Dossier zur Nutzenbewertung gemäß § 35a SGB V

Ertugliflozin (STEGLATRO®)

MSD Sharp & Dohme GmbH

Modul 4 B

Anhang 4-G: Weitere Ergebnisse

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

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Inhaltsverzeichnis

Seite

Tabellenverzeichnis

Abbildungsverzeichnis

Es konnten keine Einträge für ein Abbildungsverzeichnis gefunden werden.

Anhang 4-G1: Ergebnisse der Subgruppen mit nicht signifikantem Interaktionstest (p ≥ 0,05) der Studie VERTIS CV

Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.2.2 die Ergebnisse der Subgruppenanalysen, für die ein nicht signifikanter Interaktionstest (p ≥ 0,05) vorliegt, dargestellt.

Anhang 4-G1.1: Mortalität

Tabelle 4G-1: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Gesamtmortalität (Ertugliflozin 5 mg) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a]	Ertugliflozin 5 mg		Glimepiride		Ertugliflozin 5 mg vs. Glimepiride		
All-Cause Mortality	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
Sex							
Female	218	0 (0.0)	211	0 (0.0)	n.c.	n.c.	n.c.
Male	227	1 (0.4)	224	0 (0.0)	n.c.	n.c.	
Age (Years)							
< 65	326	0 (0.0)	332	0 (0.0)	n.c.	n.c.	n.c.
≥ 65	119	1 (0.8)	103	0 (0.0)	n.c.	n.c.	
Region							
WHO Stratum A	153	1 (0.7)	148	0 (0.0)	n.c.	n.c.	n.c.
Rest of the World	292	0 (0.0)	287	0 (0.0)	n.c.	n.c.	

a: Database Cutoff of week 26: randomization till the earliest of the data cut-off date (first dose date+182 days), last contact date, or date of the death

b: Number of participants: all-participants-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the control arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the control arm, report ″n.a.″

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report ″n.a.″

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as ″n.a.″

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary); WHO: World Health Organization

Tabelle 4G-2: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Gesamtmortalität (Ertugliflozin 15 mg) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a]	**Ertugliflozin 15 mg**		**Glimepiride**		**Ertugliflozin 15 mg vs. Glimepiride**		
All-Cause Mortality	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**Treatment Effect p-Value[d]**	**Interaction Test p-Value[e]**
Sex							
Female	244	0 (0.0)	211	0 (0.0)	n.c.	n.c.	n.c.
Male	191	1 (0.5)	224	0 (0.0)	n.c.	n.c.	
Age (Years)							
< 65	323	0 (0.0)	332	0 (0.0)	n.c.	n.c.	n.c.
≥ 65	112	1 (0.9)	103	0 (0.0)	n.c.	n.c.	
Region							
WHO Stratum A	148	1 (0.7)	148	0 (0.0)	n.c.	n.c.	n.c.
Rest of the World	287	0 (0.0)	287	0 (0.0)	n.c.	n.c.	

a: Database Cutoff of week 26: randomization till the earliest of the data cut-off date (first dose date+182 days), last contact date, or date of the death

b: Number of participants: all-participants-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the control arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the control arm, report ″n.a.″

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report ″n.a.″

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as ″n.a.″

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary); WHO: World Health Organization

Anhang 4-G1.2: Morbidität

Tabelle 4G-3: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Endpunkt MACE plus (Ertugliflozin 5 mg) aus RCT mit dem zu bewertenden Arzneimittel (Ertugliflozin 5 mg)

Study: VERTIS SU[a]	Ertugliflozin 5 mg		Glimepiride		Ertugliflozin 5 mg vs. Glimepiride		
MACE-plus[f]	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
Sex							
Female	218	1 (0.5)	211	1 (0.5)	n.c.	n.c.	n.c.
Male	227	2 (0.9)	224	0 (0.0)	n.c.	n.c.	
Age (Years)							
< 65	326	1 (0.3)	332	1 (0.3)	n.c.	n.c.	n.c.
≥ 65	119	2 (1.7)	103	0 (0.0)	n.c.	n.c.	
Region							
WHO Stratum A	153	2 (1.3)	148	0 (0.0)	n.c.	n.c.	n.c.
Rest of the World	292	1 (0.3)	287	1 (0.3)	n.c.	n.c.	

a: Database Cutoff of week 26: randomization till the earliest of the data cut-off date (first dose date+182 days), last contact date, or date of the death

b: Number of participants: all-participants-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the control arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the control arm, report ″n.a.″

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report ″n.a.″

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as ″n.a.″

f: MACE-plus: CV death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina

CI: Confidence Interval; CV: Cardiovascular; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary); WHO: World Health Organization

Tabelle 4G-4: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Endpunkt Kardiovaskulärer Tod (Ertugliflozin 5 mg) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a]	Ertugliflozin 5 mg		Glimepiride		Ertugliflozin 5 mg vs. Glimepiride		
Cardiovascular Death	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
Sex							
Female	218	0 (0.0)	211	0 (0.0)	n.c.	n.c.	n.c.
Male	227	1 (0.4)	224	0 (0.0)	n.c.	n.c.	
Age (Years)							
< 65	326	0 (0.0)	332	0 (0.0)	n.c.	n.c.	n.c.
≥ 65	119	1 (0.8)	103	0 (0.0)	n.c.	n.c.	
Region							
WHO Stratum A	153	1 (0.7)	148	0 (0.0)	n.c.	n.c.	n.c.

Study: VERTIS SU[a]	Ertugliflozin 5 mg		Glimepiride		Ertugliflozin 5 mg vs. Glimepiride		
Cardiovascular Death	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
Rest of the World	292	0 (0.0)	287	0 (0.0)	n.c.	n.c.	

a: Database Cutoff of week 26: randomization till the earliest of the data cut-off date (first dose date+182 days), last contact date, or date of the death

b: Number of participants: all-participants-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the control arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the control arm, report ″n.a.″

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report ″n.a.″

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as ″n.a.″

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary); WHO: World Health Organization

Tabelle 4G-5: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Nicht-tödlicher Herzinfarkt (Ertugliflozin 5 mg) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a]	Ertugliflozin 5 mg		Glimepiride		Ertugliflozin 5 mg vs. Glimepiride		
Non-fatal Myocardial Infarction	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
Sex							
Female	218	0 (0.0)	211	0 (0.0)	n.c.	n.c.	n.c.
Male	227	0 (0.0)	224	0 (0.0)	n.c.	n.c.	
Age (Years)							
< 65	326	0 (0.0)	332	0 (0.0)	n.c.	n.c.	n.c.
≥ 65	119	0 (0.0)	103	0 (0.0)	n.c.	n.c.	
Region							
WHO Stratum A	153	0 (0.0)	148	0 (0.0)	n.c.	n.c.	n.c.
Rest of the World	292	0 (0.0)	287	0 (0.0)	n.c.	n.c.	

a: Database Cutoff of week 26: randomization till the earliest of the data cut-off date (first dose date+182 days), last contact date, or date of the death

b: Number of participants: all-participants-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the control arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the control arm, report ″n.a.″

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report ″n.a.″

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as ″n.a.″

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary); WHO: World Health Organization

Tabelle 4G-6: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Nicht-tödlicher Schlaganfall (Ertugliflozin 5 mg) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a]	**Ertugliflozin 5 mg**		**Glimepiride**		**Ertugliflozin 5 mg vs. Glimepiride**		
Non-fatal Stroke	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**Treatment Effect p-Value[d]**	**Interaction Test p-Value[e]**
Sex							
Female	218	1 (0.5)	211	1 (0.5)	n.c.	n.c.	n.c.
Male	227	1 (0.4)	224	0 (0.0)	n.c.	n.c.	
Age (Years)							
< 65	326	1 (0.3)	332	1 (0.3)	n.c.	n.c.	n.c.
≥ 65	119	1 (0.8)	103	0 (0.0)	n.c.	n.c.	
Region							
WHO Stratum A	153	1 (0.7)	148	0 (0.0)	n.c.	n.c.	n.c.
Rest of the World	292	1 (0.3)	287	1 (0.3)	n.c.	n.c.	

a: Database Cutoff of week 26: randomization till the earliest of the data cut-off date (first dose date+182 days), last contact date, or date of the death

b: Number of participants: all-participants-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the control arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the control arm, report ″n.a.″

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report ″n.a.″

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as ″n.a.″

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary); WHO: World Health Organization

Tabelle 4G-7: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Hospitalisierung wegen instabiler Angina pectoris (Ertugliflozin 5 mg) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a]	**Ertugliflozin 5 mg**		**Glimepiride**		**Ertugliflozin 5 mg vs. Glimepiride**		
Hospitalization for Unstable Angina	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**Treatment Effect p-Value[d]**	**Interaction Test p-Value[e]**
Sex							
Female	218	0 (0.0)	211	0 (0.0)	n.c.	n.c.	n.c.
Male	227	0 (0.0)	224	0 (0.0)	n.c.	n.c.	
Age (Years)							
< 65	326	0 (0.0)	332	0 (0.0)	n.c.	n.c.	n.c.
≥ 65	119	0 (0.0)	103	0 (0.0)	n.c.	n.c.	
Region							
WHO Stratum A	153	0 (0.0)	148	0 (0.0)	n.c.	n.c.	n.c.
Rest of the World	292	0 (0.0)	287	0 (0.0)	n.c.	n.c.	

a: Database Cutoff of week 26: randomization till the earliest of the data cut-off date (first dose date+182 days), last contact date, or date of the death

Study: VERTIS SU[a]	Ertugliflozin 5 mg		Glimepiride		Ertugliflozin 5 mg vs. Glimepiride		
Hospitalization for Unstable Angina	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]

b: Number of participants: all-participants-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the control arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the control arm, report ″n.a.″

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report ″n.a.″

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as ″n.a.″

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary); WHO: World Health Organization

Tabelle 4G-8: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Hospitalisierung wegen Herzinsuffizienz (Ertugliflozin 5 mg) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a]	Ertugliflozin 5 mg		Glimepiride		Ertugliflozin 5 mg vs. Glimepiride		
Hospitalization for Heart Failure	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
Sex							
Female	218	1 (0.5)	211	0 (0.0)	n.c.	n.c.	n.c.
Male	227	0 (0.0)	224	0 (0.0)	n.c.	n.c.	
Age (Years)							
< 65	326	1 (0.3)	332	0 (0.0)	n.c.	n.c.	n.c.
≥ 65	119	0 (0.0)	103	0 (0.0)	n.c.	n.c.	
Region							
WHO Stratum A	153	0 (0.0)	148	0 (0.0)	n.c.	n.c.	n.c.
Rest of the World	292	1 (0.3)	287	0 (0.0)	n.c.	n.c.	

a: Database Cutoff of week 26: randomization till the earliest of the data cut-off date (first dose date+182 days), last contact date, or date of the death

b: Number of participants: all-participants-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the control arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the control arm, report ″n.a.″

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report ″n.a.″

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as ″n.a.″

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary); WHO: World Health Organization

