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Dossier zur Nutzenbewertung gemäß § 35a SGB V

Semaglutid (Rybelsus®/Ozempic®)

Novo Nordisk Pharma GmbH

Modul 4 B – Anhang 4-G

Zur Behandlung von erwachsenen Patienten mit Typ 2 Diabetes mellitus in der Zweifachtherapie

Medizinischer Nutzen und
medizinischer Zusatznutzen,
Patientengruppen mit therapeutisch
bedeutsamem Zusatznutzen

Stand: 26.10.2020

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Anhang 4-G: Ergänzende Analysen

1. Responderanalysen SF-36v2

Tabelle 4G-1: Ergebnisse für Anteil der Responder für den SF-36v2 aus RCT mit dem zu bewertenden Arzneimittel

Anteil der Responder für den SF-36v2						
Behandlung	**N**	**n (%)**	**RR [95 %-KI]**	**OR [95 %-KI]**	**RD [95 %-KI]**	**p-Wert[1]**
PIONEER 2 (FAS, *In-trial*) – Woche 52						
Körperliche Funktionsfähigkeit (MID = 4,3)						
Semaglutid oral	411	67 (17,4)	0,96 [0,71; 1,31]	0,96 [0,66; 1,38]	-0,66 [-6,05; 4,74]	0,8503¤¤
Empagliflozin	410	69 (18,0)				
Körperliche Rollenfunktion (MID = 4,0)						
Semaglutid oral	411	80 (20,7)	0,73 [0,57; 0,94]	0,66 [0,48; 0,92]	-7,55 [-13,61; -1,49]	0,0186¤¤
Empagliflozin	410	108 (28,3)				
Körperliche Schmerzen (MID = 5,5)						
Semaglutid oral	411	99 (25,6)	0,91 [0,72; 1,15]	0,88 [0,64; 1,21]	-2,55 [-8,82; 3,72]	0,4644¤¤
Empagliflozin	410	108 (28,2)				
Allgemeiner Gesundheitszustand (MID = 7,0)						
Semaglutid oral	411	93 (24,1)	1,25 [0,95; 1,63]	1,33 [0,94; 1,87]	4,77 [-1,04; 10,59]	0,1158¤¤
Empagliflozin	410	74 (19,3)				
Vitalität (MID = 6,7)						
Semaglutid oral	411	78 (20,2)	1,01 [0,76; 1,33]	1,01 [0,71; 1,43]	0,10 [-5,57; 5,77]	1,0000¤¤
Empagliflozin	410	77 (20,1)				
Soziale Funktionsfähigkeit (MID = 6,2)						
Semaglutid oral	411	58 (15,0)	1,05 [0,74; 1,47]	1,05 [0,71; 1,57]	0,67 [-4,34; 5,67]	0,8388¤¤
Empagliflozin	410	55 (14,4)				
Emotionale Rollenfunktion (MID = 4,6)						
Semaglutid oral	411	85 (22,0)	1,01 [0,78; 1,32]	1,02 [0,72; 1,43]	0,29 [-5,55; 6,14]	0,9307¤¤
Empagliflozin	410	83 (21,7)				
Mentaler Gesundheitszustand (MID = 6,7)						
Semaglutid oral	411	74 (19,2)	0,97 [0,72; 1,29]	0,96 [0,67; 1,37]	-0,67 [-6,27; 4,93]	0,8557¤¤
Empagliflozin	410	76 (19,8)				

not est.: Nicht bestimmbar

1: Nicht-adjustierter zweiseitiger p-Wert aus dem Test einer 2x2-Kontingenztafel (¤: Barnards unbedingter exakter Test; ¤¤: Fishers exakter Test)

Post-hoc-Analyse

2. Subgruppenanalysen – Morbidität

2.1. HbA1c (%) - multiple imputation - Pioneer 2 - week 52 - in-trial - full analysis set

	Oral Sema 14 mg						Empa 25 mg						Oral Sema 14 mg vs. Empa 25 mg		
Subgroup	N	Nbase	N week 52	Mean base (SD)	Mean week 52 (SD)	Est. CFB (SE)	N	Nbase	N week 52	Mean base (SD)	Mean week 52 (SD)	Est. CFB (SE)	ETD [95%-CI] p-value	Hedges' g [95%-CI]	p-value int.
All subjects (total)	411	411	384	8.14 (0.9)	6.80 (1.0)	-1.30 (0.0)	410	410	382	8.14 (0.9)	7.21 (0.9)	-0.89 (0.0)	-0.40 [-0.54;-0.27] <0.0001	-0.35 [-0.49;-0.21]	
Gender															0.0881
Female	205	205	190	8.17 (1.0)	6.70 (1.0)	-1.37 (0.1)	201	201	187	8.16 (0.9)	7.25 (0.9)	-0.85 (0.1)	-0.52 [-0.71;-0.33] <0.0001	-0.48 [-0.68;-0.27]	
Male	206	206	194	8.10 (0.9)	6.89 (1.1)	-1.22 (0.1)	209	209	195	8.11 (0.9)	7.17 (0.9)	-0.93 (0.1)	-0.29 [-0.48;-0.10] 0.0026	-0.23 [-0.43;-0.03]	
Age															0.4160
< 65	306	306	281	8.23 (1.0)	6.84 (1.1)	-1.27 (0.1)	300	300	283	8.23 (0.9)	7.23 (0.9)	-0.90 (0.1)	-0.37 [-0.53;-0.21] <0.0001	-0.32 [-0.49;-0.15]	
65 <=	105	105	103	7.86 (0.8)	6.68 (0.7)	-1.37 (0.1)	110	110	99	7.87 (0.9)	7.14 (0.9)	-0.87 (0.1)	-0.50 [-0.76;-0.24] 0.0002	-0.47 [-0.75;-0.20]	
Region A															0.7443
West Europe	78	78	76	7.93 (0.8)	6.74 (0.9)	-1.31 (0.1)	89	89	87	7.92 (0.8)	7.20 (0.8)	-0.86 (0.1)	-0.45 [-0.74;-0.16] 0.0023	-0.47 [-0.78;-0.16]	
Rest of World	333	333	308	8.18 (1.0)	6.81 (1.1)	-1.29 (0.1)	321	321	295	8.20 (1.0)	7.21 (0.9)	-0.90 (0.1)	-0.39 [-0.55;-0.24] <0.0001	-0.32 [-0.48;-0.15]	

N: number of subjects in the analysis set, Nbase: number of subjects with an observation at baseline, N week 52: number of subjects with an observation at week 52, base: baseline, CI: confidence interval, Est. CFB: estimated change from baseline, ETD: estimated treatment difference, Mean: observed arithmetic mean, SD: standard deviation, SE: standard error, p-value: unadjusted two-sided p-value for test of no difference from 0 (t-test), p-value int.: unadjusted two-sided p-value for test of no treatment by subgroup interaction (F-test), *: p-value int. < 0,05
Missing post-baseline values were imputed by a pattern mixture model using multiple imputation. Change from baseline was analysed using an ANCOVA model with treatment, (region, if applicable), (subgroup, and interaction between treatment and subgroup, if applicable) as fixed factors and the corresponding baseline value as a covariate for each of the 1000 imputed complete datasets, and pooled by Rubin's rule to draw inference.
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HbA1c (%) - multiple imputation - Pioneer 2 - week 52 - in-trial - full analysis set

	Oral Sema 14 mg						Empa 25 mg						Oral Sema 14 mg vs. Empa 25 mg		
Subgroup	N	Nbase	N week 52	Mean base (SD)	Mean week 52 (SD)	Est. CFB (SE)	N	Nbase	N week 52	Mean base (SD)	Mean week 52 (SD)	Est. CFB (SE)	ETD [95%-CI] p-value	Hedges' g [95%-CI]	p-value int.
HbA1c at baseline (disease severity)															0.7390
<= 7.5	134	134	129	7.19 (0.2)	6.52 (0.7)	-0.66 (0.1)	131	131	122	7.20 (0.2)	6.92 (0.6)	-0.23 (0.1)	-0.44 [-0.67;-0.21] 0.0002	-0.56 [-0.81;-0.31]	
7.5 <	277	277	255	8.59 (0.8)	6.94 (1.1)	-1.60 (0.1)	279	279	260	8.58 (0.8)	7.34 (0.9)	-1.21 (0.1)	-0.39 [-0.56;-0.22] <0.0001	-0.36 [-0.54;-0.19]	

N: number of subjects in the analysis set, Nbase: number of subjects with an observation at baseline, N week 52: number of subjects with an observation at week 52, base: baseline, CI: confidence interval, Est. CFB: estimated change from baseline, ETD: estimated treatment difference, Mean: observed arithmetic mean, SD: standard deviation, SE: standard error, p-value: unadjusted two-sided p-value for test of no difference from 0 (t-test), p-value int.: unadjusted two-sided p-value for test of no treatment by subgroup interaction (F-test), *: p-value int. < 0,05
Missing post-baseline values were imputed by a pattern mixture model using multiple imputation. Change from baseline was analysed using an ANCOVA model with treatment, (region, if applicable), (subgroup, and interaction between treatment and subgroup, if applicable) as fixed factors and the corresponding baseline value as a covariate for each of the 1000 imputed complete datasets, and pooled by Rubin's rule to draw inference.

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2.2. Body weight (kg) - multiple imputation - Pioneer 2 - week 52 - in-trial - full analysis set

	Oral Sema 14 mg						Empa 25 mg						Oral Sema 14 mg vs. Empa 25 mg		
Subgroup	N	Nbase	N week 52	Mean base (SD)	Mean week 52 (SD)	Est. CFB (SE)	N	Nbase	N week 52	Mean base (SD)	Mean week 52 (SD)	Est. CFB (SE)	ETD [95%-CI] p-value	Hedges' g [95%-CI]	p-value int.
All subjects (total)	411	411	386	91.93 (20.5)	87.94 (20.2)	-3.79 (0.3)	410	410	383	91.30 (20.1)	87.75 (19.6)	-3.62 (0.3)	-0.18 [-0.88;0.53] 0.6231	-0.06 [-0.20;0.09]	
Gender															0.0085*
Female	205	205	192	86.98 (21.0)	81.82 (20.3)	-5.05 (0.4)	201	201	188	85.14 (18.0)	81.50 (17.4)	-3.96 (0.4)	-1.08 [-2.06;-0.11] 0.0293	-0.24 [-0.44;-0.04]	
Male	206	206	194	96.85 (18.8)	94.00 (18.3)	-2.54 (0.4)	209	209	195	97.21 (20.2)	93.77 (19.9)	-3.28 (0.4)	0.74 [-0.22;1.71] 0.1319	0.16 [-0.03;0.36]	
Age															0.4885
< 65	306	306	283	94.32 (21.3)	90.16 (21.0)	-3.85 (0.3)	300	300	284	92.94 (20.6)	89.19 (20.2)	-3.53 (0.3)	-0.32 [-1.14;0.49] 0.4395	-0.11 [-0.27;0.06]	
65 <=	105	105	103	84.95 (16.3)	81.84 (16.6)	-3.62 (0.5)	110	110	99	86.81 (18.0)	83.60 (17.4)	-3.85 (0.5)	0.23 [-1.12;1.59] 0.7347	0.11 [-0.17;0.38]	
Region A															0.3710
West Europe	78	78	76	87.88 (17.9)	82.09 (15.4)	-4.56 (0.6)	89	89	88	88.51 (19.0)	84.82 (18.8)	-3.73 (0.5)	-0.83 [-2.34;0.69] 0.2843	-0.20 [-0.51;0.11]	
Rest of World	333	333	310	92.87 (21.0)	89.38 (21.0)	-3.62 (0.3)	321	321	295	92.07 (20.3)	88.62 (19.8)	-3.57 (0.3)	-0.05 [-0.84;0.75] 0.9080	-0.02 [-0.18;0.14]	

N: number of subjects in the analysis set, Nbase: number of subjects with an observation at baseline, N week 52: number of subjects with an observation at week 52, base: baseline, CI: confidence interval, Est. CFB: estimated change from baseline, ETD: estimated treatment difference, Mean: observed arithmetic mean, SD: standard deviation, SE: standard error, p-value: unadjusted two-sided p-value for test of no difference from 0 (t-test), p-value int.: unadjusted two-sided p-value for test of no treatment by subgroup interaction (F-test), *: p-value int. < 0,05
Missing post-baseline values were imputed by a pattern mixture model using multiple imputation. Change from baseline was analysed using an ANCOVA model with treatment, (region, if applicable), (subgroup, and interaction between treatment and subgroup, if applicable) as fixed factors and the corresponding baseline value as a covariate for each of the 1000 imputed complete datasets, and pooled by Rubin's rule to draw inference.

