemia
				Hypocoagulable state
				Hypofibrinogenaemia
				Hypoprothrombinaemia
				Hypothrombinaemia
				Hypothromboplastinaemia
				Icterus index increased
				Immune-mediated cholangitis
				Immune-mediated hepatic disorder
				Immune-mediated hepatitis
				International normalised ratio abnormal
				International normalised ratio increased
				Intestinal varices
				Intestinal varices haemorrhage
				Ischaemic hepatitis
				Jaundice
				Jaundice cholestatic
				Jaundice hepatocellular
				Kayser-Fleischer ring
				Liver carcinoma ruptured
				Liver dialysis
				Liver disorder
				Liver function test abnormal
				Liver function test decreased
				Liver function test increased
				Liver induration
				Liver injury
				Liver operation
				Liver palpable
				Liver scan abnormal
				Liver tenderness
				Liver transplant
				Liver-kidney microsomal antibody positive
				Lupoid hepatic cirrhosis

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Hepatobiliary	Hepatic disorders combined	Drug related hepatic disorders - comprehensive search (SMQ narrow)	SMQ - narrow	Lupus hepatitis
				Magnetic resonance imaging hepatobiliary abnormal
				Magnetic resonance proton density fat fraction measurement
				Mitochondrial aspartate aminotransferase increased
				Mixed hepatocellular cholangiocarcinoma
				Mixed liver injury
				Molar ratio of total branched-chain amino acid to tyrosine
				Nodular regenerative hyperplasia
				Non-alcoholic fatty liver
				Non-alcoholic steatohepatitis
				Non-cirrhotic portal hypertension
				Ocular icterus
				Oedema due to hepatic disease
				Oesophageal varices haemorrhage
				Omental oedema
				Parenteral nutrition associated liver disease
				Perihepatic discomfort
				Peripancreatic varices
				Portal fibrosis
				Portal hypertension
				Portal hypertensive colopathy
				Portal hypertensive enteropathy
				Portal hypertensive gastropathy
				Portal vein cavernous transformation
				Portal vein dilatation
				Portopulmonary hypertension
				Primary biliary cholangitis
				Protein C decreased
				Protein S abnormal
				Protein S decreased
				Prothrombin level abnormal
				Prothrombin level decreased
				Prothrombin time abnormal
				Prothrombin time prolonged
				Prothrombin time ratio abnormal
				Prothrombin time ratio increased

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Hepatobiliary	Hepatic disorders combined	Drug related hepatic disorders - comprehensive search (SMQ narrow)	SMQ - narrow	Radiation hepatitis
				Regenerative siderotic hepatic nodule
				Renal and liver transplant
				Retrograde portal vein flow
				Reye's syndrome
				Reynold's syndrome
				Splenic varices
				Splenic varices haemorrhage
				Spontaneous bacterial peritonitis
				Steatohepatitis
				Subacute hepatic failure
				Sugiura procedure
				Thrombin time abnormal
				Thrombin time prolonged
				Total bile acids increased
				Transaminases abnormal
				Transaminases increased
				Ultrasound liver abnormal
				Urine bilirubin increased
				Varices oesophageal
				Varicose veins of abdominal wall
				White nipple sign
				X-ray hepatobiliary abnormal
		Hepatitis, non-infectious (SMQ narrow)	SMQ - narrow	Acute graft versus host disease in liver
				Allergic hepatitis
				Alloimmune hepatitis
				Autoimmune hepatitis
				Chronic graft versus host disease in liver
				Chronic hepatitis
				Graft versus host disease in liver
				Hepatic cytolysis
				Hepatitis
				Hepatitis acute
				Hepatitis cholestatic
				Hepatitis chronic active
				Hepatitis chronic persistent
				Hepatitis fulminant

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Hepatobiliary	Hepatic disorders combined	Hepatitis, non-infectious (SMQ narrow)	SMQ - narrow	Hepatitis toxic
				Immune-mediated hepatitis
				Ischaemic hepatitis
				Lupus hepatitis
				Non-alcoholic steatohepatitis
				Radiation hepatitis
				Steatohepatitis
		Liver related investigations, signs and symptoms (SMQ broad)	SMQ - broad	5'nucleotidase increased
				AST to platelet ratio index increased
				AST/ALT ratio abnormal
				Acquired factor V deficiency
				Alanine aminotransferase abnormal
				Alanine aminotransferase increased
				Ammonia abnormal
				Ammonia increased
				Anti-liver cytosol antibody type 1 positive
				Ascites
				Aspartate aminotransferase abnormal
				Aspartate aminotransferase increased
				Bacterascites
				Bile output abnormal
				Bile output decreased
				Biliary ascites
				Bilirubin conjugated abnormal
				Bilirubin conjugated increased
				Bilirubin urine present
				Biopsy liver abnormal
				Blood alkaline phosphatase abnormal
				Blood alkaline phosphatase increased
				Blood bilirubin abnormal
				Blood bilirubin increased
				Blood bilirubin unconjugated increased
				Blood cholinesterase abnormal
				Blood cholinesterase decreased
				Bromosulphthalein test abnormal
				Child-Pugh-Turcotte score abnormal
				Child-Pugh-Turcotte score increased
				Computerised tomogram liver abnormal

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Hepatobiliary	Hepatic disorders combined	Liver related investigations, signs and symptoms (SMQ broad)	SMQ - broad	Congestive hepatopathy
				Cytokeratin 18 increased
				Deficiency of bile secretion
				Foetor hepaticus
				Galactose elimination capacity test abnormal
				Galactose elimination capacity test decreased
				Gamma-glutamyltransferase abnormal
				Gamma-glutamyltransferase increased
				Glutamate dehydrogenase increased
				Glycocholic acid increased
				Guanase increased
				Haemorrhagic ascites
				Hepaplastin abnormal
				Hepaplastin decreased
				Hepatic artery flow decreased
				Hepatic enzyme abnormal
				Hepatic enzyme decreased
				Hepatic enzyme increased
				Hepatic fibrosis marker abnormal
				Hepatic fibrosis marker increased
				Hepatic function abnormal
				Hepatic hydrothorax
				Hepatic hypertrophy
				Hepatic hypoperfusion
				Hepatic lymphocytic infiltration
				Hepatic mass
				Hepatic pain
				Hepatic sequestration
				Hepatic vascular resistance increased
				Hepatic venous pressure gradient abnormal
				Hepatic venous pressure gradient increased
				Hepatitis A immunity confirmed
				Hepatitis B immunity confirmed
				Hepatitis E immunity confirmed
				Hepatobiliary scan abnormal
				Hepatomegaly
				Hepatosplenomegaly
				Hyperammonaemia

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Hepatobiliary	Hepatic disorders combined	Liver related investigations, signs and symptoms (SMQ broad)	SMQ - broad	Hyperbilirubinaemia
				Hypercholia
				Hypertransaminasaemia
				Hypoalbuminaemia
				Kayser-Fleischer ring
				Leucine aminopeptidase increased
				Liver function test abnormal
				Liver function test decreased
				Liver function test increased
				Liver induration
				Liver iron concentration abnormal
				Liver iron concentration increased
				Liver opacity
				Liver palpable
				Liver scan abnormal
				Liver tenderness
				Liver-kidney microsomal antibody positive
				Magnetic resonance imaging hepatobiliary abnormal
				Magnetic resonance proton density fat fraction measurement
				Mitochondrial aspartate aminotransferase increased
				Model for end stage liver disease score abnormal
				Model for end stage liver disease score increased
				Molar ratio of total branched-chain amino acid to tyrosine
				Oedema due to hepatic disease
				Osteopontin increased
				Perihepatic discomfort
				Periportal oedema
				Peritoneal fluid protein abnormal
				Peritoneal fluid protein decreased
				Peritoneal fluid protein increased
				Pneumobilia
				Portal vein flow decreased
				Portal vein pressure increased
				Retinol binding protein decreased
				Retrograde portal vein flow

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Hepatobiliary	Hepatic disorders combined	Liver related investigations, signs and symptoms (SMQ broad)	SMQ - broad	Total bile acids increased
				Transaminases abnormal
				Transaminases increased
				Ultrasound liver abnormal
				Urine bilirubin increased
				Urobilinogen urine decreased
				Urobilinogen urine increased
				White nipple sign
				X-ray hepatobiliary abnormal
	Hepatic failure		SMQ - narrow	Acquired hepatocerebral degeneration
				Acute hepatic failure
				Acute on chronic liver failure
				Acute yellow liver atrophy
				Ascites
				Asterixis
				Bacterascites
				Biliary cirrhosis
				Biliary fibrosis
				Cardiohepatic syndrome
				Cholestatic liver injury
				Chronic hepatic failure
				Coma hepatic
				Cryptogenic cirrhosis
				Diabetic hepatopathy
				Drug-induced liver injury
				Duodenal varices
				Flood syndrome
				Gallbladder varices
				Gastric variceal injection
				Gastric variceal ligation
				Gastric varices
				Gastric varices haemorrhage
				Gastrooesophageal variceal haemorrhage prophylaxis
				Hepatectomy
				Hepatic atrophy
				Hepatic calcification
				Hepatic cirrhosis
				Hepatic cytolysis
				Hepatic encephalopathy

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Hepatobiliary	Hepatic failure		SMQ - narrow	Hepatic encephalopathy prophylaxis
				Hepatic failure
				Hepatic fibrosis
				Hepatic hydrothorax
				Hepatic infiltration eosinophilic
				Hepatic lesion
				Hepatic necrosis
				Hepatic steato-fibrosis
				Hepatic steatosis
				Hepatitis fulminant
				Hepatobiliary disease
				Hepatocellular foamy cell syndrome
				Hepatocellular injury
				Hepatopulmonary syndrome
				Hepatorenal failure
				Hepatorenal syndrome
				Hepatotoxicity
				Immune-mediated cholangitis
				Immune-mediated hepatic disorder
				Intestinal varices
				Intestinal varices haemorrhage
				Liver dialysis
				Liver disorder
				Liver injury
				Liver operation
				Liver transplant
				Lupoid hepatic cirrhosis
				Mixed liver injury
				Nodular regenerative hyperplasia
				Non-alcoholic fatty liver
				Non-alcoholic steatohepatitis
				Non-cirrhotic portal hypertension
				Oedema due to hepatic disease
				Oesophageal varices haemorrhage
				Omental oedema
				Peripancreatic varices
				Portal fibrosis
				Portal hypertension
				Portal hypertensive colopathy
				Portal hypertensive enteropathy
				Portal hypertensive gastropathy
				Portal vein cavernous transformation
				Portal vein dilatation
				Portopulmonary hypertension

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
MedDRA version: 25.0

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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Hepatobiliary	Hepatic failure		SMQ - narrow	Primary biliary cholangitis Regenerative siderotic hepatic nodule Renal and liver transplant Retrograde portal vein flow Reye's syndrome Reynold's syndrome Splenic varices Splenic varices haemorrhage Spontaneous bacterial peritonitis Steatohepatitis Subacute hepatic failure Sugiura procedure Varices oesophageal Varicose veins of abdominal wall White nipple sign
Infections	Lower respiratory tract infection		Group of MedDRA PTs	Actinomycotic pulmonary infection Acute interstitial pneumonitis Acute pulmonary histoplasmosis Allergic bronchopulmonary mycosis Amoebic lung abscess Aspergilloma Atypical mycobacterial lower respiratory tract infection Atypical mycobacterial pneumonia Atypical pneumonia Bronchiectasis Bronchitis Bronchitis bacterial Bronchitis fungal Bronchitis haemophilus Bronchitis moraxella Bronchitis mycoplasmal Bronchitis pneumococcal Bronchitis viral Bronchopulmonary aspergillosis Bronchopulmonary aspergillosis allergic COVID-19 pneumonia Candidiasis of trachea Chronic pulmonary histoplasmosis Coccidioidomycosis

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
MedDRA version: 25.0

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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Infections	Lower respiratory tract infection		Group of MedDRA PTs	Congenital pneumonia
				Embolic pneumonia
				Enterobacter pneumonia
				H1N1 influenza
				H3N2 influenza
				Haemorrhagic pneumonia
				Hantavirus pulmonary infection
				Herpes simplex pneumonia
				Infectious pleural effusion
				Infective exacerbation of chronic obstructive airways disease
				Lower respiratory tract herpes infection
				Lower respiratory tract infection
				Lower respiratory tract infection bacterial
				Lower respiratory tract infection fungal
				Lower respiratory tract infection viral
				Lung abscess
				Mediastinal abscess
				Metapneumovirus infection
				Middle East respiratory syndrome
				Miliary pneumonia
				Neonatal pneumonia
				Paracancerous pneumonia
				Paragonimiasis
				Parasitic pneumonia
				Pleural infection
				Pleural infection bacterial
				Pneumocystis jirovecii pneumonia
				Pneumonia
				Pneumonia acinetobacter
				Pneumonia adenoviral
				Pneumonia anthrax
				Pneumonia bacterial
				Pneumonia bordetella
				Pneumonia chlamydial
				Pneumonia cryptococcal
				Pneumonia cytomegaloviral
				Pneumonia escherichia
				Pneumonia fungal
				Pneumonia haemophilus
				Pneumonia helminthic
				Pneumonia herpes viral

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
MedDRA version: 25.0

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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Infections	Lower respiratory tract infection		Group of MedDRA PTs	Pneumonia influenzal
				Pneumonia klebsiella
				Pneumonia legionella
				Pneumonia measles
				Pneumonia moraxella
				Pneumonia mycoplasmal
				Pneumonia necrotising
				Pneumonia parainfluenzae viral
				Pneumonia pneumococcal
				Pneumonia proteus
				Pneumonia pseudomonal
				Pneumonia respiratory syncytial viral
				Pneumonia salmonella
				Pneumonia serratia
				Pneumonia staphylococcal
				Pneumonia streptococcal
				Pneumonia toxoplasmal
				Pneumonia tularaemia
				Pneumonia viral
				Post procedural pneumonia
				Pseudomonas bronchitis
				Pulmonary blastomycosis
				Pulmonary echinococciasis
				Pulmonary nocardiosis
				Pulmonary paracoccidioidomycosis
				Pulmonary sepsis
				Pulmonary sporotrichosis
				Pulmonary syphilis
				Pulmonary trichosporonosis
				Pulmonary tuberculoma
				Pulmonary tuberculosis
				Pyopneumothorax
				Respiratory moniliasis
				Respiratory syncytial virus bronchiolitis
				Severe acute respiratory syndrome
				Sputum purulent
				Tracheobronchitis bacterial
				Varicella zoster pneumonia
				Young’s syndrome

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
MedDRA version: 25.0

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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Infections	Upper and not otherwise specified respiratory tract infection		Group of MedDRA PTs	Acute sinusitis
				Adenoiditis
				Cellulitis laryngeal
				Cellulitis pharyngeal
				Chronic rhinosinusitis with nasal polyps
				Chronic sinusitis
				Chronic tonsillitis
				Epiglottitis
				Epiglottitis obstructive
				Fungal pharyngitis
				Fungal rhinitis
				Herpes pharyngitis
				Herpes simplex pharyngitis
				Herpes zoster pharyngitis
				Laryngitis
				Laryngitis fungal
				Laryngotracheitis obstructive
				Nasal abscess
				Nasal candidiasis
				Nasal herpes
				Nasal vestibulitis
				Nasopharyngitis
				Oropharyngeal candidiasis
				Oropharyngitis fungal
				Parainfluenzae virus infection
				Paranasal sinus abscess
				Peritonsillar abscess
				Peritonsillitis
				Pharyngeal abscess
				Pharyngeal chlamydia infection
				Pharyngeal haematoma
				Pharyngitis
				Pharyngitis mycoplasmal
				Pharyngoconjunctival fever of children
				Pharyngotonsillitis
				Reflux laryngitis
				Respiratory tract infection
				Respiratory tract infection bacterial
				Respiratory tract infection fungal
				Respiratory tract infection viral
				Rhinitis
				Rhinolaryngitis

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
MedDRA version: 25.0

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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Infections	Upper and not otherwise specified respiratory tract infection		Group of MedDRA PTs	Rhinotracheitis
				Sinobronchitis
				Sinonasal obstruction
				Sinusitis
				Sinusitis aspergillus
				Sinusitis fungal
				Subglottic laryngitis
				Tonsillitis
				Tonsillitis fungal
				Tracheal abscess
				Tracheitis
				Tracheitis obstructive
				Tracheobronchitis
				Tracheobronchitis bacterial
				Tracheobronchitis mycoplasmal
				Upper aerodigestive tract infection
				Upper respiratory fungal infection
				Upper respiratory tract infection
				Upper respiratory tract infection bacterial
				Upper respiratory tract infection helminthic
				Viral epiglottitis
				Viral upper respiratory tract infection
Liver laboratories	Alanine aminotransferase increased		Group of MedDRA PTs	Alanine aminotransferase abnormal
				Alanine aminotransferase increased
	Aspartate aminotransferase increased		Group of MedDRA PTs	Aspartate aminotransferase abnormal
				Aspartate aminotransferase increased
	Blood alkaline phosphatase increased		Group of MedDRA PTs	Blood alkaline phosphatase abnormal
				Blood alkaline phosphatase increased

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
MedDRA version: 25.0

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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Liver laboratories	Gamma-glutamyltransferase increased		Group of MedDRA PTs	Gamma-glutamyltransferase abnormal Gamma-glutamyltransferase increased
	Hepatic enzyme increased		Group of MedDRA PTs	Alanine aminotransferase abnormal Alanine aminotransferase increased Aspartate aminotransferase abnormal Aspartate aminotransferase increased Blood alkaline phosphatase abnormal Blood alkaline phosphatase increased Gamma-glutamyltransferase abnormal Gamma-glutamyltransferase increased Hepatic enzyme abnormal Hepatic enzyme increased Hepatic function abnormal Hypertransaminasaemia Liver function test abnormal Liver function test increased Transaminases abnormal Transaminases increased
	Hyperbilirubinaemia		Group of MedDRA PTs	Bilirubin conjugated abnormal Bilirubin conjugated increased Blood bilirubin abnormal Blood bilirubin increased Blood bilirubin unconjugated increased Hyperbilirubinaemia Icterus index increased Jaundice Jaundice hepatocellular
Metabolic	Decreased appetite		Single MedDRA PT	Decreased appetite
	Weight decreased		Group of MedDRA PTs	Abnormal loss of weight Weight decreased
Musculoskeletal	Growth plate disorders		Group of MedDRA PTs	Bone scan abnormal

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
MedDRA version: 25.0

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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Musculoskeletal	Growth plate disorders		Group of MedDRA PTs	Congenital syphilitic osteochondritis Epiphyseal disorder Epiphyseal injury Epiphyses delayed fusion Epiphyses premature fusion Epiphysiolysis Epiphysitis Perthes disease X-ray limb abnormal
	Impact on growth		Group of MedDRA PTs	Body height abnormal Body height below normal Body height decreased Growth disorder Growth failure Growth retardation Short stature
Psychiatric	Depression		SMQ - narrow	Activation syndrome Adjustment disorder with depressed mood Adjustment disorder with mixed anxiety and depressed mood Agitated depression Anhedonia Antidepressant therapy Childhood depression Decreased interest Depressed mood Depression Depression postoperative Depression rating scale score increased Depressive symptom Discouragement Dysphoria Electroconvulsive therapy Feeling guilty Feeling of despair Feelings of worthlessness Helplessness Major depression Menopausal depression

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
MedDRA version: 25.0

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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Psychiatric	Depression		SMQ - narrow	Mixed anxiety and depressive disorder Perinatal depression Persistent depressive disorder Post stroke depression Postictal depression
	Suicide		SMQ - narrow	Assisted suicide Columbia suicide severity rating scale abnormal Completed suicide Depression suicidal Intentional overdose Intentional self-injury Poisoning deliberate Self-injurious ideation Suicidal behaviour Suicidal ideation Suicide attempt Suicide threat Suspected suicide Suspected suicide attempt
Renal	Glomerulonephritis (narrow)		MedDRA HLT	Anti-LRP2 nephropathy Anti-glomerular basement membrane disease C1q nephropathy C3 glomerulopathy Chronic autoimmune glomerulonephritis Fibrillary glomerulonephritis Focal segmental glomerulosclerosis Glomerulonephritis Glomerulonephritis acute Glomerulonephritis chronic Glomerulonephritis membranoproliferative Glomerulonephritis membranous Glomerulonephritis minimal lesion Glomerulonephritis proliferative Glomerulonephritis rapidly progressive Goodpasture's syndrome Henoch-Schonlein purpura nephritis

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
MedDRA version: 25.0

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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Renal	Glomerulonephritis (narrow)		MedDRA HLT	IgA nephropathy
				IgM nephropathy
				Immunotactoid glomerulonephritis
				Membranous-like glomerulopathy with masked IgG-kappa deposits
				Mesangiolipidosis
				Mesangioproliferative glomerulonephritis
				Nephritic syndrome
				Nephritis allergic
				Nephrotic syndrome
				Paraneoplastic glomerulonephritis
				Paraneoplastic nephrotic syndrome
				Post infection glomerulonephritis
				Post streptococcal glomerulonephritis
				Pulmonary renal syndrome
	Proteinuria		SMQ - narrow	Albumin globulin ratio increased
				Albumin urine present
				Albuminuria
				Bence Jones protein urine present
				Bence Jones proteinuria
				Beta 2 microglobulin urine increased
				Globulinuria
				Microalbuminuria
				Myoglobinuria
				Orthostatic proteinuria
				Protein urine
				Protein urine present
				Proteinuria
				Urine albumin/creatinine ratio increased
				Urine protein/creatinine ratio abnormal
				Urine protein/creatinine ratio increased
	Renal failure		SMQ - narrow	Acute kidney injury
				Acute phosphate nephropathy
				Anuria
				Azotaemia
				Continuous haemodiafiltration
				Dialysis
				Foetal renal impairment
				Haemodialysis