Tabelle 4G-9: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Veränderung des HbA1c-Wertes (Ertugliflozin 5 mg) zu Woche 26 aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a] Hemoglobin A1C (%) (ER)	N[b]	N[c]	Mean at Baseline of Study (SD)	Mean at Week 26 (SD)	Mean Change from Week 26 (SE)[d]	Ertugliflozin 5 mg vs. Glimepiride			p-Value for Interaction Test[f]
						Mean Difference[d] [95 %-CI]	p-Value[d]	Standardized Mean Difference[e] [95 %-CI]	
Sex									
Female									
Ertugliflozin 5 mg	218	218	7.79 (0.585)	7.28 (0.715)	-0.49 (0.049)	0.38	< 0.001	0.50	0.107
Glimepiride	211	211	7.79 (0.637)	6.92 (0.762)	-0.86 (0.050)	[0.24; 0.51]		[0.33; 0.68]	
Male									
Ertugliflozin 5 mg	227	227	7.82 (0.623)	7.17 (0.798)	-0.61 (0.058)	0.36	< 0.001	0.40	
Glimepiride	224	224	7.73 (0.563)	6.77 (0.956)	-0.97 (0.058)	[0.20; 0.52]		[0.23; 0.58]	
Region									
WHO Stratum A									
Ertugliflozin 5 mg	153	153	7.90 (0.628)	7.35 (0.780)	-0.45 (0.075)	0.36	< 0.001	0.38	0.098
Glimepiride	148	148	7.74 (0.574)	6.96 (1.043)	-0.81 (0.076)	[0.15; 0.57]		[0.16; 0.60]	
Rest of the World									
Ertugliflozin 5 mg	292	292	7.76 (0.586)	7.16 (0.745)	-0.60 (0.044)	0.37	< 0.001	0.48	
Glimepiride	287	287	7.77 (0.614)	6.79 (0.776)	-0.97 (0.044)	[0.25; 0.49]		[0.33; 0.64]	
Race									
Asian									
Ertugliflozin 5 mg	79	79	7.77 (0.568)	7.17 (0.619)	-0.62 (0.070)	0.43	< 0.001	0.70	0.318
Glimepiride	71	71	7.82 (0.569)	6.74 (0.605)	-1.05 (0.073)	[0.24; 0.61]		[0.40; 1.00]	
Other									
Ertugliflozin 5 mg	32	32	7.89 (0.638)	7.04 (0.627)	-0.73 (0.123)	0.03	0.847	-	
Glimepiride	44	44	7.80	7.02	-0.76	[-0.29; 0.35]		-	

Study: VERTIS SU[a] Hemoglobin A1C (%) (ER)	N[b]	N[c]	Mean at Baseline of Study (SD)	Mean at Week 26 (SD)	Mean Change from Week 26 (SE)[d]	Ertugliflozin 5 mg vs. Glimepiride			p-Value for Interaction Test[f]
						Mean Difference[d] [95 %-CI]	p-Value[d]	Standardized Mean Difference[e] [95 %-CI]	
			(0.691)	(0.790)	(0.107)				
White									
Ertugliflozin 5 mg	317	317	7.79 (0.600)	7.25 (0.802)	-0.52 (0.047)	0.39	< 0.001	0.45	
Glimepiride	312	312	7.75 (0.593)	6.84 (0.930)	-0.90 (0.048)	[0.26; 0.52]		[0.30; 0.59]	
Ethnicity									
Hispanic or Latino									
Ertugliflozin 5 mg	89	89	7.91 (0.663)	7.30 (0.888)	-0.57 (0.114)	0.01	0.958	-	0.767
Glimepiride	88	88	7.71 (0.628)	7.21 (1.193)	-0.57 (0.113)	[-0.30; 0.32]		-	
Not Hispanic or Latino									
Ertugliflozin 5 mg	356	356	7.78 (0.587)	7.20 (0.729)	-0.55 (0.039)	0.45	< 0.001	0.60	
Glimepiride	347	347	7.77 (0.594)	6.76 (0.759)	-1.00 (0.039)	[0.35; 0.55]		[0.46; 0.73]	
Body Mass Index									
≤ Median									
Ertugliflozin 5 mg	203	203	7.75 (0.577)	7.21 (0.720)	-0.54 (0.059)	0.39	< 0.001	0.46	0.658
Glimepiride	230	230	7.78 (0.624)	6.83 (0.938)	-0.92 (0.056)	[0.23; 0.54]		[0.28; 0.64]	
>Median									
Ertugliflozin 5 mg	242	242	7.86 (0.623)	7.23 (0.794)	-0.57 (0.050)	0.34	< 0.001	0.41	
Glimepiride	205	205	7.74 (0.574)	6.85 (0.793)	-0.90 (0.054)	[0.20; 0.48]		[0.24; 0.59]	
Prior Antihyperglycemic Therapy									
Monotherapy									
Ertugliflozin 5 mg	368	368	7.75 (0.581)	7.17 (0.740)	-0.57 (0.042)	0.36	< 0.001	0.44	0.277
Glimepiride	354	354	7.76 (0.614)	6.80 (0.888)	-0.93 (0.042)	[0.25; 0.47]		[0.30; 0.58]	

Study: VERTIS SU[a] Hemoglobin A1C (%) (ER)	N[b]	N[c]	Mean at Baseline of Study (SD)	Mean at Week 26 (SD)	Mean Change from Week 26 (SE)[d]	Ertugliflozin 5 mg vs. Glimepiride Mean Difference[d] [95 %-CI]	p-Value[d]	Standardized Mean Difference[e] [95 %-CI]	p-Value for Interaction Test[f]
Dual Therapy									
Ertugliflozin 5 mg	77	77	8.08 (0.641)	7.46 (0.818)	-0.46 (0.098)	0.41	0.002	0.48	
Glimepiride	81	81	7.79 (0.542)	7.00 (0.784)	-0.86 (0.093)	[0.15; 0.67]		[0.18; 0.78]	

a: Database Cutoff of week 26 is the week 26 visit
b: Number of participants in subgroup: full-analysis-set population
c: Number of patients with data available for the analysis
d: Based on constrained longitudinal data analysis model that include fixed effects for treatment, time, prior AHAs (monotherapy or dual therapy), baseline eGFR (continuous), and the interaction of time by treatment, where time was treated as categorical variable. Values of eGFR that were >120 mL/min/1.73 m^2 were set to 120 mL/min/1.73 m^2
e: Standardized mean difference (Hedges´s g) is only calculated if confidence interval for mean difference does not include zero
f: P-Value of the interaction, based on constrained longitudinal data analysis model that include fixed effects for treatment, time, prior AHAs (monotherapy or dual therapy), baseline eGFR (continuous), subgroup, the interaction of time by treatment , treatment by subgroup, and time by treatment by subgroup, where time was treated as categorical variable
AHAs: Anti-Hyperglycemic Agents; CI: Confidence Interval; cLDA: Constrained Longitudinal Data Analysis; eGFR: Estimated Glomerular Filtration Rate; ER: Excluding Rescue; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

Tabelle 4G-10: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Veränderung des Körpergewichts (Ertugliflozin 5 mg) zu Woche 26 aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a] Weight (kg) (ER)	N[b]	N[c]	Mean at Baseline of Study (SD)	Mean at Week 26 (SD)	Mean Change from Week 26 (SE)[d]	Ertugliflozin 5 mg vs. Glimepiride Mean Difference[d] [95 %-CI]	p-Value[d]	Standardized Mean Difference[e] [95 %-CI]	p-Value for Interaction Test[f]
Sex									
Female									
Ertugliflozin 5 mg	218	218	81.24 (16.594)	78.78 (16.555)	-2.72 (0.173)	-3.49	< 0.001	-0.18	0.340
Glimepiride	211	211	81.08 (21.158)	81.78 (21.080)	0.77 (0.176)	[-3.97; -3.00]		[-0.21; -0.16]	
Male									
Ertugliflozin 5 mg	227	227	94.51	90.93	-2.99	-3.56	< 0.001	-0.19	

Study: VERTIS SU[a] Weight (kg) (ER)	N[b]	N[c]	Mean at Baseline of Study (SD)	Mean at Week 26 (SD)	Mean Change from Week 26 (SE)[d]	Ertugliflozin 5 mg vs. Glimepiride Mean Difference[d] [95 %-CI]	p-Value[d]	Standardized Mean Difference[e] [95 %-CI]	p-Value for Interaction Test[f]
			(18.870)	(18.643)	(0.230)				
Glimepiride	224	224	92.39 (18.841)	92.83 (18.166)	0.57 (0.229)	[-4.19; -2.93]		[-0.23; -0.16]	
Age Group (Years)									
< 65									
Ertugliflozin 5 mg	326	326	89.39 (19.089)	86.30 (18.803)	-2.93 (0.170)	-3.69	< 0.001	-0.18	0.393
Glimepiride	332	332	87.94 (21.928)	88.60 (21.540)	0.76 (0.169)	[-4.16; -3.22]		[-0.21; -0.16]	
≥ 65									
Ertugliflozin 5 mg	119	119	84.24 (18.199)	81.37 (17.812)	-2.65 (0.276)	-3.06	< 0.001	-0.18	
Glimepiride	103	103	83.56 (16.087)	84.59 (15.812)	0.41 (0.289)	[-3.85; -2.28]		[-0.22; -0.13]	
Region									
WHO Stratum A									
Ertugliflozin 5 mg	153	153	91.64 (19.858)	88.70 (19.895)	-2.84 (0.264)	-4.01	< 0.001	-0.19	0.975
Glimepiride	148	148	91.91 (23.246)	93.49 (22.910)	1.16 (0.265)	[-4.74; -3.27]		[-0.22; -0.15]	
Rest of the World									
Ertugliflozin 5 mg	292	292	86.11 (18.239)	83.32 (17.839)	-2.85 (0.173)	-3.30	< 0.001	-0.18	
Glimepiride	287	287	84.32 (18.886)	84.89 (18.444)	0.45 (0.174)	[-3.78; -2.82]		[-0.21; -0.15]	

a: Database Cutoff of week 26 is the week 26 visit

b: Number of participants in subgroup: full-analysis-set population

c: Number of patients with data available for the analysis

d: Based on constrained longitudinal data analysis model that include fixed effects for treatment, time, prior AHAs (monotherapy or dual therapy), baseline eGFR (continuous), and the interaction of time by treatment, where time was treated as categorical variable. Values of eGFR that were >120 mL/min/1.73 m^2 were set to 120 mL/min/1.73 m^2

e: Standardized mean difference (Hedges´s g) is only calculated if confidence interval for mean difference does not include zero

f: P-Value of the interaction, based on constrained longitudinal data analysis model that include fixed effects for treatment, time, prior AHAs (monotherapy or dual therapy), baseline eGFR (continuous), subgroup, the interaction of time by treatment , treatment by subgroup, and time by treatment by subgroup, where time was treated as categorical variable

AHAs: Anti-Hyperglycemic Agents; CI: Confidence Interval; cLDA: Constrained Longitudinal Data Analysis; eGFR: Estimated Glomerular Filtration Rate; ER: Excluding Rescue; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

Tabelle 4G-11: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Veränderung des systolischen Blutdrucks (Ertugliflozin 5 mg) zu Woche 26 aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a] **Sitting Systolic Blood Pressure (mmHg) (ER)**	**N[b]**	**N[c]**	**Mean at Baseline of Study (SD)**	**Mean at Week 26 (SD)**	**Mean Change from Week 26 (SE)[d]**	**Ertugliflozin 5 mg vs. Glimepiride**			**p-Value for Interaction Test[f]**
						Mean Difference[d] [95 %-CI]	**p-Value[d]**	**Standardized Mean Difference[e] [95 %-CI]**	
Sex									
Female									
Ertugliflozin 5 mg	218	218	129.60 (13.298)	127.80 (14.193)	-1.86 (0.859)	-3.71	0.002	-0.26	0.287
Glimepiride	211	211	128.66 (13.121)	130.81 (14.560)	1.85 (0.877)	[-6.03; -1.39]		[-0.42; -0.10]	
Male									
Ertugliflozin 5 mg	227	227	130.75 (12.375)	127.46 (13.444)	-3.18 (0.730)	-2.94	0.003	-0.23	
Glimepiride	224	224	131.13 (10.879)	130.77 (11.603)	-0.25 (0.726)	[-4.88; -0.99]		[-0.39; -0.08]	
Age Group (Years)									
< 65									
Ertugliflozin 5 mg	326	326	128.83 (13.021)	126.56 (13.835)	-2.33 (0.622)	-2.92	< 0.001	-0.22	0.484
Glimepiride	332	332	129.01 (12.326)	129.62 (12.744)	0.59 (0.619)	[-4.58; -1.26]		[-0.34; -0.09]	
≥ 65									
Ertugliflozin 5 mg	119	119	133.91 (11.566)	130.63 (13.305)	-3.28 (1.238)	-4.59	0.008	-0.34	
Glimepiride	103	103	132.89 (10.729)	134.37 (13.453)	1.31 (1.288)	[-7.95; -1.23]		[-0.59; -0.09]	
Region									
WHO Stratum A									
Ertugliflozin 5 mg	153	153	127.84 (12.746)	125.82 (12.871)	-1.70 (1.002)	-3.56	0.010	-0.27	0.298
Glimepiride	148	148	127.96 (11.991)	129.68 (13.496)	1.86 (1.006)	[-6.25; -0.88]		[-0.47; -0.07]	