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Body weight (kg) - multiple imputation - Pioneer 2 - week 52 - in-trial - full analysis set

	Oral Sema 14 mg						Empa 25 mg						Oral Sema 14 mg vs. Empa 25 mg		
Subgroup	N	Nbase	N week 52	Mean base (SD)	Mean week 52 (SD)	Est. CFB (SE)	N	Nbase	N week 52	Mean base (SD)	Mean week 52 (SD)	Est. CFB (SE)	ETD [95%-CI] p-value	Hedges' g [95%-CI]	p-value int.
HbA1c at baseline (disease severity)															0.5224
<= 7.5	134	134	131	89.52 (19.8)	85.85 (19.8)	-4.06 (0.4)	131	131	123	89.99 (19.9)	86.92 (19.9)	-3.56 (0.4)	-0.50 [-1.71;0.71] 0.4164	-0.09 [-0.34;0.15]	
7.5 <	277	277	255	93.09 (20.8)	89.01 (20.4)	-3.66 (0.3)	279	279	260	91.91 (20.2)	88.14 (19.5)	-3.64 (0.3)	-0.02 [-0.88;0.84] 0.9644	-0.04 [-0.21;0.14]	

N: number of subjects in the analysis set, Nbase: number of subjects with an observation at baseline, N week 52: number of subjects with an observation at week 52, base: baseline, CI: confidence interval, Est. CFB: estimated change from baseline, ETD: estimated treatment difference, Mean: observed arithmetic mean, SD: standard deviation, SE: standard error, p-value: unadjusted two-sided p-value for test of no difference from 0 (t-test), p-value int.: unadjusted two-sided p-value for test of no treatment by subgroup interaction (F-test), *: p-value int. < 0,05

Missing post-baseline values were imputed by a pattern mixture model using multiple imputation. Change from baseline was analysed using an ANCOVA model with treatment, (region, if applicable), (subgroup, and interaction between treatment and subgroup, if applicable) as fixed factors and the corresponding baseline value as a covariate for each of the 1000 imputed complete datasets, and pooled by Rubin's rule to draw inference.

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3. Subgruppenanalysen – Lebensqualität

3.1. SF-36v2 (acute version) - Physical component summary - multiple imputation - Pioneer 2 - week 52 - in-trial - full analysis set

	Oral Sema 14 mg						Empa 25 mg						Oral Sema 14 mg vs. Empa 25 mg		
Subgroup	N	Nbase	N week 52	Mean base (SD)	Mean week 52 (SD)	Est. CFB (SE)	N	Nbase	N week 52	Mean base (SD)	Mean week 52 (SD)	Est. CFB (SE)	ETD [95%-CI] p-value	Hedges' g [95%-CI]	p-value int.
All subjects (total)	411	411	386	50.00 (7.5)	50.59 (7.9)	0.44 (0.3)	410	410	382	49.31 (8.0)	50.88 (7.8)	1.44 (0.3)	-1.00 [-1.88;-0.12] 0.0263	-0.14 [-0.28;-0.00]	
Gender															0.4521
Female	205	205	192	48.96 (8.2)	49.61 (8.5)	-0.03 (0.4)	201	201	188	48.64 (8.2)	50.34 (8.3)	1.30 (0.4)	-1.33 [-2.56;-0.10] 0.0347	-0.19 [-0.39;0.01]	
Male	206	206	194	51.03 (6.6)	51.57 (7.1)	0.91 (0.4)	209	209	194	49.95 (7.7)	51.41 (7.4)	1.58 (0.4)	-0.67 [-1.90;0.55] 0.2822	-0.10 [-0.30;0.10]	
Age															0.2359
< 65	306	306	283	50.12 (7.5)	51.09 (7.7)	0.69 (0.4)	300	300	284	49.95 (8.0)	51.27 (7.8)	1.39 (0.4)	-0.70 [-1.71;0.32] 0.1773	-0.07 [-0.23;0.10]	
65 <=	105	105	103	49.64 (7.6)	49.23 (8.2)	-0.30 (0.6)	110	110	98	47.56 (7.5)	49.76 (7.9)	1.57 (0.6)	-1.87 [-3.56;-0.19] 0.0296	-0.34 [-0.62;-0.07]	
Region A															0.9201
West Europe	78	78	76	51.21 (7.9)	51.45 (6.8)	0.84 (0.7)	89	89	87	50.40 (7.4)	51.94 (7.4)	1.70 (0.6)	-0.87 [-2.73;1.00] 0.3633	-0.15 [-0.46;0.16]	
Rest of World	333	333	310	49.72 (7.4)	50.39 (8.1)	0.37 (0.4)	321	321	295	49.01 (8.1)	50.57 (8.0)	1.34 (0.4)	-0.97 [-1.98;0.03] 0.0576	-0.14 [-0.30;0.02]	

N: number of subjects in the analysis set, Nbase: number of subjects with an observation at baseline, N week 52: number of subjects with an observation at week 52, base: baseline, CI: confidence interval, Est. CFB: estimated change from baseline, ETD: estimated treatment difference, Mean: observed arithmetic mean, SD: standard deviation, SE: standard error, p-value: unadjusted two-sided p-value for test of no difference from 0 (t-test), p-value int.: unadjusted two-sided p-value for test of no treatment by subgroup interaction (F-test), *: p-value int. < 0,05
Missing post-baseline values were imputed by a pattern mixture model using multiple imputation. Change from baseline was analysed using an ANCOVA model with treatment, (region, if applicable), (subgroup, and interaction between treatment and subgroup, if applicable) as fixed factors and the corresponding baseline value as a covariate for each of the 1000 imputed complete datasets, and pooled by Rubin's rule to draw inference.

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SF-36v2 (acute version) - Physical component summary - multiple imputation - Pioneer 2 - week 52 - in-trial - full analysis set

	Oral Sema 14 mg						Empa 25 mg						Oral Sema 14 mg vs. Empa 25 mg		
Subgroup	N	Nbase	N week 52	Mean base (SD)	Mean week 52 (SD)	Est. CFB (SE)	N	Nbase	N week 52	Mean base (SD)	Mean week 52 (SD)	Est. CFB (SE)	ETD [95%-CI] p-value	Hedges' g [95%-CI]	p-value int.
HbA1c at baseline (disease severity)															0.6939
<= 7.5	134	134	131	50.14 (7.4)	50.41 (7.7)	0.38 (0.5)	131	131	122	49.87 (8.5)	51.40 (8.0)	1.63 (0.5)	-1.25 [-2.74;0.24] 0.1003	-0.19 [-0.44;0.06]	
7.5 <	277	277	255	49.93 (7.6)	50.69 (8.0)	0.47 (0.4)	279	279	260	49.05 (7.7)	50.64 (7.8)	1.35 (0.4)	-0.88 [-1.96;0.20] 0.1094	-0.12 [-0.29;0.05]	

N: number of subjects in the analysis set, Nbase: number of subjects with an observation at baseline, N week 52: number of subjects with an observation at week 52, base: baseline, CI: confidence interval, Est. CFB: estimated change from baseline, ETD: estimated treatment difference, Mean: observed arithmetic mean, SD: standard deviation, SE: standard error, p-value: unadjusted two-sided p-value for test of no difference from 0 (t-test), p-value int.: unadjusted two-sided p-value for test of no treatment by subgroup interaction (F-test), *: p-value int. < 0,05
Missing post-baseline values were imputed by a pattern mixture model using multiple imputation. Change from baseline was analysed using an ANCOVA model with treatment, (region, if applicable), (subgroup, and interaction between treatment and subgroup, if applicable) as fixed factors and the corresponding baseline value as a covariate for each of the 1000 imputed complete datasets, and pooled by Rubin's rule to draw inference.

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3.2. SF-36v2 (acute version) - Mental component summary - multiple imputation - Pioneer 2 - week 52 - in-trial - full analysis set

	Oral Sema 14 mg						Empa 25 mg						Oral Sema 14 mg vs. Empa 25 mg		
Subgroup	N	Nbase	N week 52	Mean base (SD)	Mean week 52 (SD)	Est. CFB (SE)	N	Nbase	N week 52	Mean base (SD)	Mean week 52 (SD)	Est. CFB (SE)	ETD [95%-CI] p-value	Hedges' g [95%-CI]	p-value int.
All subjects (total)	411	411	386	49.76 (9.0)	50.17 (9.2)	0.23 (0.4)	410	410	382	50.13 (9.8)	50.02 (9.7)	0.02 (0.4)	0.20 [-0.93;1.33] 0.7240	0.05 [-0.09;0.19]	
Gender															0.4439
Female	205	205	192	48.43 (9.3)	48.59 (10.1)	-0.64 (0.6)	201	201	188	48.48 (10.5)	48.77 (10.7)	-0.41 (0.6)	-0.23 [-1.80;1.34] 0.7772	-0.01 [-0.21;0.19]	
Male	206	206	194	51.07 (8.5)	51.73 (8.0)	1.08 (0.6)	209	209	194	51.72 (8.8)	51.24 (8.4)	0.45 (0.6)	0.63 [-0.94;2.20] 0.4335	0.12 [-0.08;0.32]	
Age															0.3020
< 65	306	306	283	49.87 (9.0)	50.17 (9.1)	0.09 (0.5)	300	300	284	49.74 (9.7)	50.07 (9.9)	0.23 (0.5)	-0.14 [-1.44;1.16] 0.8297	-0.01 [-0.18;0.15]	
65 <=	105	105	103	49.42 (9.0)	50.17 (9.5)	0.63 (0.8)	110	110	98	51.19 (10.0)	49.87 (8.8)	-0.54 (0.8)	1.18 [-1.00;3.35] 0.2897	0.23 [-0.04;0.51]	
Region A															0.4203
West Europe	78	78	76	47.32 (9.8)	49.03 (9.7)	0.79 (0.9)	89	89	87	50.55 (10.2)	49.89 (9.0)	-0.34 (0.8)	1.13 [-1.27;3.52] 0.3558	0.28 [-0.03;0.59]	
Rest of World	333	333	310	50.33 (8.7)	50.45 (9.1)	0.11 (0.4)	321	321	295	50.02 (9.7)	50.06 (9.9)	0.10 (0.5)	0.01 [-1.28;1.30] 0.9890	-0.01 [-0.16;0.15]	

N: number of subjects in the analysis set, Nbase: number of subjects with an observation at baseline, N week 52: number of subjects with an observation at week 52, base: baseline, CI: confidence interval, Est. CFB: estimated change from baseline, ETD: estimated treatment difference, Mean: observed arithmetic mean, SD: standard deviation, SE: standard error, p-value: unadjusted two-sided p-value for test of no difference from 0 (t-test), p-value int.: unadjusted two-sided p-value for test of no treatment by subgroup interaction (F-test), *: p-value int. < 0,05
Missing post-baseline values were imputed by a pattern mixture model using multiple imputation. Change from baseline was analysed using an ANCOVA model with treatment, (region, if applicable), (subgroup, and interaction between treatment and subgroup, if applicable) as fixed factors and the corresponding baseline value as a covariate for each of the 1000 imputed complete datasets, and pooled by Rubin's rule to draw inference.