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
MedDRA version: 25.0

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Listing 3.1.1 Adverse event groupings by system and safety topic

System	Safety topic	Subcategory	Type of grouping	Preferred term
Renal	Renal failure		SMQ - narrow	Haemofiltration Neonatal anuria Nephropathy toxic Oliguria Peritoneal dialysis Prerenal failure Renal failure Renal failure neonatal Renal impairment Renal impairment neonatal Subacute kidney injury

For groupings based on MedDRA SOC or HLT only the primary path of the MedDRA hierarchy is considered.
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Anhang 4-G4: Weitere Ergebnisse zu Unerwünschten Ereignissen aus der Studie InPedILD®

Anhang 4-G4.1: UE

Table 4.1.1 Proportion of patients with any adverse event during double-blind period overall and by subgroup
Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk diff. (95% CI)	Odds ratio	Odds ratio (95% CI)
Overall	13	11	84.6	26	22	84.6	1.0000	0.00	(-0.24, 0.32)	1.00	(0.11, 6.56)
Sex											
Male	5	5	100.0	10	8	80.0	0.4363	-0.20	(-0.56, 0.33)	0.00	(0.00, 4.34)
Female	8	6	75.0	16	14	87.5	0.5075	0.13	(-0.21, 0.53)	2.33	(0.20, 26.01)
Age											
6-<12	4	4	100.0	8	6	75.0	0.4249	-0.25	(-0.65, 0.37)	0.00	(0.00, 4.34)
12-<18	9	7	77.8	18	16	88.9	0.5106	0.11	(-0.20, 0.49)	2.29	(0.20, 24.97)
Region											
Europe	4	3	75.0	15	12	80.0	1.0000	0.05	(-0.36, 0.61)	1.33	(0.04, 18.23)
Rest of World	9	8	88.9	11	10	90.9	1.0000	0.02	(-0.31, 0.39)	1.25	(0.03, 53.37)
Corticosteroid Baseline Use											
Yes	4	4	100.0	9	7	77.8	0.4656	-0.22	(-0.60, 0.36)	0.00	(0.00, 4.94)
No	9	7	77.8	17	15	88.2	0.7585	0.10	(-0.21, 0.48)	2.14	(0.18, 23.53)

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Table 4.1.1 Proportion of patients with any adverse event during double-blind period overall and by subgroup
Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	1.00	(0.74, 1.60)	(0.75, 1.33)	
Sex				0.1700
Male	0.80	(0.44, 1.65)	(0.59, 1.09)	
Female	1.17	(0.76, 2.68)	(0.75, 1.81)	
Age				0.1373
6-<12	0.75	(0.35, 1.70)	(0.50, 1.12)	
12-<18	1.14	(0.79, 2.25)	(0.78, 1.68)	
Region				0.9045
Europe	1.07	(0.62, 3.96)	(0.57, 1.98)	
Rest of World	1.02	(0.65, 1.79)	(0.76, 1.38)	
Corticosteroid Baseline Use				0.1576
Yes	0.78	(0.40, 2.12)	(0.55, 1.10)	
No	1.13	(0.77, 2.15)	(0.77, 1.68)	

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Anhang 4-G4.2: SUE

Table 4.2.1 Proportion of patients with any serious adverse event during double-blind period overall and by subgroup
Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Overall	13	1	7.7	26	2	7.7	1.0000	0.00	(-0.28, 0.20)	1.00	(0.07, 31.83)
Sex											
Male	5	0	0.0	10	0	0.0					
Female	8	1	12.5	16	2	12.5					
Age											
6-<12	4	0	0.0	8	0	0.0					
12-<18	9	1	11.1	18	2	11.1					
Region											
Europe	4	0	0.0	15	1	6.7					
Rest of World	9	1	11.1	11	1	9.1					
Corticosteroid Baseline Use											
Yes	4	0	0.0	9	0	0.0					
No	9	1	11.1	17	2	11.8					

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Table 4.2.1 Proportion of patients with any serious adverse event during double-blind period overall and by subgroup
Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	1.00	(0.10, 27.11)	(0.10, 10.04)	
Sex				
Male				
Female				
Age				
6-<12				
12-<18				
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Anhang 4-G4.3: UE, die zum Therapieabbruch führten

Table 4.3.1 Proportion of patients with any adverse event leading to treatment discontinuation during double-blind period overall and by subgroup
Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk diff. (95% CI)	Odds ratio	Odds ratio (95% CI)
Overall	13	0	0.0	26	2	7.7	0.4373	0.08	(-0.17, 0.26)	inf	(0.23, inf)
Sex											
Male	5	0	0.0	10	1	10.0					
Female	8	0	0.0	16	1	6.3					
Age											
6-<12	4	0	0.0	8	2	25.0					
12-<18	9	0	0.0	18	0	0.0					
Region											
Europe	4	0	0.0	15	1	6.7					
Rest of World	9	0	0.0	11	1	9.1					
Corticosteroid Baseline Use											
Yes	4	0	0.0	9	1	11.1					
No	9	0	0.0	17	1	5.9					

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Treatment discontinuations are premature and permanent.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Table 4.3.1 Proportion of patients with any adverse event leading to treatment discontinuation during double-blind period overall and by subgroup
Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	inf 2.55	(0.20, inf)	(0.13, 49.39)	
Sex				
Male				
Female				
Age				
6-<12				
12-<18				
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Treatment discontinuations are premature and permanent.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Anhang 4-G4.4: Diarrhö differenziert nach Schweregrad (CTCAE, Grad 1, Grad 2 und ≥ Grad 3)

Table 4.4.1 Proportion of patients with any diarrhoea CTCAE-Grade 1 adverse event during double-blind period overall and by subgroup
Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk (95% CI)	Odds ratio	Odds (95% CI)
Overall	13	1	7.7	26	6	23.1	0.3665	0.15	(-0.15, 0.38)	3.60	(0.44, 89.87)
Sex											
Male	5	0	0.0	10	4	40.0					
Female	8	1	12.5	16	2	12.5					
Age											
6-<12	4	0	0.0	8	0	0.0					
12-<18	9	1	11.1	18	6	33.3					
Region											
Europe	4	0	0.0	15	2	13.3					
Rest of World	9	1	11.1	11	4	36.4					
Corticosteroid Baseline Use											
Yes	4	0	0.0	9	2	22.2					
No	9	1	11.1	17	4	23.5					

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
Each patient is considered only once with the worst grade for the analysis of patients with Diarrhoea by CTCAE-Grade.
inf=infinity

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Table 4.4.1 Proportion of patients with any diarrhoea CTCAE-Grade 1 adverse event during double-blind period overall and by subgroup
Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	3.00	(0.51, 77.09)	(0.40, 22.38)	
Sex				
Male				
Female				
Age				
6-<12				
12-<18				
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
Each patient is considered only once with the worst grade for the analysis of patients with Diarrhoea by CTCAE-Grade.
inf=infinity

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Table 4.4.2 Proportion of patients with any diarrhoea CTCAE-Grade 2 adverse event during double-blind period overall and by subgroup
Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk (95% CI)	Odds ratio	Odds (95% CI)
Overall	13	1	7.7	26	3	11.5	0.8713	0.04	(-0.26, 0.25)	1.57	(0.15, 44.45)
Sex											
Male	5	1	20.0	10	1	10.0					
Female	8	0	0.0	16	2	12.5					
Age											
6-<12	4	0	0.0	8	2	25.0					
12-<18	9	1	11.1	18	1	5.6					
Region											
Europe	4	0	0.0	15	1	6.7					
Rest of World	9	1	11.1	11	2	18.2					
Corticosteroid Baseline Use											
Yes	4	1	25.0	9	0	0.0					
No	9	0	0.0	17	3	17.6					

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
Each patient is considered only once with the worst grade for the analysis of patients with Diarrhoea by CTCAE-Grade.
inf=infinity

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Table 4.4.2 Proportion of patients with any diarrhoea CTCAE-Grade 2 adverse event during double-blind period overall and by subgroup
Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	1.50	(0.17, 38.59)	(0.17, 13.05)	
Sex				
Male				
Female				
Age				
6-<12				
12-<18				
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
Each patient is considered only once with the worst grade for the analysis of patients with Diarrhoea by CTCAE-Grade.
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Table 4.4.3 Proportion of patients with any diarrhoea CTCAE-Grade >=3 adverse event during double-blind period overall and by subgroup
Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff. (95% CI)	Odds ratio (95% CI)
Overall	13	0	0.0	26	0	0.0			
Sex									
Male	5	0	0.0	10	0	0.0			
Female	8	0	0.0	16	0	0.0			
Age									
6-<12	4	0	0.0	8	0	0.0			
12-<18	9	0	0.0	18	0	0.0			
Region									
Europe	4	0	0.0	15	0	0.0			
Rest of World	9	0	0.0	11	0	0.0			
Corticosteroid Baseline Use									
Yes	4	0	0.0	9	0	0.0			
No	9	0	0.0	17	0	0.0			

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
Each patient is considered only once with the worst grade for the analysis of patients with Diarrhoea by CTCAE-Grade.
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Table 4.4.3 Proportion of patients with any diarrhoea CTCAE-Grade >=3 adverse event during double-blind period overall and by subgroup
Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall				
Sex				
Male				
Female				
Age				
6-<12				
12-<18				
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
Each patient is considered only once with the worst grade for the analysis of patients with Diarrhoea by CTCAE-Grade.
inf=infinity

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Anhang 4-G4.5: UE, SUE und Diarrhö differenziert nach Schweregrad unter Ausschluss erkrankungsbezogenen Ereignissen

Table 4.5.1 Proportion of patients with any adverse event excluding disease-related events during double-blind period overall and by subgroup
Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk diff. (95% CI)	Odds ratio	Odds ratio (95% CI)
Overall	13	11	84.6	26	22	84.6	1.0000	0.00	(-0.24, 0.32)	1.00	(0.11, 6.56)
Sex											
Male	5	5	100.0	10	8	80.0	0.4363	-0.20	(-0.56, 0.33)	0.00	(0.00, 4.34)
Female	8	6	75.0	16	14	87.5	0.5075	0.13	(-0.21, 0.53)	2.33	(0.20, 26.01)
Age											
6-<12	4	4	100.0	8	6	75.0	0.4249	-0.25	(-0.65, 0.37)	0.00	(0.00, 4.34)
12-<18	9	7	77.8	18	16	88.9	0.5106	0.11	(-0.20, 0.49)	2.29	(0.20, 24.97)
Region											
Europe	4	3	75.0	15	12	80.0	1.0000	0.05	(-0.36, 0.61)	1.33	(0.04, 18.23)
Rest of World	9	8	88.9	11	10	90.9	1.0000	0.02	(-0.31, 0.39)	1.25	(0.03, 53.37)
Corticosteroid Baseline Use											
Yes	4	4	100.0	9	7	77.8	0.4656	-0.22	(-0.60, 0.36)	0.00	(0.00, 4.94)
No	9	7	77.8	17	15	88.2	0.7585	0.10	(-0.21, 0.48)	2.14	(0.18, 23.53)

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.5.1 Proportion of patients with any adverse event excluding disease-related events during double-blind period overall and by subgroup
Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	1.00	(0.74, 1.60)	(0.75, 1.33)	
Sex				0.1700
Male	0.80	(0.44, 1.65)	(0.59, 1.09)	
Female	1.17	(0.76, 2.68)	(0.75, 1.81)	
Age				0.1373
6-<12	0.75	(0.35, 1.70)	(0.50, 1.12)	
12-<18	1.14	(0.79, 2.25)	(0.78, 1.68)	
Region				0.9045
Europe	1.07	(0.62, 3.96)	(0.57, 1.98)	
Rest of World	1.02	(0.65, 1.79)	(0.76, 1.38)	
Corticosteroid Baseline Use				0.1576
Yes	0.78	(0.40, 2.12)	(0.55, 1.10)	
No	1.13	(0.77, 2.15)	(0.77, 1.68)	

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Table 4.5.2 Proportion of patients with any serious adverse event excluding disease-related events during double-blind period overall and by subgroup - Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk (95% CI)	Odds ratio	Odds (95% CI)
Overall	13	1	7.7	26	1	3.8	0.7861	-0.04	(-0.32, 0.15)	0.48	(0.01, 20.22)
Sex											
Male	5	0	0.0	10	0	0.0					
Female	8	1	12.5	16	1	6.3					
Age											
6-<12	4	0	0.0	8	0	0.0					
12-<18	9	1	11.1	18	1	5.6					
Region											
Europe	4	0	0.0	15	1	6.7					
Rest of World	9	1	11.1	11	0	0.0					
Corticosteroid Baseline Use											
Yes	4	0	0.0	9	0	0.0					
No	9	1	11.1	17	1	5.9					

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Table 4.5.2 Proportion of patients with any serious adverse event excluding disease-related events during double-blind period overall and by subgroup - Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	0.50	(0.02, 16.57)	(0.03, 7.37)	
Sex				
Male				
Female				
Age				
6-<12				
12-<18				
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.5.3 Proportion of patients with any diarrhoea CTCAE-Grade 1 adverse event excluding disease-related events during double-blind period overall and by subgroup - Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk diff. (95% CI)	Odds ratio	Odds ratio (95% CI)
Overall	13	1	7.7	26	6	23.1	0.3665	0.15	(-0.15, 0.38)	3.60	(0.44, 89.87)
Sex											
Male	5	0	0.0	10	4	40.0					
Female	8	1	12.5	16	2	12.5					
Age											
6-<12	4	0	0.0	8	0	0.0					
12-<18	9	1	11.1	18	6	33.3					
Region											
Europe	4	0	0.0	15	2	13.3					
Rest of World	9	1	11.1	11	4	36.4					
Corticosteroid Baseline Use											
Yes	4	0	0.0	9	2	22.2					
No	9	1	11.1	17	4	23.5					

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
Each patient is considered only once with the worst grade for the analysis of patients with Diarrhoea by CTCAE-Grade.
inf=infinity

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Table 4.5.3 Proportion of patients with any diarrhoea CTCAE-Grade 1 adverse event excluding disease-related events during double-blind period overall and by subgroup - Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	3.00	(0.51, 77.09)	(0.40, 22.38)	
Sex				
Male				
Female				
Age				
6-<12				
12-<18				
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
Each patient is considered only once with the worst grade for the analysis of patients with Diarrhoea by CTCAE-Grade.
inf=infinity

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Table 4.5.4 Proportion of patients with any diarrhoea CTCAE-Grade 2 adverse event excluding disease-related events during double-blind period overall and by subgroup - Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk diff. (95% CI)	Odds ratio	Odds ratio (95% CI)
Overall	13	1	7.7	26	3	11.5	0.8713	0.04	(-0.26, 0.25)	1.57	(0.15, 44.45)
Sex											
Male	5	1	20.0	10	1	10.0					
Female	8	0	0.0	16	2	12.5					
Age											
6-<12	4	0	0.0	8	2	25.0					
12-<18	9	1	11.1	18	1	5.6					
Region											
Europe	4	0	0.0	15	1	6.7					
Rest of World	9	1	11.1	11	2	18.2					
Corticosteroid Baseline Use											
Yes	4	1	25.0	9	0	0.0					
No	9	0	0.0	17	3	17.6					

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
Each patient is considered only once with the worst grade for the analysis of patients with Diarrhoea by CTCAE-Grade.
inf=infinity

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Table 4.5.4 Proportion of patients with any diarrhoea CTCAE-Grade 2 adverse event excluding disease-related events during double-blind period overall and by subgroup - Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	1.50	(0.17, 38.59)	(0.17, 13.05)	
Sex				
Male				
Female				
Age				
6-<12				
12-<18				
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
Each patient is considered only once with the worst grade for the analysis of patients with Diarrhoea by CTCAE-Grade.
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Table 4.5.5 Proportion of patients with any diarrhoea CTCAE-Grade >=3 adverse event excluding disease-related events during double-blind period overall and by subgroup - Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk (95% CI)	Odds ratio	Odds (95% CI)
Overall	13	0	0.0	26	0	0.0					
Sex											
Male	5	0	0.0	10	0	0.0					
Female	8	0	0.0	16	0	0.0					
Age											
6-<12	4	0	0.0	8	0	0.0					
12-<18	9	0	0.0	18	0	0.0					
Region											
Europe	4	0	0.0	15	0	0.0					
Rest of World	9	0	0.0	11	0	0.0					
Corticosteroid Baseline Use											
Yes	4	0	0.0	9	0	0.0					
No	9	0	0.0	17	0	0.0					

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
Each patient is considered only once with the worst grade for the analysis of patients with Diarrhoea by CTCAE-Grade.
inf=infinity

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Table 4.5.5 Proportion of patients with any diarrhoea CTCAE-Grade >=3 adverse event excluding disease-related events during double-blind period overall and by subgroup - Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall				
Sex				
Male				
Female				
Age				
6-<12				
12-<18				
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
Each patient is considered only once with the worst grade for the analysis of patients with Diarrhoea by CTCAE-Grade.
inf=infinity

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Anhang 4-G4.6: Safety Topics

Table 4.6.1 Proportion of patients with any adverse event by safety topic during double-blind period overall and by subgroup
Treated Set
Safety topic: Abdominal pain (MedDRA HLT)

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk (95% CI)	Odds ratio	Odds (95% CI)
Overall	13	4	30.8	26	6	23.1	0.7861	-0.08	(-0.40, 0.21)	0.68	(0.15, 3.35)
Sex											
Male	5	1	20.0	10	3	30.0					
Female	8	3	37.5	16	3	18.8					
Age											
6-<12	4	3	75.0	8	2	25.0					
12-<18	9	1	11.1	18	4	22.2					
Region											
Europe	4	0	0.0	15	1	6.7					
Rest of World	9	4	44.4	11	5	45.5					
Corticosteroid Baseline Use											
Yes	4	1	25.0	9	2	22.2					
No	9	3	33.3	17	4	23.5					

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 4.6.1 Proportion of patients with any adverse event by safety topic during double-blind period overall and by subgroup
Treated Set
Safety topic: Abdominal pain (MedDRA HLT)

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	0.75	(0.25, 2.81)	(0.26, 2.20)	
Sex				
Male				
Female				
Age				
6-<12				
12-<18				
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 4.6.1 Proportion of patients with any adverse event by safety topic during double-blind period overall and by subgroup
Treated Set
Safety topic: Bleeding

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk (95% CI)	Odds ratio	Odds (95% CI)
Overall	13	2	15.4	26	1	3.8	0.3665	-0.12	(-0.41, 0.09)	0.22	(0.01, 3.28)
Sex											
Male	5	1	20.0	10	0	0.0					
Female	8	1	12.5	16	1	6.3					
Age											
6-<12	4	2	50.0	8	1	12.5					
12-<18	9	0	0.0	18	0	0.0					
Region											
Europe	4	0	0.0	15	1	6.7					
Rest of World	9	2	22.2	11	0	0.0					
Corticosteroid Baseline Use											
Yes	4	0	0.0	9	1	11.1					
No	9	2	22.2	17	0	0.0					

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 4.6.1 Proportion of patients with any adverse event by safety topic during double-blind period overall and by subgroup
Treated Set
Safety topic: Bleeding

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	0.25	(0.01, 2.63)	(0.02, 2.51)	
Sex				
Male				
Female				
Age				
6-<12				
12-<18				
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 4.6.1 Proportion of patients with any adverse event by safety topic during double-blind period overall and by subgroup
Treated Set
Safety topic: Decreased appetite (Single MedDRA PT)

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk (95% CI)	Odds ratio	Odds (95% CI)
Overall	13	0	0.0	26	1	3.8	0.7724	0.04	(-0.21, 0.20)	inf	(0.06, inf)
Sex											
Male	5	0	0.0	10	0	0.0					
Female	8	0	0.0	16	1	6.3					
Age											
6-<12	4	0	0.0	8	0	0.0					
12-<18	9	0	0.0	18	1	5.6					
Region											
Europe	4	0	0.0	15	0	0.0					
Rest of World	9	0	0.0	11	1	9.1					
Corticosteroid Baseline Use											
Yes	4	0	0.0	9	0	0.0					
No	9	0	0.0	17	1	5.9					

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 4.6.1 Proportion of patients with any adverse event by safety topic during double-blind period overall and by subgroup
Treated Set
Safety topic: Decreased appetite (Single MedDRA PT)

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	inf 1.53	(0.04, inf)	(0.07, 35.06)	
Sex				
Male				
Female				
Age				
6-<12				
12-<18				
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 4.6.1 Proportion of patients with any adverse event by safety topic during double-blind period overall and by subgroup
Treated Set
Safety topic: Dental disorders (Group of MedDRA PTs)

Subgroup	Placebo			Nintedanib			Nintedanib vs Placebo				
Category	N	n	%	N	n	%	p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Overall	13	7	53.8	26	9	34.6	0.3665	-0.19	(-0.51, 0.15)	0.45	(0.11, 1.85)
Sex											
Male	5	4	80.0	10	2	20.0	0.0425	-0.60	(-0.91,-0.02)	0.06	(0.00, 0.99)
Female	8	3	37.5	16	7	43.8	0.8907	0.06	(-0.37, 0.45)	1.30	(0.22, 8.57)
Age											
6-<12	4	3	75.0	8	3	37.5	0.3525	-0.38	(-0.81, 0.28)	0.20	(0.01, 3.21)
12-<18	9	4	44.4	18	6	33.3	0.7845	-0.11	(-0.50, 0.28)	0.63	(0.11, 3.58)
Region											
Europe	4	2	50.0	15	7	46.7					
Rest of World	9	5	55.6	11	2	18.2					
Corticosteroid Baseline Use											
Yes	4	3	75.0	9	1	11.1	0.0662	-0.64	(-0.95, 0.01)	0.04	(0.00, 1.03)
No	9	4	44.4	17	8	47.1	0.9724	0.03	(-0.38, 0.42)	1.11	(0.21, 6.18)