Study: VERTIS SU[a] **Sitting Systolic Blood Pressure (mmHg) (ER)**	**N[b]**	**N[c]**	**Mean at Baseline of Study (SD)**	**Mean at Week 26 (SD)**	**Mean Change from Week 26 (SE)[d]**	**Ertugliflozin 5 mg vs. Glimepiride**			**p-Value for Interaction Test[f]**
						Mean Difference[d] [95 %-CI]	**p-Value[d]**	**Standardized Mean Difference[e] [95 %-CI]**	
Rest of the World									
Ertugliflozin 5 mg	292	292	131.42 (12.730)	128.45 (14.149)	-2.99 (0.681)	-3.22	< 0.001	-0.24	
Glimepiride	287	287	130.95 (12.003)	131.31 (12.855)	0.23 (0.687)	[-5.05; -1.38]		[-0.37; -0.10]	

a: Database Cutoff of week 26 is the week 26 visit

b: Number of participants in subgroup: full-analysis-set population

c: Number of patients with data available for the analysis

d: Based on constrained longitudinal data analysis model that include fixed effects for treatment, time, prior AHAs (monotherapy or dual therapy), baseline eGFR (continuous), and the interaction of time by treatment, where time was treated as categorical variable. Values of eGFR that were >120 mL/min/1.73 m^2 were set to 120 mL/min/1.73 m^2

e: Standardized mean difference (Hedges´s g) is only calculated if confidence interval for mean difference does not include zero

f: P-Value of the interaction, based on constrained longitudinal data analysis model that include fixed effects for treatment, time, prior AHAs (monotherapy or dual therapy), baseline eGFR (continuous), subgroup, the interaction of time by treatment , treatment by subgroup, and time by treatment by subgroup, where time was treated as categorical variable

AHAs: Anti-Hyperglycemic Agents; CI: Confidence Interval; cLDA: Constrained Longitudinal Data Analysis; eGFR: Estimated Glomerular Filtration Rate; ER: Excluding Rescue; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

Tabelle 4G-12: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Endpunkt MACE plus (Ertugliflozin 15 mg) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a] MACE-plus[f]	Ertugliflozin 15 mg		Glimepiride		Ertugliflozin 15 mg vs. Glimepiride		
	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
Sex							
Female	244	0 (0.0)	211	1 (0.5)	n.c.	n.c.	n.c.
Male	191	1 (0.5)	224	0 (0.0)	n.c.	n.c.	
Age (Years)							
< 65	323	0 (0.0)	332	1 (0.3)	n.c.	n.c.	n.c.
≥ 65	112	1 (0.9)	103	0 (0.0)	n.c.	n.c.	
Region							
WHO Stratum A	148	1 (0.7)	148	0 (0.0)	n.c.	n.c.	n.c.
Rest of the World	287	0 (0.0)	287	1 (0.3)	n.c.	n.c.	

a: Database Cutoff of week 26: randomization till the earliest of the data cut-off date (first dose date+182 days), last contact date, or date of the death

b: Number of participants: all-participants-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the control arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the control arm, report ″n.a.″

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report ″n.a.″

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as ″n.a.″

f: MACE-plus: CV death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina

CI: Confidence Interval; CV: Cardiovascular; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary); WHO: World Health Organization

Tabelle 4G-13: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Endpunkt Kardiovaskulärer Tod (Ertugliflozin 15 mg) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a] Cardiovascular Death	Ertugliflozin 15 mg		Glimepiride		Ertugliflozin 15 mg vs. Glimepiride		
	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
Sex							
Female	244	0 (0.0)	211	0 (0.0)	n.c.	n.c.	n.c.
Male	191	1 (0.5)	224	0 (0.0)	n.c.	n.c.	
Age (Years)							
< 65	323	0 (0.0)	332	0 (0.0)	n.c.	n.c.	n.c.
≥ 65	112	1 (0.9)	103	0 (0.0)	n.c.	n.c.	
Region							
WHO Stratum A	148	1 (0.7)	148	0 (0.0)	n.c.	n.c.	n.c.
Rest of the World	287	0 (0.0)	287	0 (0.0)	n.c.	n.c.	

a: Database Cutoff of week 26: randomization till the earliest of the data cut-off date (first dose date+182 days), last contact date,

Study: VERTIS SU[a]	Ertugliflozin 15 mg		Glimepiride		Ertugliflozin 15 mg vs. Glimepiride		
Cardiovascular Death	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
or date of the death							
b: Number of participants: all-participants-as-treated population							
c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the control arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the control arm, report ″n.a.″							
d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report ″n.a.″							
e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as ″n.a.″							
CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary); WHO: World Health Organization							

Tabelle 4G-14: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Nicht-tödlicher Herzinfarkt (Ertugliflozin 15 mg) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a]	Ertugliflozin 15 mg		Glimepiride		Ertugliflozin 15 mg vs. Glimepiride		
Non-fatal Myocardial Infarction	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
Sex							
Female	244	0 (0.0)	211	0 (0.0)	n.c.	n.c.	n.c.
Male	191	0 (0.0)	224	0 (0.0)	n.c.	n.c.	
Age (Years)							
< 65	323	0 (0.0)	332	0 (0.0)	n.c.	n.c.	n.c.
≥ 65	112	0 (0.0)	103	0 (0.0)	n.c.	n.c.	
Region							
WHO Stratum A	148	0 (0.0)	148	0 (0.0)	n.c.	n.c.	n.c.
Rest of the World	287	0 (0.0)	287	0 (0.0)	n.c.	n.c.	
a: Database Cutoff of week 26: randomization till the earliest of the data cut-off date (first dose date+182 days), last contact date, or date of the death							
b: Number of participants: all-participants-as-treated population							
c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the control arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the control arm, report ″n.a.″							
d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report ″n.a.″							
e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as ″n.a.″							
CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary); WHO: World Health Organization							

Tabelle 4G-15: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Nicht-tödlicher Schlaganfall (Ertugliflozin 15 mg) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a]	**Ertugliflozin 15 mg**		**Glimepiride**		**Ertugliflozin 15 mg vs. Glimepiride**		
Non-fatal Stroke	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**Treatment Effect p-Value[d]**	**Interaction Test p-Value[e]**
Sex							
Female	244	0 (0.0)	211	1 (0.5)	n.c.	n.c.	n.c.
Male	191	0 (0.0)	224	0 (0.0)	n.c.	n.c.	
Age (Years)							
< 65	323	0 (0.0)	332	1 (0.3)	n.c.	n.c.	n.c.
≥ 65	112	0 (0.0)	103	0 (0.0)	n.c.	n.c.	
Region							
WHO Stratum A	148	0 (0.0)	148	0 (0.0)	n.c.	n.c.	n.c.
Rest of the World	287	0 (0.0)	287	1 (0.3)	n.c.	n.c.	

a: Database Cutoff of week 26: randomization till the earliest of the data cut-off date (first dose date+182 days), last contact date, or date of the death

b: Number of participants: all-participants-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the control arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the control arm, report ″n.a.″

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report ″n.a.″

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as ″n.a.″

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary); WHO: World Health Organization

Tabelle 4G-16: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Hospitalisierung wegen instabiler Angina pectoris (Ertugliflozin 15 mg) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a]	**Ertugliflozin 15 mg**		**Glimepiride**		**Ertugliflozin 15 mg vs. Glimepiride**		
Hospitalization for Unstable Angina	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**Treatment Effect p-Value[d]**	**Interaction Test p-Value[e]**
Sex							
Female	244	0 (0.0)	211	0 (0.0)	n.c.	n.c.	n.c.
Male	191	0 (0.0)	224	0 (0.0)	n.c.	n.c.	
Age (Years)							
< 65	323	0 (0.0)	332	0 (0.0)	n.c.	n.c.	n.c.
≥ 65	112	0 (0.0)	103	0 (0.0)	n.c.	n.c.	
Region							
WHO Stratum A	148	0 (0.0)	148	0 (0.0)	n.c.	n.c.	n.c.
Rest of the World	287	0 (0.0)	287	0 (0.0)	n.c.	n.c.	

a: Database Cutoff of week 26: randomization till the earliest of the data cut-off date (first dose date+182 days), last contact date, or date of the death

Study: VERTIS SU[a]	Ertugliflozin 15 mg		Glimepiride		Ertugliflozin 15 mg vs. Glimepiride		
Hospitalization for Unstable Angina	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]

b: Number of participants: all-participants-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the control arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the control arm, report ″n.a.″

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report ″n.a.″

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as ″n.a.″

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary); WHO: World Health Organization

Tabelle 4G-17: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Hospitalisierung wegen Herzinsuffizienz (Ertugliflozin 15 mg) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a]	Ertugliflozin 15 mg		Glimepiride		Ertugliflozin 15 mg vs. Glimepiride		
Hospitalization for Heart Failure	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
Sex							
Female	244	0 (0.0)	211	0 (0.0)	n.c.	n.c.	n.c.
Male	191	0 (0.0)	224	0 (0.0)	n.c.	n.c.	
Age (Years)							
< 65	323	0 (0.0)	332	0 (0.0)	n.c.	n.c.	n.c.
≥ 65	112	0 (0.0)	103	0 (0.0)	n.c.	n.c.	
Region							
WHO Stratum A	148	0 (0.0)	148	0 (0.0)	n.c.	n.c.	n.c.
Rest of the World	287	0 (0.0)	287	0 (0.0)	n.c.	n.c.	

a: Database Cutoff of week 26: randomization till the earliest of the data cut-off date (first dose date+182 days), last contact date, or date of the death

b: Number of participants: all-participants-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the control arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the control arm, report ″n.a.″

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report ″n.a.″

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as ″n.a.″

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 subjects per subgroup and at least 10 events in one of the subgroups necessary); WHO: World Health Organization

Tabelle 4G-18: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Veränderung des HbA1c-Wertes (Ertugliflozin 15 mg) zu Woche 26 aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a] **Hemoglobin A1C (%) (ER)**	**N[b]**	**N[c]**	**Mean at Baseline of Study (SD)**	**Mean at Week 26 (SD)**	**Mean Change from Week 26 (SE)[d]**	**Ertugliflozin 15 mg vs. Glimepiride**			**p-Value for Interaction Test[f]**
						Mean Difference[d] [95 %-CI]	**p-Value[d]**	**Standardized Mean Difference[e] [95 %-CI]**	
Sex									
Female									
Ertugliflozin 15 mg	244	244	7.80 (0.599)	7.17 (0.717)	-0.61 (0.048)	0.26	< 0.001	0.34	0.459
Glimepiride	211	211	7.79 (0.637)	6.92 (0.762)	-0.86 (0.052)	[0.12; 0.39]		[0.16; 0.52]	
Male									
Ertugliflozin 15 mg	191	191	7.81 (0.607)	7.12 (0.742)	-0.67 (0.062)	0.30	< 0.001	0.34	
Glimepiride	224	224	7.73 (0.563)	6.77 (0.956)	-0.97 (0.057)	[0.14; 0.46]		[0.16; 0.53]	
Region									
WHO Stratum A									
Ertugliflozin 15 mg	148	148	7.80 (0.634)	7.26 (0.768)	-0.53 (0.075)	0.26	0.014	0.28	0.078
Glimepiride	148	148	7.74 (0.574)	6.96 (1.043)	-0.79 (0.075)	[0.05; 0.46]		[0.06; 0.50]	
Rest of the World									
Ertugliflozin 15 mg	287	287	7.80 (0.586)	7.10 (0.704)	-0.68 (0.044)	0.29	< 0.001	0.39	
Glimepiride	287	287	7.77 (0.614)	6.79 (0.776)	-0.98 (0.044)	[0.18; 0.41]		[0.24; 0.55]	
Race									
Asian									
Ertugliflozin 15 mg	83	83	7.91 (0.666)	7.09 (0.785)	-0.79 (0.078)	0.31	0.005	0.43	0.117
Glimepiride	71	71	7.82 (0.569)	6.74 (0.605)	-1.10 (0.084)	[0.10; 0.52]		[0.13; 0.73]	
Other									
Ertugliflozin 15 mg	38	38	7.69 (0.581)	6.97 (0.577)	-0.71 (0.106)	0.01	0.953	-	
Glimepiride	44	44	7.80	7.02	-0.72	[-0.28; 0.29]		-	