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SF-36v2 (acute version) - Mental component summary - multiple imputation - Pioneer 2 - week 52 - in-trial - full analysis set

	Oral Sema 14 mg						Empa 25 mg						Oral Sema 14 mg vs. Empa 25 mg		
Subgroup	N	Nbase	N week 52	Mean base (SD)	Mean week 52 (SD)	Est. CFB (SE)	N	Nbase	N week 52	Mean base (SD)	Mean week 52 (SD)	Est. CFB (SE)	ETD [95%-CI] p-value	Hedges' g [95%-CI]	p-value int.
HbA1c at baseline (disease severity)															0.6962
<= 7.5	134	134	131	50.25 (8.4)	49.97 (9.1)	-0.11 (0.7)	131	131	122	49.86 (10.1)	50.00 (10.0)	0.00 (0.7)	-0.11 [-2.03;1.81] 0.9103	-0.03 [-0.27;0.22]	
7.5 <	277	277	255	49.52 (9.3)	50.27 (9.3)	0.39 (0.5)	279	279	260	50.26 (9.6)	50.03 (9.5)	0.03 (0.5)	0.36 [-1.02;1.73] 0.6125	0.10 [-0.08;0.27]	

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N: number of subjects in the analysis set, Nbase: number of subjects with an observation at baseline, N week 52: number of subjects with an observation at week 52, base: baseline, CI: confidence interval, Est. CFB: estimated change from baseline, ETD: estimated treatment difference, Mean: observed arithmetic mean, SD: standard deviation, SE: standard error, p-value: unadjusted two-sided p-value for test of no difference from 0 (t-test), p-value int.: unadjusted two-sided p-value for test of no treatment by subgroup interaction (F-test), *: p-value int. < 0,05

Missing post-baseline values were imputed by a pattern mixture model using multiple imputation. Change from baseline was analysed using an ANCOVA model with treatment, (region, if applicable), (subgroup, and interaction between treatment and subgroup, if applicable) as fixed factors and the corresponding baseline value as a covariate for each of the 1000 imputed complete datasets, and pooled by Rubin's rule to draw inference.

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4. Subgruppenanalysen – Sicherheit

4.1. Diabetic retinopathy and related complications - pre-defined MedDRA search - analysis of 2x2 tables - Pioneer 2 - in-trial - safety analysis set

	Oral Sema 14 mg			Empa 25 mg			Oral Sema 14 mg vs. Empa 25 mg				
Subgroup	N	n (%)	E	N	n (%)	E	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	p-value interaction
All subjects (total)	410	14 (3.4%)	14	409	5 (1.2%)	5	2.79 [1.02;7.68]	2.86 [1.02;8.01]	2.19 [0.14;4.25]	0.0390¤	
Gender											0.0274*
Female	204	8 (3.9%)	8	200	0 (0.0%)	0	16.67 [0.97;286.87]	17.35 [0.99;302.57]	3.92 [1.26;6.59]	0.0047¤	
Male	206	6 (2.9%)	6	209	5 (2.4%)	5	1.22 [0.38;3.93]	1.22 [0.37;4.07]	0.52 [-2.57;3.61]	0.8078¤	
Age											0.7935
< 65	305	12 (3.9%)	12	299	4 (1.3%)	4	2.94 [0.96;9.02]	3.02 [0.96;9.47]	2.60 [0.06;5.14]	0.0478¤	
65 <=	105	2 (1.9%)	2	110	1 (0.9%)	1	2.10 [0.19;22.76]	2.12 [0.19;23.70]	1.00 [-2.16;4.16]	0.5996¤	
Region A											0.3306
West Europe	77	2 (2.6%)	2	89	0 (0.0%)	0	5.77 [0.28;118.36]	5.93 [0.28;125.38]	2.60 [-0.96;6.15]	0.1581¤	
Rest of World	333	12 (3.6%)	12	320	5 (1.6%)	5	2.31 [0.82;6.47]	2.36 [0.82;6.76]	2.04 [-0.38;4.46]	0.1090¤	
HbA1c at baseline (disease severity)											0.7283
<= 7.5	133	4 (3.0%)	4	130	1 (0.8%)	1	3.91 [0.44;34.52]	4.00 [0.44;36.28]	2.24 [-1.03;5.51]	0.2455¤	
7.5 <	277	10 (3.6%)	10	279	4 (1.4%)	4	2.52 [0.80;7.93]	2.57 [0.80;8.31]	2.18 [-0.43;4.78]	0.1126¤	

N: number of subjects in the analysis set, n: number of subjects with at least one event, %: proportion of subjects with at least one event, E: number of events, RR: relative risk, OR: odds ratio, RD: risk difference in percentage points, CI: confidence interval, p-value: unadjusted two-sided p-value from test for 2x2 contingency table (¤: Barnard's unconditional exact test, ¤¤: Fisher's exact test), p-value interaction: unadjusted p-value for test of no interaction effect (Breslow-Day test for stratified 2x2 contingency tables), *: p-value interaction < 0,05, not est.: not estimated
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table.

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t_bin_p2.sas/t_bin_dr_meddra_p2.txt

4.2. Adverse events - analysis of 2x2 tables - Pioneer 2 - in-trial - safety analysis set

	Oral Sema 14 mg			Empa 25 mg			Oral Sema 14 mg vs. Empa 25 mg				
Subgroup	N	n (%)	E	N	n (%)	E	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	p-value interaction
All subjects (total)	410	292 (71.2%)	1089	409	284 (69.4%)	976	1.03 [0.94;1.12]	1.09 [0.81;1.47]	1.78 [-4.47;8.04]	0.5929¤¤	
Gender											0.1485
Female	204	145 (71.1%)	549	200	129 (64.5%)	440	1.10 [0.96;1.26]	1.35 [0.89;2.06]	6.58 [-2.51;15.67]	0.1673¤¤	
Male	206	147 (71.4%)	540	209	155 (74.2%)	536	0.96 [0.86;1.08]	0.87 [0.56;1.34]	-2.80 [-11.37;5.76]	0.5815¤¤	
Age											0.3613
< 65	305	215 (70.5%)	757	299	200 (66.9%)	673	1.05 [0.95;1.17]	1.18 [0.84;1.67]	3.60 [-3.79;10.99]	0.3802¤¤	
65 <=	105	77 (73.3%)	332	110	84 (76.4%)	303	0.96 [0.82;1.12]	0.85 [0.46;1.58]	-3.03 [-14.63;8.57]	0.6395¤¤	
Region A											0.0556
West Europe	77	50 (64.9%)	224	89	67 (75.3%)	279	0.86 [0.70;1.06]	0.61 [0.31;1.19]	-10.35 [-24.27;3.58]	0.1737¤	
Rest of World	333	242 (72.7%)	865	320	217 (67.8%)	697	1.07 [0.97;1.18]	1.26 [0.90;1.77]	4.86 [-2.15;11.87]	0.1988¤¤	
HbA1c at baseline (disease severity)											0.6898
<= 7.5	133	95 (71.4%)	394	130	93 (71.5%)	334	1.00 [0.86;1.16]	0.99 [0.58;1.70]	-0.11 [-11.02;10.80]	1.0000¤¤	
7.5 <	277	197 (71.1%)	695	279	191 (68.5%)	642	1.04 [0.93;1.16]	1.13 [0.79;1.63]	2.66 [-4.97;10.29]	0.5187¤¤	

N: number of subjects in the analysis set, n: number of subjects with at least one event, %: proportion of subjects with at least one event, E: number of events, RR: relative risk, OR: odds ratio, RD: risk difference in percentage points, CI: confidence interval, p-value: unadjusted two-sided p-value from test for 2x2 contingency table (¤: Barnard's unconditional exact test, ¤¤: Fisher's exact test), p-value interaction: unadjusted p-value for test of no interaction effect (Breslow-Day test for stratified 2x2 contingency tables), *: p-value interaction < 0,05, not est.: not estimated
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table.

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4.3. Serious adverse events - analysis of 2x2 tables - Pioneer 2 - in-trial - safety analysis set

	Oral Sema 14 mg			Empa 25 mg			Oral Sema 14 mg vs. Empa 25 mg				
Subgroup	N	n (%)	E	N	n (%)	E	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	p-value interaction
All subjects (total)	410	28 (6.8%)	44	409	37 (9.0%)	56	0.75 [0.47;1.21]	0.74 [0.44;1.23]	-2.22 [-5.92;1.48]	0.2478¤¤	
Gender											0.2780
Female	204	16 (7.8%)	22	200	16 (8.0%)	26	0.98 [0.50;1.91]	0.98 [0.48;2.02]	-0.16 [-5.42;5.11]	1.0000¤¤	
Male	206	12 (5.8%)	22	209	21 (10.0%)	30	0.58 [0.29;1.15]	0.55 [0.26;1.16]	-4.22 [-9.40;0.96]	0.1461¤¤	
Age											0.5731
< 65	305	21 (6.9%)	26	299	25 (8.4%)	36	0.82 [0.47;1.44]	0.81 [0.44;1.48]	-1.48 [-5.71;2.76]	0.5412¤¤	
65 <=	105	7 (6.7%)	18	110	12 (10.9%)	20	0.61 [0.25;1.49]	0.58 [0.22;1.54]	-4.24 [-11.77;3.29]	0.3395¤¤	
Region A											0.7923
West Europe	77	8 (10.4%)	12	89	13 (14.6%)	17	0.71 [0.31;1.63]	0.68 [0.27;1.73]	-4.22 [-14.23;5.80]	0.5319¤	
Rest of World	333	20 (6.0%)	32	320	24 (7.5%)	39	0.80 [0.45;1.42]	0.79 [0.43;1.46]	-1.49 [-5.35;2.36]	0.5328¤¤	
HbA1c at baseline (disease severity)											0.1966
<= 7.5	133	16 (12.0%)	29	130	15 (11.5%)	20	1.04 [0.54;2.02]	1.05 [0.50;2.22]	0.49 [-7.30;8.28]	1.0000¤¤	
7.5 <	277	12 (4.3%)	15	279	22 (7.9%)	36	0.55 [0.28;1.09]	0.53 [0.26;1.09]	-3.55 [-7.52;0.42]	0.1101¤¤	

N: number of subjects in the analysis set, n: number of subjects with at least one event, %: proportion of subjects with at least one event, E: number of events, RR: relative risk, OR: odds ratio, RD: risk difference in percentage points, CI: confidence interval, p-value: unadjusted two-sided p-value from test for 2x2 contingency table (¤: Barnard's unconditional exact test, ¤¤: Fisher's exact test), p-value interaction: unadjusted p-value for test of no interaction effect (Breslow-Day test for stratified 2x2 contingency tables), *: p-value interaction < 0,05, not est.: not estimated
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table.
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4.4. Severe adverse events - analysis of 2x2 tables - Pioneer 2 - in-trial - safety analysis set