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 4.6.1 Proportion of patients with any adverse event by safety topic during double-blind period overall and by subgroup
Treated Set
Safety topic: Dental disorders (Group of MedDRA PTs)

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	0.64	(0.29, 1.53)	(0.31, 1.33)	
Sex				0.0731
Male	0.25	(0.04, 0.91)	(0.07, 0.93)	
Female	1.17	(0.40, 7.24)	(0.41, 3.34)	
Age				0.5817
6-<12	0.50	(0.13, 1.90)	(0.17, 1.44)	
12-<18	0.75	(0.26, 2.72)	(0.28, 2.00)	
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				0.0699
Yes	0.15	(0.01, 1.01)	(0.02, 1.02)	
No	1.06	(0.44, 4.41)	(0.44, 2.57)	

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 4.6.1 Proportion of patients with any adverse event by safety topic during double-blind period overall and by subgroup
Treated Set
Safety topic: Diarrhoea (Single MedDRA PT)

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk (95% CI)	Odds ratio	Odds (95% CI)
Overall	13	2	15.4	26	10	38.5	0.1776	0.23	(-0.10, 0.49)	3.44	(0.65, 26.21)
Sex											
Male	5	1	20.0	10	5	50.0					
Female	8	1	12.5	16	5	31.3					
Age											
6-<12	4	0	0.0	8	2	25.0	0.4249	0.25	(-0.37, 0.65)	inf	(0.23, inf)
12-<18	9	2	22.2	18	8	44.4	0.3635	0.22	(-0.21, 0.55)	2.80	(0.45, 23.53)
Region											
Europe	4	0	0.0	15	3	20.0					
Rest of World	9	2	22.2	11	7	63.6					
Corticosteroid Baseline Use											
Yes	4	1	25.0	9	2	22.2					
No	9	1	11.1	17	8	47.1					

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 4.6.1 Proportion of patients with any adverse event by safety topic during double-blind period overall and by subgroup
Treated Set
Safety topic: Diarrhoea (Single MedDRA PT)

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	2.50	(0.73, 27.11)	(0.64, 9.78)	
Sex				
Male				
Female				
Age				0.8598
6-<12	inf 2.65	(0.20, inf)	(0.16, 44.11)	
12-<18	2.00	(0.62, 16.49)	(0.53, 7.54)	
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 4.6.1 Proportion of patients with any adverse event by safety topic during double-blind period overall and by subgroup
Treated Set
Safety topic: Growth plate disorders (Group of MedDRA PTs)

Subgroup	Placebo			Nintedanib			Nintedanib vs Placebo				
Category	N	n	%	N	n	%	p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Overall	13	2	15.4	26	1	3.8	0.3665	-0.12	(-0.41, 0.09)	0.22	(0.01, 3.28)
Sex											
Male	5	1	20.0	10	1	10.0					
Female	8	1	12.5	16	0	0.0					
Age											
6-<12	4	1	25.0	8	1	12.5					
12-<18	9	1	11.1	18	0	0.0					
Region											
Europe	4	2	50.0	15	1	6.7					
Rest of World	9	0	0.0	11	0	0.0					
Corticosteroid Baseline Use											
Yes	4	1	25.0	9	1	11.1					
No	9	1	11.1	17	0	0.0					

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 4.6.1 Proportion of patients with any adverse event by safety topic during double-blind period overall and by subgroup
Treated Set
Safety topic: Growth plate disorders (Group of MedDRA PTs)

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	0.25	(0.01, 2.63)	(0.02, 2.51)	
Sex				
Male				
Female				
Age				
6-<12				
12-<18				
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 4.6.1 Proportion of patients with any adverse event by safety topic during double-blind period overall and by subgroup
Treated Set
Safety topic: Hepatic disorders combined

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk (95% CI)	Odds ratio	Odds (95% CI)
Overall	13	0	0.0	26	2	7.7	0.4373	0.08	(-0.17, 0.26)	inf	(0.23, inf)
Sex											
Male	5	0	0.0	10	0	0.0					
Female	8	0	0.0	16	2	12.5					
Age											
6-<12	4	0	0.0	8	1	12.5					
12-<18	9	0	0.0	18	1	5.6					
Region											
Europe	4	0	0.0	15	0	0.0					
Rest of World	9	0	0.0	11	2	18.2					
Corticosteroid Baseline Use											
Yes	4	0	0.0	9	0	0.0					
No	9	0	0.0	17	2	11.8					

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 4.6.1 Proportion of patients with any adverse event by safety topic during double-blind period overall and by subgroup
Treated Set
Safety topic: Hepatic disorders combined

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	inf 2.55	(0.20, inf)	(0.13, 49.39)	
Sex				
Male				
Female				
Age				
6-<12				
12-<18				
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 4.6.1 Proportion of patients with any adverse event by safety topic during double-blind period overall and by subgroup
Treated Set
Safety topic: Hepatic enzyme increased (Group of MedDRA PTs)

Subgroup	Placebo			Nintedanib			Nintedanib vs Placebo				
Category	N	n	%	N	n	%	p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Overall	13	0	0.0	26	1	3.8	0.7724	0.04	(-0.21, 0.20)	inf	(0.06, inf)
Sex											
Male	5	0	0.0	10	0	0.0					
Female	8	0	0.0	16	1	6.3					
Age											
6-<12	4	0	0.0	8	0	0.0					
12-<18	9	0	0.0	18	1	5.6					
Region											
Europe	4	0	0.0	15	0	0.0					
Rest of World	9	0	0.0	11	1	9.1					
Corticosteroid Baseline Use											
Yes	4	0	0.0	9	0	0.0					
No	9	0	0.0	17	1	5.9					

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 4.6.1 Proportion of patients with any adverse event by safety topic during double-blind period overall and by subgroup
Treated Set
Safety topic: Hepatic enzyme increased (Group of MedDRA PTs)

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	inf 1.53	(0.04, inf)	(0.07, 35.06)	
Sex				
Male				
Female				
Age				
6-<12				
12-<18				
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.6.1 Proportion of patients with any adverse event by safety topic during double-blind period overall and by subgroup
Treated Set
Safety topic: Hepatic failure (SMQ - narrow)

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk (95% CI)	Odds ratio	Odds (95% CI)
Overall	13	0	0.0	26	1	3.8	0.7724	0.04	(-0.21, 0.20)	inf	(0.06, inf)
Sex											
Male	5	0	0.0	10	0	0.0					
Female	8	0	0.0	16	1	6.3					
Age											
6-<12	4	0	0.0	8	1	12.5					
12-<18	9	0	0.0	18	0	0.0					
Region											
Europe	4	0	0.0	15	0	0.0					
Rest of World	9	0	0.0	11	1	9.1					
Corticosteroid Baseline Use											
Yes	4	0	0.0	9	0	0.0					
No	9	0	0.0	17	1	5.9					

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 4.6.1 Proportion of patients with any adverse event by safety topic during double-blind period overall and by subgroup
Treated Set
Safety topic: Hepatic failure (SMQ - narrow)

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	inf 1.53	(0.04, inf)	(0.07, 35.06)	
Sex				
Male				
Female				
Age				
6-<12				
12-<18				
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 4.6.1 Proportion of patients with any adverse event by safety topic during double-blind period overall and by subgroup
Treated Set
Safety topic: Nausea (Single MedDRA PT)

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk (95% CI)	Odds ratio	Odds (95% CI)
Overall	13	3	23.1	26	5	19.2	0.8921	-0.04	(-0.36, 0.22)	0.79	(0.15, 4.77)
Sex											
Male	5	1	20.0	10	2	20.0					
Female	8	2	25.0	16	3	18.8					
Age											
6-<12	4	2	50.0	8	0	0.0					
12-<18	9	1	11.1	18	5	27.8					
Region											
Europe	4	0	0.0	15	2	13.3					
Rest of World	9	3	33.3	11	3	27.3					
Corticosteroid Baseline Use											
Yes	4	2	50.0	9	2	22.2					
No	9	1	11.1	17	3	17.6					

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 4.6.1 Proportion of patients with any adverse event by safety topic during double-blind period overall and by subgroup
Treated Set
Safety topic: Nausea (Single MedDRA PT)

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	0.83	(0.23, 7.22)	(0.23, 2.96)	
Sex				
Male				
Female				
Age				
6-<12				
12-<18				
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.6.1 Proportion of patients with any adverse event by safety topic during double-blind period overall and by subgroup
Treated Set
Safety topic: Tooth developmental disorders (MedDRA HLT)

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk (95% CI)	Odds ratio	Odds (95% CI)
Overall	13	4	30.8	26	3	11.5	0.1687	-0.19	(-0.50, 0.08)	0.29	(0.05, 1.75)
Sex											
Male	5	3	60.0	10	1	10.0					
Female	8	1	12.5	16	2	12.5					
Age											
6-<12	4	2	50.0	8	1	12.5					
12-<18	9	2	22.2	18	2	11.1					
Region											
Europe	4	1	25.0	15	2	13.3					
Rest of World	9	3	33.3	11	1	9.1					
Corticosteroid Baseline Use											
Yes	4	1	25.0	9	0	0.0					
No	9	3	33.3	17	3	17.6					

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.6.1 Proportion of patients with any adverse event by safety topic during double-blind period overall and by subgroup
Treated Set
Safety topic: Tooth developmental disorders (MedDRA HLT)

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	0.38	(0.07, 1.58)	(0.10, 1.43)	
Sex				
Male				
Female				
Age				
6-<12				
12-<18				
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.6.1 Proportion of patients with any adverse event by safety topic during double-blind period overall and by subgroup
Treated Set
Safety topic: Upper and not otherwise specified respiratory tract infection (Group of MedDRA PTs)

Subgroup	Placebo			Nintedanib			Nintedanib vs Placebo				
Category	N	n	%	N	n	%	p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Overall	13	1	7.7	26	5	19.2	0.4667	0.12	(-0.18, 0.34)	2.86	(0.34, 73.29)
Sex											
Male	5	0	0.0	10	1	10.0					
Female	8	1	12.5	16	4	25.0					
Age											
6-<12	4	0	0.0	8	3	37.5					
12-<18	9	1	11.1	18	2	11.1					
Region											
Europe	4	0	0.0	15	3	20.0					
Rest of World	9	1	11.1	11	2	18.2					
Corticosteroid Baseline Use											
Yes	4	0	0.0	9	2	22.2					
No	9	1	11.1	17	3	17.6					

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.6.1 Proportion of patients with any adverse event by safety topic during double-blind period overall and by subgroup
Treated Set
Safety topic: Upper and not otherwise specified respiratory tract infection (Group of MedDRA PTs)

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	2.50	(0.41, 63.68)	(0.32, 19.25)	
Sex				
Male				
Female				
Age				
6-<12				
12-<18				
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 4.6.1 Proportion of patients with any adverse event by safety topic during double-blind period overall and by subgroup
Treated Set
Safety topic: Vomiting (Single MedDRA PT)

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk (95% CI)	Odds ratio	Odds (95% CI)
Overall	13	3	23.1	26	7	26.9	0.9040	0.04	(-0.30, 0.31)	1.23	(0.26, 6.94)
Sex											
Male	5	1	20.0	10	3	30.0					
Female	8	2	25.0	16	4	25.0					
Age											
6-<12	4	2	50.0	8	2	25.0					
12-<18	9	1	11.1	18	5	27.8					
Region											
Europe	4	0	0.0	15	3	20.0					
Rest of World	9	3	33.3	11	4	36.4					
Corticosteroid Baseline Use											
Yes	4	2	50.0	9	3	33.3					
No	9	1	11.1	17	4	23.5					

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.6.1 Proportion of patients with any adverse event by safety topic during double-blind period overall and by subgroup
Treated Set
Safety topic: Vomiting (Single MedDRA PT)

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	1.17	(0.36, 7.34)	(0.36, 3.79)	
Sex				
Male				
Female				
Age				
6-<12				
12-<18				
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 4.6.2 Proportion of patients with any serious adverse event by safety topic during double-blind period overall and by subgroup
Treated Set

---------- No data satisfied to be displayed ----------

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Anhang 4-G4.7: UE nach SOC

Table 4.7.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on SOC level during double-blind period overall and by subgroup - Treated Set
System Organ Class: Gastrointestinal disorders

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk (95% CI)	Odds ratio	Odds (95% CI)
Overall	13	11	84.6	26	22	84.6	1.0000	0.00	(-0.24, 0.32)	1.00	(0.11, 6.56)

Subgroups for analyses by SOC are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity
MedDRA version: 25.0

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Table 4.7.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on SOC level during double-blind period overall and by subgroup - Treated Set
System Organ Class: Gastrointestinal disorders

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	1.00	(0.74, 1.60)	(0.75, 1.33)	

Subgroups for analyses by SOC are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity
MedDRA version: 25.0

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Table 4.7.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on SOC level during double-blind period overall and by subgroup - Treated Set
System Organ Class: General disorders and administration site conditions

Subgroup	Placebo			Nintedanib			Nintedanib vs Placebo				
Category	N	n	%	N	n	%	p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Overall	13	3	23.1	26	8	30.8	0.7861	0.08	(-0.26, 0.35)	1.48	(0.32, 8.20)

Subgroups for analyses by SOC are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity
MedDRA version: 25.0

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Table 4.7.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on SOC level during double-blind period overall and by subgroup - Treated Set
System Organ Class: General disorders and administration site conditions

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	1.33	(0.44, 7.38)	(0.42, 4.20)	

Subgroups for analyses by SOC are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity
MedDRA version: 25.0

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Table 4.7.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on SOC level during double-blind period overall and by subgroup - Treated Set
System Organ Class: Infections and infestations

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk (95% CI)	Odds ratio	Odds (95% CI)
Overall	13	3	23.1	26	10	38.5	0.4373	0.15	(-0.18, 0.43)	2.08	(0.46, 11.22)

Subgroups for analyses by SOC are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity
MedDRA version: 25.0

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Table 4.7.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on SOC level during double-blind period overall and by subgroup - Treated Set
System Organ Class: Infections and infestations

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	1.67	(0.58, 7.40)	(0.55, 5.03)	

Subgroups for analyses by SOC are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.7.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on SOC level during double-blind period overall and by subgroup - Treated Set
System Organ Class: Investigations

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk (95% CI)	Odds ratio	Odds (95% CI)
Overall	13	3	23.1	26	2	7.7	0.3041	-0.15	(-0.45, 0.10)	0.28	(0.03, 2.21)

Subgroups for analyses by SOC are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity
MedDRA version: 25.0

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Table 4.7.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on SOC level during double-blind period overall and by subgroup - Treated Set
System Organ Class: Investigations

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	0.33	(0.03, 1.90)	(0.06, 1.75)	

Subgroups for analyses by SOC are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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MedDRA version: 25.0

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Table 4.7.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on SOC level during double-blind period overall and by subgroup - Treated Set
System Organ Class: Musculoskeletal and connective tissue disorders

Subgroup	Placebo			Nintedanib			Nintedanib vs Placebo				
Category	N	n	%	N	n	%	p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Overall	13	2	15.4	26	6	23.1	0.7861	0.08	(-0.24, 0.32)	1.65	(0.29, 13.46)

Subgroups for analyses by SOC are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.7.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on SOC level during double-blind period overall and by subgroup - Treated Set
System Organ Class: Musculoskeletal and connective tissue disorders

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	1.50	(0.37, 16.57)	(0.35, 6.43)	

Subgroups for analyses by SOC are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.7.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on SOC level during double-blind period overall and by subgroup - Treated Set
System Organ Class: Nervous system disorders

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk (95% CI)	Odds ratio	Odds (95% CI)
Overall	13	3	23.1	26	3	11.5	0.4667	-0.12	(-0.42, 0.14)	0.43	(0.07, 2.99)

Subgroups for analyses by SOC are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.7.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on SOC level during double-blind period overall and by subgroup - Treated Set
System Organ Class: Nervous system disorders

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	0.50	(0.09, 2.81)	(0.12, 2.14)	

Subgroups for analyses by SOC are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.7.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on SOC level during double-blind period overall and by subgroup - Treated Set
System Organ Class: Respiratory, thoracic and mediastinal disorders

Subgroup	Placebo			Nintedanib			Nintedanib vs Placebo				
Category	N	n	%	N	n	%	p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Overall	13	4	30.8	26	4	15.4	0.3667	-0.15	(-0.47, 0.12)	0.41	(0.08, 2.23)

Subgroups for analyses by SOC are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.7.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on SOC level during double-blind period overall and by subgroup - Treated Set
System Organ Class: Respiratory, thoracic and mediastinal disorders

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	0.50	(0.13, 2.00)	(0.15, 1.69)	

Subgroups for analyses by SOC are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.7.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on SOC level during double-blind period overall and by subgroup - Treated Set
System Organ Class: Skin and subcutaneous tissue disorders

Subgroup	Placebo			Nintedanib			Nintedanib vs Placebo				
Category	N	n	%	N	n	%	p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Overall	13	2	15.4	26	2	7.7	0.5178	-0.08	(-0.38, 0.14)	0.46	(0.04, 4.99)

Subgroups for analyses by SOC are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.7.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on SOC level during double-blind period overall and by subgroup - Treated Set
System Organ Class: Skin and subcutaneous tissue disorders

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	0.50	(0.03, 7.34)	(0.08, 3.16)	

Subgroups for analyses by SOC are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Anhang 4-G4.8: SUE nach SOC

Table 4.8.1 Proportion of patients with any serious adverse event occurring in >= 5% of the patients in either treatment arm in the overall population on SOC level during double-blind period overall and by subgroup - Treated Set
System Organ Class: Nervous system disorders

Subgroup	Placebo			Nintedanib			Nintedanib vs Placebo				
Category	N	n	%	N	n	%	p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Overall	13	1	7.7	26	0	0.0	0.3017	-0.08	(-0.36, 0.07)	0.00	(0.00, 4.50)

Subgroups for analyses by SOC are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.8.1 Proportion of patients with any serious adverse event occurring in >= 5% of the patients in either treatment arm in the overall population on SOC level during double-blind period overall and by subgroup - Treated Set
System Organ Class: Nervous system disorders

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	0.00 0.17	(0.00, 7.22)	(0.01, 3.90)	

Subgroups for analyses by SOC are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Anhang 4-G4.9: UE nach SOC und PT

Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Gastrointestinal disorders
Preferred term: Abdominal pain

Subgroup	Placebo			Nintedanib			Nintedanib vs Placebo				
Category	N	n	%	N	n	%	p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Overall	13	3	23.1	26	5	19.2	0.8921	-0.04	(-0.36, 0.22)	0.79	(0.15, 4.77)

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity
MedDRA version: 25.0

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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Gastrointestinal disorders
Preferred term: Abdominal pain

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	0.83	(0.23, 7.22)	(0.23, 2.96)	

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Gastrointestinal disorders
Preferred term: Dental caries

Subgroup	Placebo			Nintedanib			Nintedanib vs Placebo				
Category	N	n	%	N	n	%	p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Overall	13	3	23.1	26	7	26.9	0.9040	0.04	(-0.30, 0.31)	1.23	(0.26, 6.94)

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Gastrointestinal disorders
Preferred term: Dental caries

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	1.17	(0.36, 7.34)	(0.36, 3.79)	

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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MedDRA version: 25.0

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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Gastrointestinal disorders
Preferred term: Diarrhoea

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk diff. (95% CI)	Odds ratio	Odds ratio (95% CI)
Overall	13	2	15.4	26	10	38.5	0.1776	0.23	(-0.10, 0.49)	3.44	(0.65, 26.21)

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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MedDRA version: 25.0

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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Gastrointestinal disorders
Preferred term: Diarrhoea

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	2.50	(0.73, 27.11)	(0.64, 9.78)	

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity
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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Gastrointestinal disorders
Preferred term: Faeces soft

Subgroup	Placebo			Nintedanib			Nintedanib vs Placebo				
Category	N	n	%	N	n	%	p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Overall	13	2	15.4	26	1	3.8	0.3665	-0.12	(-0.41, 0.09)	0.22	(0.01, 3.28)

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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MedDRA version: 25.0

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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Gastrointestinal disorders
Preferred term: Faeces soft

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	0.25	(0.01, 2.63)	(0.02, 2.51)	

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Gastrointestinal disorders
Preferred term: Nausea

Subgroup	Placebo			Nintedanib			Nintedanib vs Placebo				
Category	N	n	%	N	n	%	p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Overall	13	3	23.1	26	5	19.2	0.8921	-0.04	(-0.36, 0.22)	0.79	(0.15, 4.77)

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Gastrointestinal disorders
Preferred term: Nausea

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	0.83	(0.23, 7.22)	(0.23, 2.96)	

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity
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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Gastrointestinal disorders
Preferred term: Tooth impacted

Subgroup	Placebo			Nintedanib			Nintedanib vs Placebo				
Category	N	n	%	N	n	%	p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Overall	13	2	15.4	26	2	7.7	0.5178	-0.08	(-0.38, 0.14)	0.46	(0.04, 4.99)

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Gastrointestinal disorders
Preferred term: Tooth impacted

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	0.50	(0.03, 7.34)	(0.08, 3.16)	

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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MedDRA version: 25.0

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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Gastrointestinal disorders
Preferred term: Vomiting

Subgroup	Placebo			Nintedanib			Nintedanib vs Placebo				
Category	N	n	%	N	n	%	p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Overall	13	3	23.1	26	7	26.9	0.9040	0.04	(-0.30, 0.31)	1.23	(0.26, 6.94)

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Gastrointestinal disorders
Preferred term: Vomiting

