Dossier zur Nutzenbewertung gemäß § 35a SGB V

Ertugliflozin (STEGLATRO®)

MSD Sharp & Dohme GmbH

Modul 4 E

Anhang 4-G: Weitere Ergebnisse

Behandlung von erwachsenen Patienten mit Typ-2-Diabetes mellitus und hohem kardiovaskulärem Risiko.

Stand: 01.12.2021

Inhaltsverzeichnis

Seite

Tabellenverzeichnis

Abbildungsverzeichnis

Anhang 4-G1: Ergebnisse der Sensitivitätsanalysen der Veränderung zum Ausgangswert der Studie VERTIS CV

Anhang 4-G1.1: Weitere Morbiditätsendpunkte

Tabelle 4G-1: Ergebnisse für die Endpunkte Veränderung des systolischen Blutdrucks (Ertugliflozin 5 mg) aus RCT mit dem zu bewertenden Arzneimittel

Change from Baseline in Sitting Systolic Blood Pressure	Study:VERTIS CV	
	Ertugliflozin 5 mg	Placebo
	N[a]=2746	N[a]=2745
Week 6		
N	2654	2633
Mean (SD)	-2.4 (12.3)	0.5 (12.6)
Median (Q1; Q3)	-1.7 (-9.7; 4.4)	0.0 (-6.7; 7.3)
Min; Max	-54.7; 49.6	-50.0; 60.4
Week 12		
N	2579	2569
Mean (SD)	-2.5 (12.8)	0.0 (13.6)
Median (Q1; Q3)	-2.0 (-10.0; 4.7)	0.0 (-7.7; 7.7)
Min; Max	-51.0; 49.3	-66.3; 79.0
Week 18		
N	2550	2535
Mean (SD)	-2.5 (13.4)	0.3 (13.9)
Median (Q1; Q3)	-2.0 (-10.4; 5.4)	0.0 (-8.0; 8.3)
Min; Max	-68.4; 43.4	-73.0; 78.0
Week 26		
N	2493	2483
Mean (SD)	-2.8 (13.9)	0.1 (13.9)
Median (Q1; Q3)	-2.3 (-10.7; 5.3)	0.0 (-8.0; 8.0)
Min; Max	-77.4; 66.7	-64.6; 86.7
Week 39		
N	2433	2415
Mean (SD)	-1.9 (13.9)	0.7 (14.1)
Median (Q1; Q3)	-1.7 (-10.0; 6.0)	0.4 (-8.0; 9.0)
Min; Max	-67.4; 62.7	-65.6; 63.0
Week 52		
N	2369	2322
Mean (SD)	-1.9 (13.8)	0.9 (14.3)
Median (Q1; Q3)	-1.4 (-10.0; 6.3)	1.0 (-7.4; 9.3)
Min; Max	-50.4; 57.4	-75.3; 53.6
Month 16		
N	2097	2015
Mean (SD)	-2.6 (14.1)	0.3 (14.9)
Median (Q1; Q3)	-2.6 (-11.3; 6.0)	0.0 (-8.7; 8.7)
Min; Max	-60.7; 70.3	-74.3; 78.0
Month 20		
N	1902	1795
Mean (SD)	-2.0 (14.5)	1.0 (14.7)
Median (Q1; Q3)	-1.4 (-10.7; 6.0)	0.7 (-7.7; 9.7)
Min; Max	-53.0; 61.3	-54.4; 57.7
Month 24		

Change from Baseline in Sitting Systolic Blood Pressure	Study:VERTIS CV	
	Ertugliflozin 5 mg N[a]=2746	Placebo N[a]=2745
N Mean (SD) Median (Q1; Q3) Min; Max	1581 -1.5 (14.3) -1.0 (-10.0; 7.0) -52.7; 53.0	1504 0.8 (15.0) 0.3 (-7.9; 9.0) -72.0; 67.7
Month 28		
N Mean (SD) Median (Q1; Q3) Min; Max	1507 -1.9 (14.7) -1.4 (-11.4; 6.7) -55.0; 66.7	1400 1.2 (14.7) 1.3 (-8.0; 10.0) -66.3; 52.0
Month 32		
N Mean (SD) Median (Q1; Q3) Min; Max	1787 -2.1 (14.7) -2.0 (-10.7; 6.6) -52.4; 64.4	1698 0.6 (15.0) 0.4 (-8.3; 9.3) -80.6; 75.7
Month 36		
N Mean (SD) Median (Q1; Q3) Min; Max	1593 -1.6 (14.6) -1.4 (-10.7; 7.6) -53.3; 64.7	1505 0.8 (14.6) 0.7 (-7.7; 9.0) -71.3; 53.6
Month 40		
N Mean (SD) Median (Q1; Q3) Min; Max	1087 -1.4 (14.9) -0.6 (-10.7; 7.7) -60.7; 60.7	1010 1.7 (15.2) 1.7 (-7.0; 10.7) -79.0; 62.0
Month 44		
N Mean (SD) Median (Q1; Q3) Min; Max	895 -1.5 (15.4) -1.0 (-11.3; 8.0) -55.0; 57.3	808 1.0 (15.7) 1.0 (-8.7; 10.3) -79.0; 60.6
Month 48		
N Mean (SD) Median (Q1; Q3) Min; Max	881 -1.9 (14.7) -2.0 (-11.4; 8.0) -44.6; 54.3	789 0.9 (15.3) 1.3 (-7.7; 11.0) -76.6; 59.0
Month 52		
N Mean (SD) Median (Q1; Q3) Min; Max	847 -1.4 (15.7) -1.0 (-11.0; 8.7) -56.0; 81.7	762 0.8 (15.7) 0.7 (-9.0; 10.4) -73.6; 52.7
Month 56		
N Mean (SD) Median (Q1; Q3) Min; Max	845 -1.3 (15.2) -1.0 (-11.0; 8.0) -52.7; 45.4	733 1.0 (15.4) 1.4 (-8.0; 10.7) -85.3; 52.0
Month 60		
N Mean (SD) Median (Q1; Q3) Min; Max	525 -2.2 (15.4) -2.0 (-12.0; 8.0) -52.0; 45.7	479 0.6 (15.9) 1.0 (-9.0; 10.7) -56.0; 61.7

Change from Baseline in Sitting Systolic Blood Pressure	Study:VERTIS CV	
	Ertugliflozin 5 mg	Placebo
	N[a]=2746	N[a]=2745
Month 64		
N	264	255
Mean (SD)	-1.1 (15.1)	0.8 (16.2)
Median (Q1; Q3)	0.0 (-11.7; 8.3)	1.0 (-8.0; 12.3)
Min; Max	-36.4; 49.6	-68.3; 45.0
Month 68		
N	88	69
Mean (SD)	-0.3 (16.4)	2.9 (19.7)
Median (Q1; Q3)	-0.4 (-11.5; 12.5)	2.7 (-9.6; 15.0)
Min; Max	-42.4; 32.0	-54.3; 52.7
Month 72		
N	13	9
Mean (SD)	1.3 (18.0)	2.7 (14.0)
Median (Q1; Q3)	0.3 (-10.3; 9.4)	0.7 (-5.0; 13.4)
Min; Max	-25.4; 30.0	-19.0; 20.7
a: Number of participants: full analysis set Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation		

Tabelle 4G-2: Ergebnisse für die Endpunkte Veränderung des systolischen Blutdrucks (Ertugliflozin 15 mg) aus RCT mit dem zu bewertenden Arzneimittel

Change from Baseline in Sitting Systolic Blood Pressure	Study:VERTIS CV	
	Ertugliflozin 15 mg	Placebo
	N[a]=2747	N[a]=2745
Week 6		
N	2647	2633
Mean (SD)	-2.7 (12.5)	0.5 (12.6)
Median (Q1; Q3)	-2.0 (-9.7; 4.3)	0.0 (-6.7; 7.3)
Min; Max	-65.4; 49.3	-50.0; 60.4
Week 12		
N	2577	2569
Mean (SD)	-2.7 (13.2)	0.0 (13.6)
Median (Q1; Q3)	-2.3 (-10.3; 5.3)	0.0 (-7.7; 7.7)
Min; Max	-68.3; 82.3	-66.3; 79.0
Week 18		
N	2528	2535
Mean (SD)	-2.7 (13.5)	0.3 (13.9)
Median (Q1; Q3)	-3.0 (-11.0; 5.3)	0.0 (-8.0; 8.3)
Min; Max	-53.7; 55.0	-73.0; 78.0
Week 26		
N	2485	2483
Mean (SD)	-2.9 (13.8)	0.1 (13.9)
Median (Q1; Q3)	-2.6 (-11.0; 5.0)	0.0 (-8.0; 8.0)
Min; Max	-48.3; 71.7	-64.6; 86.7
Week 39		
N	2417	2415
Mean (SD)	-2.3 (13.9)	0.7 (14.1)
Median (Q1; Q3)	-2.4 (-11.0; 5.7)	0.4 (-8.0; 9.0)

Change from Baseline in Sitting Systolic Blood Pressure	Study:VERTIS CV	
	Ertugliflozin 15 mg	Placebo
	N[a]=2747	N[a]=2745
Min; Max	-57.4; 51.0	-65.6; 63.0
Week 52		
N	2353	2322
Mean (SD)	-2.4 (13.9)	0.9 (14.3)
Median (Q1; Q3)	-2.3 (-10.7; 5.7)	1.0 (-7.4; 9.3)
Min; Max	-63.0; 61.0	-75.3; 53.6
Month 16		
N	2091	2015
Mean (SD)	-2.5 (14.1)	0.3 (14.9)
Median (Q1; Q3)	-2.4 (-10.7; 6.0)	0.0 (-8.7; 8.7)
Min; Max	-61.0; 64.6	-74.3; 78.0
Month 20		
N	1839	1795
Mean (SD)	-1.8 (14.7)	1.0 (14.7)
Median (Q1; Q3)	-1.4 (-10.7; 6.7)	0.7 (-7.7; 9.7)
Min; Max	-68.3; 73.7	-54.4; 57.7
Month 24		
N	1547	1504
Mean (SD)	-2.0 (14.8)	0.8 (15.0)
Median (Q1; Q3)	-1.7 (-11.3; 6.4)	0.3 (-7.9; 9.0)
Min; Max	-69.3; 81.0	-72.0; 67.7
Month 28		
N	1490	1400
Mean (SD)	-1.5 (14.2)	1.2 (14.7)
Median (Q1; Q3)	-1.6 (-10.0; 6.7)	1.3 (-8.0; 10.0)
Min; Max	-51.0; 47.7	-66.3; 52.0
Month 32		
N	1762	1698
Mean (SD)	-1.7 (15.1)	0.6 (15.0)
Median (Q1; Q3)	-1.6 (-10.7; 7.4)	0.4 (-8.3; 9.3)
Min; Max	-76.3; 64.6	-80.6; 75.7
Month 36		
N	1580	1505
Mean (SD)	-1.2 (15.1)	0.8 (14.6)
Median (Q1; Q3)	-1.3 (-10.3; 7.3)	0.7 (-7.7; 9.0)
Min; Max	-61.7; 61.4	-71.3; 53.6
Month 40		
N	1107	1010
Mean (SD)	-1.4 (14.6)	1.7 (15.2)
Median (Q1; Q3)	-2.0 (-10.4; 7.0)	1.7 (-7.0; 10.7)
Min; Max	-53.7; 91.4	-79.0; 62.0
Month 44		
N	890	808
Mean (SD)	-1.6 (15.5)	1.0 (15.7)
Median (Q1; Q3)	-2.6 (-11.0; 7.4)	1.0 (-8.7; 10.3)
Min; Max	-59.6; 65.4	-79.0; 60.6
Month 48		
N	868	789
Mean (SD)	-1.9 (15.3)	0.9 (15.3)

Change from Baseline in Sitting Systolic Blood Pressure	Study:VERTIS CV	
	Ertugliflozin 15 mg N[a]=2747	Placebo N[a]=2745
Median (Q1; Q3)	-2.0 (-11.4; 7.0)	1.3 (-7.7; 11.0)
Min; Max	-62.3; 56.0	-76.6; 59.0
Month 52		
N	841	762
Mean (SD)	-1.8 (15.3)	0.8 (15.7)
Median (Q1; Q3)	-1.7 (-11.0; 6.7)	0.7 (-9.0; 10.4)
Min; Max	-55.0; 66.0	-73.6; 52.7
Month 56		
N	817	733
Mean (SD)	-1.7 (15.3)	1.0 (15.4)
Median (Q1; Q3)	-1.3 (-10.6; 8.0)	1.4 (-8.0; 10.7)
Min; Max	-65.0; 49.3	-85.3; 52.0
Month 60		
N	529	479
Mean (SD)	-1.9 (15.0)	0.6 (15.9)
Median (Q1; Q3)	-2.0 (-11.3; 7.7)	1.0 (-9.0; 10.7)
Min; Max	-46.3; 44.7	-56.0; 61.7
Month 64		
N	286	255
Mean (SD)	-1.9 (15.7)	0.8 (16.2)
Median (Q1; Q3)	-1.3 (-14.0; 8.0)	1.0 (-8.0; 12.3)
Min; Max	-44.7; 46.7	-68.3; 45.0
Month 68		
N	81	69
Mean (SD)	-2.0 (14.0)	2.9 (19.7)
Median (Q1; Q3)	-2.0 (-11.3; 8.0)	2.7 (-9.6; 15.0)
Min; Max	-34.0; 29.0	-54.3; 52.7
Month 72		
N	12	9
Mean (SD)	-3.5 (14.4)	2.7 (14.0)
Median (Q1; Q3)	-6.6 (-13.7; 7.0)	0.7 (-5.0; 13.4)
Min; Max	-25.6; 22.0	-19.0; 20.7

a: Number of participants: full analysis set
Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation

Anhang 4-G2: Kaplan-Meier-Kurven der Sensitivitätsanalysen der Morbidität

Anhang 4-G2.1: Kardiale und zerebrale Morbidität

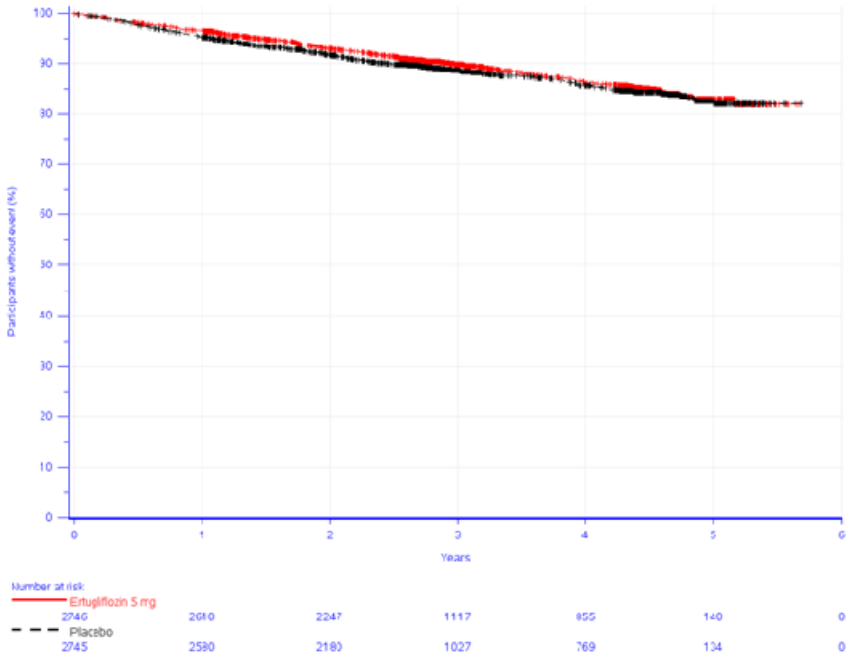

Abbildung 4G-1: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt MACE in der Studie VERTIS CV (FAS) (Ertugliflozin 5 mg)

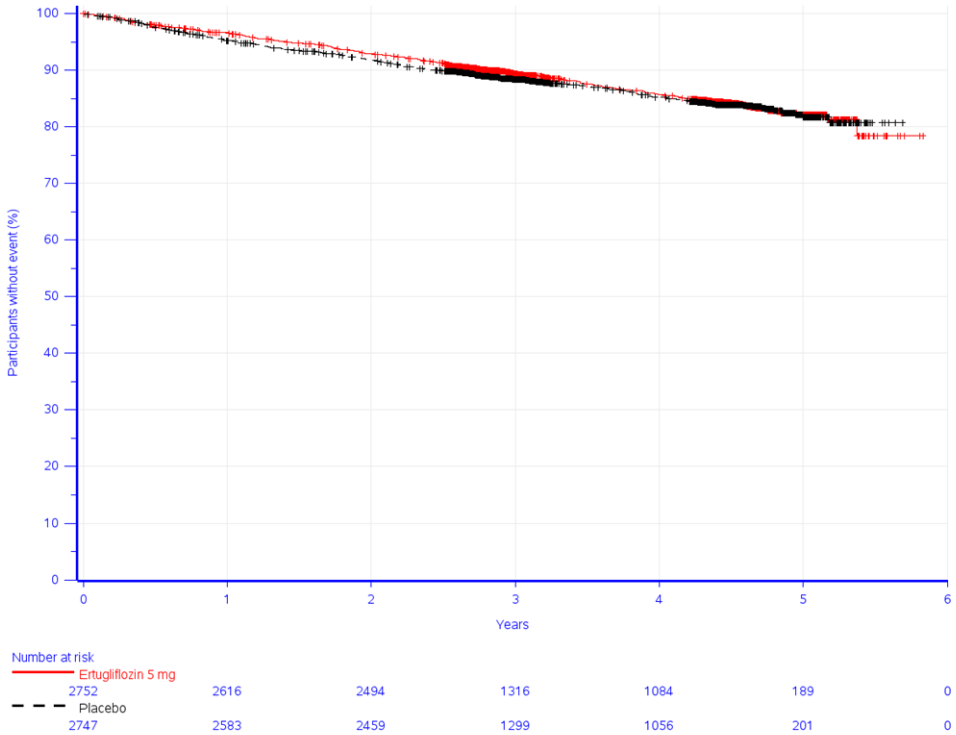

Abbildung 4G-2: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt MACE in der Studie VERTIS CV (ITT) (Ertugliflozin 5 mg)

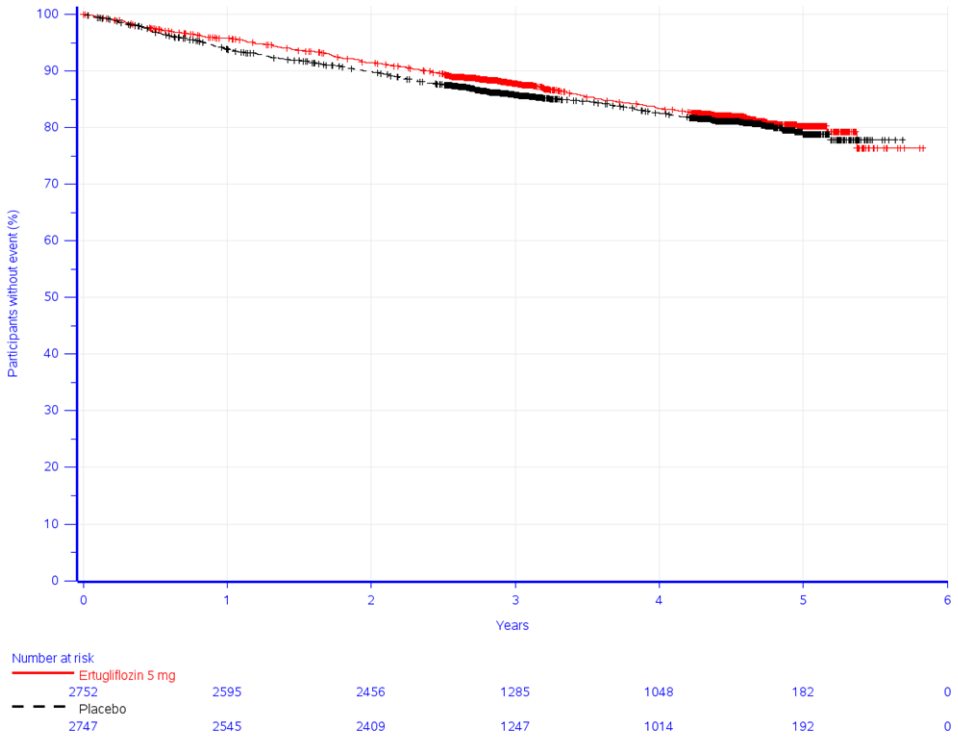

Abbildung 4G-3: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt MACE plus in der Studie VERTIS CV (ITT) (Ertugliflozin 5 mg)

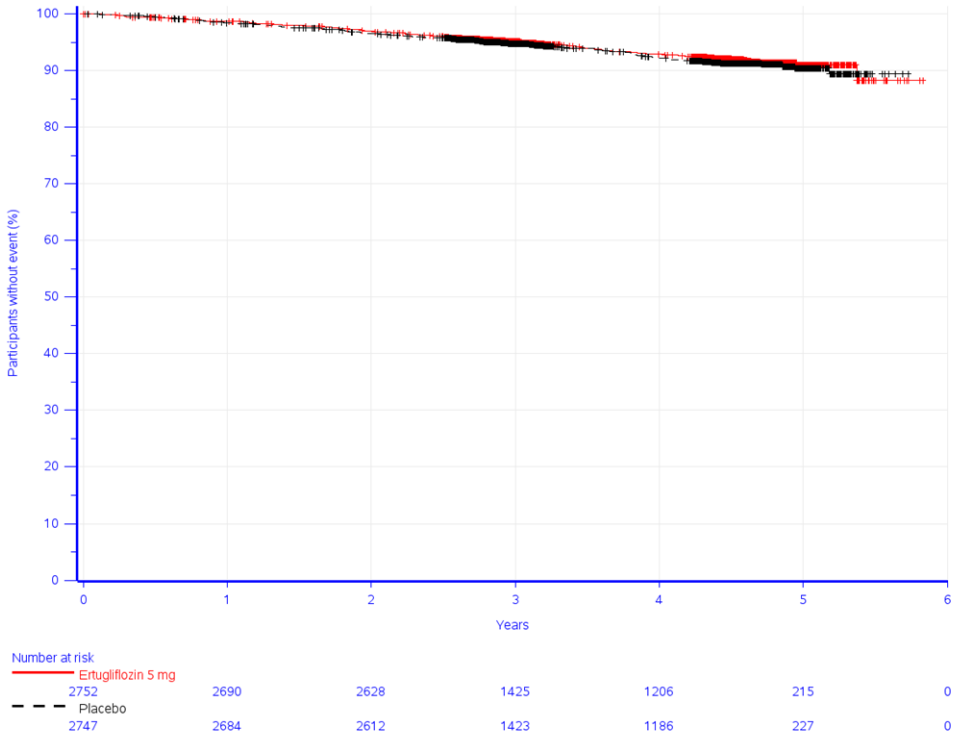

Abbildung 4G-4: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt kardiovaskulärer Tod in der Studie VERTIS CV (Ertugliflozin 5 mg)

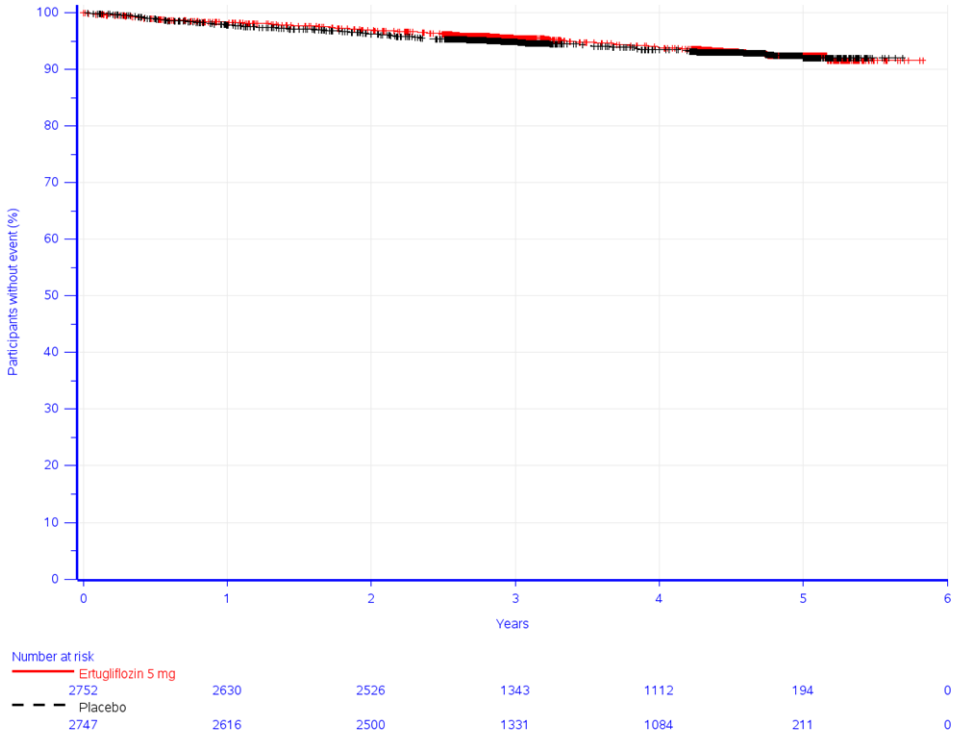

Abbildung 4G-5: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den kombinierten Endpunkt Herzinfarkt in der Studie VERTIS CV (Ertugliflozin 5 mg)