Study: VERTIS SU[a] Hemoglobin A1C (%) (ER)	N[b]	N[c]	Mean at Baseline of Study (SD)	Mean at Week 26 (SD)	Mean Change from Week 26 (SE)[d]	Ertugliflozin 15 mg vs. Glimepiride Mean Difference[d] [95 %-CI]	p-Value[d]	Standardized Mean Difference[e] [95 %-CI]	p-Value for Interaction Test[f]
			(0.691)	(0.790)	(0.103)				
White									
Ertugliflozin 15 mg	299	299	7.79 (0.589)	7.19 (0.727)	-0.58 (0.048)	0.32	< 0.001	0.38	
Glimepiride	312	312	7.75 (0.593)	6.84 (0.930)	-0.90 (0.047)	[0.19; 0.45]		[0.23; 0.53]	
Ethnicity									
Hispanic or Latino									
Ertugliflozin 15 mg	87	87	7.81 (0.580)	7.12 (0.744)	-0.68 (0.109)	-0.13	0.382	-	0.402
Glimepiride	88	88	7.71 (0.628)	7.21 (1.193)	-0.55 (0.107)	[-0.43; 0.16]		-	
Not Hispanic or Latino									
Ertugliflozin 15 mg	347	347	7.80 (0.609)	7.15 (0.726)	-0.62 (0.040)	0.38	< 0.001	0.51	
Glimepiride	347	347	7.77 (0.594)	6.76 (0.759)	-1.01 (0.040)	[0.27; 0.49]		[0.37; 0.65]	
Body Mass Index									
≤ Median									
Ertugliflozin 15 mg	226	226	7.81 (0.622)	7.13 (0.730)	-0.66 (0.056)	0.28	< 0.001	0.33	0.486
Glimepiride	230	230	7.78 (0.624)	6.83 (0.938)	-0.94 (0.056)	[0.13; 0.43]		[0.15; 0.51]	
>Median									
Ertugliflozin 15 mg	209	209	7.80 (0.581)	7.17 (0.727)	-0.60 (0.053)	0.29	< 0.001	0.37	
Glimepiride	205	205	7.74 (0.574)	6.85 (0.793)	-0.89 (0.053)	[0.14; 0.43]		[0.19; 0.56]	
Prior Antihyperglycemic Therapy									
Monotherapy									
Ertugliflozin 15 mg	354	354	7.80 (0.601)	7.14 (0.751)	-0.64 (0.043)	0.30	< 0.001	0.37	0.748
Glimepiride	354	354	7.76 (0.614)	6.80 (0.888)	-0.94 (0.043)	[0.19; 0.42]		[0.23; 0.51]	

Study: VERTIS SU[a] **Hemoglobin A1C (%) (ER)**	**N[b]**	**N[c]**	**Mean at Baseline of Study (SD)**	**Mean at Week 26 (SD)**	**Mean Change from Week 26 (SE)[d]**	**Ertugliflozin 15 mg vs. Glimepiride**			**p-Value for Interaction Test[f]**
						Mean Difference[d] [95 %-CI]	**p-Value[d]**	**Standardized Mean Difference[e] [95 %-CI]**	
Dual Therapy									
Ertugliflozin 15 mg	81	81	7.82 (0.608)	7.18 (0.618)	-0.60 (0.087)	0.21	0.075	-	
Glimepiride	81	81	7.79 (0.542)	7.00 (0.784)	-0.80 (0.087)	[-0.02; 0.43]		-	
Time since Diagnosis of Diabetes									
≤ Median									
Ertugliflozin 15 mg	226	226	7.82 (0.607)	7.17 (0.786)	-0.63 (0.052)	0.30	< 0.001	0.37	0.966
Glimepiride	221	221	7.75 (0.600)	6.81 (0.797)	-0.93 (0.053)	[0.16; 0.44]		[0.20; 0.55]	
>Median									
Ertugliflozin 15 mg	209	209	7.79 (0.597)	7.13 (0.657)	-0.64 (0.058)	0.26	< 0.001	0.32	
Glimepiride	214	214	7.77 (0.602)	6.87 (0.944)	-0.90 (0.056)	[0.11; 0.41]		[0.13; 0.50]	

a: Database Cutoff of week 26 is the week 26 visit

b: Number of participants in subgroup: full-analysis-set population

c: Number of patients with data available for the analysis

d: Based on constrained longitudinal data analysis model that include fixed effects for treatment, time, prior AHAs (monotherapy or dual therapy), baseline eGFR (continuous), and the interaction of time by treatment, where time was treated as categorical variable. Values of eGFR that were >120 mL/min/1.73 m^2 were set to 120 mL/min/1.73 m^2

e: Standardized mean difference (Hedges´s g) is only calculated if confidence interval for mean difference does not include zero

f: P-Value of the interaction, based on constrained longitudinal data analysis model that include fixed effects for treatment, time, prior AHAs (monotherapy or dual therapy), baseline eGFR (continuous), subgroup, the interaction of time by treatment , treatment by subgroup, and time by treatment by subgroup, where time was treated as categorical variable

AHAs: Anti-Hyperglycemic Agents; CI: Confidence Interval; cLDA: Constrained Longitudinal Data Analysis; eGFR: Estimated Glomerular Filtration Rate; ER: Excluding Rescue; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

Tabelle 4G-19: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Veränderung des Körpergewichts (Ertugliflozin 15 mg) zu Woche 26 aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a] Weight (kg) (ER)	N[b]	N[c]	Mean at Baseline of Study (SD)	Mean at Week 26 (SD)	Mean Change from Week 26 (SE)[d]	Ertugliflozin 15 mg vs. Glimepiride			p-Value for Interaction Test[f]
						Mean Difference[d] [95 %-CI]	p-Value[d]	Standardized Mean Difference[e] [95 %-CI]	
Sex									
Female									
Ertugliflozin 15 mg	244	244	81.38 (18.027)	78.44 (17.725)	-3.15 (0.172)	-3.91	< 0.001	-0.20	0.833
Glimepiride	211	211	81.08 (21.158)	81.78 (21.080)	0.77 (0.185)	[-4.41; -3.42]		[-0.23; -0.18]	
Male									
Ertugliflozin 15 mg	191	191	91.14 (19.084)	87.82 (18.888)	-3.21 (0.234)	-3.84	< 0.001	-0.21	
Glimepiride	224	224	92.39 (18.841)	92.83 (18.166)	0.63 (0.214)	[-4.46; -3.23]		[-0.24; -0.17]	
Age Group (Years)									
< 65									
Ertugliflozin 15 mg	323	323	86.90 (19.983)	84.31 (19.732)	-3.22 (0.163)	-4.00	< 0.001	-0.19	0.593
Glimepiride	332	332	87.94 (21.928)	88.60 (21.540)	0.78 (0.161)	[-4.45; -3.56]		[-0.21; -0.17]	
≥ 65									
Ertugliflozin 15 mg	112	112	82.11 (15.843)	77.71 (14.876)	-3.06 (0.294)	-3.49	< 0.001	-0.22	
Glimepiride	103	103	83.56 (16.087)	84.59 (15.812)	0.44 (0.298)	[-4.31; -2.67]		[-0.28; -0.17]	
Region									
WHO Stratum A									
Ertugliflozin 15 mg	148	148	89.99 (20.080)	87.33 (19.632)	-3.38 (0.231)	-4.56	< 0.001	-0.22	0.310
Glimepiride	148	148	91.91 (23.246)	93.49 (22.910)	1.17 (0.228)	[-5.19; -3.92]		[-0.25; -0.19]	
Rest of the World									
Ertugliflozin 15 mg	287	287	83.44 (18.215)	80.43 (18.043)	-3.08 (0.179)	-3.57	< 0.001	-0.19	
Glimepiride	287	287	84.32	84.89	0.49	[-4.06; -3.07]		[-0.22; -0.17]	

Study: VERTIS SU[a] Weight (kg) (ER)	N[b]	N[c]	Mean at Baseline of Study (SD)	Mean at Week 26 (SD)	Mean Change from Week 26 (SE)[d]	Ertugliflozin 15 mg vs. Glimepiride			p-Value for Interaction Test[f]
						Mean Difference[d] [95 %-CI]	p-Value[d]	Standardized Mean Difference[e] [95 %-CI]	
			(18.886)	(18.444)	(0.178)				

a: Database Cutoff of week 26 is the week 26 visit

b: Number of participants in subgroup: full-analysis-set population

c: Number of patients with data available for the analysis

d: Based on constrained longitudinal data analysis model that include fixed effects for treatment, time, prior AHAs (monotherapy or dual therapy), baseline eGFR (continuous), and the interaction of time by treatment, where time was treated as categorical variable. Values of eGFR that were >120 mL/min/1.73 m^2 were set to 120 mL/min/1.73 m^2

e: Standardized mean difference (Hedges´s g) is only calculated if confidence interval for mean difference does not include zero

f: P-Value of the interaction, based on constrained longitudinal data analysis model that include fixed effects for treatment, time, prior AHAs (monotherapy or dual therapy), baseline eGFR (continuous), subgroup, the interaction of time by treatment , treatment by subgroup, and time by treatment by subgroup, where time was treated as categorical variable

AHAs: Anti-Hyperglycemic Agents; CI: Confidence Interval; cLDA: Constrained Longitudinal Data Analysis; eGFR: Estimated Glomerular Filtration Rate; ER: Excluding Rescue; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

Tabelle 4G-20: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Veränderung des systolischen Blutdrucks (Ertugliflozin 15 mg) zu Woche 26 aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a] **Sitting Systolic Blood Pressure (mmHg) (ER)**	**N[b]**	**N[c]**	**Mean at Baseline of Study (SD)**	**Mean at Week 26 (SD)**	**Mean Change from Week 26 (SE)[d]**	**Ertugliflozin 15 mg vs. Glimepiride**			**p-Value for Interaction Test[f]**
						Mean Difference[d] [95 %-CI]	**p-Value[d]**	**Standardized Mean Difference[e] [95 %-CI]**	
Sex									
Female									
Ertugliflozin 15 mg	244	244	130.32 (12.565)	126.21 (13.015)	-3.57 (0.831)	-5.22	< 0.001	-0.38	0.483
Glimepiride	211	211	128.66 (13.121)	130.81 (14.560)	1.65 (0.888)	[-7.50; -2.94]		[-0.54; -0.21]	
Male									
Ertugliflozin 15 mg	191	191	131.34 (12.176)	128.27 (13.714)	-2.93 (0.785)	-2.57	0.013	-0.20	
Glimepiride	224	224	131.13 (10.879)	130.77 (11.603)	-0.36 (0.720)	[-4.59; -0.55]		[-0.37; -0.04]	
Age Group (Years)									
< 65									
Ertugliflozin 15 mg	323	323	130.09 (12.154)	126.37 (13.570)	-3.40 (0.654)	-3.78	< 0.001	-0.29	0.935
Glimepiride	332	332	129.01 (12.326)	129.62 (12.744)	0.38 (0.646)	[-5.52; -2.05]		[-0.42; -0.15]	
≥ 65									
Ertugliflozin 15 mg	112	112	132.72 (12.913)	129.34 (12.503)	-3.28 (1.201)	-4.89	0.003	-0.37	
Glimepiride	103	103	132.89 (10.729)	134.37 (13.453)	1.61 (1.214)	[-8.08; -1.70]		[-0.62; -0.13]	
Region									
WHO Stratum A									
Ertugliflozin 15 mg	148	148	128.32 (12.765)	125.57 (13.199)	-2.36 (1.021)	-4.17	0.003	-0.31	0.263
Glimepiride	148	148	127.96 (11.991)	129.68 (13.496)	1.82 (1.015)	[-6.90; -1.44]		[-0.51; -0.11]	
Rest of the World									
Ertugliflozin 15 mg	287	287	132.03 (12.023)	127.86 (13.388)	-3.86 (0.698)	-3.98	< 0.001	-0.30	