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	1.17	(0.36, 7.34)	(0.36, 3.79)	

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: General disorders and administration site conditions
Preferred term: Fatigue

Subgroup	Placebo			Nintedanib			Nintedanib vs Placebo				
Category	N	n	%	N	n	%	p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Overall	13	2	15.4	26	2	7.7	0.5178	-0.08	(-0.38, 0.14)	0.46	(0.04, 4.99)

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity
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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: General disorders and administration site conditions
Preferred term: Fatigue

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	0.50	(0.03, 7.34)	(0.08, 3.16)	

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity
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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: General disorders and administration site conditions
Preferred term: Pyrexia

Subgroup	Placebo			Nintedanib			Nintedanib vs Placebo				
Category	N	n	%	N	n	%	p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Overall	13	1	7.7	26	3	11.5	0.8713	0.04	(-0.26, 0.25)	1.57	(0.15, 44.45)

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity
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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: General disorders and administration site conditions
Preferred term: Pyrexia

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	1.50	(0.17, 38.59)	(0.17, 13.05)	

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity
MedDRA version: 25.0

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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Infections and infestations
Preferred term: COVID-19

Subgroup	Placebo			Nintedanib			Nintedanib vs Placebo				
Category	N	n	%	N	n	%	p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Overall	13	1	7.7	26	5	19.2	0.4667	0.12	(-0.18, 0.34)	2.86	(0.34, 73.29)

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity
MedDRA version: 25.0

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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Infections and infestations
Preferred term: COVID-19

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	2.50	(0.41, 63.68)	(0.32, 19.25)	

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity
MedDRA version: 25.0

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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Infections and infestations
Preferred term: Rhinitis

Subgroup	Placebo			Nintedanib			Nintedanib vs Placebo				
Category	N	n	%	N	n	%	p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Overall	13	0	0.0	26	3	11.5	0.3665	0.12	(-0.15, 0.31)	inf	(0.44, inf)

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity
MedDRA version: 25.0

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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Infections and infestations
Preferred term: Rhinitis

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	inf 3.57	(0.35, inf)	(0.20, 64.15)	

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity
MedDRA version: 25.0

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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Investigations
Preferred term: X-ray limb abnormal

Subgroup	Placebo			Nintedanib			Nintedanib vs Placebo				
Category	N	n	%	N	n	%	p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Overall	13	2	15.4	26	0	0.0	0.0772	-0.15	(-0.45, 0.02)	0.00	(0.00, 1.04)

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Investigations
Preferred term: X-ray limb abnormal

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	0.00 0.10	(0.00, 1.29)	(0.01, 1.98)	

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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MedDRA version: 25.0

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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Nervous system disorders
Preferred term: Headache

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk (95% CI)	Odds ratio	Odds (95% CI)
Overall	13	1	7.7	26	3	11.5	0.8713	0.04	(-0.26, 0.25)	1.57	(0.15, 44.45)

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Nervous system disorders
Preferred term: Headache

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	1.50	(0.17, 38.59)	(0.17, 13.05)	

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity
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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Epistaxis

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Overall	13	2	15.4	26	0	0.0	0.0772	-0.15	(-0.45, 0.02)	0.00	(0.00, 1.04)

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity
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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Epistaxis

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	0.00 0.10	(0.00, 1.29)	(0.01, 1.98)	

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity
MedDRA version: 25.0

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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Oropharyngeal pain

Subgroup	Placebo			Nintedanib			Nintedanib vs Placebo				
Category	N	n	%	N	n	%	p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Overall	13	2	15.4	26	1	3.8	0.3665	-0.12	(-0.41, 0.09)	0.22	(0.01, 3.28)

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity
MedDRA version: 25.0

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Table 4.9.1 Proportion of patients with any adverse event occurring in >= 10% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Oropharyngeal pain

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	0.25	(0.01, 2.63)	(0.02, 2.51)	

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity
MedDRA version: 25.0

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Anhang 4-G4.10: SUE nach SOC und PT

Table 4.10.1 Proportion of patients with any serious adverse event occurring in >= 5% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Nervous system disorders
Preferred term: Frontal lobe epilepsy

Subgroup	Placebo			Nintedanib			Nintedanib vs Placebo				
Category	N	n	%	N	n	%	p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Overall	13	1	7.7	26	0	0.0	0.3017	-0.08	(-0.36, 0.07)	0.00	(0.00, 4.50)

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity
MedDRA version: 25.0

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Table 4.10.1 Proportion of patients with any serious adverse event occurring in >= 5% of the patients in either treatment arm in the overall population on PT level during double-blind period overall and by subgroup - Treated Set
System organ class: Nervous system disorders
Preferred term: Frontal lobe epilepsy

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	0.00 0.17	(0.00, 7.22)	(0.01, 3.90)	

Subgroups for analyses by SOC and PT are not displayed because overall test for treatment is not significant on 5% level

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity
MedDRA version: 25.0

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Anhang 4-G4.11: UE, die zum Therapieabbruch führten nach SOC und PT

Table 4.11.1 Frequency of adverse events leading to treatment discontinuation during double-blind period by treatment, primary system organ class and preferred term - Treated Set

System organ class/ Preferred term	Placebo N	Placebo %	Nintedanib N	Nintedanib %
Number of patients	13	100.0	26	100.0
Number of patients with at least one adverse event leading to discontinuation of trial drug	0	0.0	2	7.7
Hepatobiliary disorders	0	0.0	1	3.8
Liver injury	0	0.0	1	3.8
Musculoskeletal and connective tissue disorders	0	0.0	1	3.8
Epiphyses premature fusion	0	0.0	1	3.8

Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Treatment discontinuations are premature and permanent.
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Anhang 4-G4.12: AESI nach SOC und PT

Table 4.12.1 Proportion of patients with any adverse event of special interest by primary SOC and preferred term as documented by the investigator during double-blind period overall and by subgroup - Treated Set
System organ class: Gastrointestinal disorders
Preferred term: Lower gastrointestinal haemorrhage

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk diff. (95% CI)	Odds ratio	Odds ratio (95% CI)
Overall	13	0	0.0	26	1	3.8	0.7724	0.04	(-0.21, 0.20)	inf	(0.06, inf)
Sex											
Male	5	0	0.0	10	0	0.0					
Female	8	0	0.0	16	1	6.3					
Age											
6-<12	4	0	0.0	8	1	12.5					
12-<18	9	0	0.0	18	0	0.0					
Region											
Europe	4	0	0.0	15	1	6.7					
Rest of World	9	0	0.0	11	0	0.0					
Corticosteroid Baseline Use											
Yes	4	0	0.0	9	1	11.1					
No	9	0	0.0	17	0	0.0					

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Protocol-specified AEs of special interest incl. pathological findings on epiphyseal growth plates imaging, stunted growth (dental imaging), AEs relating to gastrointestinal perforation, bleeding, hepatic injury. Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. AsymptoticCIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 4.12.1 Proportion of patients with any adverse event of special interest by primary SOC and preferred term as documented by the investigator during double-blind period overall and by subgroup - Treated Set
System organ class: Gastrointestinal disorders
Preferred term: Lower gastrointestinal haemorrhage

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	inf 1.53	(0.04, inf)	(0.07, 35.06)	
Sex				
Male				
Female				
Age				
6-<12				
12-<18				
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Protocol-specified AEs of special interest incl. pathological findings on epiphyseal growth plates imaging, stunted growth (dental imaging), AEs relating to gastrointestinal perforation, bleeding, hepatic injury. Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. AsymptoticCIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.12.1 Proportion of patients with any adverse event of special interest by primary SOC and preferred term as documented by the investigator during double-blind period overall and by subgroup - Treated Set
System organ class: Gastrointestinal disorders
Preferred term: Rectal haemorrhage

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk diff. (95% CI)	Odds ratio	Odds ratio (95% CI)
Overall	13	1	7.7	26	0	0.0	0.3017	-0.08	(-0.36, 0.07)	0.00	(0.00, 4.50)
Sex											
Male	5	0	0.0	10	0	0.0					
Female	8	1	12.5	16	0	0.0					
Age											
6-<12	4	1	25.0	8	0	0.0					
12-<18	9	0	0.0	18	0	0.0					
Region											
Europe	4	0	0.0	15	0	0.0					
Rest of World	9	1	11.1	11	0	0.0					
Corticosteroid Baseline Use											
Yes	4	0	0.0	9	0	0.0					
No	9	1	11.1	17	0	0.0					

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Protocol-specified AEs of special interest incl. pathological findings on epiphyseal growth plates imaging, stunted growth (dental imaging), AEs relating to gastrointestinal perforation, bleeding, hepatic injury. Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. AsymptoticCIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.12.1 Proportion of patients with any adverse event of special interest by primary SOC and preferred term as documented by the investigator during double-blind period overall and by subgroup - Treated Set
System organ class: Gastrointestinal disorders
Preferred term: Rectal haemorrhage

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	0.00 0.17	(0.00, 7.22)	(0.01, 3.90)	
Sex				
Male				
Female				
Age				
6-<12				
12-<18				
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Protocol-specified AEs of special interest incl. pathological findings on epiphyseal growth plates imaging, stunted growth (dental imaging), AEs relating to gastrointestinal perforation, bleeding, hepatic injury. Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. AsymptoticCIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 4.12.1 Proportion of patients with any adverse event of special interest by primary SOC and preferred term as documented by the investigator during double-blind period overall and by subgroup - Treated Set
System organ class: Hepatobiliary disorders
Preferred term: Liver injury

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk diff. (95% CI)	Odds ratio	Odds ratio (95% CI)
Overall	13	0	0.0	26	1	3.8	0.7724	0.04	(-0.21, 0.20)	inf	(0.06, inf)
Sex											
Male	5	0	0.0	10	0	0.0					
Female	8	0	0.0	16	1	6.3					
Age											
6-<12	4	0	0.0	8	1	12.5					
12-<18	9	0	0.0	18	0	0.0					
Region											
Europe	4	0	0.0	15	0	0.0					
Rest of World	9	0	0.0	11	1	9.1					
Corticosteroid Baseline Use											
Yes	4	0	0.0	9	0	0.0					
No	9	0	0.0	17	1	5.9					

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Protocol-specified AEs of special interest incl. pathological findings on epiphyseal growth plates imaging, stunted growth (dental imaging), AEs relating to gastrointestinal perforation, bleeding, hepatic injury. Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. AsymptoticCIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 4.12.1 Proportion of patients with any adverse event of special interest by primary SOC and preferred term as documented by the investigator during double-blind period overall and by subgroup - Treated Set
System organ class: Hepatobiliary disorders
Preferred term: Liver injury

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	inf 1.53	(0.04, inf)	(0.07, 35.06)	
Sex				
Male				
Female				
Age				
6-<12				
12-<18				
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Protocol-specified AEs of special interest incl. pathological findings on epiphyseal growth plates imaging, stunted growth (dental imaging), AEs relating to gastrointestinal perforation, bleeding, hepatic injury. Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. AsymptoticCIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 4.12.1 Proportion of patients with any adverse event of special interest by primary SOC and preferred term as documented by the investigator during double-blind period overall and by subgroup - Treated Set
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Epistaxis

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk diff. (95% CI)	Odds ratio	Odds ratio (95% CI)
Overall	13	2	15.4	26	0	0.0	0.0772	-0.15	(-0.45, 0.02)	0.00	(0.00, 1.04)
Sex											
Male	5	1	20.0	10	0	0.0					
Female	8	1	12.5	16	0	0.0					
Age											
6-<12	4	2	50.0	8	0	0.0					
12-<18	9	0	0.0	18	0	0.0					
Region											
Europe	4	0	0.0	15	0	0.0					
Rest of World	9	2	22.2	11	0	0.0					
Corticosteroid Baseline Use											
Yes	4	0	0.0	9	0	0.0					
No	9	2	22.2	17	0	0.0					

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Protocol-specified AEs of special interest incl. pathological findings on epiphyseal growth plates imaging, stunted growth (dental imaging), AEs relating to gastrointestinal perforation, bleeding, hepatic injury. Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. AsymptoticCIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 4.12.1 Proportion of patients with any adverse event of special interest by primary SOC and preferred term as documented by the investigator during double-blind period overall and by subgroup - Treated Set
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Epistaxis

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	0.00 0.10	(0.00, 1.29)	(0.01, 1.98)	
Sex				
Male				
Female				
Age				
6-<12				
12-<18				
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Protocol-specified AEs of special interest incl. pathological findings on epiphyseal growth plates imaging, stunted growth (dental imaging), AEs relating to gastrointestinal perforation, bleeding, hepatic injury. Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. AsymptoticCIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 4.12.2 Proportion of patients with any serious adverse event of special interest by primary SOC and preferred term as documented by the investigator during double-blind period overall and by subgroup - Treated Set

---------- No data satisfied to be displayed ----------

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Anhang 4-G4.13: Weitere Sicherheitsendpunkte

Table 4.13.1 Proportion of patients with any treatment-emergent pathological findings of epiphyseal growth plate on imaging up to week 24 (during double-blind period) overall and by subgroup - Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk diff. (95% CI)	Odds ratio	Odds ratio (95% CI)
Overall	13	1	7.7	26	2	7.7	1.0000	0.00	(-0.28, 0.20)	1.00	(0.07, 31.83)
Sex											
Male	5	1	20.0	10	1	10.0					
Female	8	0	0.0	16	1	6.3					
Age											
6-<12	4	0	0.0	8	1	12.5					
12-<18	9	1	11.1	18	1	5.6					
Region											
Europe	4	0	0.0	15	2	13.3					
Rest of World	9	1	11.1	11	0	0.0					
Corticosteroid Baseline Use											
Yes	4	1	25.0	9	0	0.0					
No	9	0	0.0	17	2	11.8					

N is the number of patients in the respective analysis set. n is the number of patients with at least one finding in the respective analysis set.
Based on central review and not on investigator decision. Pathological findings which were already present at baseline will NOT be considered treatment-emergent in this analysis, in spite of being identified after start of treatment (baseline time window: day -84 until day 15).
All findings after this time window and up to week 24 are considered in this analysis.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Table 4.13.1 Proportion of patients with any treatment-emergent pathological findings of epiphyseal growth plate on imaging up to week 24 (during double-blind period) overall and by subgroup - Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	1.00	(0.10, 27.11)	(0.10, 10.04)	
Sex				
Male				
Female				
Age				
6-<12				
12-<18				
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

N is the number of patients in the respective analysis set. n is the number of patients with at least one finding in the respective analysis set.
Based on central review and not on investigator decision. Pathological findings which were already present at baseline will NOT be considered treatment-emergent in this analysis, in spite of being identified after start of treatment (baseline time window: day -84 until day 15).
All findings after this time window and up to week 24 are considered in this analysis.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Table 4.13.2 Proportion of patients with any treatment-emergent pathological findings on dental examination up to week 24 (during double-blind period) overall and by subgroup - Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk diff. (95% CI)	Odds ratio	Odds ratio (95% CI)
Overall	13	1	7.7	26	5	19.2	0.4667	0.12	(-0.18, 0.34)	2.86	(0.34, 73.29)
Sex											
Male	5	1	20.0	10	1	10.0					
Female	8	0	0.0	16	4	25.0					
Age											
6-<12	4	0	0.0	8	1	12.5					
12-<18	9	1	11.1	18	4	22.2					
Region											
Europe	4	0	0.0	15	3	20.0					
Rest of World	9	1	11.1	11	2	18.2					
Corticosteroid Baseline Use											
Yes	4	1	25.0	9	2	22.2					
No	9	0	0.0	17	3	17.6					

N is the number of patients in the respective analysis set. n is the number of patients with at least one finding in the respective analysis set.
Dental examination done by dentist. Pathological findings which were already present at baseline will NOT be considered treatment-emergent in this analysis, in spite of being identified after start of treatment (baseline time window: day -84 until day 15).
All findings after this time window and up to week 24 are considered in this analysis.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Table 4.13.2 Proportion of patients with any treatment-emergent pathological findings on dental examination up to week 24 (during double-blind period) overall and by subgroup - Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	2.50	(0.41, 63.68)	(0.32, 19.25)	
Sex				
Male				
Female				
Age				
6-<12				
12-<18				
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

N is the number of patients in the respective analysis set. n is the number of patients with at least one finding in the respective analysis set.
Dental examination done by dentist. Pathological findings which were already present at baseline will NOT be considered
treatment-emergent in this analysis, in spite of being identified after start of treatment (baseline time window: day -84 until day 15).
All findings after this time window and up to week 24 are considered in this analysis.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the
modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Table 4.13.3 Proportion of patients with any treatment-emergent pathological findings on dental imaging up to week 24 (during double-blind period) overall and by subgroup - Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk diff. (95% CI)	Odds ratio	Odds ratio (95% CI)
Overall	13	4	30.8	26	9	34.6	0.9105	0.04	(-0.30, 0.33)	1.19	(0.28, 5.54)
Sex											
Male	5	1	20.0	10	1	10.0	0.7809	-0.10	(-0.62, 0.32)	0.44	(0.01, 21.51)
Female	8	3	37.5	16	8	50.0	0.7839	0.13	(-0.31, 0.51)	1.67	(0.28, 10.89)
Age											
6-<12	4	2	50.0	8	1	12.5	0.3510	-0.38	(-0.84, 0.21)	0.14	(0.00, 3.26)
12-<18	9	2	22.2	18	8	44.4	0.3635	0.22	(-0.21, 0.55)	2.80	(0.45, 23.53)
Region											
Europe	4	2	50.0	15	4	26.7					
Rest of World	9	2	22.2	11	5	45.5					
Corticosteroid Baseline Use											
Yes	4	1	25.0	9	5	55.6					
No	9	3	33.3	17	4	23.5					

N is the number of patients in the respective analysis set. n is the number of patients with at least one finding in the respective analysis set.
Based on central review and not on investigator decision. Pathological findings which were already present at baseline will NOT be considered treatment-emergent in this analysis, in spite of being identified after start of treatment (baseline time window: day -84 until day 15).
All findings after this time window and up to week 24 are considered in this analysis.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Table 4.13.3 Proportion of patients with any treatment-emergent pathological findings on dental imaging up to week 24 (during double-blind period) overall and by subgroup - Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Overall	1.13	(0.43, 6.80)	(0.43, 2.97)	
Sex				0.4848
Male	0.50	(0.02, 16.28)	(0.04, 6.44)	
Female	1.33	(0.50, 7.28)	(0.48, 3.70)	
Age				0.0984
6-<12	0.25	(0.01, 2.36)	(0.03, 2.00)	
12-<18	2.00	(0.62, 16.49)	(0.53, 7.54)	
Region				
Europe				
Rest of World				
Corticosteroid Baseline Use				
Yes				
No				

N is the number of patients in the respective analysis set. n is the number of patients with at least one finding in the respective analysis set.
Based on central review and not on investigator decision. Pathological findings which were already present at baseline will NOT be considered treatment-emergent in this analysis, in spite of being identified after start of treatment (baseline time window: day -84 until day 15).
All findings after this time window and up to week 24 are considered in this analysis.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Table 4.13.4 Adjusted mean (SE) of absolute change from baseline in height-for-age z-score (HAZ) at week 24 by subgroup
Treated Set

Subgroup/ Category/ Treatment	N	Baseline [1] Mean	SD	24 weeks [1] Mean	SD	Change from baseline to 24 weeks: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	Comparison vs. Randomised Placebo: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	p-value [3]
Sex														0.3102
Male														
Placebo	4	-1.204	0.754	-1.271	0.707	-0.110	0.070	-0.253	0.033					
Nintedanib	8	-0.650	1.589	-0.718	1.631	-0.053	0.050	-0.154	0.047	0.057	0.086	-0.119	0.232	
Female														
Placebo	8	-1.084	1.714	-1.073	1.716	0.010	0.051	-0.095	0.115					
Nintedanib	14	-0.890	1.117	-0.939	1.053	-0.044	0.038	-0.121	0.034	-0.053	0.064	-0.184	0.077	
Age														
6-<12														
Placebo	3	0.011	1.896	-0.077	1.857									
Nintedanib	6	-0.531	1.120	-0.597	1.149									
12-<18														
Placebo	9	-1.503	1.116	-1.493	1.162									
Nintedanib	16	-0.904	1.350	-0.957	1.319									
Region														0.5597
Europe														
Placebo	3	-2.107	1.820	-2.033	2.016	0.012	0.083	-0.157	0.182					
Nintedanib	14	-0.422	1.087	-0.481	1.076	-0.053	0.040	-0.135	0.028	-0.066	0.095	-0.258	0.127	
Rest of World														
Placebo	9	-0.797	1.216	-0.841	1.167	-0.043	0.048	-0.142	0.057					
Nintedanib	8	-1.469	1.376	-1.520	1.347	-0.036	0.051	-0.139	0.066	0.006	0.071	-0.137	0.150	
Corticosteroid at Baseline														0.3697
Yes														
Placebo	3	-0.314	1.282	-0.381	1.182	-0.112	0.081	-0.277	0.053					
Nintedanib	7	-1.781	1.237	-1.835	1.169	-0.048	0.056	-0.161	0.065	0.064	0.100	-0.139	0.267	
No														
Placebo	9	-1.394	1.432	-1.391	1.463	0.001	0.050	-0.101	0.102					
Nintedanib	15	-0.346	1.042	-0.403	1.045	-0.048	0.039	-0.127	0.030	-0.049	0.065	-0.181	0.083	

The age in months at the respective time point is used to determine the z-score of a given patient.
[1] Based on the number of patients having available data at baseline and at the respective visit.
[2] Based on Mixed Model for Repeated Measures (MMRM), with fixed categorical effect age-group and the fixed continuous effects of baseline value at each visit, (randomized) treatment-by-visit-by-subgroup interaction, and random effect for patient. [3] Interaction p-value.
Visit is treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
Adjusted mean is based on all analysed patients in the model (i.e. on patients with a baseline and at least one post-baseline measurement - not only on patients with a baseline and measurement at the respective visit).
For derivation of the MMRM available data from all visits up to week 52 is used. Only on-treatment data are considered.