	Oral Sema 14 mg			Empa 25 mg			Oral Sema 14 mg vs. Empa 25 mg				
Subgroup	N	n (%)	E	N	n (%)	E	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	p-value interaction
All subjects (total)	410	25 (6.1%)	37	409	24 (5.9%)	40	1.04 [0.60;1.79]	1.04 [0.58;1.86]	0.23 [-3.02;3.48]	1.0000¤¤	
Gender											0.0933
Female	204	8 (3.9%)	11	200	13 (6.5%)	19	0.60 [0.26;1.42]	0.59 [0.24;1.45]	-2.58 [-6.91;1.75]	0.2695¤¤	
Male	206	17 (8.3%)	26	209	11 (5.3%)	21	1.57 [0.75;3.27]	1.62 [0.74;3.55]	2.99 [-1.84;7.81]	0.2456¤¤	
Age											0.5205
< 65	305	16 (5.2%)	23	299	17 (5.7%)	31	0.92 [0.48;1.79]	0.92 [0.46;1.85]	-0.44 [-4.07;3.19]	0.8592¤¤	
65 <=	105	9 (8.6%)	14	110	7 (6.4%)	9	1.35 [0.52;3.49]	1.38 [0.49;3.85]	2.21 [-4.83;9.24]	0.6089¤¤	
Region A											0.3712
West Europe	77	7 (9.1%)	10	89	5 (5.6%)	5	1.62 [0.54;4.89]	1.68 [0.51;5.53]	3.47 [-4.53;11.48]	0.5319¤	
Rest of World	333	18 (5.4%)	27	320	19 (5.9%)	35	0.91 [0.49;1.70]	0.91 [0.47;1.76]	-0.53 [-4.08;3.02]	0.8659¤¤	
HbA1c at baseline (disease severity)											0.0831
<= 7.5	133	11 (8.3%)	17	130	5 (3.8%)	5	2.15 [0.77;6.02]	2.25 [0.76;6.68]	4.42 [-1.31;10.16]	0.1418¤	
7.5 <	277	14 (5.1%)	20	279	19 (6.8%)	35	0.74 [0.38;1.45]	0.73 [0.36;1.48]	-1.76 [-5.68;2.17]	0.4734¤¤	

N: number of subjects in the analysis set, n: number of subjects with at least one event, %: proportion of subjects with at least one event, E: number of events, RR: relative risk, OR: odds ratio, RD: risk difference in percentage points, CI: confidence interval, p-value: unadjusted two-sided p-value from test for 2x2 contingency table (¤: Barnard's unconditional exact test, ¤¤: Fisher's exact test), p-value interaction: unadjusted p-value for test of no interaction effect (Breslow-Day test for stratified 2x2 contingency tables), *: p-value interaction < 0,05, not est.: not estimated
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table.
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t_bin_p2.sas/t_bin_sev_ae_p2.txt

4.5. Moderate adverse events - analysis of 2x2 tables - Pioneer 2 - in-trial - safety analysis set

	Oral Sema 14 mg			Empa 25 mg			Oral Sema 14 mg vs. Empa 25 mg				
Subgroup	N	n (%)	E	N	n (%)	E	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	p-value interaction
All subjects (total)	410	142 (34.6%)	310	409	120 (29.3%)	214	1.18 [0.97;1.44]	1.28 [0.95;1.71]	5.29 [-1.08;11.67]	0.1157¤¤	
Gender											0.1787
Female	204	76 (37.3%)	139	200	55 (27.5%)	110	1.35 [1.02;1.81]	1.57 [1.03;2.38]	9.75 [0.68;18.83]	0.0433¤¤	
Male	206	66 (32.0%)	171	209	65 (31.1%)	104	1.03 [0.78;1.37]	1.04 [0.69;1.58]	0.94 [-8.01;9.88]	0.9159¤¤	
Age											0.6805
< 65	305	99 (32.5%)	200	299	79 (26.4%)	142	1.23 [0.96;1.58]	1.34 [0.94;1.90]	6.04 [-1.21;13.29]	0.1088¤¤	
65 <=	105	43 (41.0%)	110	110	41 (37.3%)	72	1.10 [0.79;1.53]	1.17 [0.67;2.02]	3.68 [-9.36;16.72]	0.6750¤¤	
Region A											0.4531
West Europe	77	16 (20.8%)	35	89	19 (21.3%)	27	0.97 [0.54;1.76]	0.97 [0.46;2.04]	-0.57 [-13.00;11.86]	0.9924¤	
Rest of World	333	126 (37.8%)	275	320	101 (31.6%)	187	1.20 [0.97;1.48]	1.32 [0.96;1.82]	6.28 [-1.01;13.56]	0.1004¤¤	
HbA1c at baseline (disease severity)											0.7144
<= 7.5	133	49 (36.8%)	119	130	43 (33.1%)	88	1.11 [0.80;1.55]	1.18 [0.71;1.96]	3.77 [-7.75;15.28]	0.6051¤¤	
7.5 <	277	93 (33.6%)	191	279	77 (27.6%)	126	1.22 [0.95;1.57]	1.33 [0.92;1.90]	5.98 [-1.67;13.62]	0.1409¤¤	

N: number of subjects in the analysis set, n: number of subjects with at least one event, %: proportion of subjects with at least one event, E: number of events, RR: relative risk, OR: odds ratio, RD: risk difference in percentage points, CI: confidence interval, p-value: unadjusted two-sided p-value from test for 2x2 contingency table (¤: Barnard's unconditional exact test, ¤¤: Fisher's exact test), p-value interaction: unadjusted p-value for test of no interaction effect (Breslow-Day test for stratified 2x2 contingency tables), *: p-value interaction < 0,05, not est.: not estimated
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table.

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t_bin_p2.sas/t_bin_mod_ae_p2.txt

4.6. Mild adverse events - analysis of 2x2 tables - Pioneer 2 - in-trial - safety analysis set

	Oral Sema 14 mg			Empa 25 mg			Oral Sema 14 mg vs. Empa 25 mg				
Subgroup	N	n (%)	E	N	n (%)	E	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	p-value interaction
All subjects (total)	410	247 (60.2%)	742	409	243 (59.4%)	722	1.01 [0.91;1.13]	1.04 [0.78;1.37]	0.83 [-5.88;7.55]	0.8309¤¤	
Gender											0.2590
Female	204	122 (59.8%)	399	200	110 (55.0%)	311	1.09 [0.92;1.29]	1.22 [0.82;1.81]	4.80 [-4.83;14.44]	0.3654¤¤	
Male	206	125 (60.7%)	343	209	133 (63.6%)	411	0.95 [0.82;1.11]	0.88 [0.59;1.31]	-2.96 [-12.29;6.37]	0.5452¤¤	
Age											0.7685
< 65	305	182 (59.7%)	534	299	174 (58.2%)	500	1.03 [0.90;1.17]	1.06 [0.77;1.47]	1.48 [-6.37;9.32]	0.7410¤¤	
65 <=	105	65 (61.9%)	208	110	69 (62.7%)	222	0.99 [0.80;1.22]	0.97 [0.56;1.68]	-0.82 [-13.78;12.14]	1.0000¤¤	
Region A											0.2038
West Europe	77	47 (61.0%)	179	89	61 (68.5%)	247	0.89 [0.71;1.12]	0.72 [0.38;1.36]	-7.50 [-22.05;7.05]	0.3628¤	
Rest of World	333	200 (60.1%)	563	320	182 (56.9%)	475	1.06 [0.93;1.20]	1.14 [0.84;1.56]	3.19 [-4.37;10.74]	0.4275¤¤	
HbA1c at baseline (disease severity)											0.9876
<= 7.5	133	82 (61.7%)	258	130	79 (60.8%)	241	1.01 [0.84;1.23]	1.04 [0.63;1.70]	0.88 [-10.89;12.66]	0.8999¤¤	
7.5 <	277	165 (59.6%)	484	279	164 (58.8%)	481	1.01 [0.88;1.16]	1.03 [0.74;1.45]	0.79 [-7.39;8.96]	0.8634¤¤	

N: number of subjects in the analysis set, n: number of subjects with at least one event, %: proportion of subjects with at least one event, E: number of events, RR: relative risk, OR: odds ratio, RD: risk difference in percentage points, CI: confidence interval, p-value: unadjusted two-sided p-value from test for 2x2 contingency table (¤: Barnard's unconditional exact test, ¤¤: Fisher's exact test), p-value interaction: unadjusted p-value for test of no interaction effect (Breslow-Day test for stratified 2x2 contingency tables), *: p-value interaction < 0,05, not est.: not estimated
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table.

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t_bin_p2.sas/t_bin_mild_ae_p2.txt

4.7. Adverse events leading to premature trial product discontinuation - analysis of 2x2 tables - Pioneer 2 - in-trial - safety analysis set

	Oral Sema 14 mg			Empa 25 mg			Oral Sema 14 mg vs. Empa 25 mg				
Subgroup	N	n (%)	E	N	n (%)	E	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	p-value interaction
All subjects (total)	410	44 (10.7%)	83	409	18 (4.4%)	30	2.44 [1.43;4.15]	2.61 [1.48;4.60]	6.33 [2.74;9.93]	0.0008¤¤	
Gender											0.1851
Female	204	23 (11.3%)	44	200	6 (3.0%)	9	3.76 [1.56;9.03]	4.11 [1.64;10.32]	8.27 [3.33;13.22]	0.0016¤¤	
Male	206	21 (10.2%)	39	209	12 (5.7%)	21	1.78 [0.90;3.51]	1.86 [0.89;3.89]	4.45 [-0.75;9.65]	0.1046¤¤	
Age											0.6821
< 65	305	28 (9.2%)	45	299	10 (3.3%)	10	2.74 [1.36;5.55]	2.92 [1.39;6.13]	5.84 [2.01;9.66]	0.0039¤¤	
65 <=	105	16 (15.2%)	38	110	8 (7.3%)	20	2.10 [0.94;4.69]	2.29 [0.94;5.61]	7.97 [-0.45;16.38]	0.0828¤¤	
Region A											0.9214
West Europe	77	6 (7.8%)	10	89	3 (3.4%)	4	2.31 [0.60;8.93]	2.42 [0.58;10.03]	4.42 [-2.64;11.49]	0.2269¤	
Rest of World	333	38 (11.4%)	73	320	15 (4.7%)	26	2.43 [1.37;4.34]	2.62 [1.41;4.86]	6.72 [2.60;10.85]	0.0023¤¤	
HbA1c at baseline (disease severity)											0.3267
<= 7.5	133	18 (13.5%)	39	130	5 (3.8%)	11	3.52 [1.35;9.20]	3.91 [1.41;10.88]	9.69 [3.00;16.38]	0.0056¤	
7.5 <	277	26 (9.4%)	44	279	13 (4.7%)	19	2.01 [1.06;3.84]	2.12 [1.07;4.22]	4.73 [0.49;8.96]	0.0315¤¤	

N: number of subjects in the analysis set, n: number of subjects with at least one event, %: proportion of subjects with at least one event, E: number of events, RR: relative risk, OR: odds ratio, RD: risk difference in percentage points, CI: confidence interval, p-value: unadjusted two-sided p-value from test for 2x2 contingency table (¤: Barnard's unconditional exact test, ¤¤: Fisher's exact test), p-value interaction: unadjusted p-value for test of no interaction effect (Breslow-Day test for stratified 2x2 contingency tables), *: p-value interaction < 0,05, not est.: not estimated
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table.
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4.8. Neoplasms - pre-defined MedDRA search - analysis of 2x2 tables - Pioneer 2 - in-trial - safety analysis set

	Oral Sema 14 mg			Empa 25 mg			Oral Sema 14 mg vs. Empa 25 mg				
Subgroup	N	n (%)	E	N	n (%)	E	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	p-value interaction
All subjects (total)	410	24 (5.9%)	39	409	13 (3.2%)	18	1.84 [0.95;3.57]	1.89 [0.95;3.77]	2.68 [-0.16;5.51]	0.0913¤¤	
Gender											0.4345
Female	204	10 (4.9%)	13	200	7 (3.5%)	10	1.40 [0.54;3.61]	1.42 [0.53;3.81]	1.40 [-2.51;5.31]	0.6218¤¤	
Male	206	14 (6.8%)	26	209	6 (2.9%)	8	2.37 [0.93;6.04]	2.47 [0.93;6.55]	3.93 [-0.19;8.04]	0.0696¤¤	
Age											0.1298
< 65	305	13 (4.3%)	18	299	10 (3.3%)	13	1.27 [0.57;2.86]	1.29 [0.56;2.98]	0.92 [-2.13;3.97]	0.6720¤¤	
65 <=	105	11 (10.5%)	21	110	3 (2.7%)	5	3.84 [1.10;13.38]	4.17 [1.13;15.41]	7.75 [1.15;14.35]	0.0217¤	
Region A											0.8623
West Europe	77	7 (9.1%)	12	89	4 (4.5%)	5	2.02 [0.62;6.65]	2.13 [0.60;7.56]	4.60 [-3.13;12.33]	0.2623¤	
Rest of World	333	17 (5.1%)	27	320	9 (2.8%)	13	1.82 [0.82;4.01]	1.86 [0.82;4.23]	2.29 [-0.69;5.27]	0.1623¤¤	
HbA1c at baseline (disease severity)											0.9701
<= 7.5	133	11 (8.3%)	21	130	6 (4.6%)	9	1.79 [0.68;4.70]	1.86 [0.67;5.20]	3.66 [-2.25;9.56]	0.3166¤¤	
7.5 <	277	13 (4.7%)	18	279	7 (2.5%)	9	1.87 [0.76;4.62]	1.91 [0.75;4.87]	2.18 [-0.91;5.28]	0.1800¤¤	