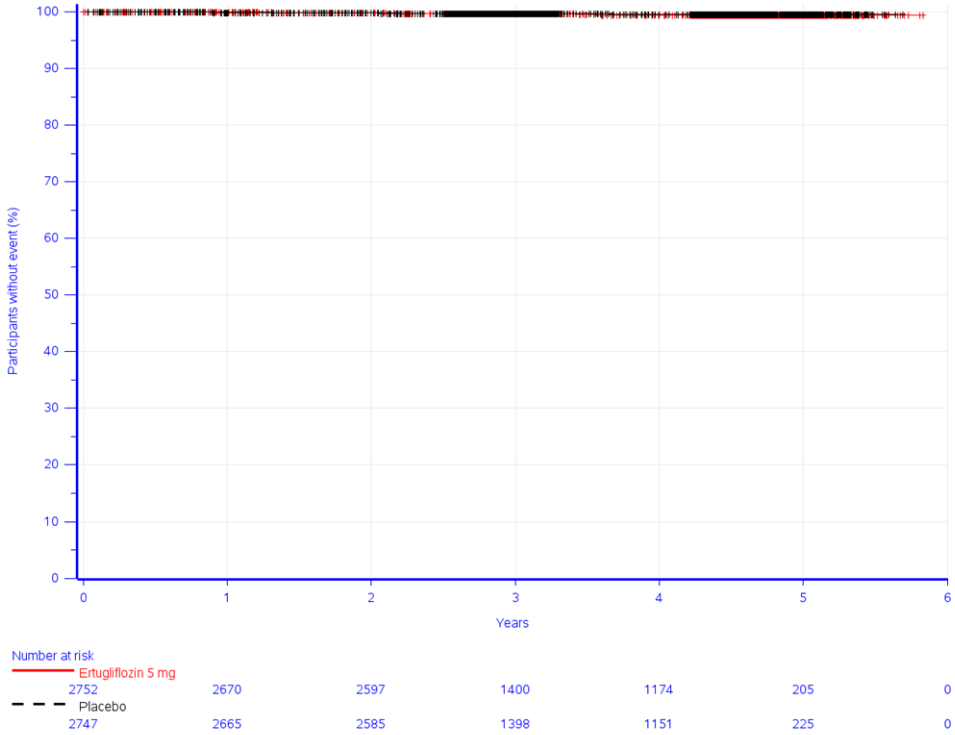

Abbildung 4G-6: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt tödlicher Herzinfarkt in der Studie VERTIS CV (Ertugliflozin 5 mg)

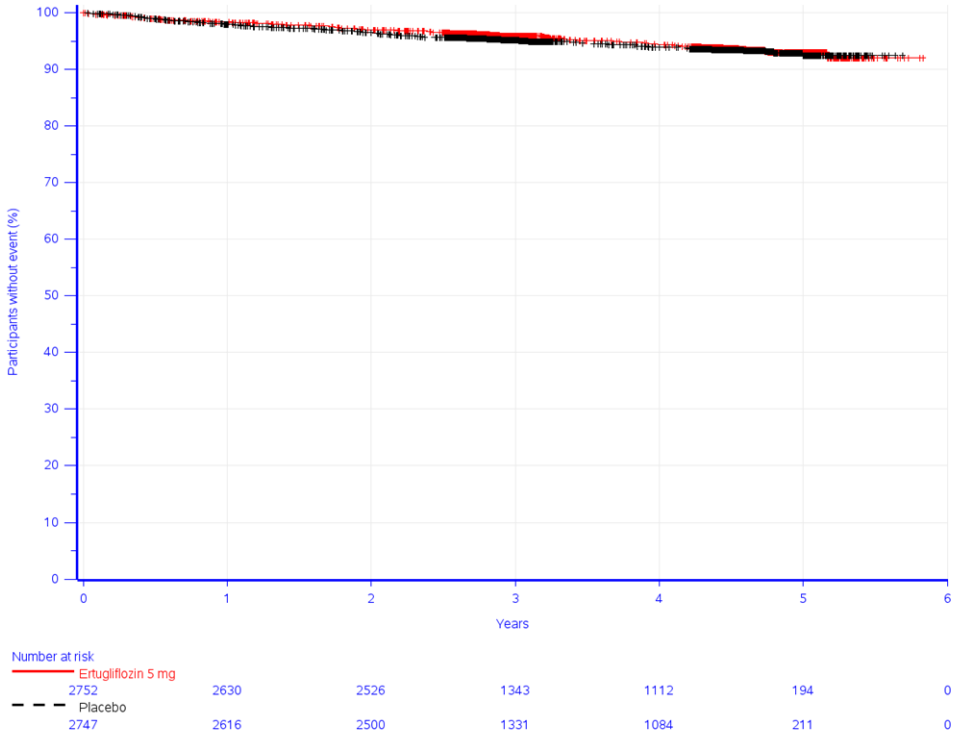

Abbildung 4G-7: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt nicht-tödlicher Herzinfarkt in der Studie VERTIS CV (Ertugliflozin 5 mg)

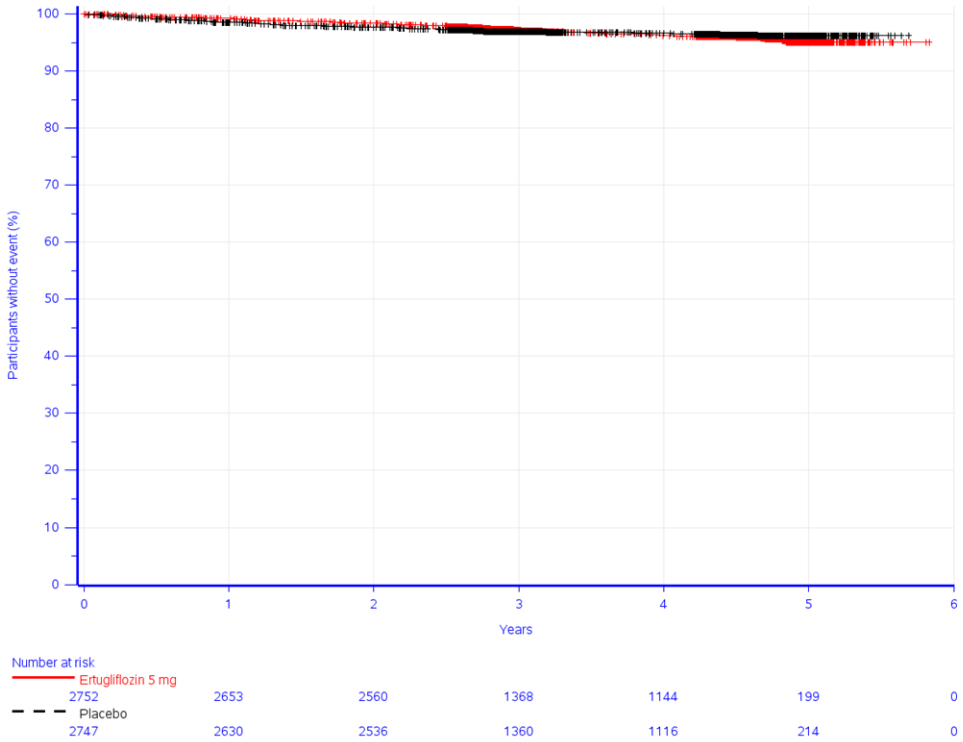

Abbildung 4G-8: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt Schlaganfall in der Studie VERTIS CV (Ertugliflozin 5 mg)

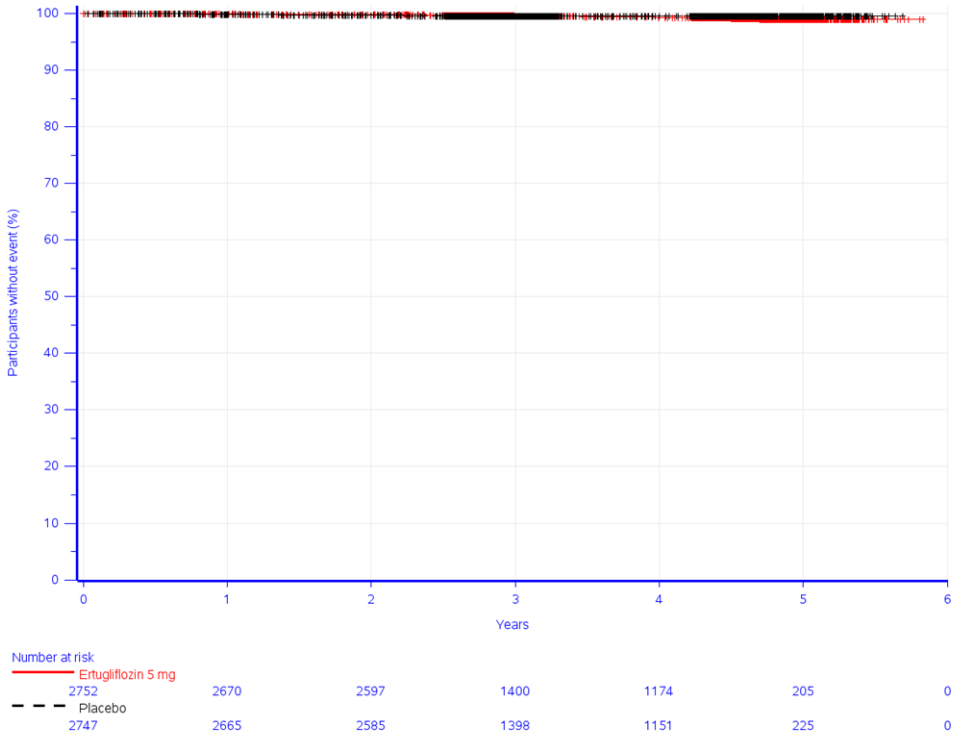

Abbildung 4G-9: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt tödlicher Schlaganfall in der Studie VERTIS CV (Ertugliflozin 5 mg)

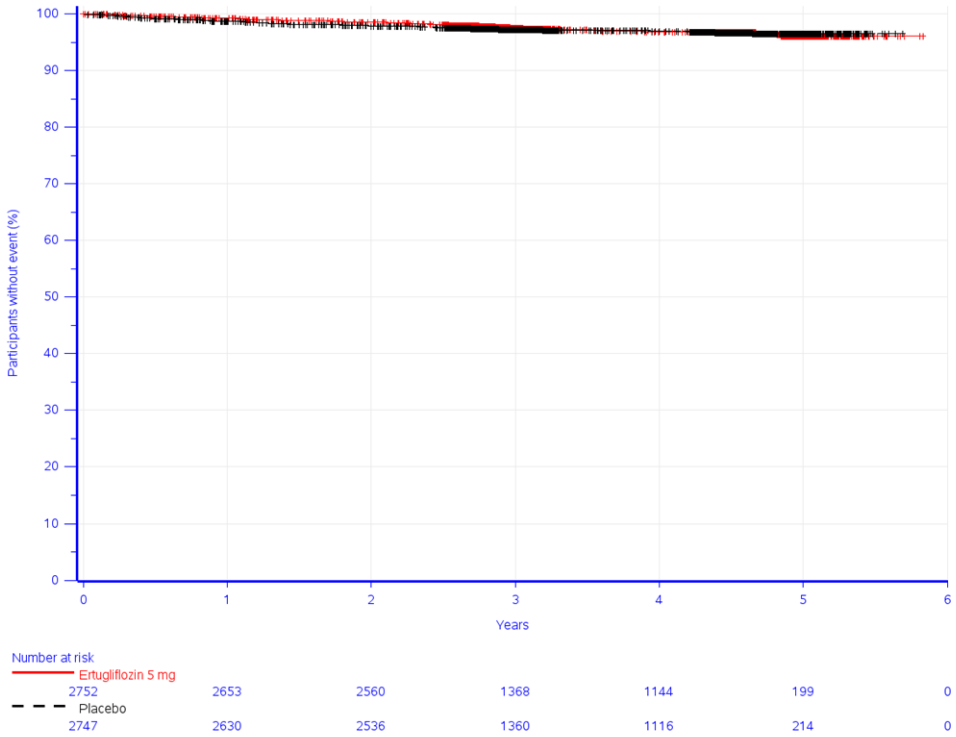

Abbildung 4G-10: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt nicht-tödlicher Schlaganfall in der Studie VERTIS CV (Ertugliflozin 5 mg)