Study: VERTIS SU[a] **Sitting Systolic Blood Pressure (mmHg) (ER)**	**N[b]**	**N[c]**	**Mean at Baseline of Study (SD)**	**Mean at Week 26 (SD)**	**Mean Change from Week 26 (SE)[d]**	**Ertugliflozin 15 mg vs. Glimepiride**			**p-Value for Interaction Test[f]**
						Mean Difference[d] [95 %-CI]	**p-Value[d]**	**Standardized Mean Difference[e] [95 %-CI]**	
Glimepiride	287	287	130.95 (12.003)	131.31 (12.855)	0.13 (0.693)	[-5.83; -2.13]		[-0.44; -0.16]	

a: Database Cutoff of week 26 is the week 26 visit

b: Number of participants in subgroup: full-analysis-set population

c: Number of patients with data available for the analysis

d: Based on constrained longitudinal data analysis model that include fixed effects for treatment, time, prior AHAs (monotherapy or dual therapy), baseline eGFR (continuous), and the interaction of time by treatment, where time was treated as categorical variable. Values of eGFR that were >120 mL/min/1.73 m^2 were set to 120 mL/min/1.73 m^2

e: Standardized mean difference (Hedges´s g) is only calculated if confidence interval for mean difference does not include zero

f: P-Value of the interaction, based on constrained longitudinal data analysis model that include fixed effects for treatment, time, prior AHAs (monotherapy or dual therapy), baseline eGFR (continuous), subgroup, the interaction of time by treatment , treatment by subgroup, and time by treatment by subgroup, where time was treated as categorical variable

AHAs: Anti-Hyperglycemic Agents; CI: Confidence Interval; cLDA: Constrained Longitudinal Data Analysis; eGFR: Estimated Glomerular Filtration Rate; ER: Excluding Rescue; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

Tabelle 4G-21: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Hypoglykämien (ER) (Ertugliflozin 5 mg)aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a]	**Ertugliflozin 5 mg**		**Glimepiride**		**Ertugliflozin 5 mg vs. Glimepiride**		
Hypoglycemia Related Endpoints	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**Treatment Effect p-Value[d]**	**Interaction Test p-Value[e]**
Documented Symptomatic Hypoglycemia < 56 mg/dL ER							
Sex							
Female	218	1 (0.5)	211	17 (8.1)	0.06 [0.01; 0.42]	< 0.001	0.441
Male	227	1 (0.4)	224	6 (2.7)	0.16 [0.02; 1.36]	0.055	
Age (Years)							
< 65	326	2 (0.6)	332	19 (5.7)	0.11 [0.03; 0.46]	< 0.001	0.491
≥ 65	119	0 (0.0)	103	4 (3.9)	0.10 [0.01; 1.77]	0.030	
Region							
WHO Stratum A	153	0 (0.0)	148	6 (4.1)	0.07 [0.00; 1.31]	0.012	0.407
Rest of the World	292	2 (0.7)	287	17 (5.9)	0.12 [0.03; 0.50]	< 0.001	
Non-Severe Hypoglycemia ER							
Sex							
Female	218	13 (6.0)	211	59 (28.0)	0.21 [0.12; 0.38]	< 0.001	0.756
Male	227	9 (4.0)	224	51 (22.8)	0.17 [0.09; 0.35]	< 0.001	
Age (Years)							
< 65	326	13 (4.0)	332	87 (26.2)	0.15 [0.09; 0.27]	< 0.001	0.083
≥ 65	119	9 (7.6)	103	23 (22.3)	0.34 [0.16; 0.70]	0.002	
Region							
WHO Stratum A	153	9 (5.9)	148	47 (31.8)	0.19 [0.09; 0.36]	< 0.001	0.675
Rest of the World	292	13 (4.5)	287	63 (22.0)	0.20 [0.11; 0.36]	< 0.001	
Severe Hypoglycemia Requiring Medical Assistance ER							
Sex							
Female	218	0 (0.0)	211	3 (1.4)	n.c.	n.c.	n.c.
Male	227	0 (0.0)	224	1 (0.4)	n.c.	n.c.	
Age (Years)							
< 65	326	0 (0.0)	332	3 (0.9)	n.c.	n.c.	n.c.
≥ 65	119	0 (0.0)	103	1 (1.0)	n.c.	n.c.	
Region							
WHO Stratum A	153	0 (0.0)	148	0 (0.0)	n.c.	n.c.	n.c.
Rest of the World	292	0 (0.0)	287	4 (1.4)	n.c.	n.c.	

a: Database Cutoff of week 26: all events from the first dose of treatment up to week 26 + 14 days of post-treatment follow-up period, and for participants that did not continue into week 26, it includes all events up to 14 days after the final dose of study medication

b: Number of participants: all-participants-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the placebo arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the placebo arm, report 'n.a.'

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report 'n.a.'

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as 'n.a.'

Study: VERTIS SU[a]	Ertugliflozin 5 mg		Glimepiride		Ertugliflozin 5 mg vs. Glimepiride		
Hypoglycemia Related Endpoints	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
CI: Confidence Interval; ER: Excluding Rescue; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 participants per subgroup and at least 10 events in one of the subgroups necessary); WHO: World Health Organization							

Tabelle 4G-22: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Hypoglykämien (ER) (Ertugliflozin 15 mg)aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a]	Ertugliflozin 15 mg		Glimepiride		Ertugliflozin 15 mg vs. Glimepiride		
Hypoglycemia Related Endpoints	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
Documented Symptomatic Hypoglycemia < 56 mg/dL ER							
Sex							
Female	244	1 (0.4)	211	17 (8.1)	0.05 [0.01; 0.38]	< 0.001	0.613
Male	191	0 (0.0)	224	6 (2.7)	0.09 [0.01; 1.59]	0.023	
Age (Years)							
< 65	323	1 (0.3)	332	19 (5.7)	0.05 [0.01; 0.40]	< 0.001	0.633
≥ 65	112	0 (0.0)	103	4 (3.9)	0.10 [0.01; 1.88]	0.036	
Region							
WHO stratum A	148	0 (0.0)	148	6 (4.1)	0.08 [0.00; 1.35]	0.013	0.558
Rest of the World	287	1 (0.3)	287	17 (5.9)	0.06 [0.01; 0.44]	< 0.001	
Non-Severe Hypoglycemia ER							
Sex							
Female	244	18 (7.4)	211	59 (28.0)	0.26 [0.16; 0.43]	< 0.001	0.666
Male	191	13 (6.8)	224	51 (22.8)	0.30 [0.17; 0.53]	< 0.001	
Age (Years)							
< 65	323	26 (8.0)	332	87 (26.2)	0.31 [0.20; 0.46]	< 0.001	0.462
≥ 65	112	5 (4.5)	103	23 (22.3)	0.20 [0.08; 0.51]	< 0.001	
Region							
WHO stratum A	148	13 (8.8)	148	47 (31.8)	0.28 [0.16; 0.49]	< 0.001	0.752
Rest of the World	287	18 (6.3)	287	63 (22.0)	0.29 [0.17; 0.47]	< 0.001	
Severe Hypoglycemia Requiring Medical Assistance ER							
Sex							
Female	244	0 (0.0)	211	3 (1.4)	n.c.	n.c.	n.c.
Male	191	0 (0.0)	224	1 (0.4)	n.c.	n.c.	
Age (Years)							
< 65	323	0 (0.0)	332	3 (0.9)	n.c.	n.c.	n.c.
≥ 65	112	0 (0.0)	103	1 (1.0)	n.c.	n.c.	
Region							
WHO stratum A	148	0 (0.0)	148	0 (0.0)	n.c.	n.c.	n.c.
Rest of the World	287	0 (0.0)	287	4 (1.4)	n.c.	n.c.	
a: Database Cutoff of week 26: all events from the first dose of treatment up to week 26 + 14 days of post-treatment follow-up							

Study: VERTIS SU[a]	Ertugliflozin 15 mg		Glimepiride		Ertugliflozin 15 mg vs. Glimepiride		
Hypoglycemia Related Endpoints	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
period, and for participants that did not continue into week 26, it includes all events up to 14 days after the final dose of study medication							
b: Number of participants: all-participant-as-treated population							
c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the placebo arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the placebo arm, report 'n.a.'							
d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report 'n.a.'							
e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as 'n.a.'							
CI: Confidence Interval; ER: Excluding Rescue; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 participants per subgroup and at least 10 events in one of the subgroups necessary); WHO: World Health Organization							

Anhang 4-G1.3: Unerwünschte Ereignisse

Unerwünschte Ereignisse

Tabelle 4G-23: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (Ertugliflozin 5 mg) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a]	Ertugliflozin 5 mg		Glimepiride		Ertugliflozin 5 mg vs. Glimepiride		
Adverse Events	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
Sex							
Female	218	105 (48.2)	211	118 (55.9)	0.86 [0.72; 1.03]	0.108	0.074
Male	227	107 (47.1)	224	96 (42.9)	1.10 [0.90; 1.35]	0.362	
Age (Years)							
< 65	326	153 (46.9)	332	166 (50.0)	0.94 [0.80; 1.10]	0.432	0.437
≥ 65	119	59 (49.6)	103	48 (46.6)	1.06 [0.81; 1.40]	0.659	
Region							
WHO stratum A	153	83 (54.2)	148	84 (56.8)	0.96 [0.78; 1.17]	0.662	0.844
Rest of the World	292	129 (44.2)	287	130 (45.3)	0.98 [0.81; 1.17]	0.787	

a: Database Cutoff of week 26: all events from the first dose of treatment up to week 26 + 14 days of post-treatment follow-up period, and for participants that did not continue into week 26, it includes all events up to 14 days after the final dose of study medication

b: Number of participants: all-participant-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the placebo arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the placebo arm, report 'n.a.'

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report 'n.a.'

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as 'n.a.'

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 participants per subgroup and at least 10 events in one of the subgroups necessary); WHO: World Health Organization

Tabelle 4G-24: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse (Ertugliflozin 5 mg) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a]	Ertugliflozin 5 mg		Glimepiride		Ertugliflozin 5 mg vs. Glimepiride		
Serious Adverse Events	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
Sex							
Female	218	5 (2.3)	211	2 (0.9)	2.42 [0.47; 12.34]	0.272	0.690
Male	227	11 (4.8)	224	3 (1.3)	3.62 [1.02; 12.80]	0.032	
Age (Years)							
< 65	326	9 (2.8)	332	4 (1.2)	2.29 [0.71; 7.37]	0.152	0.403
≥ 65	119	7 (5.9)	103	1 (1.0)	6.06 [0.76; 48.43]	0.051	

Study: VERTIS SU[a]	Ertugliflozin 5 mg		Glimepiride		Ertugliflozin 5 mg vs. Glimepiride		
Serious Adverse Events	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
Region							
WHO stratum A	153	5 (3.3)	148	2 (1.4)	2.42 [0.48; 12.27]	0.271	0.703
Rest of the World	292	11 (3.8)	287	3 (1.0)	3.60 [1.02; 12.78]	0.033	

a: Database Cutoff of week 26: all events from the first dose of treatment up to week 26 + 14 days of post-treatment follow-up period, and for participants that did not continue into week 26, it includes all events up to 14 days after the final dose of study medication

b: Number of participants: all-participant-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the placebo arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the placebo arm, report 'n.a.'