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Table 4.13.5 Adjusted mean (SE) of absolute change from baseline in BMI-for-age z-score (BAZ) at week 24 by subgroup
Treated Set

Subgroup/ Category/ Treatment	N	Baseline [1] Mean	Baseline [1] SD	24 weeks [1] Mean	24 weeks [1] SD	Change from baseline to 24 weeks: Adjusted mean [2]	SE	95% confidence interval Lower	95% confidence interval Upper	Comparison vs. Randomised Placebo: Adjusted mean [2]	SE	95% confidence interval Lower	95% confidence interval Upper	p-value [3]
Sex														0.2498
Male														
Placebo	4	0.778	1.505	0.893	1.571	0.254	0.203	-0.159	0.666					
Nintedanib	8	-0.197	2.429	-0.534	2.422	-0.362	0.142	-0.651	-0.074	-0.616	0.246	-1.116	-0.116	
Female														
Placebo	8	-1.063	2.368	-1.061	2.265	-0.012	0.153	-0.325	0.301					
Nintedanib	14	-0.371	0.781	-0.649	1.000	-0.262	0.109	-0.486	-0.039	-0.251	0.188	-0.635	0.134	
Age														
6-<12														
Placebo	3	-1.312	1.028	-0.755	0.442									
Nintedanib	6	-0.474	2.469	-0.551	2.458									
12-<18														
Placebo	9	-0.161	2.500	-0.295	2.565									
Nintedanib	16	-0.245	1.116	-0.628	1.263									
Region														0.8159
Europe														
Placebo	3	-1.959	3.697	-2.082	3.678	0.007	0.241	-0.483	0.498					
Nintedanib	14	-0.387	1.664	-0.669	1.708	-0.310	0.114	-0.543	-0.077	-0.317	0.268	-0.863	0.229	
Rest of World														
Placebo	9	0.054	1.526	0.148	1.381	0.099	0.145	-0.197	0.395					
Nintedanib	8	-0.168	1.372	-0.500	1.516	-0.299	0.140	-0.584	-0.014	-0.398	0.202	-0.810	0.015	
Corticosteroid at Baseline														0.0034
Yes														
Placebo	3	0.439	2.380	1.164	1.574	0.739	0.190	0.352	1.126					
Nintedanib	7	-0.553	1.029	-0.752	1.339	-0.258	0.124	-0.512	-0.005	-0.997	0.227	-1.460	-0.535	
No														
Placebo	9	-0.745	2.253	-0.934	2.198	-0.187	0.117	-0.426	0.051					
Nintedanib	15	-0.193	1.741	-0.540	1.756	-0.323	0.087	-0.502	-0.145	-0.136	0.146	-0.435	0.163	

The age in months at the respective time point is used to determine the z-score of a given patient.
[1] Based on the number of patients having available data at baseline and at the respective visit.
[2] Based on Mixed Model for Repeated Measures (MMRM), with fixed categorical effect age-group and the fixed continuous effects of baseline value at each visit, (randomized) treatment-by-visit-by-subgroup interaction, and random effect for patient. [3] Interaction p-value.
Visit is treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
Adjusted mean is based on all analysed patients in the model (i.e. on patients with a baseline and at least one post-baseline measurement - not only on patients with a baseline and measurement at the respective visit).
For derivation of the MMRM available data from all visits up to week 52 is used. Only on-treatment data are considered.

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Anhang 4-G5: Baselinecharakteristika

Anhang 4-G5.1: Kriterien für eine klinische Progression

Table 5.1.1 Number of criteria for clinical progression over time at baseline
Treated Set

	Placebo		Nintedanib		Total	
Number of subjects (N, %)	13	100.0	26	100.0	39	100.0
Number of criteria for clinical progression over time (N, %)						
0	1	7.7	3	11.5	4	10.3
>=1	12	92.3	22	84.6	34	87.2
Missing	0	0.0	1	3.8	1	2.6

Criteria for clinical progression over time are: 5-10% relative decline in FVC % predicted with worsening symptoms, >=10% relative decline in FVC % predicted, Increased fibrosis on HRCT, Other measures of clinical worsening

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Anhang 4-G6: Weitere Ergebnisse zur Wirksamkeit nach zugrundeliegender ILD Diagnose

Anhang 4-G6.1: FVC

Table 6.1.1 Proportion of patients with absolute increase in FVC % predicted (>=5%) from baseline at week 24 by underlying ILD diagnosis
Treated Set

	Placebo			Nintedanib			Randomised Nintedanib vs. Placebo							
	N	n	%	N	n	%	Risk ratio [1]	95% confidence interval [1] Lower	Upper	p-value [1]	Odds ratio [2]	95% confidence interval [2] Lower	Upper	p-value [1][3]
Underlying ILD diagnosis														
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	0	0.0	6	0	0.0								
Chronic Hypersensitivity Pneumonitis (cHP)	0			2	1	50.0								
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	1	33.3								
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0			1	0	0.0								
Juvenile Rheumatoid Arthritis (RA)	0			1	1	100.0								
Juvenile Idiopathic Arthritis	1	0	0.0	0										
Systemic Sclerosis (SSc)	3	0	0.0	4	0	0.0								
Dermatomyositis	0			1	0	0.0								
Mixed Connective Tissue Disease	0			0										
Sarcoidosis	0			0										
Other Childhood ILD	2	0	0.0	5	2	40.0								

N represents the number of patients in the Treated Set with an available FVC value at baseline and at the respective visit based on observed data.
n represents the number of patients meeting the response criterion based on observed data.
[1] Based on a log-linked Poisson model with robust estimate of variance^.
[2] Based on a logistic regression model^ showing Wald confidence intervals.
[3] Interaction p-value from log-linked Poisson model with robust estimate of variance^.
^ All models contain continuous covariate baseline value and categorical covariate age-group. Subgroup and treatment by subgroup interaction term are additionally included for the subgroup analyses.
All model results are based on pooled results following multiple imputation procedure (m=100 imputations) as described in TSAP Section 6.6.2.3.
inf=infinity; NC=not calculabe because of errors/warnings in at least one of the 100 regression models.

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Table 6.1.2 Proportion of patients with absolute increase in FVC % predicted (>=10%) from baseline at week 24 by underlying ILD diagnosis
Treated Set

	Placebo			Nintedanib			Randomised Nintedanib vs. Placebo						
	N	n	%	N	n	%	Risk ratio [1]	95% confidence interval [1] Lower	Upper	p-value [1]	Odds ratio [2]	95% confidence interval [2] Lower	Upper	p-value [1][3]
Underlying ILD diagnosis														
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	0	0.0	6	0	0.0								
Chronic Hypersensitivity Pneumonitis (cHP)	0			2	0	0.0								
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	0	0.0								
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0			1	0	0.0								
Juvenile Rheumatoid Arthritis (RA)	0			1	0	0.0								
Juvenile Idiopathic Arthritis	1	0	0.0	0										
Systemic Sclerosis (SSc)	3	0	0.0	4	0	0.0								
Dermatomyositis	0			1	0	0.0								
Mixed Connective Tissue Disease	0			0										
Sarcoidosis	0			0										
Other Childhood ILD	2	0	0.0	5	1	20.0								

N represents the number of patients in the Treated Set with an available FVC value at baseline and at the respective visit.
n represents the number of patients meeting the response criterion.
[1] Based on a log-linked Poisson model with robust estimate of variance^.
[2] Based on a logistic regression model^ showing Wald confidence intervals.
[3] Interaction p-value from log-linked Poisson model with robust estimate of variance^.
^ All models contain continuous covariate baseline value and categorical covariate age-group. Subgroup and treatment by subgroup interaction term are additionally included for the subgroup analyses.
All model results are based on pooled results following multiple imputation procedure (m=100 imputations) as described in TSAP Section 6.6.2.3.
inf=infinity; NC=not calculabe because of errors/warnings in at least one of the 100 regression models.

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Table 6.1.3 Adjusted mean (SE) of absolute change from baseline in FVC % predicted at week 24 by underlying ILD diagnosis
Treated Set

Subgroup/ Category/ Treatment	N	Baseline [1] Mean	Baseline [1] SD	24 weeks [1] Mean	24 weeks [1] SD	Change from baseline to 24 weeks: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	Comparison vs. Randomised Placebo: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	p-value [3]
Underlying ILD diagnosis														
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)														
Placebo	5	62.6284	29.0144	63.2522	31.3794									
Nintedanib	6	57.3013	17.5943	56.9143	18.1066									
Chronic Hypersensitivity Pneumonitis (cHP)														
Placebo	0													
Nintedanib	2	51.4450	31.2329	56.8440	30.4409									
Toxic/Radiation/Drug Induced Pneumonitis														
Placebo	1	52.5210		53.8220										
Nintedanib	3	44.8843	18.7089	46.8433	23.6443									
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis														
Placebo	0													
Nintedanib	1	22.2250		23.1600										
Juvenile Rheumatoid Arthritis (RA)														
Placebo	0													
Nintedanib	1	69.9460		77.8380										
Juvenile Idiopathic Arthritis														
Placebo	1	70.5080		74.6510										
Nintedanib	0													
Systemic Sclerosis (SSc)														
Placebo	3	80.2513	19.6296	79.4417	20.6267									
Nintedanib	4	52.5028	28.9019	44.5798	20.2568									
Dermatomyositis														
Placebo	0													
Nintedanib	1	64.9780		62.1210										
Mixed Connective Tissue Disease														
Placebo	0													
Nintedanib	0													
Sarcoidosis														
Placebo	0													
Nintedanib	0													
Other Childhood ILD														

[1] Based on the number of patients having available data at baseline and at the respective visit.
[2] Based on Mixed Model for Repeated Measures (MMRM), with fixed categorical effect age-group and the fixed continuous effects of baseline value at each visit, (randomized) treatment-by-visit-by-subgroup interaction, and random effect for patient. [3] Interaction p-value.
Visit is treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
Adjusted mean is based on all analysed patients in the model (i.e. on patients with a baseline and at least one post-baseline measurement - not only on patients with a baseline and measurement at the respective visit).
For derivation of the MMRM available data from all visits up to week 52 is used.

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Table 6.1.3 Adjusted mean (SE) of absolute change from baseline in FVC % predicted at week 24 by underlying ILD diagnosis
Treated Set

Subgroup/ Category/ Treatment	N	Baseline [1] Mean	Baseline [1] SD	24 weeks [1] Mean	24 weeks [1] SD	Change from baseline to 24 weeks: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	Comparison vs. Randomised Placebo: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	p-value [3]
Placebo	2	50.2970	10.3167	47.1670	13.8225									
Nintedanib	5	71.5766	24.8876	74.0198	25.8824									

[1] Based on the number of patients having available data at baseline and at the respective visit.
[2] Based on Mixed Model for Repeated Measures (MMRM), with fixed categorical effect age-group and the fixed continuous effects of baseline value at each visit, (randomized) treatment-by-visit-by-subgroup interaction, and random effect for patient. [3] Interaction p-value.
Visit is treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
Adjusted mean is based on all analysed patients in the model (i.e. on patients with a baseline and at least one post-baseline measurement - not only on patients with a baseline and measurement at the respective visit).
For derivation of the MMRM available data from all visits up to week 52 is used.

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Table 6.1.4 Adjusted mean (SE) of absolute change from baseline in FVC z-score at week 24 by underlying ILD diagnosis
Treated Set

Subgroup/ Category/ Treatment	N	Baseline Mean	Baseline SD [1]	24 weeks Mean	24 weeks SD [1]	Change from baseline to 24 weeks: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	Comparison vs. Randomised Placebo: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	p-value [3]
Underlying ILD diagnosis														
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)														
Placebo	5	-3.190	2.440	-3.126	2.635									
Nintedanib	6	-3.566	1.411	-3.618	1.479									
Chronic Hypersensitivity Pneumonitis (cHP)														
Placebo	0													
Nintedanib	2	-4.101	2.683	-3.675	2.660									
Toxic/Radiation/Drug Induced Pneumonitis														
Placebo	1	-4.022		-3.898										
Nintedanib	3	-4.663	1.768	-4.493	2.147									
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis														
Placebo	0													
Nintedanib	1	-7.120		-7.033										
Juvenile Rheumatoid Arthritis (RA)														
Placebo	0													
Nintedanib	1	-2.590		-1.906										
Juvenile Idiopathic Arthritis														
Placebo	1	-2.577		-2.213										
Nintedanib	0													
Systemic Sclerosis (SSc)														
Placebo	3	-1.703	1.687	-1.772	1.771									
Nintedanib	4	-4.129	2.540	-4.806	1.774									
Dermatomyositis														
Placebo	0													
Nintedanib	1	-2.918		-3.148										
Mixed Connective Tissue Disease														
Placebo	0													
Nintedanib	0													
Sarcoidosis														
Placebo	0													
Nintedanib	0													
Other Childhood ILD														

[1] Based on the number of patients having available data at baseline and at the respective visit.
[2] Based on Mixed Model for Repeated Measures (MMRM), with fixed categorical effect age-group and the fixed continuous effects of baseline value at each visit, (randomized) treatment-by-visit-by-subgroup interaction, and random effect for patient. [3] Interaction p-value.
Visit is treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
Adjusted mean is based on all analysed patients in the model (i.e. on patients with a baseline and at least one post-baseline measurement - not only on patients with a baseline and measurement at the respective visit).
For derivation of the MMRM available data from all visits up to week 52 is used.

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Table 6.1.4 Adjusted mean (SE) of absolute change from baseline in FVC z-score at week 24 by underlying ILD diagnosis
Treated Set

Subgroup/ Category/ Treatment	N	Baseline Mean	Baseline SD [1]	24 weeks Mean	24 weeks SD [1]	Change from baseline to 24 weeks: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	Comparison vs. Randomised Placebo: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	p-value [3]
Placebo	2	-4.385	0.970	-4.653	1.271									
Nintedanib	5	-2.370	2.072	-2.162	2.161									

[1] Based on the number of patients having available data at baseline and at the respective visit.
[2] Based on Mixed Model for Repeated Measures (MMRM), with fixed categorical effect age-group and the fixed continuous effects of baseline value at each visit, (randomized) treatment-by-visit-by-subgroup interaction, and random effect for patient. [3] Interaction p-value.
Visit is treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
Adjusted mean is based on all analysed patients in the model (i.e. on patients with a baseline and at least one post-baseline measurement - not only on patients with a baseline and measurement at the respective visit).
For derivation of the MMRM available data from all visits up to week 52 is used.

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Anhang 4-G6.2: SpO2

Table 6.3.1 Proportion of patients with increase (>4%) in SpO2 on room air at rest from baseline at week 24 by underlying ILD diagnosis
Treated Set

	Placebo			Nintedanib			Randomised Nintedanib vs. Placebo						
	N	n	%	N	n	%	Risk ratio [1]	95% confidence interval [1] Lower	Upper	p-value [1]	Odds ratio [2]	95% confidence interval [2] Lower	Upper	p-value [1][3]
Underlying ILD diagnosis														
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	2	0	0.0	1	0	0.0								
Chronic Hypersensitivity Pneumonitis (cHP)	0			0										
Toxic/Radiation/Drug Induced Pneumonitis	0			1	0	0.0								
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0			1	0	0.0								
Juvenile Rheumatoid Arthritis (RA)	0			0										
Juvenile Idiopathic Arthritis	0			0										
Systemic Sclerosis (SSc)	0			2	1	50.0								
Dermatomyositis	0			0										
Mixed Connective Tissue Disease	0			0										
Sarcoidosis	0			0										
Other Childhood ILD	0			2	0	0.0								

N represents the number of patients in the Treated Set with an available SpO2 value at baseline <96% and at the respective visit.
n represents the number of patients meeting the response criterion.
[1] Based on a log-linked Poisson model with robust estimate of variance^.
[2] Based on a logistic regression model^ showing Wald confidence intervals.
[3] Interaction p-value from log-linked Poisson model with robust estimate of variance^.
^ All models contain continuous covariate baseline value and categorical covariate age-group. Subgroup and treatment by subgroup interaction term are additionally included for the subgroup analyses.
All model results are based on pooled results following multiple imputation procedure (m=100 imputations) as described in TSAP Section 6.6.2.3.
inf=infinity; NC=not calculabe because of errors/warnings in at least one of the 100 regression models.

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Table 6.3.2 Adjusted mean (SE) of absolute change from baseline in SpO2 on room air at rest at week 24 by underlying ILD diagnosis
Treated Set

Subgroup/ Category/ Treatment	N	Baseline Mean	Baseline SD [1]	24 weeks Mean	24 weeks SD [1]	Change from baseline to 24 weeks: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	Comparison vs. Randomised Placebo: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	p-value [3]
Underlying ILD diagnosis														
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)														
Placebo	5	94.60	5.68	93.80	6.98									
Nintedanib	7	97.14	3.02	97.14	3.13									
Chronic Hypersensitivity Pneumonitis (cHP)														
Placebo	0													
Nintedanib	2	99.50	0.71	98.00	1.41									
Toxic/Radiation/Drug Induced Pneumonitis														
Placebo	1	100.00		99.00										
Nintedanib	3	96.67	3.21	96.33	4.04									
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis														
Placebo	0													
Nintedanib	1	95.00		83.00										
Juvenile Rheumatoid Arthritis (RA)														
Placebo	0													
Nintedanib	1	99.00		99.00										
Juvenile Idiopathic Arthritis														
Placebo	1	98.00		99.00										
Nintedanib	0													
Systemic Sclerosis (SSc)														
Placebo	3	98.67	1.15	98.67	1.53									
Nintedanib	4	94.50	4.80	96.75	3.59									
Dermatomyositis														
Placebo	0													
Nintedanib	1	96.00		99.00										
Mixed Connective Tissue Disease														
Placebo	0													
Nintedanib	0													
Sarcoidosis														
Placebo	0													
Nintedanib	0													
Other Childhood ILD														

[1] Based on the number of patients having available data at baseline and at the respective visit.
[2] Based on Mixed Model for Repeated Measures (MMRM), with fixed categorical effect age-group and the fixed continuous effects of baseline value at each visit, (randomized) treatment-by-visit-by-subgroup interaction, and random effect for patient. [3] Interaction p-value.
Visit is treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
Adjusted mean is based on all analysed patients in the model (i.e. on patients with a baseline and at least one post-baseline measurement - not only on patients with a baseline and measurement at the respective visit).
For derivation of the MMRM available data from all visits up to week 52 is used.

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Table 6.3.2 Adjusted mean (SE) of absolute change from baseline in SpO2 on room air at rest at week 24 by underlying ILD diagnosis
Treated Set

Subgroup/ Category/ Treatment	N	Baseline Mean	Baseline SD [1]	24 weeks Mean	24 weeks SD [1]	Change from baseline to 24 weeks: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	Comparison vs. Randomised Placebo: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	p-value [3]
Placebo	2	98.00	0.00	91.00	8.49									
Nintedanib	5	95.80	1.92	96.20	3.49									

[1] Based on the number of patients having available data at baseline and at the respective visit.
[2] Based on Mixed Model for Repeated Measures (MMRM), with fixed categorical effect age-group and the fixed continuous effects of baseline value at each visit, (randomized) treatment-by-visit-by-subgroup interaction, and random effect for patient. [3] Interaction p-value.
Visit is treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
Adjusted mean is based on all analysed patients in the model (i.e. on patients with a baseline and at least one post-baseline measurement - not only on patients with a baseline and measurement at the respective visit).
For derivation of the MMRM available data from all visits up to week 52 is used.

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Table 6.3.3 Adjusted mean (SE) of absolute change from baseline in SpO2 on room air with exertion at week 24 by underlying ILD diagnosis
Treated Set

Subgroup/ Category/ Treatment	N	Baseline Mean	Baseline SD [1]	24 weeks Mean	24 weeks SD [1]	Change from baseline to 24 weeks: Adjusted mean [2]	SE	95% confidence interval Lower	95% confidence interval Upper	Comparison vs. Randomised Placebo: Adjusted mean [2]	SE	95% confidence interval Lower	95% confidence interval Upper	p-value [3]
Underlying ILD diagnosis														
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)														
Placebo	4	91.00	5.72	88.75	6.65									
Nintedanib	6	85.33	5.24	87.67	7.55									
Chronic Hypersensitivity Pneumonitis (cHP)														
Placebo	0													
Nintedanib	2	85.50	0.71	87.50	4.95									
Toxic/Radiation/Drug Induced Pneumonitis														
Placebo	1	84.00		80.00										
Nintedanib	2	87.50	6.36	95.00	1.41									
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis														
Placebo	0													
Nintedanib	0													
Juvenile Rheumatoid Arthritis (RA)														
Placebo	0													
Nintedanib	1	95.00		95.00										
Juvenile Idiopathic Arthritis														
Placebo	1	96.00		97.00										
Nintedanib	0													
Systemic Sclerosis (SSc)														
Placebo	3	84.00	19.08	96.67	3.51									
Nintedanib	2	92.50	0.71	93.00	5.66									
Dermatomyositis														
Placebo	0													
Nintedanib	1	72.00		85.00										
Mixed Connective Tissue Disease														
Placebo	0													
Nintedanib	0													
Sarcoidosis														
Placebo	0													
Nintedanib	0													
Other Childhood ILD														

[1] Based on the number of patients having available data at baseline and at the respective visit.
[2] Based on Mixed Model for Repeated Measures (MMRM), with fixed categorical effect age-group and the fixed continuous effects of baseline value at each visit, (randomized) treatment-by-visit-by-subgroup interaction, and random effect for patient. [3] Interaction p-value.
Visit is treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
Adjusted mean is based on all analysed patients in the model (i.e. on patients with a baseline and at least one post-baseline measurement - not only on patients with a baseline and measurement at the respective visit).
For derivation of the MMRM available data from all visits up to week 52 is used.