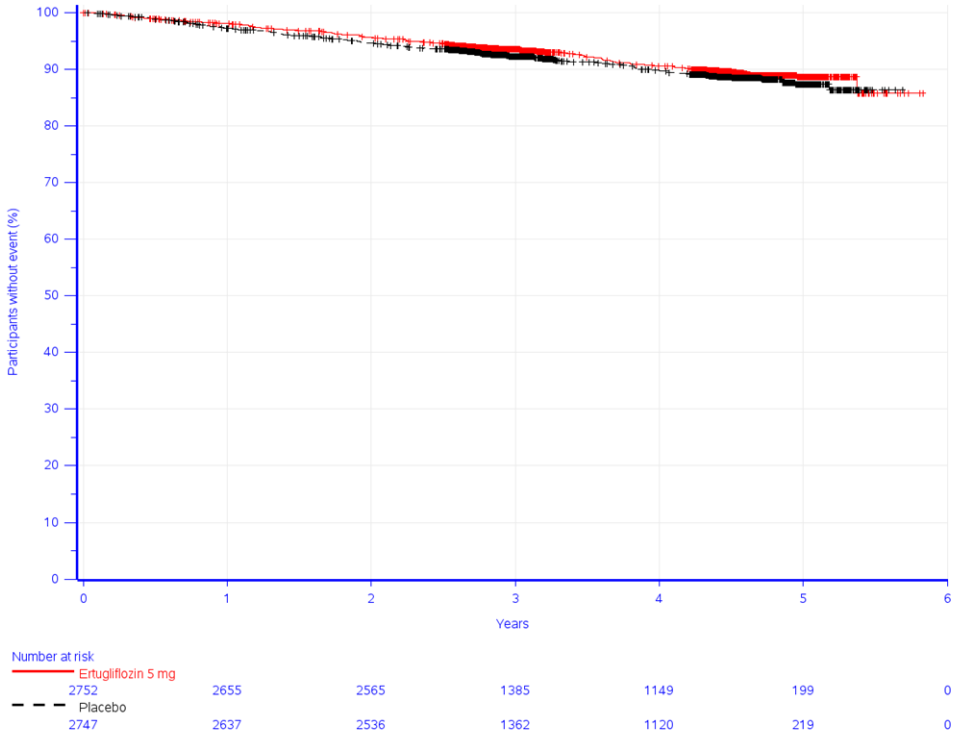

Abbildung 4G-11: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt Kardiovaskulärer Tod oder Hospitalisierung wegen Herzinsuffizienz in der Studie VERTIS CV (Ertugliflozin 5 mg)

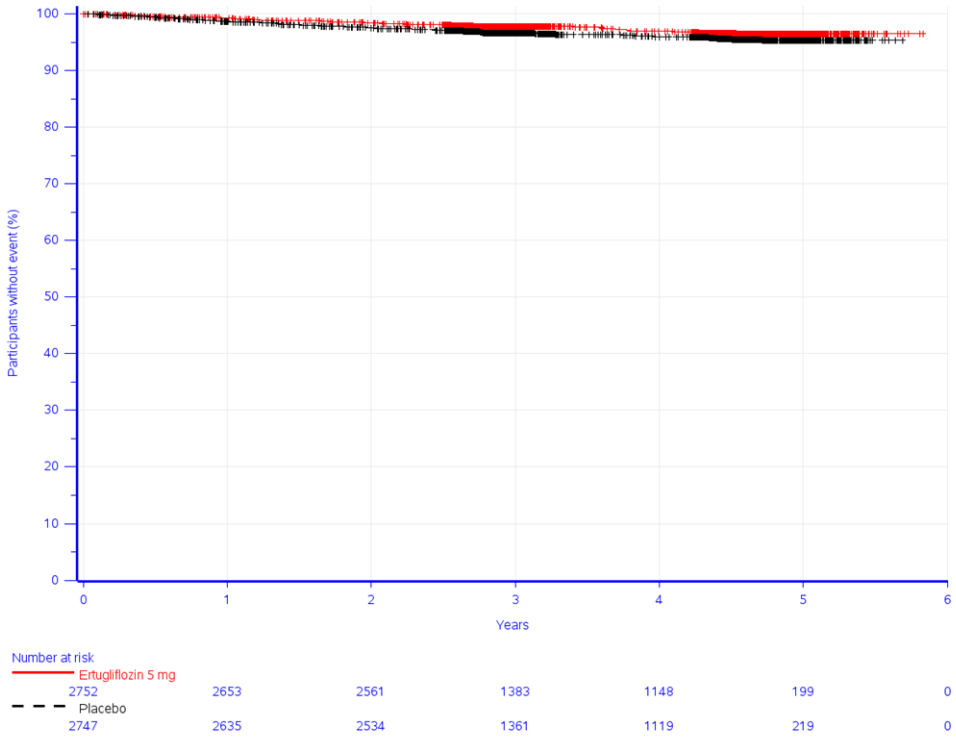

Abbildung 4G-12: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt Hospitalisierung wegen Herzinsuffizienz in der Studie VERTIS CV (Ertugliflozin 5 mg)

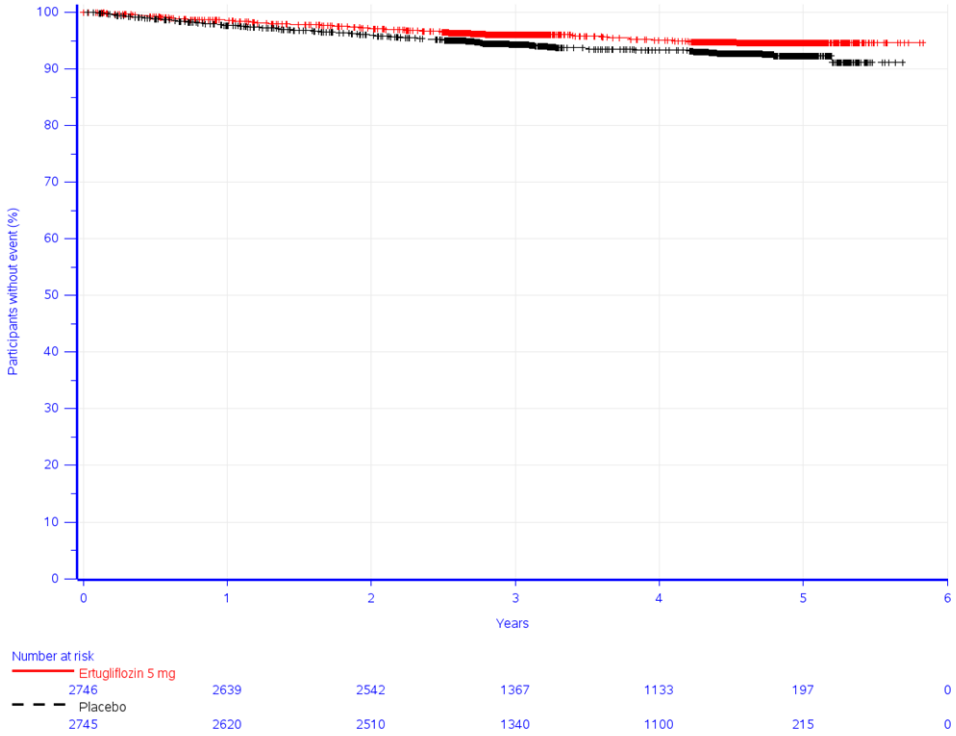

Abbildung 4G-13: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt Schwere Herzinsuffizienz (SMQ cradiac failure) (Ertugliflozin 5 mg)

Anhang 4-G2.2: Renale Morbidität

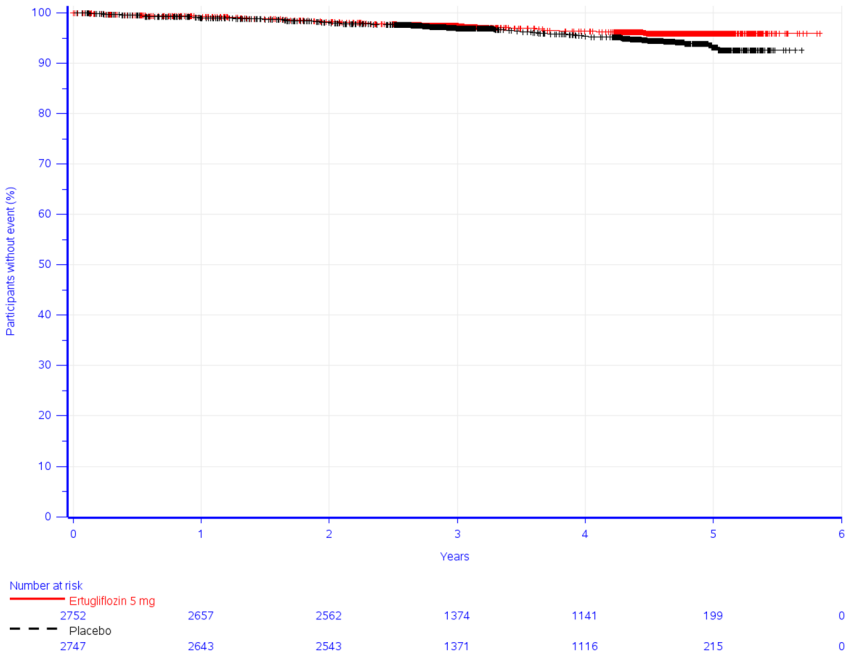

Abbildung 4G-14: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt Kombinierter renaler Endpunkt (Kreatinin) in der Studie VERTIS CV (Ertugliflozin 5 mg)

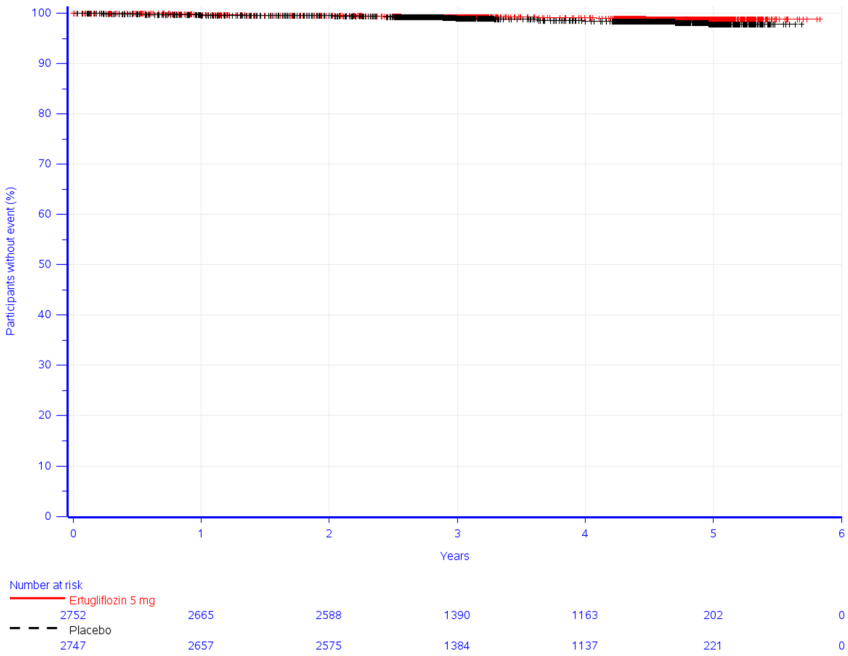

Abbildung 4G-15: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt Kombinierter renaler Endpunkt (Kreatinin Sensitivität) in der Studie VERTIS CV (Ertugliflozin 5 mg)

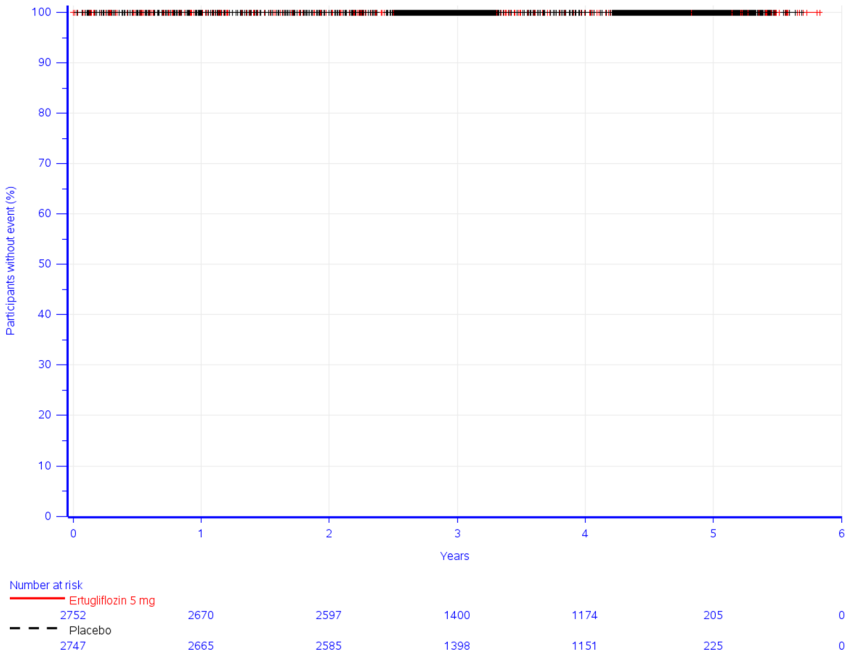

Abbildung 4G-16: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt Tod renaler Ursache in der Studie VERTIS CV (Ertugliflozin 5 mg)