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N: number of subjects in the analysis set, n: number of subjects with at least one event, %: proportion of subjects with at least one event, E: number of events, RR: relative risk, OR: odds ratio, RD: risk difference in percentage points, CI: confidence interval, p-value: unadjusted two-sided p-value from test for 2x2 contingency table (¤: Barnard's unconditional exact test, ¤¤: Fisher's exact test), p-value interaction: unadjusted p-value for test of no interaction effect (Breslow-Day test for stratified 2x2 contingency tables), *: p-value interaction < 0,05, not est.: not estimated
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table.
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4.9. Symptomatic hypoglycaemia with blood glucose < 56 mg/dL - analysis of 2x2 tables - Pioneer 2 - in-trial - safety analysis set

	Oral Sema 14 mg			Empa 25 mg			Oral Sema 14 mg vs. Empa 25 mg				
Subgroup	N	n (%)	E	N	n (%)	E	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	p-value interaction
All subjects (total)	410	8 (2.0%)	14	409	7 (1.7%)	8	1.14 [0.42;3.11]	1.14 [0.41;3.18]	0.24 [-1.60;2.08]	1.0000¤¤	
Gender											0.4496
Female	204	7 (3.4%)	13	200	5 (2.5%)	6	1.37 [0.44;4.25]	1.39 [0.43;4.44]	0.93 [-2.37;4.24]	0.6828¤	
Male	206	1 (0.5%)	1	209	2 (1.0%)	2	0.51 [0.05;5.55]	0.50 [0.05;5.61]	-0.47 [-2.10;1.15]	0.6828¤	
Age											0.2800
< 65	305	5 (1.6%)	6	299	6 (2.0%)	6	0.82 [0.25;2.65]	0.81 [0.25;2.70]	-0.37 [-2.50;1.77]	0.8080¤	
65 <=	105	3 (2.9%)	8	110	1 (0.9%)	2	3.14 [0.33;29.74]	3.21 [0.33;31.32]	1.95 [-1.70;5.59]	0.3243¤	
Region A											0.5056
West Europe	77	2 (2.6%)	3	89	1 (1.1%)	1	2.31 [0.21;25.00]	2.35 [0.21;26.39]	1.47 [-2.70;5.65]	0.5923¤	
Rest of World	333	6 (1.8%)	11	320	6 (1.9%)	7	0.96 [0.31;2.95]	0.96 [0.31;3.01]	-0.07 [-2.13;1.99]	1.0000¤¤	
HbA1c at baseline (disease severity)											0.1469
<= 7.5	133	4 (3.0%)	10	130	1 (0.8%)	1	3.91 [0.44;34.52]	4.00 [0.44;36.28]	2.24 [-1.03;5.51]	0.2455¤	
7.5 <	277	4 (1.4%)	4	279	6 (2.2%)	7	0.67 [0.19;2.35]	0.67 [0.19;2.39]	-0.71 [-2.91;1.50]	0.5641¤	

N: number of subjects in the analysis set, n: number of subjects with at least one event, %: proportion of subjects with at least one event, E: number of events, RR: relative risk, OR: odds ratio, RD: risk difference in percentage points, CI: confidence interval, p-value: unadjusted two-sided p-value from test for 2x2 contingency table (¤: Barnard's unconditional exact test, ¤¤: Fisher's exact test), p-value interaction: unadjusted p-value for test of no interaction effect (Breslow-Day test for stratified 2x2 contingency tables), *: p-value interaction < 0,05, not est.: not estimated
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table.

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t_bin_p2.sas/t_bin_ae_hypo_meddra_p2.txt

4.10. Adverse events by system organ class - analysis of 2x2 tables - Pioneer 2 - in-trial – safety analysis set

System Organ Class	Subgroup	Oral Sema 14 mg N	Oral Sema 14 mg n (%)	Oral Sema 14 mg E	Empa 25 mg N	Empa 25 mg n (%)	Empa 25 mg E	Oral Sema 14 mg vs. Empa 25 mg RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	p-value interaction
Gastrointestinal disorders	All subjects (total)	410	167 (40.7%)	345	409	58 (14.2%)	93	2.87 [2.20;3.75]	4.16 [2.96;5.85]	26.55 [20.72;32.39]	<0.0001¤¤	
	Gender											0.9419
	Female	204	83 (40.7%)	172	200	28 (14.0%)	53	2.91 [1.98;4.26]	4.21 [2.59;6.86]	26.69 [18.41;34.97]	<0.0001¤¤	
	Male	206	84 (40.8%)	173	209	30 (14.4%)	40	2.84 [1.96;4.11]	4.11 [2.55;6.61]	26.42 [18.20;34.65]	<0.0001¤¤	
	Age											0.2166
	< 65	305	120 (39.3%)	244	299	45 (15.1%)	76	2.61 [1.93;3.54]	3.66 [2.48;5.42]	24.29 [17.48;31.11]	<0.0001¤¤	
	65 <=	105	47 (44.8%)	101	110	13 (11.8%)	17	3.79 [2.18;6.58]	6.05 [3.02;12.12]	32.94 [21.68;44.21]	<0.0001¤¤	
	Region A											0.3084
	West Europe	77	29 (37.7%)	59	89	15 (16.9%)	24	2.23 [1.30;3.85]	2.98 [1.45;6.13]	20.81 [7.48;34.14]	0.0025¤	
	Rest of World	333	138 (41.4%)	286	320	43 (13.4%)	69	3.08 [2.27;4.19]	4.56 [3.09;6.72]	28.00 [21.53;34.48]	<0.0001¤¤	
	HbA1c at baseline (disease severity)											0.6874
	<= 7.5	133	56 (42.1%)	121	130	21 (16.2%)	30	2.61 [1.68;4.04]	3.77 [2.11;6.74]	25.95 [15.44;36.46]	<0.0001¤¤	
	7.5 <	277	111 (40.1%)	224	279	37 (13.3%)	63	3.02 [2.17;4.22]	4.37 [2.87;6.66]	26.81 [19.80;33.82]	<0.0001¤¤	

N: number of subjects in the analysis set, n: number of subjects with at least one event, %: proportion of subjects with at least one event, E: number of events, RR: relative risk, OR: odds ratio, RD: risk difference in percentage points, CI: confidence interval, p-value: unadjusted two-sided p-value from test for 2x2 contingency table (¤: Barnard's unconditional exact test, ¤¤: Fisher's exact test), p-value interaction: unadjusted p-value for test of no interaction effect (Breslow-Day test for stratified 2x2 contingency tables), *: p-value interaction < 0,05, not est.: not estimated
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table.
Subgroup analyses were only performed if p-value < 0,05 for all subjects (total).

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4.11. Adverse events by system organ class - analysis of 2x2 tables - Pioneer 2 - in-trial – safety analysis set

System Organ Class	Subgroup	Oral Sema 14 mg N	Oral Sema 14 mg n (%)	Oral Sema 14 mg E	Empa 25 mg N	Empa 25 mg n (%)	Empa 25 mg E	Oral Sema 14 mg vs. Empa 25 mg RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	p-value interaction
Infections and infestations	All subjects (total)	410	102 (24.9%)	174	409	131 (32.0%)	205	0.78 [0.62;0.97]	0.70 [0.52;0.95]	-7.15 [-13.31;-0.99]	0.0248¤¤	
	Gender											0.6146
	Female	204	52 (25.5%)	95	200	69 (34.5%)	108	0.74 [0.55;1.00]	0.65 [0.42;1.00]	-9.01 [-17.91;-0.11]	0.0512¤¤	
	Male	206	50 (24.3%)	79	209	62 (29.7%)	97	0.82 [0.59;1.13]	0.76 [0.49;1.17]	-5.39 [-13.92;3.13]	0.2256¤¤	
	Age											0.9163
	< 65	305	73 (23.9%)	128	299	93 (31.1%)	146	0.77 [0.59;1.00]	0.70 [0.49;1.00]	-7.17 [-14.27;-0.07]	0.0556¤¤	
	65 <=	105	29 (27.6%)	46	110	38 (34.5%)	59	0.80 [0.53;1.20]	0.72 [0.40;1.29]	-6.93 [-19.26;5.41]	0.3042¤¤	
	Region A											0.4910
	West Europe	77	26 (33.8%)	50	89	33 (37.1%)	55	0.91 [0.60;1.38]	0.87 [0.46;1.64]	-3.31 [-17.88;11.26]	0.7193¤	
	Rest of World	333	76 (22.8%)	124	320	98 (30.6%)	150	0.75 [0.58;0.96]	0.67 [0.47;0.95]	-7.80 [-14.57;-1.03]	0.0269¤¤	
	HbA1c at baseline (disease severity)											0.1512
	<= 7.5	133	28 (21.1%)	41	130	45 (34.6%)	63	0.61 [0.41;0.91]	0.50 [0.29;0.87]	-13.56 [-24.28;-2.84]	0.0189¤¤	
	7.5 <	277	74 (26.7%)	133	279	86 (30.8%)	142	0.87 [0.67;1.13]	0.82 [0.57;1.18]	-4.11 [-11.63;3.41]	0.3035¤¤	

N: number of subjects in the analysis set, n: number of subjects with at least one event, %: proportion of subjects with at least one event, E: number of events, RR: relative risk, OR: odds ratio, RD: risk difference in percentage points, CI: confidence interval, p-value: unadjusted two-sided p-value from test for 2x2 contingency table (¤: Barnard's unconditional exact test, ¤¤: Fisher's exact test), p-value interaction: unadjusted p-value for test of no interaction effect (Breslow-Day test for stratified 2x2 contingency tables), *: p-value interaction < 0,05, not est.: not estimated
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table.
Subgroup analyses were only performed if p-value < 0,05 for all subjects (total).
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4.12. Adverse events by system organ class - analysis of 2x2 tables - Pioneer 2 - in-trial – safety analysis set