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Table 6.3.3 Adjusted mean (SE) of absolute change from baseline in SpO2 on room air with exertion at week 24 by underlying ILD diagnosis
Treated Set

Subgroup/ Category/ Treatment	N	Baseline [1] Mean	Baseline [1] SD	24 weeks [1] Mean	24 weeks [1] SD	Change from baseline to 24 weeks: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	Comparison vs. Randomised Placebo: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	p-value [3]
Placebo	1	89.00		85.00										
Nintedanib	4	91.25	3.30	92.75	3.40									

[1] Based on the number of patients having available data at baseline and at the respective visit.
[2] Based on Mixed Model for Repeated Measures (MMRM), with fixed categorical effect age-group and the fixed continuous effects of baseline value at each visit, (randomized) treatment-by-visit-by-subgroup interaction, and random effect for patient. [3] Interaction p-value.
Visit is treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
Adjusted mean is based on all analysed patients in the model (i.e. on patients with a baseline and at least one post-baseline measurement - not only on patients with a baseline and measurement at the respective visit).
For derivation of the MMRM available data from all visits up to week 52 is used.

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Anhang 4-G6.3: 6-MWT

Table 6.4.1 Adjusted mean (SE) of absolute change from baseline in 6-min walk distance at week 24 by underlying ILD diagnosis
Treated Set

Subgroup/ Category/ Treatment	N	Baseline [1] Mean	Baseline [1] SD	24 weeks [1] Mean	24 weeks [1] SD	Change from baseline to 24 weeks: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	Comparison vs. Randomised Placebo: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	p-value [3]
Underlying ILD diagnosis														
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)														
Placebo	5	374.8	167.7	383.1	175.4									
Nintedanib	6	404.7	182.8	429.7	147.8									
Chronic Hypersensitivity Pneumonitis (cHP)														
Placebo	0													
Nintedanib	2	567.5	31.8	441.0	25.5									
Toxic/Radiation/Drug Induced Pneumonitis														
Placebo	1	513.0		521.0										
Nintedanib	2	446.5	105.4	517.5	116.7									
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis														
Placebo	0													
Nintedanib	1	270.0		270.0										
Juvenile Rheumatoid Arthritis (RA)														
Placebo	0													
Nintedanib	1	357.0		444.0										
Juvenile Idiopathic Arthritis														
Placebo	1	213.4		234.7										
Nintedanib	0													
Systemic Sclerosis (SSc)														
Placebo	3	434.8	57.7	467.5	105.1									
Nintedanib	3	323.3	76.4	356.0	77.4									
Dermatomyositis														
Placebo	0													
Nintedanib	1	555.0		477.0										
Mixed Connective Tissue Disease														
Placebo	0													
Nintedanib	0													
Sarcoidosis														
Placebo	0													
Nintedanib	0													
Other Childhood ILD														

[1] Based on the number of patients having available data at baseline and at the respective visit.
[2] Based on Mixed Model for Repeated Measures (MMRM), with fixed categorical effect age-group and the fixed continuous effects of baseline value at each visit, (randomized) treatment-by-visit-by-subgroup interaction, and random effect for patient. [3] Interaction p-value.
Visit is treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
Adjusted mean is based on all analysed patients in the model (i.e. on patients with a baseline and at least one post-baseline measurement - not only on patients with a baseline and measurement at the respective visit).
For derivation of the MMRM available data from all visits up to week 52 is used.

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Table 6.4.1 Adjusted mean (SE) of absolute change from baseline in 6-min walk distance at week 24 by underlying ILD diagnosis
Treated Set

Subgroup/ Category/ Treatment	N	Baseline [1] Mean	Baseline [1] SD	24 weeks [1] Mean	24 weeks [1] SD	Change from baseline to 24 weeks: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	Comparison vs. Randomised Placebo: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	p-value [3]
Placebo	1	329.8		301.8										
Nintedanib	5	351.9	79.3	397.1	117.4									

[1] Based on the number of patients having available data at baseline and at the respective visit.
[2] Based on Mixed Model for Repeated Measures (MMRM), with fixed categorical effect age-group and the fixed continuous effects of baseline value at each visit, (randomized) treatment-by-visit-by-subgroup interaction, and random effect for patient. [3] Interaction p-value.
Visit is treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
Adjusted mean is based on all analysed patients in the model (i.e. on patients with a baseline and at least one post-baseline measurement - not only on patients with a baseline and measurement at the respective visit).
For derivation of the MMRM available data from all visits up to week 52 is used.

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Anhang 4-G6.4: PedsQL™

Table 6.2.1 Proportion of patients with increase in PedsQL (parent report) total score (>=4.4 points) from baseline at week 24 by underlying ILD diagnosis - Treated Set

	Placebo			Nintedanib			Randomised Nintedanib vs. Placebo						
							Risk ratio [1]	95% confidence interval [1]		p-value [1]	Odds ratio [2]	95% confidence interval [2]		p-value [1][3]
	N	n	%	N	n	%		Lower	Upper			Lower	Upper	
Underlying ILD diagnosis														
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	4	80.0	6	1	16.7								
Chronic Hypersensitivity Pneumonitis (cHP)	0			2	0	0.0								
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	2	2	100.0								
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0			1	0	0.0								
Juvenile Rheumatoid Arthritis (RA)	0			1	0	0.0								
Juvenile Idiopathic Arthritis	1	0	0.0	0										
Systemic Sclerosis (SSc)	3	1	33.3	3	3	100.0								
Dermatomyositis	0			1	1	100.0								
Mixed Connective Tissue Disease	0			0										
Sarcoidosis	0			0										
Other Childhood ILD	1	1	100.0	5	3	60.0								

N represents the number of patients in the Treated Set with an available PedsQL total score at baseline and at the respective visit.
n represents the number of patients meeting the response criterion.
[1] Based on a log-linked Poisson model with robust estimate of variance^.
[2] Based on a logistic regression model^ showing Wald confidence intervals.
[3] Interaction p-value from log-linked Poisson model with robust estimate of variance^.
^ All models contain continuous covariate baseline value and categorical covariate age-group. Subgroup and treatment by subgroup interaction term are additionally included for the subgroup analyses.
All model results are based on pooled results following multiple imputation procedure (m=100 imputations) as described in TSAP Section 6.6.2.3.
inf=infinity; NC=not calculabe because of errors/warnings in at least one of the 100 regression models.

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Table 6.2.2 Proportion of patients with increase in PedsQL (parent report) total score (>=15 points) from baseline at week 24 by underlying ILD diagnosis - Treated Set

	Placebo			Nintedanib			Randomised Nintedanib vs. Placebo						
							Risk ratio [1]	95% confidence interval [1]		p-value [1]	Odds ratio [2]	95% confidence interval [2]		p-value [1][3]
	N	n	%	N	n	%		Lower	Upper			Lower	Upper	
Underlying ILD diagnosis														
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	0	0.0	6	1	16.7								
Chronic Hypersensitivity Pneumonitis (cHP)	0			2	0	0.0								
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	2	1	50.0								
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0			1	0	0.0								
Juvenile Rheumatoid Arthritis (RA)	0			1	0	0.0								
Juvenile Idiopathic Arthritis	1	0	0.0	0										
Systemic Sclerosis (SSc)	3	0	0.0	3	2	66.7								
Dermatomyositis	0			1	0	0.0								
Mixed Connective Tissue Disease	0			0										
Sarcoidosis	0			0										
Other Childhood ILD	1	0	0.0	5	1	20.0								

N represents the number of patients in the Treated Set with an available PedsQL total score at baseline and at the respective visit.
n represents the number of patients meeting the response criterion.
[1] Based on a log-linked Poisson model with robust estimate of variance^.
[2] Based on a logistic regression model^ showing Wald confidence intervals.
[3] Interaction p-value from log-linked Poisson model with robust estimate of variance^.
^ All models contain continuous covariate baseline value and categorical covariate age-group. Subgroup and treatment by subgroup interaction term are additionally included for the subgroup analyses.
All model results are based on pooled results following multiple imputation procedure (m=100 imputations) as described in TSAP Section 6.6.2.3.
inf=infinity; NC=not calculabe because of errors/warnings in at least one of the 100 regression models.

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Table 6.2.3 Proportion of patients with decrease in PedsQL (parent report) total score (>=4.4 points) from baseline at week 24 by underlying ILD diagnosis - Treated Set

	Placebo			Nintedanib			Randomised Nintedanib vs. Placebo							
	N	n	%	N	n	%	Risk ratio [1]	95% confidence interval [1] Lower	Upper	p-value [1]	Odds ratio [2]	95% confidence interval [2] Lower	Upper	p-value [1][3]
Underlying ILD diagnosis														
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	0	0.0	6	2	33.3								
Chronic Hypersensitivity Pneumonitis (cHP)	0			2	1	50.0								
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	2	0	0.0								
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0			1	0	0.0								
Juvenile Rheumatoid Arthritis (RA)	0			1	0	0.0								
Juvenile Idiopathic Arthritis	1	1	100.0	0										
Systemic Sclerosis (SSc)	3	0	0.0	3	0	0.0								
Dermatomyositis	0			1	0	0.0								
Mixed Connective Tissue Disease	0			0										
Sarcoidosis	0			0										
Other Childhood ILD	1	0	0.0	5	1	20.0								

N represents the number of patients in the Treated Set with an available PedsQL total score at baseline and at the respective visit.
n represents the number of patients meeting the response criterion.
[1] Based on a log-linked Poisson model with robust estimate of variance^.
[2] Based on a logistic regression model^ showing Wald confidence intervals.
[3] Interaction p-value from log-linked Poisson model with robust estimate of variance^.
^ All models contain continuous covariate baseline value and categorical covariate age-group. Subgroup and treatment by subgroup interaction term are additionally included for the subgroup analyses.
All model results are based on pooled results following multiple imputation procedure (m=100 imputations) as described in TSAP Section 6.6.2.3.
inf=infinity; NC=not calculabe because of errors/warnings in at least one of the 100 regression models.

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Table 6.2.4 Proportion of patients with decrease in PedsQL (parent report) total score (>=15 points) from baseline at week 24 by underlying ILD diagnosis - Treated Set

	Placebo			Nintedanib			Randomised Nintedanib vs. Placebo						
	N	n	%	N	n	%	Risk ratio [1]	95% confidence interval [1] Lower	Upper	p-value [1]	Odds ratio [2]	95% confidence interval [2] Lower	Upper	p-value [1][3]
Underlying ILD diagnosis														
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	0	0.0	6	2	33.3								
Chronic Hypersensitivity Pneumonitis (cHP)	0			2	0	0.0								
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	2	0	0.0								
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0			1	0	0.0								
Juvenile Rheumatoid Arthritis (RA)	0			1	0	0.0								
Juvenile Idiopathic Arthritis	1	0	0.0	0										
Systemic Sclerosis (SSc)	3	0	0.0	3	0	0.0								
Dermatomyositis	0			1	0	0.0								
Mixed Connective Tissue Disease	0			0										
Sarcoidosis	0			0										
Other Childhood ILD	1	0	0.0	5	0	0.0								

N represents the number of patients in the Treated Set with an available PedsQL total score at baseline and at the respective visit.
n represents the number of patients meeting the response criterion.
[1] Based on a log-linked Poisson model with robust estimate of variance^.
[2] Based on a logistic regression model^ showing Wald confidence intervals.
[3] Interaction p-value from log-linked Poisson model with robust estimate of variance^.
^ All models contain continuous covariate baseline value and categorical covariate age-group. Subgroup and treatment by subgroup interaction term are additionally included for the subgroup analyses.
All model results are based on pooled results following multiple imputation procedure (m=100 imputations) as described in TSAP Section 6.6.2.3.
inf=infinity; NC=not calculabe because of errors/warnings in at least one of the 100 regression models.

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Table 6.2.5 Proportion of patients with increase in PedsQL (patient report) total score (>=4.4 points) from baseline at week 24 by underlying ILD diagnosis - Treated Set

	Placebo			Nintedanib			Randomised Nintedanib vs. Placebo							
							Risk ratio [1]	95% confidence interval [1]		p-value [1]	Odds ratio [2]	95% confidence interval [2]		p-value [1][3]
	N	n	%	N	n	%		Lower	Upper			Lower	Upper	
Underlying ILD diagnosis														
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	4	80.0	6	2	33.3								
Chronic Hypersensitivity Pneumonitis (cHP)	0			2	0	0.0								
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	2	1	50.0								
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0			1	0	0.0								
Juvenile Rheumatoid Arthritis (RA)	0			1	1	100.0								
Juvenile Idiopathic Arthritis	1	1	100.0	0										
Systemic Sclerosis (SSc)	3	2	66.7	3	3	100.0								
Dermatomyositis	0			1	1	100.0								
Mixed Connective Tissue Disease	0			0										
Sarcoidosis	0			0										
Other Childhood ILD	1	1	100.0	5	3	60.0								

N represents the number of patients in the Treated Set with an available PedsQL total score at baseline and at the respective visit.
n represents the number of patients meeting the response criterion.
[1] Based on a log-linked Poisson model with robust estimate of variance^.
[2] Based on a logistic regression model^ showing Wald confidence intervals.
[3] Interaction p-value from log-linked Poisson model with robust estimate of variance^.
^ All models contain continuous covariate baseline value and categorical covariate age-group. Subgroup and treatment by subgroup interaction term are additionally included for the subgroup analyses.
All model results are based on pooled results following multiple imputation procedure (m=100 imputations) as described in TSAP Section 6.6.2.3.
inf=infinity; NC=not calculabe because of errors/warnings in at least one of the 100 regression models.

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Table 6.2.6 Proportion of patients with increasee in PedsQL (patient report) total score (>=15 points) from baseline at week 24 by underlying ILD diagnosis - Treated Set

	Placebo			Nintedanib			Randomised Nintedanib vs. Placebo							
	N	n	%	N	n	%	Risk ratio [1]	95% confidence interval [1] Lower	Upper	p-value [1]	Odds ratio [2]	95% confidence interval [2] Lower	Upper	p-value [1][3]
Underlying ILD diagnosis														
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	1	20.0	6	1	16.7								
Chronic Hypersensitivity Pneumonitis (cHP)	0			2	0	0.0								
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	2	0	0.0								
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0			1	0	0.0								
Juvenile Rheumatoid Arthritis (RA)	0			1	0	0.0								
Juvenile Idiopathic Arthritis	1	0	0.0	0										
Systemic Sclerosis (SSc)	3	0	0.0	3	1	33.3								
Dermatomyositis	0			1	0	0.0								
Mixed Connective Tissue Disease	0			0										
Sarcoidosis	0			0										
Other Childhood ILD	1	0	0.0	5	2	40.0								

N represents the number of patients in the Treated Set with an available PedsQL total score at baseline and at the respective visit.
n represents the number of patients meeting the response criterion.
[1] Based on a log-linked Poisson model with robust estimate of variance^.
[2] Based on a logistic regression model^ showing Wald confidence intervals.
[3] Interaction p-value from log-linked Poisson model with robust estimate of variance^.
^ All models contain continuous covariate baseline value and categorical covariate age-group. Subgroup and treatment by subgroup interaction term are additionally included for the subgroup analyses.
All model results are based on pooled results following multiple imputation procedure (m=100 imputations) as described in TSAP Section 6.6.2.3.
inf=infinity; NC=not calculabe because of errors/warnings in at least one of the 100 regression models.

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Table 6.2.7 Proportion of patients with decrease in PedsQL (patient report) total score (>=4.4 points) from baseline at week 24 by underlying ILD diagnosis - Treated Set

	Placebo			Nintedanib			Randomised Nintedanib vs. Placebo							
	N	n	%	N	n	%	Risk ratio [1]	95% confidence interval [1] Lower	Upper	p-value [1]	Odds ratio [2]	95% confidence interval [2] Lower	Upper	p-value [1][3]
Underlying ILD diagnosis														
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	1	20.0	6	1	16.7								
Chronic Hypersensitivity Pneumonitis (cHP)	0			2	1	50.0								
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	2	0	0.0								
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0			1	0	0.0								
Juvenile Rheumatoid Arthritis (RA)	0			1	0	0.0								
Juvenile Idiopathic Arthritis	1	0	0.0	0										
Systemic Sclerosis (SSc)	3	1	33.3	3	0	0.0								
Dermatomyositis	0			1	0	0.0								
Mixed Connective Tissue Disease	0			0										
Sarcoidosis	0			0										
Other Childhood ILD	1	0	0.0	5	0	0.0								

N represents the number of patients in the Treated Set with an available PedsQL total score at baseline and at the respective visit.
n represents the number of patients meeting the response criterion.
[1] Based on a log-linked Poisson model with robust estimate of variance^.
[2] Based on a logistic regression model^ showing Wald confidence intervals.
[3] Interaction p-value from log-linked Poisson model with robust estimate of variance^.
^ All models contain continuous covariate baseline value and categorical covariate age-group. Subgroup and treatment by subgroup interaction term are additionally included for the subgroup analyses.
All model results are based on pooled results following multiple imputation procedure (m=100 imputations) as described in TSAP Section 6.6.2.3.
inf=infinity; NC=not calculabe because of errors/warnings in at least one of the 100 regression models.

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Table 6.2.8 Proportion of patients with decrease in PedsQL (patient report) total score (>=15 points) from baseline at week 24 by underlying ILD diagnosis - Treated Set

	Placebo			Nintedanib			Randomised Nintedanib vs. Placebo							
	N	n	%	N	n	%	Risk ratio [1]	95% confidence interval [1] Lower	Upper	p-value [1]	Odds ratio [2]	95% confidence interval [2] Lower	Upper	p-value [1][3]
Underlying ILD diagnosis														
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	1	20.0	6	0	0.0								
Chronic Hypersensitivity Pneumonitis (cHP)	0			2	0	0.0								
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	2	0	0.0								
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0			1	0	0.0								
Juvenile Rheumatoid Arthritis (RA)	0			1	0	0.0								
Juvenile Idiopathic Arthritis	1	0	0.0	0										
Systemic Sclerosis (SSc)	3	0	0.0	3	0	0.0								
Dermatomyositis	0			1	0	0.0								
Mixed Connective Tissue Disease	0			0										
Sarcoidosis	0			0										
Other Childhood ILD	1	0	0.0	5	0	0.0								

N represents the number of patients in the Treated Set with an available PedsQL total score at baseline and at the respective visit.
n represents the number of patients meeting the response criterion.
[1] Based on a log-linked Poisson model with robust estimate of variance^.
[2] Based on a logistic regression model^ showing Wald confidence intervals.
[3] Interaction p-value from log-linked Poisson model with robust estimate of variance^.
^ All models contain continuous covariate baseline value and categorical covariate age-group. Subgroup and treatment by subgroup interaction term are additionally included for the subgroup analyses.
All model results are based on pooled results following multiple imputation procedure (m=100 imputations) as described in TSAP Section 6.6.2.3.
inf=infinity; NC=not calculabe because of errors/warnings in at least one of the 100 regression models.

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Table 6.2.9 Adjusted mean (SE) of absolute change from baseline in PedsQL (parent report) at week 24 by underlying ILD diagnosis
Treated Set

Subgroup/ Category/ Treatment	N	Baseline [1] Mean	Baseline [1] SD	24 weeks [1] Mean	24 weeks [1] SD	Change from baseline to 24 weeks: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	Comparison vs. Randomised Placebo: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	p-value [3]
Underlying ILD diagnosis														
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)														
Placebo	5	57.391	18.974	64.565	16.206									
Nintedanib	6	63.768	21.241	62.681	16.393									
Chronic Hypersensitivity Pneumonitis (cHP)														
Placebo	0													
Nintedanib	2	58.152	2.306	54.348	1.537									
Toxic/Radiation/Drug Induced Pneumonitis														
Placebo	1	91.304		89.130										
Nintedanib	2	59.239	6.917	72.826	0.000									
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis														
Placebo	0													
Nintedanib	1	60.870		65.217										
Juvenile Rheumatoid Arthritis (RA)														
Placebo	0													
Nintedanib	1	47.826		50.000										
Juvenile Idiopathic Arthritis														
Placebo	1	55.435		48.913										
Nintedanib	0													
Systemic Sclerosis (SSc)														
Placebo	3	86.594	8.302	90.217	12.249									
Nintedanib	3	50.725	4.901	67.029	10.668									
Dermatomyositis														
Placebo	0													
Nintedanib	1	85.870		93.478										
Mixed Connective Tissue Disease														
Placebo	0													
Nintedanib	0													
Sarcoidosis														
Placebo	0													
Nintedanib	0													
Other Childhood ILD														

[1] Based on the number of patients having available data at baseline and at the respective visit.
[2] Based on Mixed Model for Repeated Measures (MMRM), with fixed categorical effect age-group and the fixed continuous effects of baseline value at each visit, (randomized) treatment-by-visit-by-subgroup interaction, and random effect for patient. [3] Interaction p-value.
Visit is treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
Adjusted mean is based on all analysed patients in the model (i.e. on patients with a baseline and at least one post-baseline measurement - not only on patients with a baseline and measurement at the respective visit).
For derivation of the MMRM available data from all visits up to week 52 is used.