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report 'n.a.'

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as 'n.a.'

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 participants per subgroup and at least 10 events in one of the subgroups necessary); WHO: World Health Organization

Tabelle 4G-25: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Nicht-schwere unerwünschte Ereignisse (Ertugliflozin 5 mg) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a]	Ertugliflozin 5 mg		Glimepiride		Ertugliflozin 5 mg vs. Glimepiride		
Non-Severe Adverse Events	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
Sex							
Female	218	103 (47.2)	211	117 (55.5)	0.85 [0.71; 1.03]	0.090	0.097
Male	227	103 (45.4)	224	95 (42.4)	1.07 [0.87; 1.32]	0.526	
Age (Years)							
< 65	326	149 (45.7)	332	164 (49.4)	0.93 [0.79; 1.09]	0.343	0.521
≥ 65	119	57 (47.9)	103	48 (46.6)	1.03 [0.78; 1.36]	0.847	
Region							
WHO stratum A	153	82 (53.6)	148	83 (56.1)	0.96 [0.78; 1.17]	0.665	0.999
Rest of the World	292	124 (42.5)	287	129 (44.9)	0.94 [0.79; 1.14]	0.548	

a: Database Cutoff of week 26: all events from the first dose of treatment up to week 26 + 14 days of post-treatment follow-up period, and for participants that did not continue into week 26, it includes all events up to 14 days after the final dose of study medication

b: Number of participants: all-participant-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the placebo arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the placebo arm, report 'n.a.'

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report 'n.a.'

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as 'n.a.'

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 participants per subgroup and at least 10 events in one of the subgroups necessary); WHO: World Health Organization

Tabelle 4G-26: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwere unerwünschte Ereignisse (Ertugliflozin 5 mg) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a]	**Ertugliflozin 5 mg**		**Glimepiride**		**Ertugliflozin 5 mg vs. Glimepiride**		
Severe Adverse Events	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**Treatment Effect p-Value[d]**	**Interaction Test p-Value[e]**
Sex							
Female	218	3 (1.4)	211	2 (0.9)	1.45 [0.25; 8.60]	0.680	0.687
Male	227	9 (4.0)	224	4 (1.8)	2.22 [0.69; 7.11]	0.167	
Age (Years)							
< 65	326	7 (2.1)	332	5 (1.5)	1.43 [0.46; 4.45]	0.539	0.351
≥ 65	119	5 (4.2)	103	1 (1.0)	4.33 [0.51; 36.45]	0.140	
Region							
WHO stratum A	153	6 (3.9)	148	2 (1.4)	2.90 [0.60; 14.15]	0.166	0.504
Rest of the World	292	6 (2.1)	287	4 (1.4)	1.47 [0.42; 5.17]	0.542	

a: Database Cutoff of week 26: all events from the first dose of treatment up to week 26 + 14 days of post-treatment follow-up period, and for participants that did not continue into week 26, it includes all events up to 14 days after the final dose of study medication

b: Number of participants: all-participant-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the placebo arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the placebo arm, report 'n.a.'

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report 'n.a.'

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as 'n.a.'

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 participants per subgroup and at least 10 events in one of the subgroups necessary); WHO: World Health Organization

Tabelle 4G-27: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse (Ertugliflozin 5 mg) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a]	**Ertugliflozin 5 mg**		**Glimepiride**		**Ertugliflozin 5 mg vs. Glimepiride**		
Adverse Events Leading to Treatment Discontinuation	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**Treatment Effect p-Value[d]**	**Interaction Test p-Value[e]**
Sex							
Female	218	6 (2.8)	211	7 (3.3)	0.83 [0.28; 2.43]	0.733	0.857
Male	227	3 (1.3)	224	3 (1.3)	0.99 [0.20; 4.84]	0.987	
Age (Years)							
< 65	326	7 (2.1)	332	8 (2.4)	0.89 [0.33; 2.43]	0.822	0.980
≥ 65	119	2 (1.7)	103	2 (1.9)	0.87 [0.12; 6.04]	0.884	
Region							

Study: VERTIS SU[a]	Ertugliflozin 5 mg		Glimepiride		Ertugliflozin 5 mg vs. Glimepiride		
Adverse Events Leading to Treatment Discontinuation	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
WHO stratum A	153	2 (1.3)	148	5 (3.4)	0.39 [0.08; 1.96]	0.234	0.199
Rest of the World	292	7 (2.4)	287	5 (1.7)	1.38 [0.44; 4.29]	0.580	

a: Database Cutoff of week 26: all events from the first dose of treatment up to week 26 + 14 days of post-treatment follow-up period, and for participants that did not continue into week 26, it includes all events up to 14 days after the final dose of study medication

b: Number of participants: all-participant-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the placebo arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the placebo arm, report 'n.a.'

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report 'n.a.'

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as 'n.a.'

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 participants per subgroup and at least 10 events in one of the subgroups necessary); WHO: World Health Organization

Tabelle 4G-28: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Unerwünschte Ereignisse gesamt (Ertugliflozin 15 mg) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a]	Ertugliflozin 15 mg		Glimepiride		Ertugliflozin 15 mg vs. Glimepiride		
Adverse Events	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
Sex							
Female	244	133 (54.5)	211	118 (55.9)	0.97 [0.83; 1.15]	0.762	0.222
Male	191	95 (49.7)	224	96 (42.9)	1.16 [0.94; 1.43]	0.161	
Age (Years)							
< 65	323	176 (54.5)	332	166 (50.0)	1.09 [0.94; 1.26]	0.251	0.553
≥ 65	112	52 (46.4)	103	48 (46.6)	1.00 [0.75; 1.33]	0.980	
Region							
WHO stratum A	148	92 (62.2)	148	84 (56.8)	1.10 [0.91; 1.32]	0.344	0.629
Rest of the World	287	136 (47.4)	287	130 (45.3)	1.05 [0.88; 1.25]	0.616	

a: Database Cutoff of week 26: all events from the first dose of treatment up to week 26 + 14 days of post-treatment follow-up period, and for participants that did not continue into week 26, it includes all events up to 14 days after the final dose of study medication

b: Number of participants: all-participant-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the placebo arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the placebo arm, report 'n.a.'

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report 'n.a.'

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as 'n.a.'

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 participants per subgroup and at least 10 events in one of the subgroups necessary); WHO: World Health Organization

Tabelle 4G-29: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschte Ereignisse (Ertugliflozin 15 mg) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a]	**Ertugliflozin 15 mg**		**Glimepiride**		**Ertugliflozin 15 mg vs. Glimepiride**		
Serious Adverse Events	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**Treatment Effect p-Value[d]**	**Interaction Test p-Value[e]**
Sex							
Female	244	5 (2.0)	211	2 (0.9)	n.c.	n.c.	n.c.
Male	191	4 (2.1)	224	3 (1.3)	n.c.	n.c.	
Age (Years)							
< 65	323	7 (2.2)	332	4 (1.2)	1.80 [0.53; 6.09]	0.338	0.988
≥ 65	112	2 (1.8)	103	1 (1.0)	1.84 [0.17; 19.98]	0.612	
Region							
WHO stratum A	148	3 (2.0)	148	2 (1.4)	n.c.	n.c.	n.c.
Rest of the World	287	6 (2.1)	287	3 (1.0)	n.c.	n.c.	

a: Database Cutoff of week 26: all events from the first dose of treatment up to week 26 + 14 days of post-treatment follow-up period, and for participants that did not continue into week 26, it includes all events up to 14 days after the final dose of study medication

b: Number of participants: all-participant-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the placebo arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the placebo arm, report 'n.a.'

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report 'n.a.'

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as 'n.a.'

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 participants per subgroup and at least 10 events in one of the subgroups necessary); WHO: World Health Organization

Tabelle 4G-30: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Nicht-schwere unerwünschte Ereignisse (Ertugliflozin 15 mg) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a]	**Ertugliflozin 15 mg**		**Glimepiride**		**Ertugliflozin 15 mg vs. Glimepiride**		
Non-Severe Adverse Events	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**Treatment Effect p-Value[d]**	**Interaction Test p-Value[e]**
Sex							
Female	244	131 (53.7)	211	117 (55.5)	0.97 [0.82; 1.15]	0.707	0.207
Male	191	94 (49.2)	224	95 (42.4)	1.16 [0.94; 1.43]	0.166	
Age (Years)							
< 65	323	175 (54.2)	332	164 (49.4)	1.10 [0.95; 1.27]	0.221	0.391
≥ 65	112	50 (44.6)	103	48 (46.6)	0.96 [0.72; 1.28]	0.774	
Region							
WHO stratum A	148	92 (62.2)	148	83 (56.1)	1.11 [0.92; 1.34]	0.288	0.500

Study: VERTIS SU[a]	Ertugliflozin 15 mg		Glimepiride		Ertugliflozin 15 mg vs. Glimepiride		
Non-Severe Adverse Events	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
Rest of the World	287	133 (46.3)	287	129 (44.9)	1.03 [0.86; 1.23]	0.738	

a: Database Cutoff of week 26: all events from the first dose of treatment up to week 26 + 14 days of post-treatment follow-up period, and for participants that did not continue into week 26, it includes all events up to 14 days after the final dose of study medication

b: Number of participants: all-participant-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the placebo arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the placebo arm, report 'n.a.'

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report 'n.a.'

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as 'n.a.'

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 participants per subgroup and at least 10 events in one of the subgroups necessary); WHO: World Health Organization

Tabelle 4G-31: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Schwere unerwünschte Ereignisse (Ertugliflozin 15 mg) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a]	Ertugliflozin 15 mg		Glimepiride		Ertugliflozin 15 mg vs. Glimepiride		
Severe Adverse Events	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
Sex							
Female	244	5 (2.0)	211	2 (0.9)	2.16 [0.42; 11.03]	0.342	0.848
Male	191	6 (3.1)	224	4 (1.8)	1.76 [0.50; 6.14]	0.370	
Age (Years)							
< 65	323	7 (2.2)	332	5 (1.5)	1.44 [0.46; 4.49]	0.528	0.442
≥ 65	112	4 (3.6)	103	1 (1.0)	3.68 [0.42; 32.38]	0.207	
Region							
WHO stratum A	148	5 (3.4)	148	2 (1.4)	2.50 [0.49; 12.68]	0.252	0.622
Rest of the World	287	6 (2.1)	287	4 (1.4)	1.50 [0.43; 5.26]	0.524	

a: Database Cutoff of week 26: all events from the first dose of treatment up to week 26 + 14 days of post-treatment follow-up period, and for participants that did not continue into week 26, it includes all events up to 14 days after the final dose of study medication

b: Number of participants: all-participant-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the placebo arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the placebo arm, report 'n.a.'

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report 'n.a.'

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as 'n.a.'

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 participants per subgroup and at least 10 events in one of the subgroups necessary); WHO: World Health Organization

Tabelle 4G-32: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse (Ertugliflozin 15 mg) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS SU[a]	**Ertugliflozin 15 mg**		**Glimepiride**		**Ertugliflozin 15 mg vs. Glimepiride**		
Adverse Events Leading to Treatment Discontinuation	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**Treatment Effect p-Value[d]**	**Interaction Test p-Value[e]**
Sex							
Female	244	15 (6.1)	211	7 (3.3)	1.85 [0.77; 4.46]	0.161	0.792
Male	191	6 (3.1)	224	3 (1.3)	2.35 [0.59; 9.25]	0.210	
Age (Years)							
< 65	323	13 (4.0)	332	8 (2.4)	1.67 [0.70; 3.98]	0.241	0.364
≥ 65	112	8 (7.1)	103	2 (1.9)	3.68 [0.80; 16.92]	0.071	
Region							
WHO stratum A	148	10 (6.8)	148	5 (3.4)	2.00 [0.70; 5.71]	0.186	0.917
Rest of the World	287	11 (3.8)	287	5 (1.7)	2.20 [0.77; 6.25]	0.129	

a: Database Cutoff of week 26: all events from the first dose of treatment up to week 26 + 14 days of post-treatment follow-up period, and for participants that did not continue into week 26, it includes all events up to 14 days after the final dose of study medication

b: Number of participants: all-participant-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the placebo arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the placebo arm, report 'n.a.'