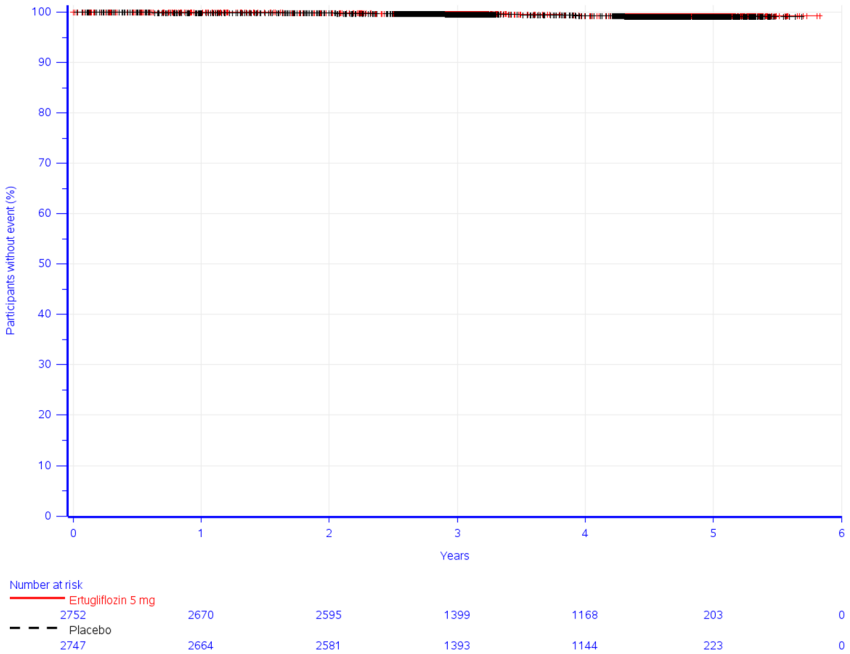

Abbildung 4G-17: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt Nierentransplantation/ Dialyse in der Studie VERTIS CV (Ertugliflozin 5 mg)

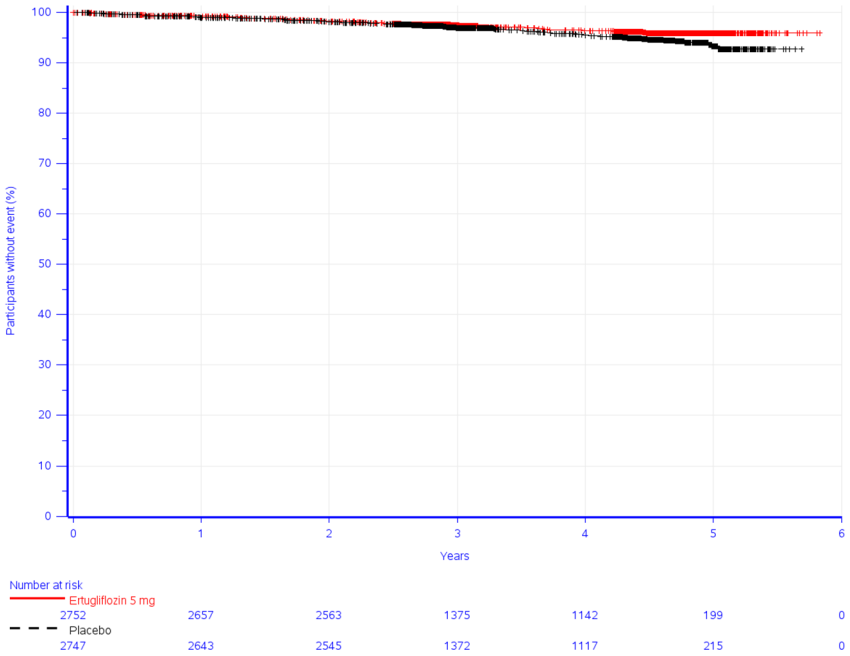

Abbildung 4G-18: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt Verdopplung der Serum-Kreatinin-Spiegels in der Studie VERTIS CV (Ertugliflozin 5 mg)

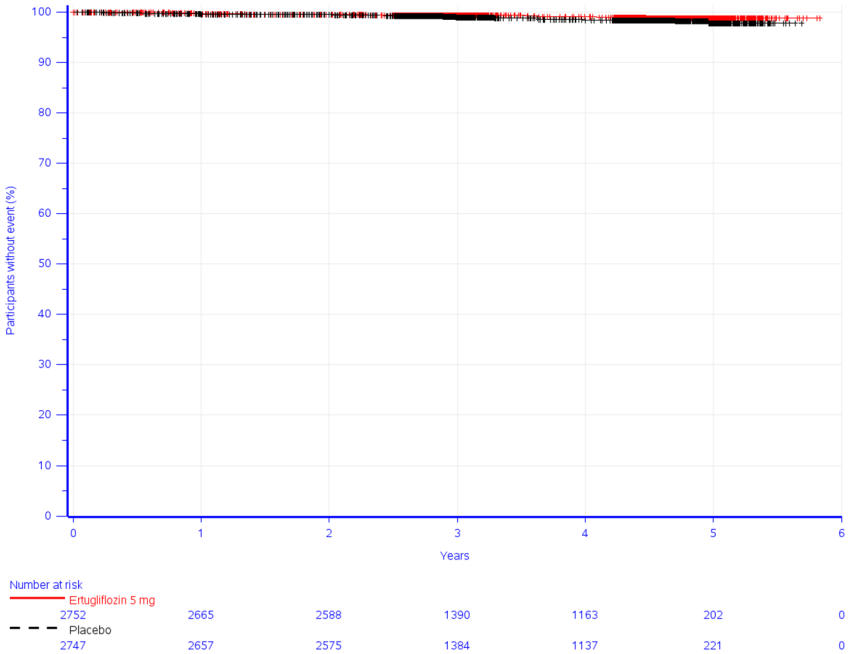

Abbildung 4G-19: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt Bestätigte Verdopplung der Serum-Kreatinin-Spiegels in der Studie VERTIS CV (Ertugliflozin 5 mg)

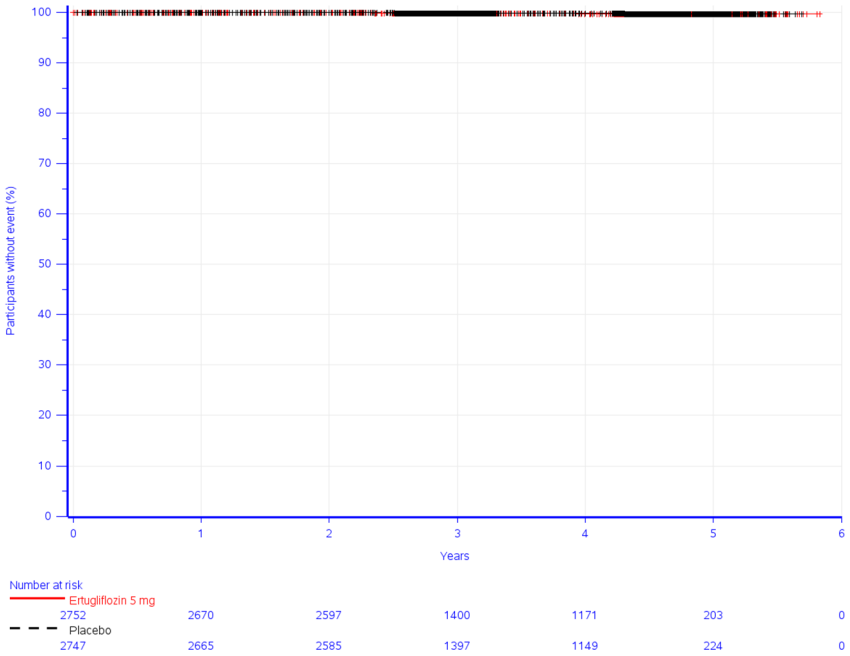

Abbildung 4G-20: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt Nierentransplantation/ Dialyse mind. 90 Tage in der Studie VERTIS CV (Ertugliflozin 5 mg)

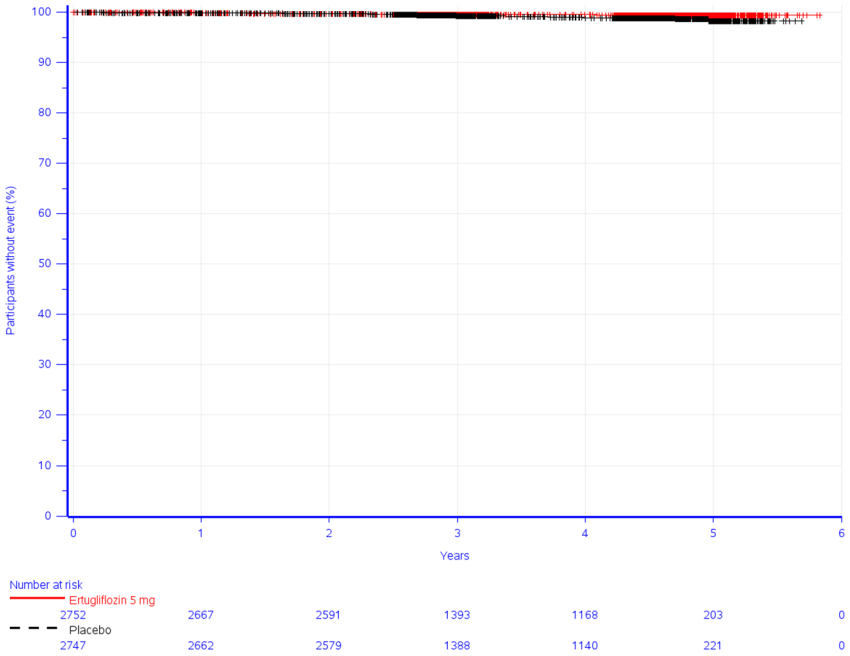

Abbildung 4G-21: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt Bestätigte Verdopplung des Serum-Kreatinin-Spiegels und eGFR ≤ 45ml/min/1.73m^2 in der Studie VERTIS CV (Ertugliflozin 5 mg)

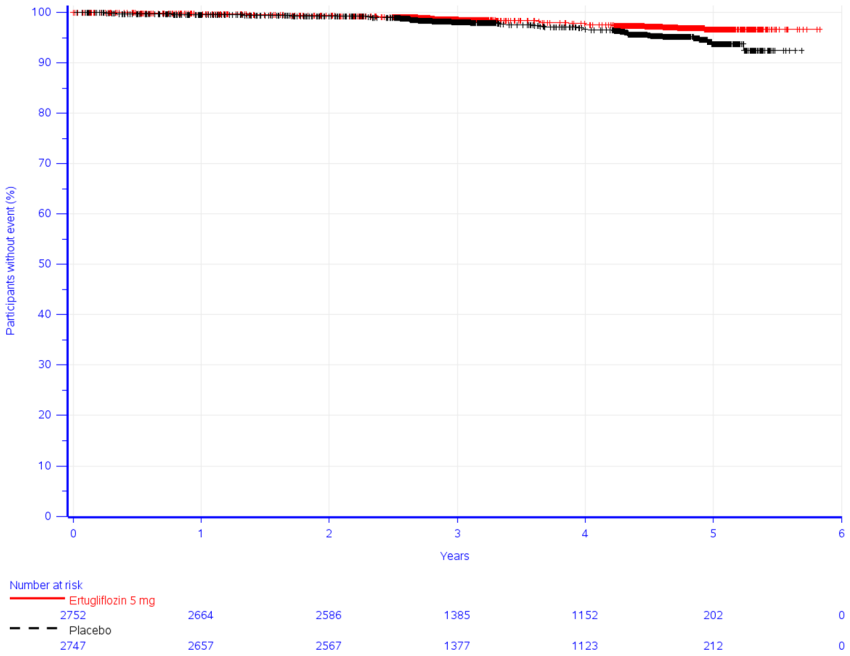

Abbildung 4G-22: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt Kombinierter renaler Endpunkt (eGFR) in der Studie VERTIS CV (Ertugliflozin 5 mg)

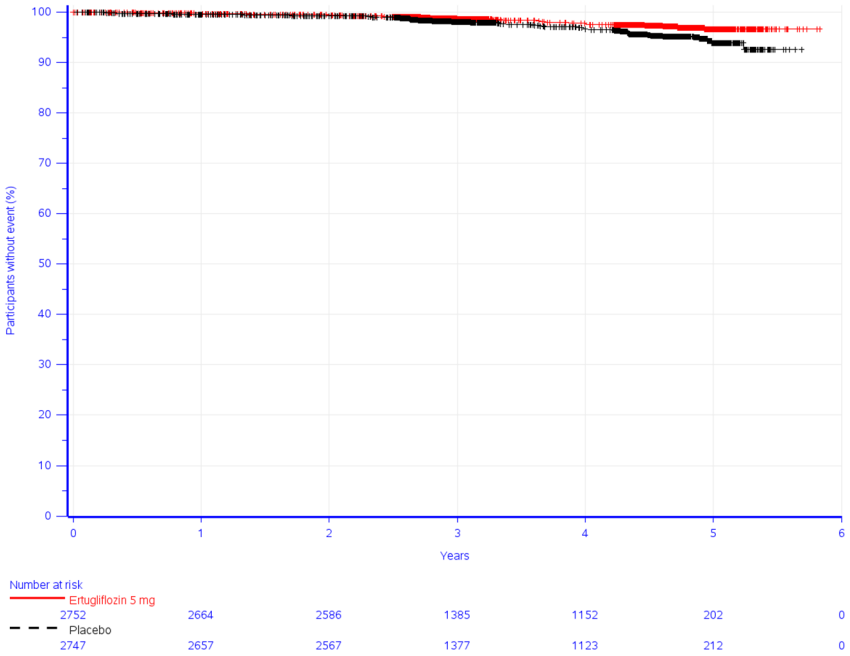

Abbildung 4G-23: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt Anhaltende Reduktion der eGFR um 40% in der Studie VERTIS CV (Ertugliflozin 5 mg)