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Table 6.2.9 Adjusted mean (SE) of absolute change from baseline in PedsQL (parent report) at week 24 by underlying ILD diagnosis
Treated Set

Subgroup/ Category/ Treatment	N	Baseline [1] Mean	Baseline [1] SD	24 weeks [1] Mean	24 weeks [1] SD	Change from baseline to 24 weeks: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	Comparison vs. Randomised Placebo: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	p-value [3]
Placebo	1	53.261		59.783										
Nintedanib	5	59.348	21.584	70.000	21.446									

[1] Based on the number of patients having available data at baseline and at the respective visit.
[2] Based on Mixed Model for Repeated Measures (MMRM), with fixed categorical effect age-group and the fixed continuous effects of baseline value at each visit, (randomized) treatment-by-visit-by-subgroup interaction, and random effect for patient. [3] Interaction p-value.
Visit is treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
Adjusted mean is based on all analysed patients in the model (i.e. on patients with a baseline and at least one post-baseline measurement - not only on patients with a baseline and measurement at the respective visit).
For derivation of the MMRM available data from all visits up to week 52 is used.

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Table 6.2.10 Adjusted mean (SE) of absolute change from baseline in PedsQL (patient report) at week 24 by underlying ILD diagnosis
Treated Set

Subgroup/ Category/ Treatment	N	Baseline [1] Mean	Baseline [1] SD	24 weeks [1] Mean	24 weeks [1] SD	Change from baseline to 24 weeks: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	Comparison vs. Randomised Placebo: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	p-value [3]
Underlying ILD diagnosis														
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)														
Placebo	5	70.217	11.672	74.348	14.391									
Nintedanib	6	72.645	17.559	77.141	15.447									
Chronic Hypersensitivity Pneumonitis (cHP)														
Placebo	0													
Nintedanib	2	52.717	16.140	50.543	6.917									
Toxic/Radiation/Drug Induced Pneumonitis														
Placebo	1	68.478		72.826										
Nintedanib	2	76.087	1.537	80.435	6.149									
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis														
Placebo	0													
Nintedanib	1	64.130		63.043										
Juvenile Rheumatoid Arthritis (RA)														
Placebo	0													
Nintedanib	1	54.348		59.783										
Juvenile Idiopathic Arthritis														
Placebo	1	54.348		63.043										
Nintedanib	0													
Systemic Sclerosis (SSc)														
Placebo	3	85.870	9.476	90.580	6.641									
Nintedanib	3	61.957	7.531	74.638	13.283									
Dermatomyositis														
Placebo	0													
Nintedanib	1	81.522		93.478										
Mixed Connective Tissue Disease														
Placebo	0													
Nintedanib	0													
Sarcoidosis														
Placebo	0													
Nintedanib	0													
Other Childhood ILD														

[1] Based on the number of patients having available data at baseline and at the respective visit.
[2] Based on Mixed Model for Repeated Measures (MMRM), with fixed categorical effect age-group and the fixed continuous effects of baseline value at each visit, (randomized) treatment-by-visit-by-subgroup interaction, and random effect for patient. [3] Interaction p-value.
Visit is treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
Adjusted mean is based on all analysed patients in the model (i.e. on patients with a baseline and at least one post-baseline measurement - not only on patients with a baseline and measurement at the respective visit).
For derivation of the MMRM available data from all visits up to week 52 is used.

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Table 6.2.10 Adjusted mean (SE) of absolute change from baseline in PedsQL (patient report) at week 24 by underlying ILD diagnosis
Treated Set

Subgroup/ Category/ Treatment	N	Baseline [1] Mean	Baseline [1] SD	24 weeks [1] Mean	24 weeks [1] SD	Change from baseline to 24 weeks: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	Comparison vs. Randomised Placebo: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	p-value [3]
Placebo	1	79.348		84.783										
Nintedanib	5	70.652	13.792	82.174	9.274									

[1] Based on the number of patients having available data at baseline and at the respective visit.
[2] Based on Mixed Model for Repeated Measures (MMRM), with fixed categorical effect age-group and the fixed continuous effects of baseline value at each visit, (randomized) treatment-by-visit-by-subgroup interaction, and random effect for patient. [3] Interaction p-value.
Visit is treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
Adjusted mean is based on all analysed patients in the model (i.e. on patients with a baseline and at least one post-baseline measurement - not only on patients with a baseline and measurement at the respective visit).
For derivation of the MMRM available data from all visits up to week 52 is used.

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Anhang 4-G7: Weitere Ergebnisse zu Unerwünschten Ereignissen nach zugrundeliegender ILD Diagnose

Anhang 4-G7.1: UE

Table 7.1.1 Proportion of patients with any adverse event during double-blind period by underlying ILD diagnosis
Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	4	80.0	7	5	71.4					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	2	100.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	1	100.0	3	3	100.0					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	1	100.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	1	100.0					
Juvenile Idiopathic Arthritis	1	1	100.0	0	0	na					
Systemic Sclerosis (SSc)	3	3	100.0	4	3	75.0					
Dermatomyositis	0	0	na	1	1	100.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	2	66.7	7	6	85.7					

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Table 7.1.1 Proportion of patients with any adverse event during double-blind period by underlying ILD diagnosis
Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Anhang 4-G7.2: SUE

Table 7.2.1 Proportion of patients with any serious adverse event during double-blind period by underlying ILD diagnosis
Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	0	0.0	7	0	0.0					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	0	0.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	1	33.3					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	0	0.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	0	0.0					
Juvenile Idiopathic Arthritis	1	0	0.0	0	0	na					
Systemic Sclerosis (SSc)	3	1	33.3	4	0	0.0					
Dermatomyositis	0	0	na	1	0	0.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	0	0.0	7	1	14.3					

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Table 7.2.1 Proportion of patients with any serious adverse event during double-blind period by underlying ILD diagnosis
Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Anhang 4-G7.3: UE, die zum Therapieabbruch führten

Table 7.3.1 Proportion of patients with any adverse event leading to treatment discontinuation during double-blind period by underlying ILD diagnosis - Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	0	0.0	7	1	14.3					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	1	50.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	0	0.0					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	0	0.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	0	0.0					
Juvenile Idiopathic Arthritis	1	0	0.0	0	0	na					
Systemic Sclerosis (SSc)	3	0	0.0	4	0	0.0					
Dermatomyositis	0	0	na	1	0	0.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	0	0.0	7	0	0.0					

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Treatment discontinuations are premature and permanent.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Table 7.3.1 Proportion of patients with any adverse event leading to treatment discontinuation during double-blind period by underlying ILD diagnosis - Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Treatment discontinuations are premature and permanent.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Anhang 4-G7.4: Diarrhö differenziert nach Schweregrad (CTCAE, Grad 1, Grad 2 und ≥ Grad 3)

Table 7.4.1 Proportion of patients with any diarrhoea CTCAE-Grade 1 adverse event during double-blind period by underlying ILD diagnosis
Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	0	0.0	7	1	14.3					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	0	0.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	0	0.0					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	1	100.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	0	0.0					
Juvenile Idiopathic Arthritis	1	0	0.0	0	0	na					
Systemic Sclerosis (SSc)	3	1	33.3	4	2	50.0					
Dermatomyositis	0	0	na	1	0	0.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	0	0.0	7	2	28.6					

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
Each patient is considered only once with the worst grade for the analysis of patients with Diarrhoea by CTCAE-Grade.
inf=infinity

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Table 7.4.1 Proportion of patients with any diarrhoea CTCAE-Grade 1 adverse event during double-blind period by underlying ILD diagnosis
Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
Each patient is considered only once with the worst grade for the analysis of patients with Diarrhoea by CTCAE-Grade.
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Table 7.4.2 Proportion of patients with any diarrhoea CTCAE-Grade 2 adverse event during double-blind period by underlying ILD diagnosis
Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	0	0.0	7	2	28.6					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	0	0.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	0	0.0					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	0	0.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	0	0.0					
Juvenile Idiopathic Arthritis	1	0	0.0	0	0	na					
Systemic Sclerosis (SSc)	3	0	0.0	4	0	0.0					
Dermatomyositis	0	0	na	1	0	0.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	1	33.3	7	1	14.3					

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
Each patient is considered only once with the worst grade for the analysis of patients with Diarrhoea by CTCAE-Grade.
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Table 7.4.2 Proportion of patients with any diarrhoea CTCAE-Grade 2 adverse event during double-blind period by underlying ILD diagnosis
Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
Each patient is considered only once with the worst grade for the analysis of patients with Diarrhoea by CTCAE-Grade.
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Table 7.4.3 Proportion of patients with any diarrhoea CTCAE-Grade >=3 adverse event during double-blind period by underlying ILD diagnosis
Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	0	0.0	7	0	0.0					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	0	0.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	0	0.0					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	0	0.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	0	0.0					
Juvenile Idiopathic Arthritis	1	0	0.0	0	0	na					
Systemic Sclerosis (SSc)	3	0	0.0	4	0	0.0					
Dermatomyositis	0	0	na	1	0	0.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	0	0.0	7	0	0.0					

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
Each patient is considered only once with the worst grade for the analysis of patients with Diarrhoea by CTCAE-Grade.
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Table 7.4.3 Proportion of patients with any diarrhoea CTCAE-Grade >=3 adverse event during double-blind period by underlying ILD diagnosis
Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
Each patient is considered only once with the worst grade for the analysis of patients with Diarrhoea by CTCAE-Grade.
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Anhang 4-G7.5: UE, SUE und Diarrhö differenziert nach Schweregrad unter Ausschluss erkrankungsbezogenen Ereignissen

Table 7.5.1 Proportion of patients with any adverse event excluding disease-related events during double-blind period by underlying ILD diagnosis
Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	4	80.0	7	5	71.4					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	2	100.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	1	100.0	3	3	100.0					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	1	100.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	1	100.0					
Juvenile Idiopathic Arthritis	1	1	100.0	0	0	na					
Systemic Sclerosis (SSc)	3	3	100.0	4	3	75.0					
Dermatomyositis	0	0	na	1	1	100.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	2	66.7	7	6	85.7					

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 7.5.1 Proportion of patients with any adverse event excluding disease-related events during double-blind period by underlying ILD diagnosis
Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
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Table 7.5.2 Proportion of patients with any serious adverse event excluding disease-related events during double-blind period by underlying ILD diagnosis - Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	0	0.0	7	0	0.0					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	0	0.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	0	0.0					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	0	0.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	0	0.0					
Juvenile Idiopathic Arthritis	1	0	0.0	0	0	na					
Systemic Sclerosis (SSc)	3	1	33.3	4	0	0.0					
Dermatomyositis	0	0	na	1	0	0.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	0	0.0	7	1	14.3					

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Table 7.5.2 Proportion of patients with any serious adverse event excluding disease-related events during double-blind period by underlying ILD diagnosis - Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Table 7.5.3 Proportion of patients with any diarrhoea CTCAE-Grade 1 adverse event excluding disease-related events during double-blind period by underlying ILD diagnosis - Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	0	0.0	7	1	14.3					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	0	0.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	0	0.0					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	1	100.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	0	0.0					
Juvenile Idiopathic Arthritis	1	0	0.0	0	0	na					
Systemic Sclerosis (SSc)	3	1	33.3	4	2	50.0					
Dermatomyositis	0	0	na	1	0	0.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	0	0.0	7	2	28.6					

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
Each patient is considered only once with the worst grade for the analysis of patients with Diarrhoea by CTCAE-Grade.
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Table 7.5.3 Proportion of patients with any diarrhoea CTCAE-Grade 1 adverse event excluding disease-related events during double-blind period by underlying ILD diagnosis - Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
Each patient is considered only once with the worst grade for the analysis of patients with Diarrhoea by CTCAE-Grade.
inf=infinity

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Table 7.5.4 Proportion of patients with any diarrhoea CTCAE-Grade 2 adverse event excluding disease-related events during double-blind period by underlying ILD diagnosis - Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff. (95% CI)	Odds ratio (95% CI)
Underlying ILD diagnosis									
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	0	0.0	7	2	28.6			
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	0	0.0			
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	0	0.0			
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	0	0.0			
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	0	0.0			
Juvenile Idiopathic Arthritis	1	0	0.0	0	0	na			
Systemic Sclerosis (SSc)	3	0	0.0	4	0	0.0			
Dermatomyositis	0	0	na	1	0	0.0			
Mixed Connective Tissue Disease	0	0	na	0	0	na			
Sarcoidosis	0	0	na	0	0	na			
Other Childhood ILD	3	1	33.3	7	1	14.3			

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
Each patient is considered only once with the worst grade for the analysis of patients with Diarrhoea by CTCAE-Grade.
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Table 7.5.4 Proportion of patients with any diarrhoea CTCAE-Grade 2 adverse event excluding disease-related events during double-blind period by underlying ILD diagnosis - Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
Each patient is considered only once with the worst grade for the analysis of patients with Diarrhoea by CTCAE-Grade.
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Table 7.5.5 Proportion of patients with any diarrhoea CTCAE-Grade >=3 adverse event excluding disease-related events during double-blind period by underlying ILD diagnosis - Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff. (95% CI)	Odds ratio (95% CI)
Underlying ILD diagnosis									
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	0	0.0	7	0	0.0			
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	0	0.0			
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	0	0.0			
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	0	0.0			
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	0	0.0			
Juvenile Idiopathic Arthritis	1	0	0.0	0	0	na			
Systemic Sclerosis (SSc)	3	0	0.0	4	0	0.0			
Dermatomyositis	0	0	na	1	0	0.0			
Mixed Connective Tissue Disease	0	0	na	0	0	na			
Sarcoidosis	0	0	na	0	0	na			
Other Childhood ILD	3	0	0.0	7	0	0.0			

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
Each patient is considered only once with the worst grade for the analysis of patients with Diarrhoea by CTCAE-Grade.
inf=infinity

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Table 7.5.5 Proportion of patients with any diarrhoea CTCAE-Grade >=3 adverse event excluding disease-related events during double-blind period by underlying ILD diagnosis - Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
Each patient is considered only once with the worst grade for the analysis of patients with Diarrhoea by CTCAE-Grade.
inf=infinity

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Anhang 4-G7.6: Safety Topics

Table 7.6.1 Proportion of patients with any adverse event by safety topic during double-blind period by underlying ILD diagnosis
Treated Set
Safety topic: Abdominal pain (MedDRA HLT)

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk (95% CI)	Odds ratio	Odds (95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	1	20.0	7	1	14.3					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	0	0.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	2	66.7					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	0	0.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	0	0.0					
Juvenile Idiopathic Arthritis	1	0	0.0	0	0	na					
Systemic Sclerosis (SSc)	3	3	100.0	4	1	25.0					
Dermatomyositis	0	0	na	1	0	0.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	0	0.0	7	2	28.6					

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.6.1 Proportion of patients with any adverse event by safety topic during double-blind period by underlying ILD diagnosis
Treated Set
Safety topic: Abdominal pain (MedDRA HLT)

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.6.1 Proportion of patients with any adverse event by safety topic during double-blind period by underlying ILD diagnosis
Treated Set
Safety topic: Bleeding

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk (95% CI)	Odds ratio	Odds (95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	1	20.0	7	0	0.0					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	0	0.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	0	0.0					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	0	0.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	1	100.0					
Juvenile Idiopathic Arthritis	1	0	0.0	0	0	na					
Systemic Sclerosis (SSc)	3	1	33.3	4	0	0.0					
Dermatomyositis	0	0	na	1	0	0.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	0	0.0	7	0	0.0					

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.6.1 Proportion of patients with any adverse event by safety topic during double-blind period by underlying ILD diagnosis
Treated Set
Safety topic: Bleeding

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.6.1 Proportion of patients with any adverse event by safety topic during double-blind period by underlying ILD diagnosis
Treated Set
Safety topic: Decreased appetite (Single MedDRA PT)

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	0	0.0	7	0	0.0					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	0	0.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	1	33.3					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	0	0.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	0	0.0					
Juvenile Idiopathic Arthritis	1	0	0.0	0	0	na					
Systemic Sclerosis (SSc)	3	0	0.0	4	0	0.0					
Dermatomyositis	0	0	na	1	0	0.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	0	0.0	7	0	0.0					

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.6.1 Proportion of patients with any adverse event by safety topic during double-blind period by underlying ILD diagnosis
Treated Set
Safety topic: Decreased appetite (Single MedDRA PT)

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.6.1 Proportion of patients with any adverse event by safety topic during double-blind period by underlying ILD diagnosis
Treated Set
Safety topic: Dental disorders (Group of MedDRA PTs)

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	4	80.0	7	3	42.9					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	2	100.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	1	33.3					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	0	0.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	0	0.0					
Juvenile Idiopathic Arthritis	1	1	100.0	0	0	na					
Systemic Sclerosis (SSc)	3	1	33.3	4	0	0.0					
Dermatomyositis	0	0	na	1	1	100.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	1	33.3	7	2	28.6					

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.6.1 Proportion of patients with any adverse event by safety topic during double-blind period by underlying ILD diagnosis
Treated Set
Safety topic: Dental disorders (Group of MedDRA PTs)

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.6.1 Proportion of patients with any adverse event by safety topic during double-blind period by underlying ILD diagnosis
Treated Set
Safety topic: Diarrhoea (Single MedDRA PT)

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk (95% CI)	Odds ratio	Odds (95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	0	0.0	7	3	42.9					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	0	0.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	1	33.3					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	1	100.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	0	0.0					
Juvenile Idiopathic Arthritis	1	0	0.0	0	0	na					
Systemic Sclerosis (SSc)	3	1	33.3	4	2	50.0					
Dermatomyositis	0	0	na	1	0	0.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	1	33.3	7	3	42.9					

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.6.1 Proportion of patients with any adverse event by safety topic during double-blind period by underlying ILD diagnosis
Treated Set
Safety topic: Diarrhoea (Single MedDRA PT)

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.6.1 Proportion of patients with any adverse event by safety topic during double-blind period by underlying ILD diagnosis
Treated Set
Safety topic: Growth plate disorders (Group of MedDRA PTs)

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	1	20.0	7	0	0.0					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	1	50.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	0	0.0					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	0	0.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	0	0.0					
Juvenile Idiopathic Arthritis	1	0	0.0	0	0	na					
Systemic Sclerosis (SSc)	3	0	0.0	4	0	0.0					
Dermatomyositis	0	0	na	1	0	0.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	1	33.3	7	0	0.0					

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.6.1 Proportion of patients with any adverse event by safety topic during double-blind period by underlying ILD diagnosis
Treated Set
Safety topic: Growth plate disorders (Group of MedDRA PTs)

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.6.1 Proportion of patients with any adverse event by safety topic during double-blind period by underlying ILD diagnosis
Treated Set
Safety topic: Hepatic disorders combined

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk (95% CI)	Odds ratio	Odds (95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	0	0.0	7	1	14.3					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	0	0.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	1	33.3					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	0	0.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	0	0.0					
Juvenile Idiopathic Arthritis	1	0	0.0	0	0	na					
Systemic Sclerosis (SSc)	3	0	0.0	4	0	0.0					
Dermatomyositis	0	0	na	1	0	0.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	0	0.0	7	0	0.0					

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.6.1 Proportion of patients with any adverse event by safety topic during double-blind period by underlying ILD diagnosis
Treated Set
Safety topic: Hepatic disorders combined

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.6.1 Proportion of patients with any adverse event by safety topic during double-blind period by underlying ILD diagnosis
Treated Set
Safety topic: Hepatic enzyme increased (Group of MedDRA PTs)

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk (95% CI)	Odds ratio	Odds (95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	0	0.0	7	0	0.0					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	0	0.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	1	33.3					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	0	0.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	0	0.0					
Juvenile Idiopathic Arthritis	1	0	0.0	0	0	na					
Systemic Sclerosis (SSc)	3	0	0.0	4	0	0.0					
Dermatomyositis	0	0	na	1	0	0.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	0	0.0	7	0	0.0					

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.6.1 Proportion of patients with any adverse event by safety topic during double-blind period by underlying ILD diagnosis
Treated Set
Safety topic: Hepatic enzyme increased (Group of MedDRA PTs)

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.6.1 Proportion of patients with any adverse event by safety topic during double-blind period by underlying ILD diagnosis
Treated Set
Safety topic: Hepatic failure (SMQ - narrow)

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk (95% CI)	Odds ratio	Odds (95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	0	0.0	7	1	14.3					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	0	0.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	0	0.0					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	0	0.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	0	0.0					
Juvenile Idiopathic Arthritis	1	0	0.0	0	0	na					
Systemic Sclerosis (SSc)	3	0	0.0	4	0	0.0					
Dermatomyositis	0	0	na	1	0	0.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	0	0.0	7	0	0.0					

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.6.1 Proportion of patients with any adverse event by safety topic during double-blind period by underlying ILD diagnosis
Treated Set
Safety topic: Hepatic failure (SMQ - narrow)

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.6.1 Proportion of patients with any adverse event by safety topic during double-blind period by underlying ILD diagnosis
Treated Set
Safety topic: Nausea (Single MedDRA PT)

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	0	0.0	7	1	14.3					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	1	50.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	1	33.3					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	1	100.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	0	0.0					
Juvenile Idiopathic Arthritis	1	1	100.0	0	0	na					
Systemic Sclerosis (SSc)	3	2	66.7	4	0	0.0					
Dermatomyositis	0	0	na	1	0	0.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	0	0.0	7	1	14.3					

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.6.1 Proportion of patients with any adverse event by safety topic during double-blind period by underlying ILD diagnosis
Treated Set
Safety topic: Nausea (Single MedDRA PT)

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.6.1 Proportion of patients with any adverse event by safety topic during double-blind period by underlying ILD diagnosis
Treated Set
Safety topic: Tooth developmental disorders (MedDRA HLT)

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	3	60.0	7	2	28.6					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	0	0.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	1	33.3					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	0	0.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	0	0.0					
Juvenile Idiopathic Arthritis	1	0	0.0	0	0	na					
Systemic Sclerosis (SSc)	3	0	0.0	4	0	0.0					
Dermatomyositis	0	0	na	1	0	0.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	1	33.3	7	0	0.0					