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report 'n.a.'

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as 'n.a.'

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 participants per subgroup and at least 10 events in one of the subgroups necessary); WHO: World Health Organization

Unerwünschte Ereignisse (gegliedert nach SOC und PT)

Tabelle 4G-33: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC) (Ertugliflozin 5 mg)

Study: VERTIS SU[a]	**Ertugliflozin 5 mg**		**Glimepiride**		**Ertugliflozin 5 mg vs. Glimepiride**		
Adverse Events[f]	**N[b]**	**Participants with Event n (%)**	**N[b]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][c]**	**Treatment Effect p-Value[d]**	**Interaction Test p-Value[e]**
SOC: Metabolism and nutrition disorders							
Sex							
Female	218	17 (7.8)	211	57 (27.0)	0.29 [0.17; 0.48]	< 0.001	0.746
Male	227	12 (5.3)	224	39 (17.4)	0.30 [0.16; 0.56]	< 0.001	
Age (Years)							
< 65	326	20 (6.1)	332	78 (23.5)	0.26 [0.16; 0.42]	< 0.001	0.237
≥ 65	119	9 (7.6)	103	18 (17.5)	0.43 [0.20; 0.92]	0.025	
Region							
WHO stratum A	153	9 (5.9)	148	35 (23.6)	0.25 [0.12; 0.50]	< 0.001	0.531

Study: VERTIS SU[a]	Ertugliflozin 5 mg		Glimepiride		Ertugliflozin 5 mg vs. Glimepiride		
Adverse Events[f]	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
Rest of the World	292	20 (6.8)	287	61 (21.3)	0.32 [0.20; 0.52]	< 0.001	
SOC: Renal and urinary disorders							
Sex							
Female	218	12 (5.5)	211	7 (3.3)	1.66 [0.67; 4.13]	0.272	0.328
Male	227	11 (4.8)	224	3 (1.3)	3.62 [1.02; 12.80]	0.032	
Age (Years)							
< 65	326	13 (4.0)	332	8 (2.4)	1.65 [0.70; 3.94]	0.250	0.255
≥ 65	119	10 (8.4)	103	2 (1.9)	4.33 [0.97; 19.30]	0.034	
Region							
WHO stratum A	153	11 (7.2)	148	6 (4.1)	1.77 [0.67; 4.67]	0.240	0.519
Rest of the World	292	12 (4.1)	287	4 (1.4)	2.95 [0.96; 9.04]	0.046	
SOC: Reproductive system and breast disorders							
Sex							
Female	218	8 (3.7)	211	3 (1.4)	2.58 [0.69; 9.60]	0.141	0.902
Male	227	6 (2.6)	224	2 (0.9)	2.96 [0.60; 14.51]	0.160	
Age (Years)							
< 65	326	14 (4.3)	332	4 (1.2)	3.56 [1.19; 10.71]	0.015	0.061
≥ 65	119	0 (0.0)	103	1 (1.0)	0.29 [0.01; 7.01]	0.282	
Region							
WHO stratum A	153	6 (3.9)	148	3 (2.0)	1.93 [0.49; 7.59]	0.335	0.503
Rest of the World	292	8 (2.7)	287	2 (0.7)	3.93 [0.84; 18.36]	0.059	

a: Database Cutoff of week 26: all events from the first dose of treatment up to week 26 + 14 days of post-treatment follow-up period, and for participants that did not continue into week 26, it includes all events up to 14 days after the final dose of study medication

b: Number of participants: all-participant-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the placebo arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the placebo arm, report 'n.a.'

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report 'n.a.'

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as 'n.a.'

f: A system organ class appears on this report only if its incidence ≥ 10% or (incidence ≥ 1% and in at least 10 participants) in one or more groups and p-value of main treatment effect smaller than 0.05

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 participants per subgroup and at least 10 events in one of the subgroups necessary); SOC: System Organ Class; WHO: World Health Organization

Tabelle 4G-34: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (PT) (Ertugliflozin 5 mg)

Study: VERTIS SU[a]	Ertugliflozin 5 mg		Glimepiride		Ertugliflozin 5 mg vs. Glimepiride		
Adverse Events[f]	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
SOC: Metabolism and nutrition disorders PT: Hypoglycaemia							
Sex							
Female	218	8 (3.7)	211	48 (22.7)	0.16 [0.08; 0.33]	< 0.001	0.945
Male	227	5 (2.2)	224	32 (14.3)	0.15 [0.06; 0.39]	< 0.001	
Age (Years)							
< 65	326	7 (2.1)	332	64 (19.3)	0.11 [0.05; 0.24]	< 0.001	0.067
≥ 65	119	6 (5.0)	103	16 (15.5)	0.32 [0.13; 0.80]	0.009	
Region							
WHO stratum A	153	5 (3.3)	148	32 (21.6)	0.15 [0.06; 0.38]	< 0.001	0.830
Rest of the World	292	8 (2.7)	287	48 (16.7)	0.16 [0.08; 0.34]	< 0.001	

a: Database Cutoff of week 26: all events from the first dose of treatment up to week 26 + 14 days of post-treatment follow-up period, and for participants that did not continue into week 26, it includes all events up to 14 days after the final dose of study medication

b: Number of participants: all-participant-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the placebo arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the placebo arm, report 'n.a.'

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report 'n.a.'

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as 'n.a.'

f: A system organ class appears on this report only if its incidence ≥ 10% or (incidence ≥ 1% and in at least 10 participants) in one or more groups and p-value of main treatment effect smaller than 0.05

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 participants per subgroup and at least 10 events in one of the subgroups necessary); PT: Preferred Term; SOC: System Organ Class; WHO: World Health Organization

Tabelle 4G-35: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Nicht-schwere unerwünschte Ereignisse gesamt (SOC) (Ertugliflozin 5 mg)

Study: VERTIS SU[a]	Ertugliflozin 5 mg		Glimepiride		Ertugliflozin 5 mg vs. Glimepiride		
Non-Severe Adverse Events[f]	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
SOC: Metabolism and nutrition disorders							
Sex							
Female	218	17 (7.8)	211	57 (27.0)	0.29 [0.17; 0.48]	< 0.001	0.746
Male	227	12 (5.3)	224	39 (17.4)	0.30 [0.16; 0.56]	< 0.001	
Age (Years)							
< 65	326	20 (6.1)	332	78 (23.5)	0.26 [0.16; 0.42]	< 0.001	0.237
≥ 65	119	9 (7.6)	103	18 (17.5)	0.43 [0.20; 0.92]	0.025	
Region							
WHO stratum A	153	9 (5.9)	148	35 (23.6)	0.25 [0.12; 0.50]	< 0.001	0.531

Study: VERTIS SU[a]	Ertugliflozin 5 mg		Glimepiride		Ertugliflozin 5 mg vs. Glimepiride		
Non-Severe Adverse Events[f]	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
Rest of the World	292	20 (6.8)	287	61 (21.3)	0.32 [0.20; 0.52]	< 0.001	
SOC: Renal and urinary disorders							
Sex							
Female	218	12 (5.5)	211	7 (3.3)	1.66 [0.67; 4.13]	0.272	0.328
Male	227	11 (4.8)	224	3 (1.3)	3.62 [1.02; 12.80]	0.032	
Age (Years)							
< 65	326	13 (4.0)	332	8 (2.4)	1.65 [0.70; 3.94]	0.250	0.255
≥ 65	119	10 (8.4)	103	2 (1.9)	4.33 [0.97; 19.30]	0.034	
Region							
WHO stratum A	153	11 (7.2)	148	6 (4.1)	1.77 [0.67; 4.67]	0.240	0.519
Rest of the World	292	12 (4.1)	287	4 (1.4)	2.95 [0.96; 9.04]	0.046	
SOC: Reproductive system and breast disorders							
Sex							
Female	218	8 (3.7)	211	3 (1.4)	2.58 [0.69; 9.60]	0.141	0.902
Male	227	6 (2.6)	224	2 (0.9)	2.96 [0.60; 14.51]	0.160	
Age (Years)							
< 65	326	14 (4.3)	332	4 (1.2)	3.56 [1.19; 10.71]	0.015	0.061
≥ 65	119	0 (0.0)	103	1 (1.0)	0.29 [0.01; 7.01]	0.282	
Region							
WHO stratum A	153	6 (3.9)	148	3 (2.0)	1.93 [0.49; 7.59]	0.335	0.503
Rest of the World	292	8 (2.7)	287	2 (0.7)	3.93 [0.84; 18.36]	0.059	

a: Database Cutoff of week 26: all events from the first dose of treatment up to week 26 + 14 days of post-treatment follow-up period, and for participants that did not continue into week 26, it includes all events up to 14 days after the final dose of study medication

b: Number of participants: all-participant-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the placebo arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the placebo arm, report 'n.a.'

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report 'n.a.'

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as 'n.a.'

f: A system organ class appears on this report only if its incidence ≥ 10% or (incidence ≥ 1% and in at least 10 participants) in one or more groups and p-value of main treatment effect smaller than 0.05

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 participants per subgroup and at least 10 events in one of the subgroups necessary); SOC: System Organ Class; WHO: World Health Organization

Tabelle 4G-36: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Nicht-schwere unerwünschte Ereignisse gesamt (PT) (Ertugliflozin 5 mg)

Study: VERTIS SU[a]	Ertugliflozin 5 mg		Glimepiride		Ertugliflozin 5 mg vs. Glimepiride		
Non-Severe Adverse Events[f]	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
SOC: Metabolism and nutrition disorders PT: Hypoglycaemia							
Sex							
Female	218	8 (3.7)	211	48 (22.7)	0.16 [0.08; 0.33]	< 0.001	0.945
Male	227	5 (2.2)	224	32 (14.3)	0.15 [0.06; 0.39]	< 0.001	
Age (Years)							
< 65	326	7 (2.1)	332	64 (19.3)	0.11 [0.05; 0.24]	< 0.001	0.067
≥ 65	119	6 (5.0)	103	16 (15.5)	0.32 [0.13; 0.80]	0.009	
Region							
WHO stratum A	153	5 (3.3)	148	32 (21.6)	0.15 [0.06; 0.38]	< 0.001	0.830
Rest of the World	292	8 (2.7)	287	48 (16.7)	0.16 [0.08; 0.34]	< 0.001	

a: Database Cutoff of week 26: all events from the first dose of treatment up to week 26 + 14 days of post-treatment follow-up period, and for participants that did not continue into week 26, it includes all events up to 14 days after the final dose of study medication

b: Number of participants: all-participant-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the placebo arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the placebo arm, report 'n.a.'

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report 'n.a.'