System Organ Class	Subgroup	Oral Sema 14 mg N	Oral Sema 14 mg n (%)	Oral Sema 14 mg E	Empa 25 mg N	Empa 25 mg n (%)	Empa 25 mg E	Oral Sema 14 mg vs. Empa 25 mg RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	p-value interaction
Renal and urinary disorders	All subjects (total)	410	26 (6.3%)	28	409	45 (11.0%)	55	0.58 [0.36;0.92]	0.55 [0.33;0.91]	-4.66 [-8.50;-0.82]	0.0185¤¤	
	Gender											0.7738
	Female	204	12 (5.9%)	12	200	19 (9.5%)	26	0.62 [0.31;1.24]	0.60 [0.28;1.26]	-3.62 [-8.81;1.57]	0.1937¤¤	
	Male	206	14 (6.8%)	16	209	26 (12.4%)	29	0.55 [0.29;1.02]	0.51 [0.26;1.01]	-5.64 [-11.29;-0.00]	0.0665¤¤	
	Age											0.0163*
	< 65	305	13 (4.3%)	15	299	34 (11.4%)	40	0.37 [0.20;0.70]	0.35 [0.18;0.67]	-7.11 [-11.36;-2.86]	0.0013¤¤	
	65 <=	105	13 (12.4%)	13	110	11 (10.0%)	15	1.24 [0.58;2.64]	1.27 [0.54;2.98]	2.38 [-6.05;10.81]	0.6669¤¤	
	Region A											0.8853
	West Europe	77	8 (10.4%)	8	89	16 (18.0%)	20	0.58 [0.26;1.28]	0.53 [0.21;1.31]	-7.59 [-18.08;2.90]	0.1754¤	
	Rest of World	333	18 (5.4%)	20	320	29 (9.1%)	35	0.60 [0.34;1.05]	0.57 [0.31;1.05]	-3.66 [-7.63;0.32]	0.0948¤¤	
	HbA1c at baseline (disease severity)											0.0754
	<= 7.5	133	15 (11.3%)	16	130	16 (12.3%)	18	0.92 [0.47;1.78]	0.91 [0.43;1.92]	-1.03 [-8.83;6.77]	0.8497¤¤	

N: number of subjects in the analysis set, n: number of subjects with at least one event, %: proportion of subjects with at least one event, E: number of events, RR: relative risk, OR: odds ratio, RD: risk difference in percentage points, CI: confidence interval, p-value: unadjusted two-sided p-value from test for 2x2 contingency table (¤: Barnard's unconditional exact test, ¤¤: Fisher's exact test), p-value interaction: unadjusted p-value for test of no interaction effect (Breslow-Day test for stratified 2x2 contingency tables), *: p-value interaction < 0,05, not est.: not estimated
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table.
Subgroup analyses were only performed if p-value < 0,05 for all subjects (total).

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4.13. Adverse events by preferred term - analysis of 2x2 tables - Pioneer 2 - in-trial – safety analysis set

		Oral Sema 14 mg			Empa 25 mg			Oral Sema 14 mg vs. Empa 25 mg				
Preferred Term	Subgroup	N	n (%)	E	N	n (%)	E	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	p-value interaction
Abdominal pain upper	All subjects (total)	410	21 (5.1%)	22	409	6 (1.5%)	7	3.49 [1.42;8.56]	3.63 [1.45;9.08]	3.65 [1.22;6.09]	0.0052¤¤	
	Gender											0.8730
	Female	204	8 (3.9%)	9	200	2 (1.0%)	2	3.92 [0.84;18.24]	4.04 [0.85;19.27]	2.92 [-0.08;5.92]	0.0616¤	
	Male	206	13 (6.3%)	13	209	4 (1.9%)	5	3.30 [1.09;9.95]	3.45 [1.11;10.77]	4.40 [0.59;8.20]	0.0243¤	
	Age											0.3148
	< 65	305	18 (5.9%)	18	299	6 (2.0%)	7	2.94 [1.18;7.31]	3.06 [1.20;7.83]	3.89 [0.81;6.98]	0.0202¤¤	
	65 <=	105	3 (2.9%)	4	110	0 (0.0%)	0	7.33 [0.38;140.22]	7.55 [0.39;147.88]	2.86 [-0.33;6.04]	0.0784¤	
	Region A											0.7853
	West Europe	77	5 (6.5%)	5	89	2 (2.2%)	3	2.89 [0.58;14.47]	3.02 [0.57;16.04]	4.25 [-2.06;10.55]	0.1900¤	
	Rest of World	333	16 (4.8%)	17	320	4 (1.3%)	4	3.84 [1.30;11.37]	3.99 [1.32;12.06]	3.55 [0.96;6.15]	0.0087¤	
	HbA1c at baseline (disease severity)											0.6832
	<= 7.5	133	9 (6.8%)	10	130	2 (1.5%)	2	4.40 [0.97;19.97]	4.65 [0.98;21.93]	5.23 [0.46;9.99]	0.0365¤	
	7.5 <	277	12 (4.3%)	12	279	4 (1.4%)	5	3.02 [0.99;9.25]	3.11 [0.99;9.77]	2.90 [0.12;5.67]	0.0419¤	

N: number of subjects in the analysis set, n: number of subjects with at least one event, %: proportion of subjects with at least one event, E: number of events, RR: relative risk, OR: odds ratio, RD: risk difference in percentage points, CI: confidence interval, p-value: unadjusted two-sided p-value from test for 2x2 contingency table (¤: Barnard's unconditional exact test, ¤¤: Fisher's exact test), p-value interaction: unadjusted p-value for test of no interaction effect (Breslow-Day test for stratified 2x2 contingency tables), *: p-value interaction < 0,05, not est.: not estimated
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table.
Subgroup analyses were only performed if p-value < 0,05 for all subjects (total).

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4.14. Adverse events by preferred term - analysis of 2x2 tables - Pioneer 2 - in-trial – safety analysis set

Preferred Term	Subgroup	Oral Sema 14 mg N	Oral Sema 14 mg n (%)	Oral Sema 14 mg E	Empa 25 mg N	Empa 25 mg n (%)	Empa 25 mg E	Oral Sema 14 mg vs. Empa 25 mg RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	p-value interaction
Balanoposthitis	All subjects (total)	410	0 (0.0%)	0	409	10 (2.4%)	12	0.05 [0.00;0.81]	0.05 [0.00;0.79]	-2.44 [-3.94;-0.95]	0.0015¤	
	Gender											not est.
	Female	204	0 (0.0%)	0	200	0 (0.0%)	0	not est.	not est.	not est.	not est.	
	Male	206	0 (0.0%)	0	209	10 (4.8%)	12	0.05 [0.00;0.82]	0.05 [0.00;0.79]	-4.78 [-7.68;-1.89]	0.0016¤	
	Age											not est.
	< 65	305	0 (0.0%)	0	299	6 (2.0%)	7	0.08 [0.00;1.33]	0.07 [0.00;1.32]	-2.01 [-3.60;-0.42]	0.0132¤	
	65 <=	105	0 (0.0%)	0	110	4 (3.6%)	5	0.12 [0.01;2.13]	0.11 [0.01;2.11]	-3.64 [-7.13;-0.14]	0.0533¤	
	Region A											not est.
	West Europe	77	0 (0.0%)	0	89	4 (4.5%)	5	0.13 [0.01;2.34]	0.12 [0.01;2.31]	-4.49 [-8.80;-0.19]	0.0620¤	
	Rest of World	333	0 (0.0%)	0	320	6 (1.9%)	7	0.07 [0.00;1.31]	0.07 [0.00;1.29]	-1.88 [-3.36;-0.39]	0.0123¤	
	HbA1c at baseline (disease severity)											not est.
	<= 7.5	133	0 (0.0%)	0	130	5 (3.8%)	6	0.09 [0.00;1.59]	0.09 [0.00;1.56]	-3.85 [-7.15;-0.54]	0.0233¤	
	7.5 <	277	0 (0.0%)	0	279	5 (1.8%)	6	0.09 [0.01;1.65]	0.09 [0.00;1.63]	-1.79 [-3.35;-0.24]	0.0256¤	

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N: number of subjects in the analysis set, n: number of subjects with at least one event, %: proportion of subjects with at least one event, E: number of events, RR: relative risk, OR: odds ratio, RD: risk difference in percentage points, CI: confidence interval, p-value: unadjusted two-sided p-value from test for 2x2 contingency table (¤: Barnard's unconditional exact test, ¤¤: Fisher's exact test), p-value interaction: unadjusted p-value for test of no interaction effect (Breslow-Day test for stratified 2x2 contingency tables), *: p-value interaction < 0,05, not est.: not estimated
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table.
Subgroup analyses were only performed if p-value < 0,05 for all subjects (total).
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4.15. Adverse events by preferred term - analysis of 2x2 tables - Pioneer 2 - in-trial – safety analysis set

		Oral Sema 14 mg			Empa 25 mg			Oral Sema 14 mg vs. Empa 25 mg				
Preferred Term	Subgroup	N	n (%)	E	N	n (%)	E	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	p-value interaction
Constipation	All subjects (total)	410	17 (4.1%)	17	409	4 (1.0%)	5	4.24 [1.44;12.49]	4.38 [1.46;13.13]	3.17 [1.02;5.32]	0.0042¤	
	Gender											0.5945
	Female	204	11 (5.4%)	11	200	2 (1.0%)	3	5.39 [1.21;24.02]	5.64 [1.23;25.79]	4.39 [1.00;7.78]	0.0126¤	
	Male	206	6 (2.9%)	6	209	2 (1.0%)	2	3.04 [0.62;14.91]	3.11 [0.62;15.57]	1.96 [-0.69;4.60]	0.1516¤	
	Age											0.2663
	< 65	305	13 (4.3%)	13	299	4 (1.3%)	5	3.19 [1.05;9.66]	3.28 [1.06;10.19]	2.92 [0.31;5.54]	0.0310¤	
	65 <=	105	4 (3.8%)	4	110	0 (0.0%)	0	9.42 [0.51;172.93]	9.80 [0.52;184.26]	3.81 [0.15;7.47]	0.0415¤	
	Region A											0.2951
	West Europe	77	1 (1.3%)	1	89	1 (1.1%)	1	1.16 [0.07;18.17]	1.16 [0.07;18.83]	0.18 [-3.17;3.52]	0.9924¤	
	Rest of World	333	16 (4.8%)	16	320	3 (0.9%)	4	5.13 [1.51;17.42]	5.33 [1.54;18.48]	3.87 [1.34;6.40]	0.0033¤	
	HbA1c at baseline (disease severity)											0.2195
	<= 7.5	133	5 (3.8%)	5	130	0 (0.0%)	0	10.75 [0.60;192.54]	11.17 [0.61;204.10]	3.76 [0.53;6.99]	0.0262¤	
	7.5 <	277	12 (4.3%)	12	279	4 (1.4%)	5	3.02 [0.99;9.25]	3.11 [0.99;9.77]	2.90 [0.12;5.67]	0.0419¤	

N: number of subjects in the analysis set, n: number of subjects with at least one event, %: proportion of subjects with at least one event, E: number of events, RR: relative risk, OR: odds ratio, RD: risk difference in percentage points, CI: confidence interval, p-value: unadjusted two-sided p-value from test for 2x2 contingency table (¤: Barnard's unconditional exact test, ¤¤: Fisher's exact test), p-value interaction: unadjusted p-value for test of no interaction effect (Breslow-Day test for stratified 2x2 contingency tables), *: p-value interaction < 0,05, not est.: not estimated
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table.
Subgroup analyses were only performed if p-value < 0,05 for all subjects (total).

nn9924/nn9924-submission-21FEB2020:08:53:56 - package/germany t_bin_soc_pt_p2.sas/t_bin_ae_pt_p2.txt