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.6.1 Proportion of patients with any adverse event by safety topic during double-blind period by underlying ILD diagnosis
Treated Set
Safety topic: Tooth developmental disorders (MedDRA HLT)

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.6.1 Proportion of patients with any adverse event by safety topic during double-blind period by underlying ILD diagnosis
Treated Set
Safety topic: Upper and not otherwise specified respiratory tract infection (Group of MedDRA PTs)

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk (95% CI)	Odds ratio	Odds (95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	0	0.0	7	1	14.3					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	2	100.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	1	33.3					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	0	0.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	1	100.0					
Juvenile Idiopathic Arthritis	1	0	0.0	0	0	na					
Systemic Sclerosis (SSc)	3	1	33.3	4	0	0.0					
Dermatomyositis	0	0	na	1	0	0.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	0	0.0	7	0	0.0					

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.6.1 Proportion of patients with any adverse event by safety topic during double-blind period by underlying ILD diagnosis
Treated Set
Safety topic: Upper and not otherwise specified respiratory tract infection (Group of MedDRA PTs)

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.6.1 Proportion of patients with any adverse event by safety topic during double-blind period by underlying ILD diagnosis
Treated Set
Safety topic: Vomiting (Single MedDRA PT)

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	0	0.0	7	3	42.9					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	0	0.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	1	33.3					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	0	0.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	0	0.0					
Juvenile Idiopathic Arthritis	1	1	100.0	0	0	na					
Systemic Sclerosis (SSc)	3	2	66.7	4	1	25.0					
Dermatomyositis	0	0	na	1	0	0.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	0	0.0	7	2	28.6					

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.6.1 Proportion of patients with any adverse event by safety topic during double-blind period by underlying ILD diagnosis
Treated Set
Safety topic: Vomiting (Single MedDRA PT)

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

User-defined AE categories are only displayed if at least one event occurred within that category

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Aggregated adverse events by safety topic are AEs categorised using Standardised MedDRA Queries (SMQs) and other pooled MedDRA terms.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.6.2 Proportion of patients with any serious adverse event by safety topic during double-blind period by underlying ILD diagnosis
Treated Set

---------- No data satisfied to be displayed ----------

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Anhang 4-G7.7: AESI nach SOC und PT

Table 7.7.1 Proportion of patients with any adverse event of special interest by primary SOC and preferred term as documented by the investigator during double-blind period by underlying ILD diagnosis - Treated Set
System organ class: Gastrointestinal disorders
Preferred term: Lower gastrointestinal haemorrhage

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	0	0.0	7	0	0.0					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	0	0.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	0	0.0					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	0	0.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	1	100.0					
Juvenile Idiopathic Arthritis	1	0	0.0	0	0	na					
Systemic Sclerosis (SSc)	3	0	0.0	4	0	0.0					
Dermatomyositis	0	0	na	1	0	0.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	0	0.0	7	0	0.0					

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Protocol-specified AEs of special interest incl. pathological findings on epiphyseal growth plates imaging, stunted growth (dental imaging), AEs relating to gastrointestinal perforation, bleeding, hepatic injury. Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. AsymptoticCIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.7.1 Proportion of patients with any adverse event of special interest by primary SOC and preferred term as documented by the investigator during double-blind period by underlying ILD diagnosis - Treated Set
System organ class: Gastrointestinal disorders
Preferred term: Lower gastrointestinal haemorrhage

Subgroup Category	Nintedanib vs Placebo Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Protocol-specified AEs of special interest incl. pathological findings on epiphyseal growth plates imaging, stunted growth (dental imaging), AEs relating to gastrointestinal perforation, bleeding, hepatic injury. Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. AsymptoticCIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.7.1 Proportion of patients with any adverse event of special interest by primary SOC and preferred term as documented by the investigator during double-blind period by underlying ILD diagnosis - Treated Set
System organ class: Gastrointestinal disorders
Preferred term: Rectal haemorrhage

Subgroup	Placebo			Nintedanib			Nintedanib vs Placebo				
Category	N	n	%	N	n	%	p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	0	0.0	7	0	0.0					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	0	0.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	0	0.0					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	0	0.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	0	0.0					
Juvenile Idiopathic Arthritis	1	0	0.0	0	0	na					
Systemic Sclerosis (SSc)	3	1	33.3	4	0	0.0					
Dermatomyositis	0	0	na	1	0	0.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	0	0.0	7	0	0.0					

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Protocol-specified AEs of special interest incl. pathological findings on epiphyseal growth plates imaging, stunted growth (dental imaging), AEs relating to gastrointestinal perforation, bleeding, hepatic injury. Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. AsymptoticCIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.7.1 Proportion of patients with any adverse event of special interest by primary SOC and preferred term as documented by the investigator during double-blind period by underlying ILD diagnosis - Treated Set
System organ class: Gastrointestinal disorders
Preferred term: Rectal haemorrhage

Subgroup Category	Nintedanib vs Placebo Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Protocol-specified AEs of special interest incl. pathological findings on epiphyseal growth plates imaging, stunted growth (dental imaging), AEs relating to gastrointestinal perforation, bleeding, hepatic injury. Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. AsymptoticCIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.7.1 Proportion of patients with any adverse event of special interest by primary SOC and preferred term as documented by the investigator during double-blind period by underlying ILD diagnosis - Treated Set
System organ class: Hepatobiliary disorders
Preferred term: Liver injury

Subgroup	Placebo			Nintedanib			Nintedanib vs Placebo				
Category	N	n	%	N	n	%	p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	0	0.0	7	1	14.3					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	0	0.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	0	0.0					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	0	0.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	0	0.0					
Juvenile Idiopathic Arthritis	1	0	0.0	0	0	na					
Systemic Sclerosis (SSc)	3	0	0.0	4	0	0.0					
Dermatomyositis	0	0	na	1	0	0.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	0	0.0	7	0	0.0					

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Protocol-specified AEs of special interest incl. pathological findings on epiphyseal growth plates imaging, stunted growth (dental imaging), AEs relating to gastrointestinal perforation, bleeding, hepatic injury. Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. AsymptoticCIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.7.1 Proportion of patients with any adverse event of special interest by primary SOC and preferred term as documented by the investigator during double-blind period by underlying ILD diagnosis - Treated Set
System organ class: Hepatobiliary disorders
Preferred term: Liver injury

Subgroup Category	Nintedanib vs Placebo Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Protocol-specified AEs of special interest incl. pathological findings on epiphyseal growth plates imaging, stunted growth (dental imaging), AEs relating to gastrointestinal perforation, bleeding, hepatic injury. Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. AsymptoticCIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.7.1 Proportion of patients with any adverse event of special interest by primary SOC and preferred term as documented by the investigator during double-blind period by underlying ILD diagnosis - Treated Set
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Epistaxis

Subgroup	Placebo			Nintedanib			Nintedanib vs Placebo				
Category	N	n	%	N	n	%	p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	1	20.0	7	0	0.0					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	0	0.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	0	0.0					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	0	0.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	0	0.0					
Juvenile Idiopathic Arthritis	1	0	0.0	0	0	na					
Systemic Sclerosis (SSc)	3	1	33.3	4	0	0.0					
Dermatomyositis	0	0	na	1	0	0.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	0	0.0	7	0	0.0					

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Protocol-specified AEs of special interest incl. pathological findings on epiphyseal growth plates imaging, stunted growth (dental imaging), AEs relating to gastrointestinal perforation, bleeding, hepatic injury. Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. AsymptoticCIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.7.1 Proportion of patients with any adverse event of special interest by primary SOC and preferred term as documented by the investigator during double-blind period by underlying ILD diagnosis - Treated Set
System organ class: Respiratory, thoracic and mediastinal disorders
Preferred term: Epistaxis

Subgroup Category	Nintedanib vs Placebo Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

N is the number of patients in the respective analysis set. n is the number of patients with at least one event in the respective analysis set.
Only treatment-emergent AEs are displayed: onset date on or after date of treatment start until the earlier of (i) first intake of open-label nintedanib (excl.) and (ii) last drug intake + 28 days.
Protocol-specified AEs of special interest incl. pathological findings on epiphyseal growth plates imaging, stunted growth (dental imaging), AEs relating to gastrointestinal perforation, bleeding, hepatic injury. Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated. AsymptoticCIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity; MedDRA version: 25.0

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Table 7.7.2 Proportion of patients with any serious adverse event of special interest by primary SOC and preferred term as documented by the investigator during double-blind period by underlying ILD diagnosis - Treated Set

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Anhang 4-G7.8: Weitere Sicherheitsendpunkte

Table 7.8.1 Proportion of patients with any treatment-emergent pathological findings of epiphyseal growth plate on imaging up to week 24 (during double-blind period) by underlying ILD diagnosis - Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	(95% CI)	Odds ratio	(95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	0	0.0	7	1	14.3					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	0	0.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	1	33.3					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	0	0.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	0	0.0					
Juvenile Idiopathic Arthritis	1	1	100.0	0	0	na					
Systemic Sclerosis (SSc)	3	0	0.0	4	0	0.0					
Dermatomyositis	0	0	na	1	0	0.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	0	0.0	7	0	0.0					

N is the number of patients in the respective analysis set. n is the number of patients with at least one finding in the respective analysis set.
Based on central review and not on investigator decision. Pathological findings which were already present at baseline will NOT be considered treatment-emergent in this analysis, in spite of being identified after start of treatment (baseline time window: day -84 until day 15).
All findings after this time window and up to week 24 are considered in this analysis.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Table 7.8.1 Proportion of patients with any treatment-emergent pathological findings of epiphyseal growth plate on imaging up to week 24 (during double-blind period) by underlying ILD diagnosis - Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

N is the number of patients in the respective analysis set. n is the number of patients with at least one finding in the respective analysis set.
Based on central review and not on investigator decision. Pathological findings which were already present at baseline will NOT be considered treatment-emergent in this analysis, in spite of being identified after start of treatment (baseline time window: day -84 until day 15).
All findings after this time window and up to week 24 are considered in this analysis.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Table 7.8.2 Proportion of patients with any treatment-emergent pathological findings on dental examination up to week 24 (during double-blind period) by underlying ILD diagnosis - Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk (95% CI)	Odds ratio	Odds (95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	0	0.0	7	0	0.0					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	2	100.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	0	0.0	3	1	33.3					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	0	0.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	0	0.0					
Juvenile Idiopathic Arthritis	1	0	0.0	0	0	na					
Systemic Sclerosis (SSc)	3	0	0.0	4	0	0.0					
Dermatomyositis	0	0	na	1	0	0.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	1	33.3	7	2	28.6					

N is the number of patients in the respective analysis set. n is the number of patients with at least one finding in the respective analysis set.
Dental examination done by dentist. Pathological findings which were already present at baseline will NOT be considered
treatment-emergent in this analysis, in spite of being identified after start of treatment (baseline time window: day -84 until day 15).
All findings after this time window and up to week 24 are considered in this analysis.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the
modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Table 7.8.2 Proportion of patients with any treatment-emergent pathological findings on dental examination up to week 24 (during double-blind period) by underlying ILD diagnosis - Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

N is the number of patients in the respective analysis set. n is the number of patients with at least one finding in the respective analysis set.
Dental examination done by dentist. Pathological findings which were already present at baseline will NOT be considered
treatment-emergent in this analysis, in spite of being identified after start of treatment (baseline time window: day -84 until day 15).
All findings after this time window and up to week 24 are considered in this analysis.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the
modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Table 7.8.3 Proportion of patients with any treatment-emergent pathological findings on dental imaging up to week 24 (during double-blind period) by underlying ILD diagnosis - Treated Set

Subgroup Category	Placebo N	Placebo n	Placebo %	Nintedanib N	Nintedanib n	Nintedanib %	Nintedanib vs Placebo p-value*	Risk diff.	Risk (95% CI)	Odds ratio	Odds (95% CI)
Underlying ILD diagnosis											
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)	5	2	40.0	7	1	14.3					
Chronic Hypersensitivity Pneumonitis (cHP)	0	0	na	2	0	0.0					
Toxic/Radiation/Drug Induced Pneumonitis	1	1	100.0	3	1	33.3					
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis	0	0	na	1	0	0.0					
Juvenile Rheumatoid Arthritis (RA)	0	0	na	1	0	0.0					
Juvenile Idiopathic Arthritis	1	0	0.0	0	0	na					
Systemic Sclerosis (SSc)	3	1	33.3	4	3	75.0					
Dermatomyositis	0	0	na	1	1	100.0					
Mixed Connective Tissue Disease	0	0	na	0	0	na					
Sarcoidosis	0	0	na	0	0	na					
Other Childhood ILD	3	0	0.0	7	3	42.9					

N is the number of patients in the respective analysis set. n is the number of patients with at least one finding in the respective analysis set.
Based on central review and not on investigator decision. Pathological findings which were already present at baseline will NOT be considered treatment-emergent in this analysis, in spite of being identified after start of treatment (baseline time window: day -84 until day 15).
All findings after this time window and up to week 24 are considered in this analysis.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Table 7.8.3 Proportion of patients with any treatment-emergent pathological findings on dental imaging up to week 24 (during double-blind period) by underlying ILD diagnosis - Treated Set

Subgroup Category	Nintedanib vs Placebo			
	Risk ratio	(exact 95% CI)	(asymp 95% CI)	p-value**
Underlying ILD diagnosis				
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)				
Chronic Hypersensitivity Pneumonitis (cHP)				
Toxic/Radiation/Drug Induced Pneumonitis				
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis				
Juvenile Rheumatoid Arthritis (RA)				
Juvenile Idiopathic Arthritis				
Systemic Sclerosis (SSc)				
Dermatomyositis				
Mixed Connective Tissue Disease				
Sarcoidosis				
Other Childhood ILD				

N is the number of patients in the respective analysis set. n is the number of patients with at least one finding in the respective analysis set.
Based on central review and not on investigator decision. Pathological findings which were already present at baseline will NOT be considered treatment-emergent in this analysis, in spite of being identified after start of treatment (baseline time window: day -84 until day 15).
All findings after this time window and up to week 24 are considered in this analysis.
Exact confidence intervals (CIs) for risk ratios and risk differences are estimated by Chan and Zhang. For odds ratios exact mid-p CIs are estimated.
Asymptotic CIs for risk ratios are Wald confidence limits. In case of zero events a continuity correction is applied to the asymptotic CI, and the modified risk ratio is additionally displayed.
*2*one-sided p value using Suissa-Shuster Z-pooled test. **Cochran's Q-test for homogeneity of risk ratios (treatment by subgroup interaction).
inf=infinity

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Table 7.8.4 Adjusted mean (SE) of absolute change from baseline in height-for-age z-score (HAZ) at week 24 by underlying ILD diagnosis
Treated Set

Subgroup/ Category/ Treatment	N	Baseline Mean [1]	Baseline SD [1]	24 weeks Mean [1]	24 weeks SD [1]	Change from baseline to 24 weeks: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	Comparison vs. Randomised Placebo: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	p-value [3]
Underlying ILD diagnosis														
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)														
Placebo	5	-1.920	1.407	-1.967	1.484									
Nintedanib	6	-0.025	1.101	-0.152	1.092									
Chronic Hypersensitivity Pneumonitis (cHP)														
Placebo	0													
Nintedanib	1	-0.740		-0.757										
Toxic/Radiation/Drug Induced Pneumonitis														
Placebo	1	-1.056		-1.092										
Nintedanib	3	0.117	1.113	0.152	1.140									
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis														
Placebo	0													
Nintedanib	1	-3.127		-3.219										
Juvenile Rheumatoid Arthritis (RA)														
Placebo	0													
Nintedanib	1	-0.522		-0.691										
Juvenile Idiopathic Arthritis														
Placebo	1	-0.613		-0.663										
Nintedanib	0													
Systemic Sclerosis (SSc)														
Placebo	3	0.422	1.184	0.383	1.061									
Nintedanib	4	-1.997	1.362	-2.043	1.330									
Dermatomyositis														
Placebo	0													
Nintedanib	1	-1.319		-1.345										
Mixed Connective Tissue Disease														
Placebo	0													
Nintedanib	0													
Sarcoidosis														
Placebo	0													
Nintedanib	0													

The age in months at the respective time point is used to determine the z-score of a given patient.
[1] Based on the number of patients having available data at baseline and at the respective visit.
[2] Based on Mixed Model for Repeated Measures (MMRM), with fixed categorical effect age-group and the fixed continuous effects of baseline value at each visit, (randomized) treatment-by-visit-by-subgroup interaction, and random effect for patient. [3] Interaction p-value.
Visit is treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
Adjusted mean is based on all analysed patients in the model (i.e. on patients with a baseline and at least one post-baseline measurement - not only on patients with a baseline and measurement at the respective visit).
For derivation of the MMRM available data from all visits up to week 52 is used. Only on-treatment data are considered.

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Table 7.8.4 Adjusted mean (SE) of absolute change from baseline in height-for-age z-score (HAZ) at week 24 by underlying ILD diagnosis
Treated Set

Subgroup/ Category/ Treatment	N	Baseline Mean	Baseline SD [1]	24 weeks Mean	24 weeks SD [1]	Change from baseline to 24 weeks: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	Comparison vs. Randomised Placebo: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	p-value [3]
Other Childhood ILD														
Placebo	2	-1.745	0.460	-1.612	0.305									
Nintedanib	5	-0.833	0.786	-0.850	0.688									

The age in months at the respective time point is used to determine the z-score of a given patient.
[1] Based on the number of patients having available data at baseline and at the respective visit.
[2] Based on Mixed Model for Repeated Measures (MMRM), with fixed categorical effect age-group and the fixed continuous effects of baseline value at each visit, (randomized) treatment-by-visit-by-subgroup interaction, and random effect for patient. [3] Interaction p-value.
Visit is treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
Adjusted mean is based on all analysed patients in the model (i.e. on patients with a baseline and at least one post-baseline measurement - not only on patients with a baseline and measurement at the respective visit).
For derivation of the MMRM available data from all visits up to week 52 is used. Only on-treatment data are considered.

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Table 7.8.5 Adjusted mean (SE) of absolute change from baseline in BMI-for-age z-score (BAZ) at week 24 by underlying ILD diagnosis
Treated Set

Subgroup/ Category/ Treatment	N	Baseline Mean [1]	Baseline SD [1]	24 weeks Mean [1]	24 weeks SD [1]	Change from baseline to 24 weeks: Adjusted mean [2]	SE	95% confidence interval Lower	95% confidence interval Upper	Comparison vs. Randomised Placebo: Adjusted mean [2]	SE	95% confidence interval Lower	95% confidence interval Upper	p-value [3]
Underlying ILD diagnosis														
Surfactant Protein Deficiency (e.g. SFTPC and ABCA3 mutations)														
Placebo	5	-1.457	2.624	-1.613	2.509									
Nintedanib	6	-0.898	1.990	-1.183	1.972									
Chronic Hypersensitivity Pneumonitis (cHP)														
Placebo	0													
Nintedanib	1	-0.688		-1.134										
Toxic/Radiation/Drug Induced Pneumonitis														
Placebo	1	2.306		2.165										
Nintedanib	3	0.943	2.179	0.753	2.038									
Post Hematopoietic Stem Cell Transplant (HSCT) Fibrosis														
Placebo	0													
Nintedanib	1	-1.795		-1.969										
Juvenile Rheumatoid Arthritis (RA)														
Placebo	0													
Nintedanib	1	0.774		0.877										
Juvenile Idiopathic Arthritis														
Placebo	1	1.717		2.206										
Nintedanib	0													
Systemic Sclerosis (SSc)														
Placebo	3	-0.863	1.255	-0.439	0.185									
Nintedanib	4	0.099	1.394	-0.619	1.716									
Dermatomyositis														
Placebo	0													
Nintedanib	1	-1.004		-1.693										
Mixed Connective Tissue Disease														
Placebo	0													
Nintedanib	0													
Sarcoidosis														
Placebo	0													
Nintedanib	0													

The age in months at the respective time point is used to determine the z-score of a given patient.
[1] Based on the number of patients having available data at baseline and at the respective visit.
[2] Based on Mixed Model for Repeated Measures (MMRM), with fixed categorical effect age-group and the fixed continuous effects of baseline value at each visit, (randomized) treatment-by-visit-by-subgroup interaction, and random effect for patient. [3] Interaction p-value.
Visit is treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
Adjusted mean is based on all analysed patients in the model (i.e. on patients with a baseline and at least one post-baseline measurement - not only on patients with a baseline and measurement at the respective visit).
For derivation of the MMRM available data from all visits up to week 52 is used. Only on-treatment data are considered.

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Table 7.8.5 Adjusted mean (SE) of absolute change from baseline in BMI-for-age z-score (BAZ) at week 24 by underlying ILD diagnosis
Treated Set

Subgroup/ Category/ Treatment	N	Baseline Mean	Baseline SD [1]	24 weeks Mean	24 weeks SD [1]	Change from baseline to 24 weeks: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	Comparison vs. Randomised Placebo: Adjusted mean [2]	SE	95% confidence interval Lower	Upper	p-value [3]
Other Childhood ILD														
Placebo	2	0.232	2.368	0.047	2.667									
Nintedanib	5	-0.379	0.837	-0.425	1.042									

The age in months at the respective time point is used to determine the z-score of a given patient.
[1] Based on the number of patients having available data at baseline and at the respective visit.
[2] Based on Mixed Model for Repeated Measures (MMRM), with fixed categorical effect age-group and the fixed continuous effects of baseline value at each visit, (randomized) treatment-by-visit-by-subgroup interaction, and random effect for patient. [3] Interaction p-value.
Visit is treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.
Adjusted mean is based on all analysed patients in the model (i.e. on patients with a baseline and at least one post-baseline measurement - not only on patients with a baseline and measurement at the respective visit).
For derivation of the MMRM available data from all visits up to week 52 is used. Only on-treatment data are considered.

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