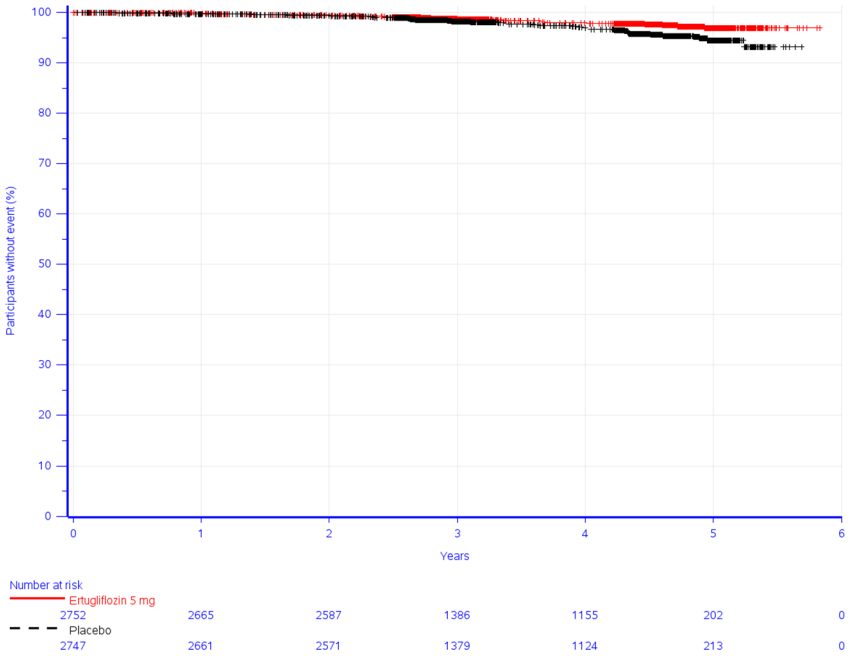

Abbildung 4G-24: Überlebenszeitanalyse: Kaplan-Meier-Kurve für den Endpunkt Anhaltende Reduktion der eGFR um 40% auf <60 ml/min/1.73m^2 in der Studie VERTIS CV (Ertugliflozin 5 mg)

Anhang 4-G2.3: Weitere Morbiditätsendpunkte

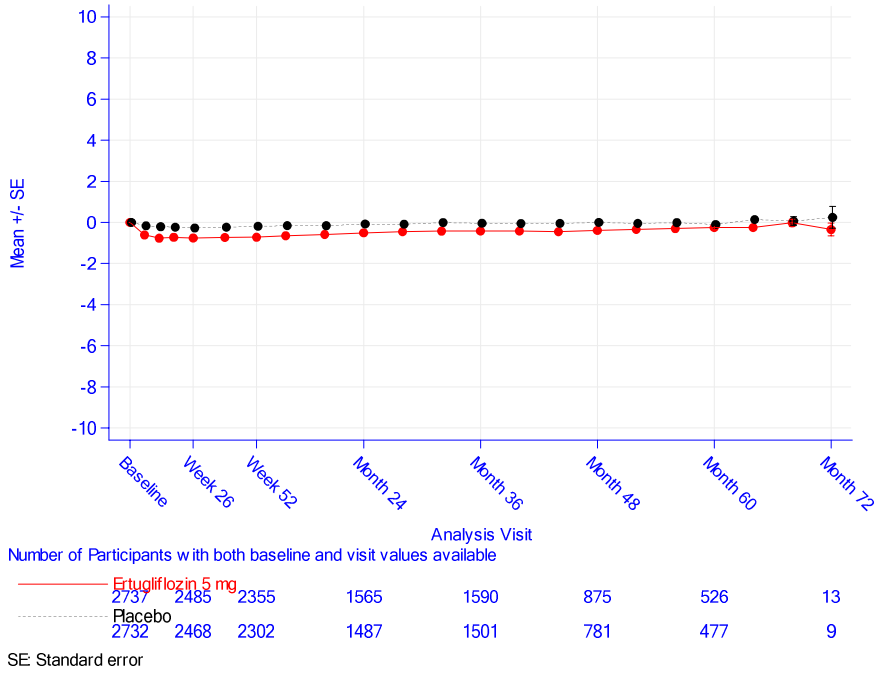

Abbildung 4G-25: Darstellung über den Zeitverlauf: Mittelwert +/- Standardfehler für den Endpunkt Veränderung des HbA1c-Wertes (Ertugliflozin 5 mg) in der Studie VERTIS CV

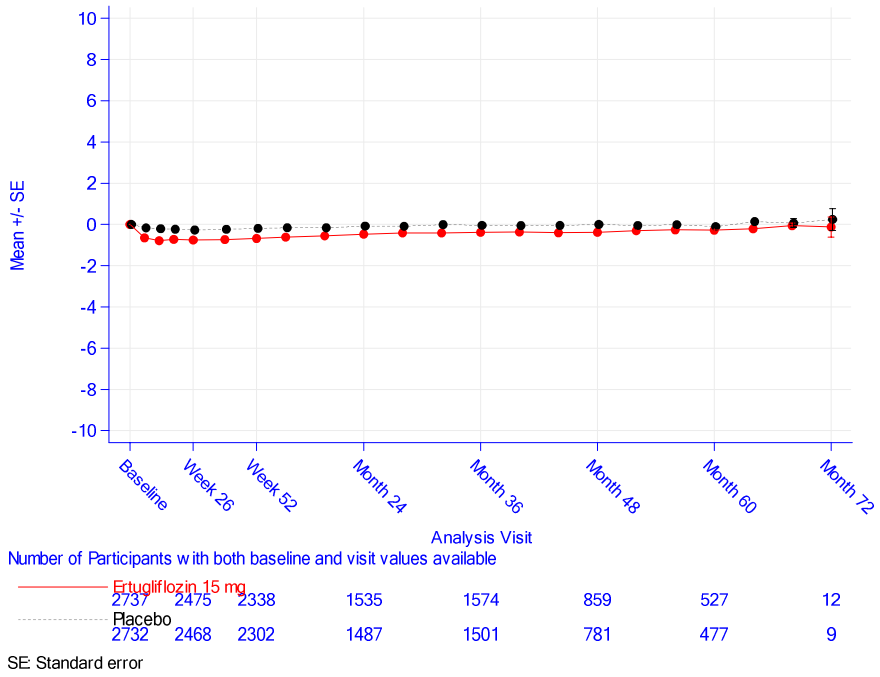

Abbildung 4G-26: Darstellung über den Zeitverlauf: Mittelwert +/- Standardfehler für den Endpunkt Veränderung des HbA1c-Wertes (Ertugliflozin 15 mg) in der Studie VERTIS CV

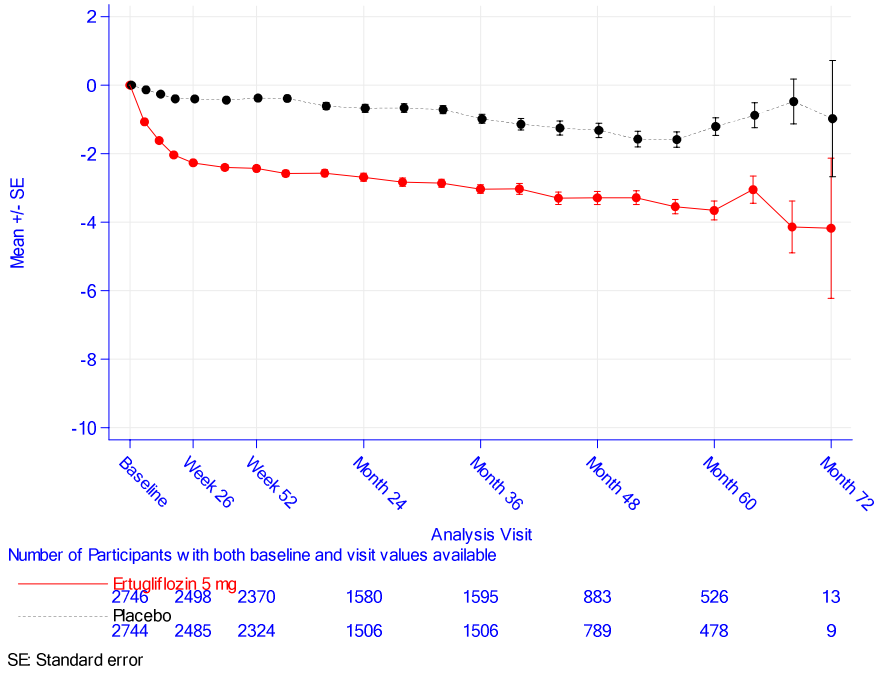

Abbildung 4G-27: Darstellung über den Zeitverlauf: Mittelwert +/- Standardfehler für den Endpunkt Veränderung des Körpergewichts (Ertugliflozin 5 mg) in der Studie VERTIS CV

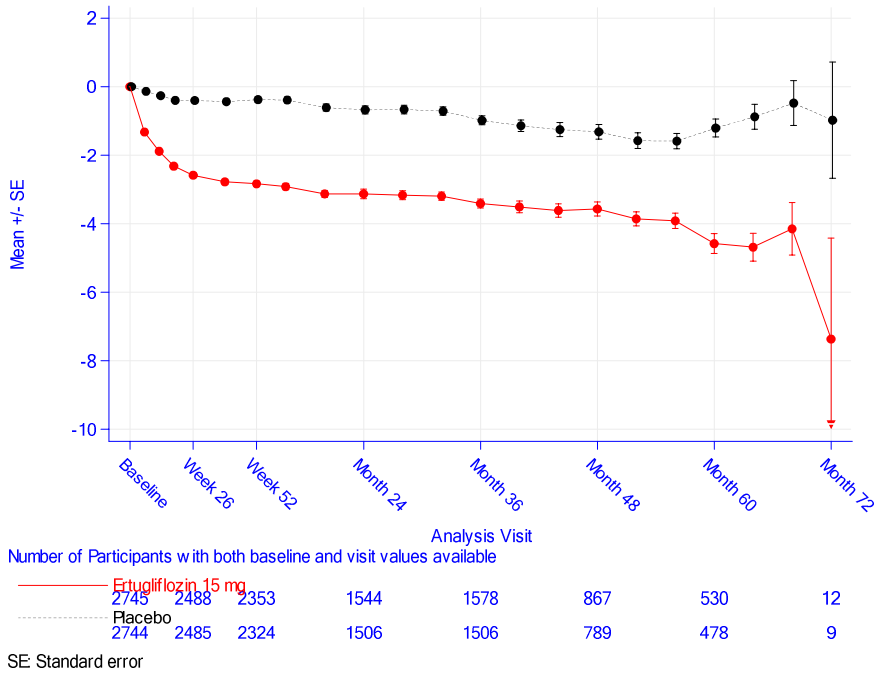

Abbildung 4G-28: Darstellung über den Zeitverlauf: Mittelwert +/- Standardfehler für den Endpunkt Veränderung des Körpergewichts (Ertugliflozin 15 mg) in der Studie VERTIS CV

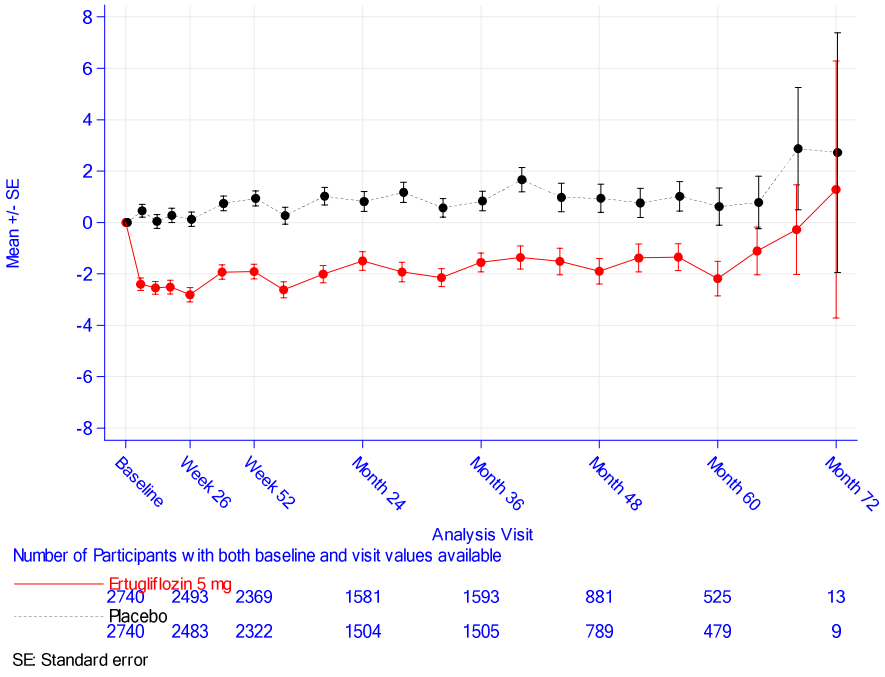

Abbildung 4G-29: Darstellung über den Zeitverlauf: Mittelwert +/- Standardfehler für den Endpunkt Veränderung des systolischen Blutdrucks (Ertugliflozin 5 mg) in der Studie VERTIS CV