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as 'n.a.'

f: A system organ class appears on this report only if its incidence ≥ 10% or (incidence ≥ 1% and in at least 10 participants) in one or more groups and p-value of main treatment effect smaller than 0.05

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 participants per subgroup and at least 10 events in one of the subgroups necessary); PT: Preferred Term; SOC: System Organ Class; WHO: World Health Organization

Tabelle 4G-37: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC) (Ertugliflozin 15 mg)

Study: VERTIS SU[a]	Ertugliflozin 15 mg		Glimepiride		Ertugliflozin 15 mg vs. Glimepiride		
Adverse Events[f]	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
SOC: Metabolism and nutrition disorders							
Sex							
Female	244	23 (9.4)	211	57 (27.0)	0.35 [0.22; 0.55]	< 0.001	0.062
Male	191	21 (11.0)	224	39 (17.4)	0.63 [0.39; 1.04]	0.064	
Age (Years)							
< 65	323	36 (11.1)	332	78 (23.5)	0.47 [0.33; 0.68]	< 0.001	0.814
≥ 65	112	8 (7.1)	103	18 (17.5)	0.41 [0.19; 0.90]	0.021	
Region							
WHO stratum A	148	15 (10.1)	148	35 (23.6)	0.43 [0.24; 0.75]	0.002	0.745

Study: VERTIS SU[a]	Ertugliflozin 15 mg		Glimepiride		Ertugliflozin 15 mg vs. Glimepiride		
Adverse Events[f]	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
Rest of the World	287	29 (10.1)	287	61 (21.3)	0.48 [0.32; 0.72]	< 0.001	
SOC: Renal and urinary disorders							
Sex							
Female	244	18 (7.4)	211	7 (3.3)	2.22 [0.95; 5.22]	0.058	0.167
Male	191	16 (8.4)	224	3 (1.3)	6.25 [1.85; 21.14]	< 0.001	
Age (Years)							
< 65	323	26 (8.0)	332	8 (2.4)	3.34 [1.54; 7.27]	0.001	0.919
≥ 65	112	8 (7.1)	103	2 (1.9)	3.68 [0.80; 16.92]	0.071	
Region							
WHO stratum A	148	16 (10.8)	148	6 (4.1)	2.67 [1.07; 6.63]	0.027	0.500
Rest of the World	287	18 (6.3)	287	4 (1.4)	4.50 [1.54; 13.13]	0.002	
SOC: Reproductive system and breast disorders							
Sex							
Female	244	9 (3.7)	211	3 (1.4)	2.59 [0.71; 9.46]	0.133	0.355
Male	191	11 (5.8)	224	2 (0.9)	6.45 [1.45; 28.74]	0.005	
Age (Years)							
< 65	323	16 (5.0)	332	4 (1.2)	4.11 [1.39; 12.17]	0.005	0.922
≥ 65	112	4 (3.6)	103	1 (1.0)	3.68 [0.42; 32.38]	0.207	
Region							
WHO stratum A	148	7 (4.7)	148	3 (2.0)	2.33 [0.62; 8.85]	0.199	0.307
Rest of the World	287	13 (4.5)	287	2 (0.7)	6.50 [1.48; 28.55]	0.004	

a: Database Cutoff of week 26: all events from the first dose of treatment up to week 26 + 14 days of post-treatment follow-up period, and for participants that did not continue into week 26, it includes all events up to 14 days after the final dose of study medication

b: Number of participants: all-participant-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the placebo arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the placebo arm, report 'n.a.'

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report 'n.a.'

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as 'n.a.'

f: A system organ class appears on this report only if its incidence ≥ 10% or (incidence ≥ 1% and in at least 10 participants) in one or more groups and p-value of main treatment effect smaller than 0.05

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 participants per subgroup and at least 10 events in one of the subgroups necessary); SOC: System Organ Class; WHO: World Health Organization

Tabelle 4G-38: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (PT) (Ertugliflozin 15 mg)

Study: VERTIS SU[a]	Ertugliflozin 15 mg		Glimepiride		Ertugliflozin 15 mg vs. Glimepiride		
Adverse Events[f]	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
SOC: Gastrointestinal disorders PT: Nausea							
Sex							
Female	244	9 (3.7)	211	3 (1.4)	2.59 [0.71; 9.46]	0.133	0.363
Male	191	2 (1.0)	224	0 (0.0)	n.a.	n.a.	
Age (Years)							
< 65	323	8 (2.5)	332	2 (0.6)	4.11 [0.88; 19.21]	0.051	0.775
≥ 65	112	3 (2.7)	103	1 (1.0)	2.76 [0.29; 26.11]	0.356	
Region							
WHO stratum A	148	4 (2.7)	148	2 (1.4)	n.c.	n.c.	n.c.
Rest of the World	287	7 (2.4)	287	1 (0.3)	n.c.	n.c.	
SOC: Metabolism and nutrition disorders PT: Hypoglycaemia							
Region							
WHO stratum A	148	7 (4.7)	148	32 (21.6)	0.22 [0.10; 0.48]	< 0.001	0.860
Rest of the World	287	11 (3.8)	287	48 (16.7)	0.23 [0.12; 0.43]	< 0.001	

a: Database Cutoff of week 26: all events from the first dose of treatment up to week 26 + 14 days of post-treatment follow-up period, and for participants that did not continue into week 26, it includes all events up to 14 days after the final dose of study medication

b: Number of participants: all-participant-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the placebo arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the placebo arm, report 'n.a.'

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report 'n.a.'

e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as 'n.a.'

f: A system organ class appears on this report only if its incidence ≥ 10% or (incidence ≥ 1% and in at least 10 participants) in one or more groups and p-value of main treatment effect smaller than 0.05

CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 participants per subgroup and at least 10 events in one of the subgroups necessary); PT: Preferred Term; SOC: System Organ Class; WHO: World Health Organization

Tabelle 4G-39: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Nicht-schwere unerwünschte Ereignisse gesamt (SOC) (Ertugliflozin 15 mg)

Study: VERTIS SU[a]	Ertugliflozin 15 mg		Glimepiride		Ertugliflozin 15 mg vs. Glimepiride		
Non-Severe Adverse Events[f]	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
SOC: Investigations							
Sex							
Female	244	14 (5.7)	211	8 (3.8)	1.51 [0.65; 3.54]	0.335	0.460
Male	191	16 (8.4)	224	8 (3.6)	2.35 [1.03; 5.36]	0.037	

Study: VERTIS SU[a]	Ertugliflozin 15 mg		Glimepiride		Ertugliflozin 15 mg vs. Glimepiride		
Non-Severe Adverse Events[f]	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
Age (Years)							
< 65	323	23 (7.1)	332	13 (3.9)	1.82 [0.94; 3.53]	0.072	0.833
≥ 65	112	7 (6.3)	103	3 (2.9)	2.15 [0.57; 8.08]	0.247	
Region							
WHO stratum A	148	9 (6.1)	148	6 (4.1)	1.50 [0.55; 4.11]	0.427	0.594
Rest of the World	287	21 (7.3)	287	10 (3.5)	2.10 [1.01; 4.38]	0.042	
SOC: Metabolism and nutrition disorders							
Sex							
Female	244	23 (9.4)	211	57 (27.0)	0.35 [0.22; 0.55]	< 0.001	0.062
Male	191	21 (11.0)	224	39 (17.4)	0.63 [0.39; 1.04]	0.064	
Age (Years)							
< 65	323	36 (11.1)	332	78 (23.5)	0.47 [0.33; 0.68]	< 0.001	0.814
≥ 65	112	8 (7.1)	103	18 (17.5)	0.41 [0.19; 0.90]	0.021	
Region							
WHO stratum A	148	15 (10.1)	148	35 (23.6)	0.43 [0.24; 0.75]	0.002	0.745
Rest of the World	287	29 (10.1)	287	61 (21.3)	0.48 [0.32; 0.72]	< 0.001	
SOC: Renal and urinary disorders							
Sex							
Female	244	17 (7.0)	211	7 (3.3)	2.10 [0.89; 4.97]	0.083	0.144
Male	191	16 (8.4)	224	3 (1.3)	6.25 [1.85; 21.14]	< 0.001	
Age (Years)							
< 65	323	25 (7.7)	332	8 (2.4)	3.21 [1.47; 7.02]	0.002	0.882
≥ 65	112	8 (7.1)	103	2 (1.9)	3.68 [0.80; 16.92]	0.071	
Region							
WHO stratum A	148	15 (10.1)	148	6 (4.1)	2.50 [1.00; 6.27]	0.042	0.441
Rest of the World	287	18 (6.3)	287	4 (1.4)	4.50 [1.54; 13.13]	0.002	
SOC: Reproductive system and breast disorders							
Sex							
Female	244	9 (3.7)	211	3 (1.4)	2.59 [0.71; 9.46]	0.133	0.413
Male	191	10 (5.2)	224	2 (0.9)	5.86 [1.30; 26.43]	0.009	
Age (Years)							
< 65	323	16 (5.0)	332	4 (1.2)	4.11 [1.39; 12.17]	0.005	0.744
≥ 65	112	3 (2.7)	103	1 (1.0)	2.76 [0.29; 26.11]	0.356	
Region							
WHO stratum A	148	6 (4.1)	148	3 (2.0)	2.00 [0.51; 7.85]	0.311	0.241
Rest of the World	287	13 (4.5)	287	2 (0.7)	6.50 [1.48; 28.55]	0.004	

a: Database Cutoff of week 26: all events from the first dose of treatment up to week 26 + 14 days of post-treatment follow-up period, and for participants that did not continue into week 26, it includes all events up to 14 days after the final dose of study medication

b: Number of participants: all-participant-as-treated population

c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the placebo arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the placebo arm, report 'n.a.'

d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report 'n.a.'

Study: VERTIS SU[a]	Ertugliflozin 15 mg		Glimepiride		Ertugliflozin 15 mg vs. Glimepiride		
Non-Severe Adverse Events[f]	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as 'n.a.'							
f: A system organ class appears on this report only if its incidence ≥ 10% or (incidence ≥ 1% and in at least 10 participants) in one or more groups and p-value of main treatment effect smaller than 0.05							
CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 participants per subgroup and at least 10 events in one of the subgroups necessary); SOC: System Organ Class; WHO: World Health Organization							

Tabelle 4G-40: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Nicht-schwere unerwünschte Ereignisse gesamt (PT) (Ertugliflozin 15 mg)

Study: VERTIS SU[a]	Ertugliflozin 15 mg		Glimepiride		Ertugliflozin 15 mg vs. Glimepiride		
Non-Severe Adverse Events[f]	N[b]	Participants with Event n (%)	N[b]	Participants with Event n (%)	Relative Risk [95 %-CI][c]	Treatment Effect p-Value[d]	Interaction Test p-Value[e]
SOC: Gastrointestinal disorders PT: Nausea							
Sex							
Female	244	9 (3.7)	211	3 (1.4)	2.59 [0.71; 9.46]	0.133	0.363
Male	191	2 (1.0)	224	0 (0.0)	n.a.	n.a.	
Age (Years)							
< 65	323	8 (2.5)	332	2 (0.6)	4.11 [0.88; 19.21]	0.051	0.775
≥ 65	112	3 (2.7)	103	1 (1.0)	2.76 [0.29; 26.11]	0.356	
Region							
WHO stratum A	148	4 (2.7)	148	2 (1.4)	n.c.	n.c.	n.c.
Rest of the World	287	7 (2.4)	287	1 (0.3)	n.c.	n.c.	
SOC: Metabolism and nutrition disorders PT: Hypoglycaemia							
Region							
WHO stratum A	148	7 (4.7)	148	32 (21.6)	0.22 [0.10; 0.48]	< 0.001	0.860
Rest of the World	287	11 (3.8)	287	48 (16.7)	0.23 [0.12; 0.43]	< 0.001	
a: Database Cutoff of week 26: all events from the first dose of treatment up to week 26 + 14 days of post-treatment follow-up period, and for participants that did not continue into week 26, it includes all events up to 14 days after the final dose of study medication							
b: Number of participants: all-participant-as-treated population							
c: Based on 2x2 contingency table, using Wald-type confidence interval. In case zero participant with event in the treatment arm (Ertugliflozin) but non-zero participants with event in the placebo arm, a correction factor (+0.5) is applied to incidence counts of participants with event in both treatment groups, and Wald modified confidence interval is applied. In case zero participant with event in the placebo arm, report 'n.a.'							
d: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report 'n.a.'							
e: Based on Breslow-Day test with subgroup as stratification factor. Subgroup category that has zero participant with event in both treatment groups is excluded from this interaction test. If the subgroup covariate has less than 2 categories that have at least 1 participant with event, p-value of interaction test is reported as 'n.a.'							
f: A system organ class appears on this report only if its incidence ≥ 10% or (incidence ≥ 1% and in at least 10 participants) in one or more groups and p-value of main treatment effect smaller than 0.05							
CI: Confidence Interval; n.a.: not applicable (when estimation not possible); n.c.: not calculated (at least 10 participants per subgroup and at least 10 events in one of the subgroups necessary); PT: Preferred Term; SOC: System Organ Class; WHO: World Health Organization							