4.16. Adverse events by preferred term - analysis of 2x2 tables - Pioneer 2 - in-trial – safety analysis set

		Oral Sema 14 mg			Empa 25 mg			Oral Sema 14 mg vs. Empa 25 mg				
Preferred Term	Subgroup	N	n (%)	E	N	n (%)	E	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	p-value interaction
Decreased appetite	All subjects (total)	410	21 (5.1%)	21	409	2 (0.5%)	2	10.47 [2.47;44.38]	10.99 [2.56;47.16]	4.63 [2.39;6.87]	<0.0001¤	
	Gender											0.9643
	Female	204	11 (5.4%)	11	200	1 (0.5%)	1	10.78 [1.41;82.76]	11.34 [1.45;88.69]	4.89 [1.64;8.14]	0.0038¤	
	Male	206	10 (4.9%)	10	209	1 (0.5%)	1	10.15 [1.31;78.54]	10.61 [1.35;83.67]	4.38 [1.30;7.46]	0.0059¤	
	Age											0.9846
	< 65	305	11 (3.6%)	11	299	1 (0.3%)	1	10.78 [1.40;83.01]	11.15 [1.43;86.91]	3.27 [1.08;5.46]	0.0040¤	
	65 <=	105	10 (9.5%)	10	110	1 (0.9%)	1	10.48 [1.36;80.42]	11.47 [1.44;91.29]	8.61 [2.73;14.50]	0.0042¤	
	Region A											0.1903
	West Europe	77	9 (11.7%)	9	89	0 (0.0%)	0	21.92 [1.30;370.61]	24.82 [1.42;433.99]	11.69 [4.51;18.86]	0.0009¤	
	Rest of World	333	12 (3.6%)	12	320	2 (0.6%)	2	5.77 [1.30;25.56]	5.94 [1.32;26.77]	2.98 [0.80;5.16]	0.0088¤	
	HbA1c at baseline (disease severity)											0.6226
	<= 7.5	133	7 (5.3%)	7	130	1 (0.8%)	1	6.84 [0.85;54.84]	7.17 [0.87;59.09]	4.49 [0.41;8.58]	0.0358¤	
	7.5 <	277	14 (5.1%)	14	279	1 (0.4%)	1	14.10 [1.87;106.50]	14.80 [1.93;113.33]	4.70 [2.02;7.37]	0.0006¤	

N: number of subjects in the analysis set, n: number of subjects with at least one event, %: proportion of subjects with at least one event, E: number of events, RR: relative risk, OR: odds ratio, RD: risk difference in percentage points, CI: confidence interval, p-value: unadjusted two-sided p-value from test for 2x2 contingency table (¤: Barnard's unconditional exact test, ¤¤: Fisher's exact test), p-value interaction: unadjusted p-value for test of no interaction effect (Breslow-Day test for stratified 2x2 contingency tables), *: p-value interaction < 0,05, not est.: not estimated
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table.
Subgroup analyses were only performed if p-value < 0,05 for all subjects (total).

nn9924/nn9924-submission-21FEB2020:08:53:56 - package/germany t_bin_soc_pt_p2.sas/t_bin_ae_pt_p2.txt

4.17. Adverse events by preferred term - analysis of 2x2 tables - Pioneer 2 - in-trial – safety analysis set

Preferred Term	Subgroup	Oral Sema 14 mg N	Oral Sema 14 mg n (%)	Oral Sema 14 mg E	Empa 25 mg N	Empa 25 mg n (%)	Empa 25 mg E	Oral Sema 14 mg vs. Empa 25 mg RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	p-value interaction
Diarrhoea	All subjects (total)	410	38 (9.3%)	48	409	13 (3.2%)	17	2.92 [1.58;5.39]	3.11 [1.63;5.93]	6.09 [2.81;9.37]	0.0004¤¤	
	Gender											0.3410
	Female	204	18 (8.8%)	21	200	8 (4.0%)	9	2.21 [0.98;4.96]	2.32 [0.99;5.47]	4.82 [0.08;9.57]	0.0666¤¤	
	Male	206	20 (9.7%)	27	209	5 (2.4%)	8	4.06 [1.55;10.61]	4.39 [1.61;11.92]	7.32 [2.77;11.86]	0.0017¤	
	Age											0.4811
	< 65	305	29 (9.5%)	39	299	11 (3.7%)	15	2.58 [1.32;5.08]	2.75 [1.35;5.61]	5.83 [1.91;9.75]	0.0049¤¤	
	65 <=	105	9 (8.6%)	9	110	2 (1.8%)	2	4.71 [1.04;21.31]	5.06 [1.07;24.01]	6.75 [0.85;12.66]	0.0256¤	
	Region A											0.9998
	West Europe	77	10 (13.0%)	12	89	4 (4.5%)	7	2.89 [0.94;8.84]	3.17 [0.95;10.56]	8.49 [-0.16;17.15]	0.0541¤	
	Rest of World	333	28 (8.4%)	36	320	9 (2.8%)	10	2.99 [1.43;6.24]	3.17 [1.47;6.83]	5.60 [2.11;9.08]	0.0021¤¤	
	HbA1c at baseline (disease severity)											0.7080
	<= 7.5	133	14 (10.5%)	21	130	4 (3.1%)	4	3.42 [1.16;10.12]	3.71 [1.19;11.58]	7.45 [1.45;13.45]	0.0189¤	
	7.5 <	277	24 (8.7%)	27	279	9 (3.2%)	13	2.69 [1.27;5.67]	2.85 [1.30;6.24]	5.44 [1.53;9.35]	0.0070¤¤	

N: number of subjects in the analysis set, n: number of subjects with at least one event, %: proportion of subjects with at least one event, E: number of events, RR: relative risk, OR: odds ratio, RD: risk difference in percentage points, CI: confidence interval, p-value: unadjusted two-sided p-value from test for 2x2 contingency table (¤: Barnard's unconditional exact test, ¤¤: Fisher's exact test), p-value interaction: unadjusted p-value for test of no interaction effect (Breslow-Day test for stratified 2x2 contingency tables), *: p-value interaction < 0,05, not est.: not estimated
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table.
Subgroup analyses were only performed if p-value < 0,05 for all subjects (total).

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4.18. Adverse events by preferred term - analysis of 2x2 tables - Pioneer 2 - in-trial – safety analysis set

Preferred Term	Subgroup	Oral Sema 14 mg N	Oral Sema 14 mg n (%)	Oral Sema 14 mg E	Empa 25 mg N	Empa 25 mg n (%)	Empa 25 mg E	Oral Sema 14 mg vs. Empa 25 mg RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	p-value interaction
Dyspepsia	All subjects (total)	410	21 (5.1%)	22	409	7 (1.7%)	7	2.99 [1.29;6.96]	3.10 [1.30;7.38]	3.41 [0.93;5.89]	0.0111¤¤	
	Gender											0.7991
	Female	204	11 (5.4%)	11	200	4 (2.0%)	4	2.70 [0.87;8.33]	2.79 [0.87;8.92]	3.39 [-0.26;7.05]	0.0732¤	
	Male	206	10 (4.9%)	11	209	3 (1.4%)	3	3.38 [0.94;12.11]	3.50 [0.95;12.92]	3.42 [0.07;6.77]	0.0495¤	
	Age											0.5337
	< 65	305	15 (4.9%)	16	299	4 (1.3%)	4	3.68 [1.23;10.95]	3.81 [1.25;11.63]	3.58 [0.83;6.33]	0.0120¤	
	65 <=	105	6 (5.7%)	6	110	3 (2.7%)	3	2.10 [0.54;8.16]	2.16 [0.53;8.88]	2.99 [-2.40;8.37]	0.2905¤	
	Region A											0.4802
	West Europe	77	5 (6.5%)	6	89	1 (1.1%)	1	5.78 [0.69;48.40]	6.11 [0.70;53.50]	5.37 [-0.55;11.29]	0.0759¤	
	Rest of World	333	16 (4.8%)	16	320	6 (1.9%)	6	2.56 [1.02;6.47]	2.64 [1.02;6.84]	2.93 [0.19;5.67]	0.0496¤¤	
	HbA1c at baseline (disease severity)											0.5018
	<= 7.5	133	12 (9.0%)	12	130	3 (2.3%)	3	3.91 [1.13;13.54]	4.20 [1.16;15.24]	6.71 [1.20;12.23]	0.0192¤	
	7.5 <	277	9 (3.2%)	10	279	4 (1.4%)	4	2.27 [0.71;7.27]	2.31 [0.70;7.59]	1.82 [-0.70;4.33]	0.1638¤	

N: number of subjects in the analysis set, n: number of subjects with at least one event, %: proportion of subjects with at least one event, E: number of events, RR: relative risk, OR: odds ratio, RD: risk difference in percentage points, CI: confidence interval, p-value: unadjusted two-sided p-value from test for 2x2 contingency table (¤: Barnard's unconditional exact test, ¤¤: Fisher's exact test), p-value interaction: unadjusted p-value for test of no interaction effect (Breslow-Day test for stratified 2x2 contingency tables), *: p-value interaction < 0,05, not est.: not estimated
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table.
Subgroup analyses were only performed if p-value < 0,05 for all subjects (total).

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4.19. Adverse events by preferred term - analysis of 2x2 tables - Pioneer 2 - in-trial – safety analysis set

		Oral Sema 14 mg			Empa 25 mg			Oral Sema 14 mg vs. Empa 25 mg				
Preferred Term	Subgroup	N	n (%)	E	N	n (%)	E	RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	p-value interaction
Influenza	All subjects (total)	410	8 (2.0%)	8	409	21 (5.1%)	23	0.38 [0.17;0.85]	0.37 [0.16;0.84]	-3.18 [-5.71;-0.66]	0.0143¤¤	
	Gender											0.8710
	Female	204	4 (2.0%)	4	200	11 (5.5%)	11	0.36 [0.12;1.10]	0.34 [0.11;1.10]	-3.54 [-7.23;0.15]	0.0644¤	
	Male	206	4 (1.9%)	4	209	10 (4.8%)	12	0.41 [0.13;1.27]	0.39 [0.12;1.28]	-2.84 [-6.30;0.61]	0.1273¤	
	Age											0.3964
	< 65	305	6 (2.0%)	6	299	12 (4.0%)	13	0.49 [0.19;1.29]	0.48 [0.18;1.30]	-2.05 [-4.76;0.67]	0.1571¤¤	
	65 <=	105	2 (1.9%)	2	110	9 (8.2%)	10	0.23 [0.05;1.05]	0.22 [0.05;1.03]	-6.28 [-12.03;-0.53]	0.0401¤	
	Region A											0.4511
	West Europe	77	1 (1.3%)	1	89	6 (6.7%)	8	0.19 [0.02;1.57]	0.18 [0.02;1.55]	-5.44 [-11.23;0.35]	0.0877¤	
	Rest of World	333	7 (2.1%)	7	320	15 (4.7%)	15	0.45 [0.19;1.09]	0.44 [0.18;1.09]	-2.59 [-5.37;0.20]	0.0828¤¤	
	HbA1c at baseline (disease severity)											0.7306
	<= 7.5	133	2 (1.5%)	2	130	4 (3.1%)	4	0.49 [0.09;2.62]	0.48 [0.09;2.67]	-1.57 [-5.19;2.04]	0.5307¤	
	7.5 <	277	6 (2.2%)	6	279	17 (6.1%)	19	0.36 [0.14;0.89]	0.34 [0.13;0.88]	-3.93 [-7.22;-0.64]	0.0311¤¤	

N: number of subjects in the analysis set, n: number of subjects with at least one event, %: proportion of subjects with at least one event, E: number of events, RR: relative risk, OR: odds ratio, RD: risk difference in percentage points, CI: confidence interval, p-value: unadjusted two-sided p-value from test for 2x2 contingency table (¤: Barnard's unconditional exact test, ¤¤: Fisher's exact test), p-value interaction: unadjusted p-value for test of no interaction effect (Breslow-Day test for stratified 2x2 contingency tables), *: p-value interaction < 0,05, not est.: not estimated
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table.
Subgroup analyses were only performed if p-value < 0,05 for all subjects (total).