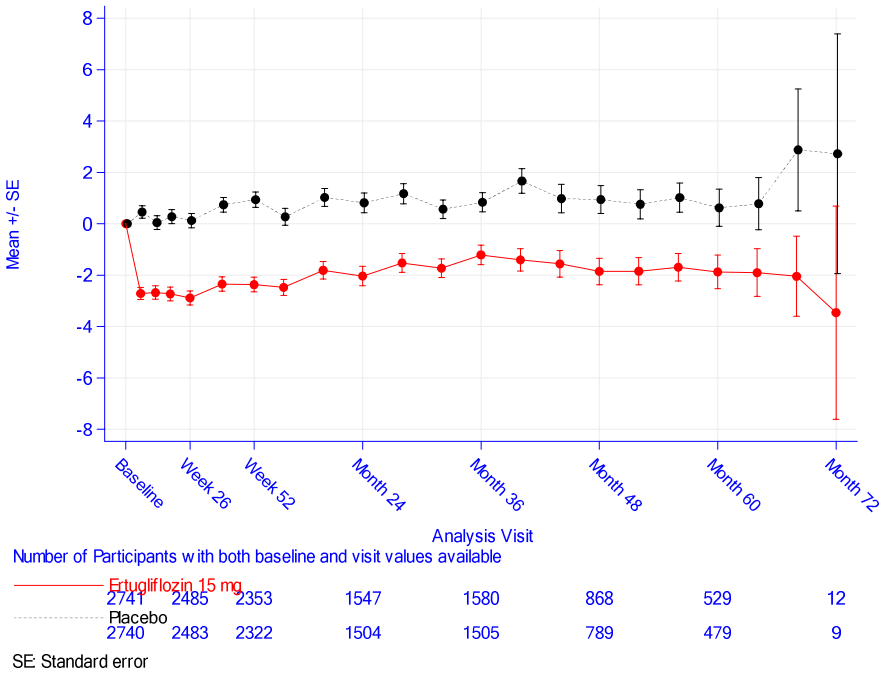

Abbildung 4G-30: Darstellung über den Zeitverlauf: Mittelwert +/- Standardfehler für den Endpunkt Veränderung des systolischen Blutdrucks (Ertugliflozin 15 mg) in der Studie VERTIS CV

Anhang 4-G3: Kaplan-Meier-Kurven der Subgruppen mit signifikantem Interaktionstest (p < 0,05) der Studie VERTIS CV

Im Folgenden werden ergänzend zu Abschnitt 4.3.1.3.2.2 die Kaplan-Meier-Kurven der Subgruppenanalysen, für die ein signifikanter Interaktionstest (p < 0,05) vorliegt, dargestellt.

Anhang 4-G3.1: Morbidität

Hauptanalyse

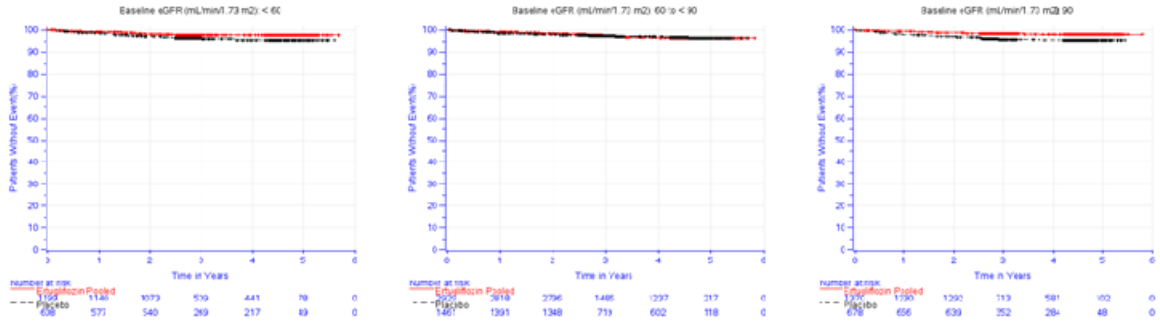

Abbildung 4G-31: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Hospitalisierung wegen instabiler Angina pectoris nach Ausmaß der chronische Niereninsuffizienz (eGFR: <60, 60 bis <90, und ≥90 ml/min/1.73m^2) der Studie VERTIS CV (Ertugliflozin gepoolt)

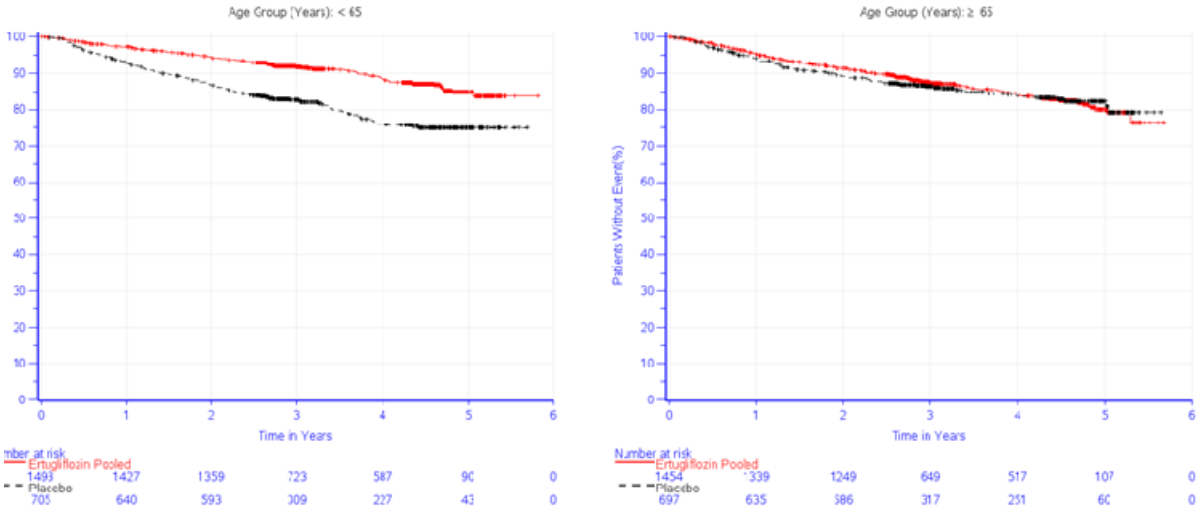

Abbildung 4G-32: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Beginn einer Insulintherapie nach Alter der Studie VERTIS CV (Ertugliflozin gepoolt)

Sensitivitätsanalyse

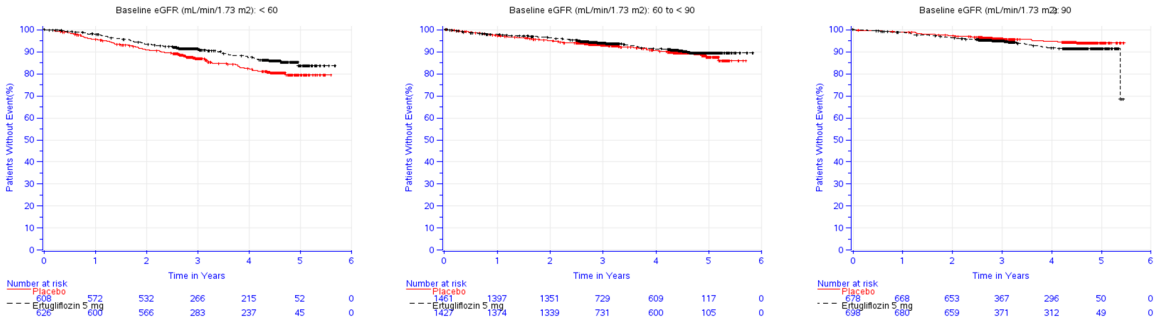

Abbildung 4G-33: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Hospitalisierung wegen Herzinsuffizienz nach Ausmaß der chronische Niereninsuffizienz (eGFR: <60, 60 bis <90, und ≥90 ml/min/1.73m^2) der Studie VERTIS CV (Ertugliflozin 5 mg)

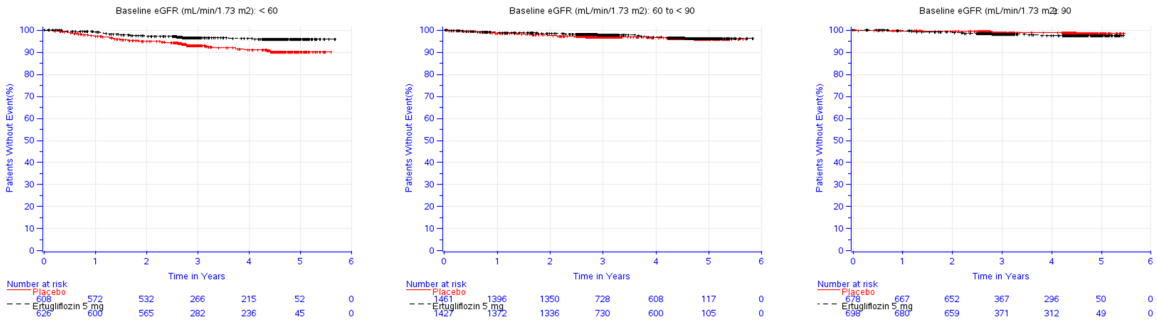

Abbildung 4G-34: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Kardiovaskulärer Tod oder Hospitalisierung wegen Herzinsuffizienz nach Ausmaß der chronische Niereninsuffizienz (eGFR: <60, 60 bis <90, und ≥90 ml/min/1.73m^2) der Studie VERTIS CV (Ertugliflozin 5 mg)

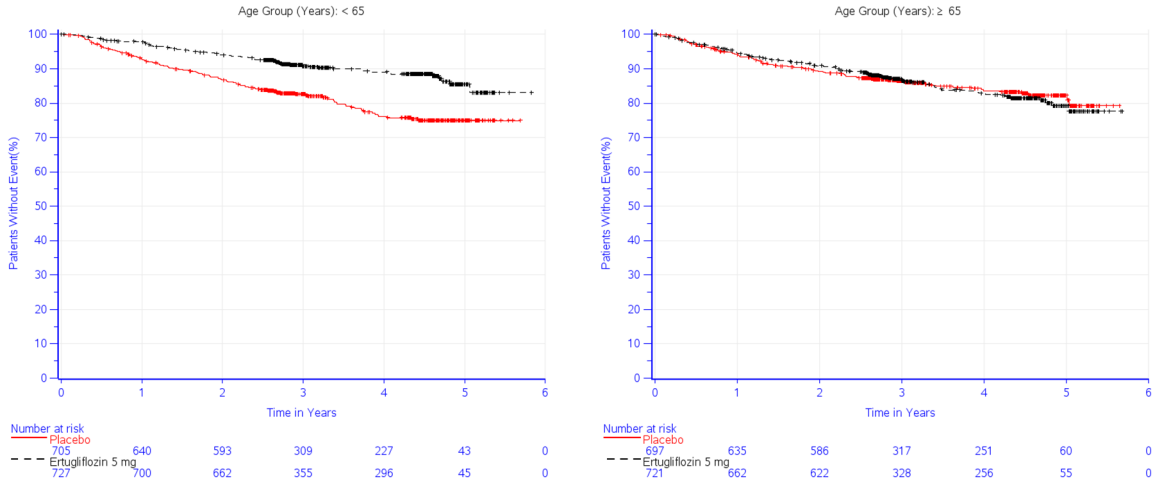

Abbildung 4G-35: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Beginn einer Insulin Therapie nach Alter der Studie VERTIS CV (Ertugliflozin 5 mg)