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4.20. Adverse events by preferred term - analysis of 2x2 tables - Pioneer 2 - in-trial – safety analysis set

Preferred Term	Subgroup	Oral Sema 14 mg N	Oral Sema 14 mg n (%)	Oral Sema 14 mg E	Empa 25 mg N	Empa 25 mg n (%)	Empa 25 mg E	Oral Sema 14 mg vs. Empa 25 mg RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	p-value nteraction
Nausea	All subjects (total)	410	81 (19.8%)	106	409	10 (2.4%)	12	8.08 [4.25;15.36]	9.82 [5.01;19.25]	17.31 [13.18;21.45]	<0.0001¤¤	
	Gender											0.9480
	Female	204	47 (23.0%)	55	200	6 (3.0%)	8	7.68 [3.36;17.56]	9.68 [4.03;23.23]	20.04 [13.80;26.28]	<0.0001¤¤	
	Male	206	34 (16.5%)	51	209	4 (1.9%)	4	8.62 [3.12;23.87]	10.13 [3.53;29.11]	14.59 [9.19;19.99]	<0.0001¤	
	Age											0.1506
	< 65	305	57 (18.7%)	73	299	9 (3.0%)	11	6.21 [3.13;12.31]	7.41 [3.59;15.26]	15.68 [10.89;20.46]	<0.0001¤¤	
	65 <=	105	24 (22.9%)	33	110	1 (0.9%)	1	25.14 [3.46;182.55]	32.30 [4.28;243.69]	21.95 [13.72;30.17]	<0.0001¤	
	Region A											0.9646
	West Europe	77	8 (10.4%)	9	89	1 (1.1%)	1	9.25 [1.18;72.29]	10.20 [1.25;83.54]	9.27 [2.11;16.42]	0.0093¤	
	Rest of World	333	73 (21.9%)	97	320	9 (2.8%)	11	7.79 [3.97;15.31]	9.70 [4.76;19.77]	19.11 [14.31;23.91]	<0.0001¤¤	
	HbA1c at baseline (disease severity)											0.3341
	<= 7.5	133	22 (16.5%)	28	130	4 (3.1%)	4	5.38 [1.90;15.17]	6.24 [2.09;18.67]	13.46 [6.49;20.44]	0.0002¤	
	7.5 <	277	59 (21.3%)	78	279	6 (2.2%)	8	9.90 [4.35;22.56]	12.31 [5.22;29.06]	19.15 [14.04;24.26]	<0.0001¤¤	

N: number of subjects in the analysis set, n: number of subjects with at least one event, %: proportion of subjects with at least one event, E: number of events, RR: relative risk, OR: odds ratio, RD: risk difference in percentage points, CI: confidence interval, p-value: unadjusted two-sided p-value from test for 2x2 contingency table (¤: Barnard's unconditional exact test, ¤¤: Fisher's exact test), p-value interaction: unadjusted p-value for test of no interaction effect (Breslow-Day test for stratified 2x2 contingency tables), *: p-value interaction < 0,05, not est.: not estimated
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table.
Subgroup analyses were only performed if p-value < 0,05 for all subjects (total).

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4.21. Adverse events by preferred term - analysis of 2x2 tables - Pioneer 2 - in-trial – safety analysis set

Preferred Term	Subgroup	Oral Sema 14 mg N	Oral Sema 14 mg n (%)	Oral Sema 14 mg E	Empa 25 mg N	Empa 25 mg n (%)	Empa 25 mg E	Oral Sema 14 mg vs. Empa 25 mg RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	p-value interaction
Pollakiuria	All subjects (total)	410	0 (0.0%)	0	409	13 (3.2%)	14	0.04 [0.00;0.62]	0.04 [0.00;0.60]	-3.18 [-4.88;-1.48]	0.0003¤	
	Gender											not est.
	Female	204	0 (0.0%)	0	200	7 (3.5%)	7	0.07 [0.00;1.14]	0.06 [0.00;1.11]	-3.50 [-6.05;-0.95]	0.0072¤	
	Male	206	0 (0.0%)	0	209	6 (2.9%)	7	0.08 [0.00;1.38]	0.08 [0.00;1.35]	-2.87 [-5.13;-0.61]	0.0144¤	
	Age											not est.
	< 65	305	0 (0.0%)	0	299	12 (4.0%)	13	0.04 [0.00;0.66]	0.04 [0.00;0.64]	-4.01 [-6.24;-1.79]	0.0004¤	
	65 <=	105	0 (0.0%)	0	110	1 (0.9%)	1	0.35 [0.01;8.47]	0.35 [0.01;8.59]	-0.91 [-2.68;0.86]	0.5150¤	
	Region A											not est.
	West Europe	77	0 (0.0%)	0	89	6 (6.7%)	6	0.09 [0.01;1.55]	0.08 [0.00;1.50]	-6.74 [-11.95;-1.53]	0.0212¤	
	Rest of World	333	0 (0.0%)	0	320	7 (2.2%)	8	0.06 [0.00;1.12]	0.06 [0.00;1.10]	-2.19 [-3.79;-0.58]	0.0069¤	
	HbA1c at baseline (disease severity)											not est.
	<= 7.5	133	0 (0.0%)	0	130	4 (3.1%)	4	0.11 [0.01;2.00]	0.11 [0.01;1.98]	-3.08 [-6.05;-0.11]	0.0430¤	
	7.5 <	277	0 (0.0%)	0	279	9 (3.2%)	10	0.05 [0.00;0.91]	0.05 [0.00;0.89]	-3.23 [-5.30;-1.15]	0.0026¤	

N: number of subjects in the analysis set, n: number of subjects with at least one event, %: proportion of subjects with at least one event, E: number of events, RR: relative risk, OR: odds ratio, RD: risk difference in percentage points, CI: confidence interval, p-value: unadjusted two-sided p-value from test for 2x2 contingency table (¤: Barnard's unconditional exact test, ¤¤: Fisher's exact test), p-value interaction: unadjusted p-value for test of no interaction effect (Breslow-Day test for stratified 2x2 contingency tables), *: p-value interaction < 0,05, not est.: not estimated
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table.
Subgroup analyses were only performed if p-value < 0,05 for all subjects (total).
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4.22. Adverse events by preferred term - analysis of 2x2 tables - Pioneer 2 - in-trial – safety analysis set

Preferred Term	Subgroup	Oral Sema 14 mg N	Oral Sema 14 mg n (%)	Oral Sema 14 mg E	Empa 25 mg N	Empa 25 mg n (%)	Empa 25 mg E	Oral Sema 14 mg vs. Empa 25 mg RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	p-value interaction
Polyuria	All subjects (total)	410	0 (0.0%)	0	409	12 (2.9%)	12	0.04 [0.00;0.67]	0.04 [0.00;0.66]	-2.93 [-4.57;-1.30]	0.0005¤	
	Gender											not est.
	Female	204	0 (0.0%)	0	200	2 (1.0%)	2	0.20 [0.01;4.06]	0.19 [0.01;4.07]	-1.00 [-2.38;0.38]	0.1587¤	
	Male	206	0 (0.0%)	0	209	10 (4.8%)	10	0.05 [0.00;0.82]	0.05 [0.00;0.79]	-4.78 [-7.68;-1.89]	0.0016¤	
	Age											not est.
	< 65	305	0 (0.0%)	0	299	11 (3.7%)	11	0.04 [0.00;0.72]	0.04 [0.00;0.70]	-3.68 [-5.81;-1.55]	0.0007¤	
	65 <=	105	0 (0.0%)	0	110	1 (0.9%)	1	0.35 [0.01;8.47]	0.35 [0.01;8.59]	-0.91 [-2.68;0.86]	0.5150¤	
	Region A											not est.
	West Europe	77	0 (0.0%)	0	89	6 (6.7%)	6	0.09 [0.01;1.55]	0.08 [0.00;1.50]	-6.74 [-11.95;-1.53]	0.0212¤	
	Rest of World	333	0 (0.0%)	0	320	6 (1.9%)	6	0.07 [0.00;1.31]	0.07 [0.00;1.29]	-1.88 [-3.36;-0.39]	0.0123¤	
	HbA1c at baseline (disease severity)											not est.
	<= 7.5	133	0 (0.0%)	0	130	3 (2.3%)	3	0.14 [0.01;2.68]	0.14 [0.01;2.67]	-2.31 [-4.89;0.27]	0.0841¤	
	7.5 <	277	0 (0.0%)	0	279	9 (3.2%)	9	0.05 [0.00;0.91]	0.05 [0.00;0.89]	-3.23 [-5.30;-1.15]	0.0026¤	

N: number of subjects in the analysis set, n: number of subjects with at least one event, %: proportion of subjects with at least one event, E: number of events, RR: relative risk, OR: odds ratio, RD: risk difference in percentage points, CI: confidence interval, p-value: unadjusted two-sided p-value from test for 2x2 contingency table (¤: Barnard's unconditional exact test, ¤¤: Fisher's exact test), p-value interaction: unadjusted p-value for test of no interaction effect (Breslow-Day test for stratified 2x2 contingency tables), *: p-value interaction < 0,05, not est.: not estimated
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table.
Subgroup analyses were only performed if p-value < 0,05 for all subjects (total).
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4.23. Adverse events by preferred term - analysis of 2x2 tables - Pioneer 2 - in-trial – safety analysis set

Preferred Term	Subgroup	Oral Sema 14 mg N	Oral Sema 14 mg n (%)	Oral Sema 14 mg E	Empa 25 mg N	Empa 25 mg n (%)	Empa 25 mg E	Oral Sema 14 mg vs. Empa 25 mg RR [95%-CI]	OR [95%-CI]	RD [95%-CI]	p-value	p-value interaction
Vomiting	All subjects (total)	410	30 (7.3%)	40	409	7 (1.7%)	7	4.28 [1.90;9.62]	4.53 [1.97;10.45]	5.61 [2.79;8.42]	0.0001¤¤	
	Gender											0.1469
	Female	204	17 (8.3%)	21	200	6 (3.0%)	6	2.78 [1.12;6.90]	2.94 [1.13;7.62]	5.33 [0.86;9.80]	0.0299¤¤	
	Male	206	13 (6.3%)	19	209	1 (0.5%)	1	13.19 [1.74;99.91]	14.01 [1.82;108.11]	5.83 [2.38;9.28]	0.0010¤	
	Age											0.4511
	< 65	305	22 (7.2%)	30	299	6 (2.0%)	6	3.59 [1.48;8.74]	3.80 [1.52;9.50]	5.21 [1.90;8.52]	0.0030¤¤	
	65 <=	105	8 (7.6%)	10	110	1 (0.9%)	1	8.38 [1.07;65.86]	8.99 [1.10;73.18]	6.71 [1.33;12.09]	0.0145¤	
	Region A											0.3470
	West Europe	77	3 (3.9%)	3	89	0 (0.0%)	0	8.08 [0.42;153.95]	8.41 [0.43;165.41]	3.90 [-0.43;8.22]	0.0656¤	
	Rest of World	333	27 (8.1%)	37	320	7 (2.2%)	7	3.71 [1.64;8.39]	3.95 [1.69;9.19]	5.92 [2.58;9.26]	0.0007¤¤	
	HbA1c at baseline (disease severity)											0.2595
	<= 7.5	133	5 (3.8%)	7	130	0 (0.0%)	0	10.75 [0.60;192.54]	11.17 [0.61;204.10]	3.76 [0.53;6.99]	0.0262¤	
	7.5 <	277	25 (9.0%)	33	279	7 (2.5%)	7	3.60 [1.58;8.18]	3.85 [1.64;9.07]	6.52 [2.68;10.36]	0.0009¤¤	

N: number of subjects in the analysis set, n: number of subjects with at least one event, %: proportion of subjects with at least one event, E: number of events, RR: relative risk, OR: odds ratio, RD: risk difference in percentage points, CI: confidence interval, p-value: unadjusted two-sided p-value from test for 2x2 contingency table (¤: Barnard's unconditional exact test, ¤¤: Fisher's exact test), p-value interaction: unadjusted p-value for test of no interaction effect (Breslow-Day test for stratified 2x2 contingency tables), *: p-value interaction < 0,05, not est.: not estimated
The relative risk, odds ratio, risk difference estimates and confidence limits were derived based on a non-parametric analysis (2x2 contingency tables) of the binary response (had an event in the in-trial observation period or not). To calculate odds ratios and relative risks in the event of zero cells, the correction value of 0.5 was added to each cell frequency of the corresponding fourfold table.
Subgroup analyses were only performed if p-value < 0,05 for all subjects (total).

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