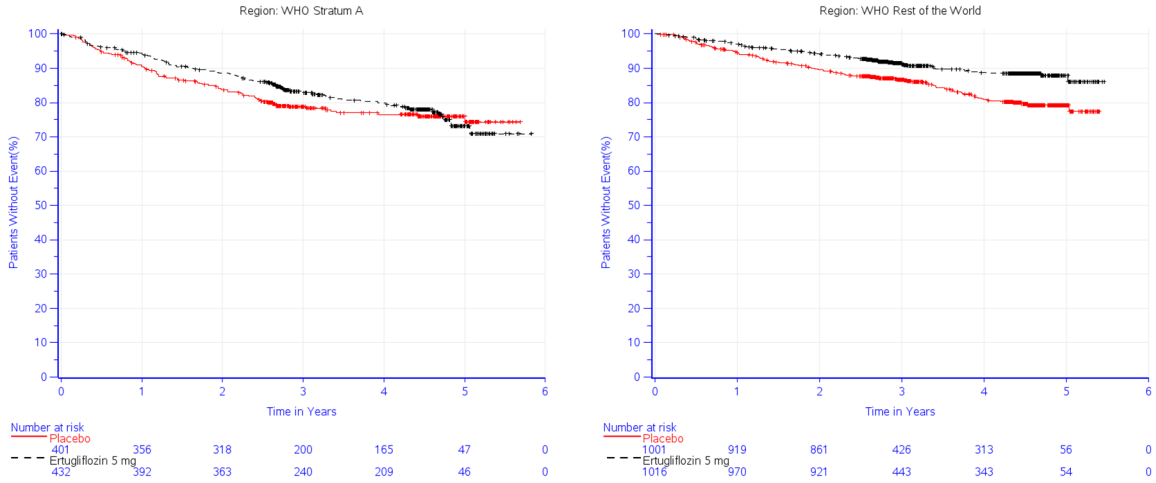

Abbildung 4G-36: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Beginn einer Insulin Therapie nach Region der Studie VERTIS CV (Ertugliflozin 5 mg)

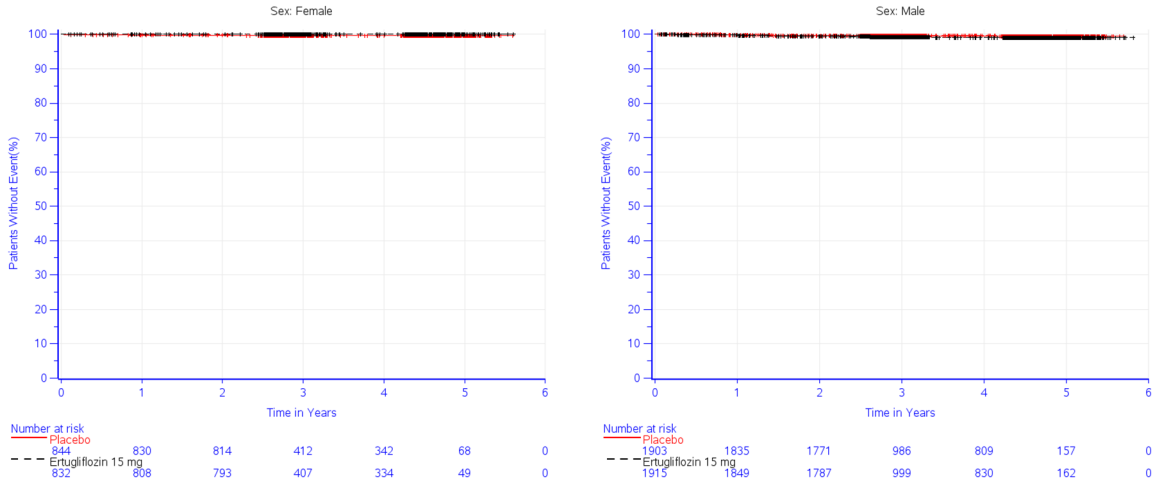

Abbildung 4G-37: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Tödlicher Schlaganfall nach Geschlecht der Studie VERTIS CV (Ertugliflozin 15 mg)

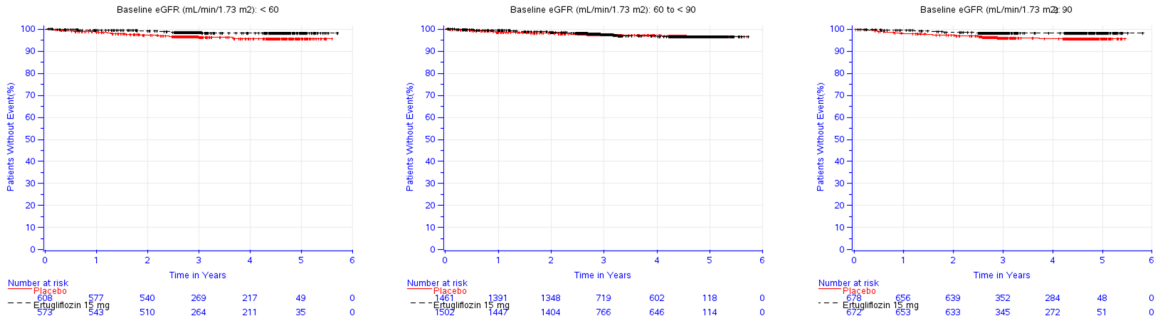

Abbildung 4G-38: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Hospitalisierung wegen instabiler Angina pectoris nach Ausmaß der chronische Niereninsuffizienz (eGFR: <60, 60 bis <90, und ≥90 ml/min/1.73m^2) der Studie VERTIS CV (Ertugliflozin 15 mg)

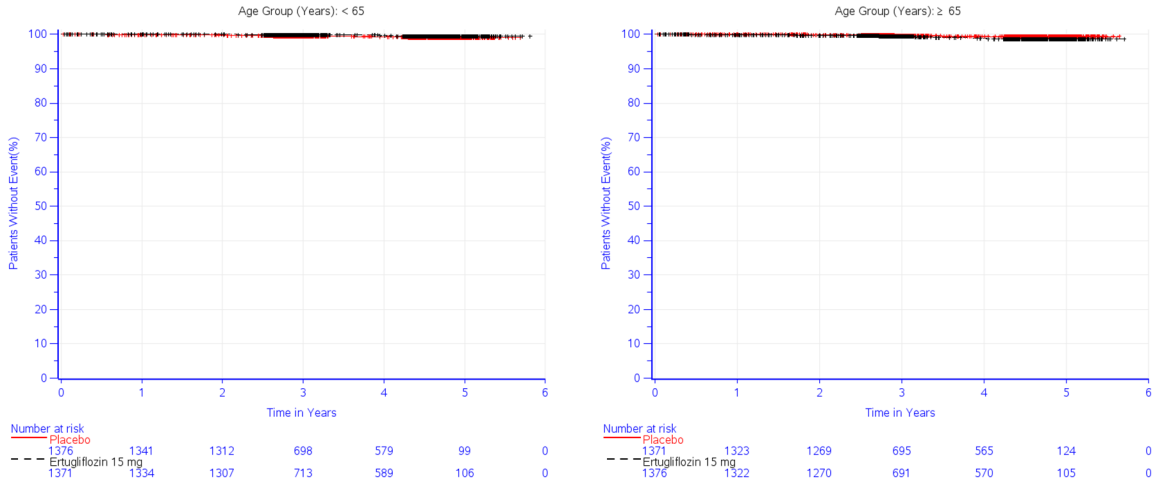

Abbildung 4G-39: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Nierentransplantation/ Dialyse nach Alter der Studie VERTIS CV (Ertugliflozin 15 mg)

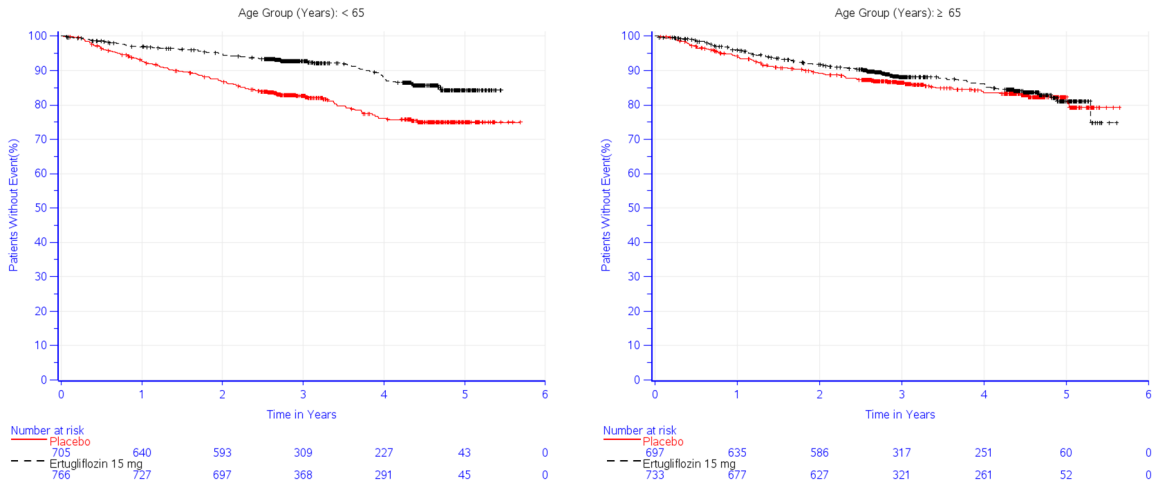

Abbildung 4G-40: Kaplan-Meier-Kurve für die Subgruppenanalyse für den Endpunkt Beginn einer Insulin Therapie nach Alter der Studie VERTIS CV (Ertugliflozin 15 mg)

Anhang 4-G4: 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-G4.1: Mortalität

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

Study: VERTIS CV	Ertugliflozin Pooled			Placebo			Ertugliflozin Pooled vs. Placebo		
All Cause Mortality Event[f]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	Hazard Ratio [95 %-CI][c]	p-Value[c,d]	p-Value for Interaction Test[e]
Sex									
Female	1,633	108 (6.6)	Not reached [-; -]	844	53 (6.3)	Not reached [-; -]	1.06 [0.76; 1.47]	0.722	0.357
Male	3,866	365 (9.4)	Not reached [-; -]	1,903	201 (10.6)	Not reached [-; -]	0.89 [0.75; 1.06]	0.183	
Age Group (Years)									
< 65	2,719	167 (6.1)	Not reached [-; -]	1,376	93 (6.8)	Not reached [-; -]	0.90 [0.70; 1.16]	0.410	0.768
≥ 65	2,780	306 (11.0)	Not reached [-; -]	1,371	161 (11.7)	Not reached [-; -]	0.94 [0.78; 1.14]	0.543	
Region									
WHO Stratum A	1,791	151 (8.4)	Not reached [-; -]	890	87 (9.8)	Not reached [-; -]	0.86 [0.66; 1.11]	0.246	0.463
WHO Rest of the World	3,708	322 (8.7)	Not reached [-; -]	1,857	167 (9.0)	Not reached [-; -]	0.97 [0.80; 1.17]	0.728	
Baseline eGFR (mL/min/1.73 m^2)									
< 60	1,199	153 (12.8)	Not reached [-; -]	608	82 (13.5)	Not reached [-; -]	0.94 [0.72; 1.23]	0.671	0.208
60 to < 90	2,929	220 (7.5)	Not reached [-; -]	1,461	131 (9.0)	Not reached [-; -]	0.83 [0.67; 1.03]	0.098	
≥ 90	1,370	100 (7.3)	Not reached [-; -]	678	41 (6.0)	Not reached [-; -]	1.21 [0.84; 1.75]	0.296	
Insulin at Baseline									
No	2,946	215 (7.3)	Not reached [-; -]	1,402	112 (8.0)	Not reached [-; -]	0.92 [0.73; 1.15]	0.460	0.840
Yes	2,553	258 (10.1)	Not reached [-; -]	1,345	142 (10.6)	Not reached [-; -]	0.95 [0.77; 1.16]	0.606	
a: Number of participants: intention-to-treat population									

Study: VERTIS CV	Ertugliflozin Pooled			Placebo			Ertugliflozin Pooled vs. Placebo		
All Cause Mortality Event[f]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	Hazard Ratio [95 %-CI][c]	p-Value[c,d]	p-Value for Interaction Test[e]

b: From product-limit (Kaplan-Meier) method for censored data

c: Based on Cox regression model With treatment as a covariate using Wald Confidence Interval

d: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)

e: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)

f: The on-study approach included confirmed events that occurred between the randomization date and the on-study censor date, which is defined as the earliest of participants´ end of study date, death date, or last contact date

CI: Confidence Interval; WHO: World Health Organization

Anhang 4-G4.2: Morbidität

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

Study: VERTIS CV	Ertugliflozin Pooled			Placebo			Ertugliflozin Pooled vs. Placebo		
MACE[f,g]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	Hazard Ratio [95 %-CI][c]	p-Value[c,d]	p-Value for Interaction Test[e]
Sex									
Female	1,633	162 (9.9)	Not reached [-; -]	844	93 (11.0)	Not reached [-; -]	0.89 [0.69; 1.15]	0.386	0.355
Male	3,866	573 (14.8)	Not reached [-; -]	1,903	275 (14.5)	Not reached [-; -]	1.02 [0.89; 1.18]	0.764	
Age Group (Years)									
< 65	2,719	285 (10.5)	Not reached [-; -]	1,376	152 (11.0)	Not reached [-; -]	0.93 [0.76; 1.13]	0.455	0.394
≥ 65	2,780	450 (16.2)	Not reached [-; -]	1,371	216 (15.8)	Not reached [-; -]	1.04 [0.88; 1.22]	0.652	
Region									
WHO Stratum A	1,791	287 (16.0)	Not reached [-; -]	890	146 (16.4)	Not reached [-; -]	0.97 [0.79; 1.18]	0.738	0.749
WHO Rest of the World	3,708	448 (12.1)	Not reached [-; -]	1,857	222 (12.0)	Not reached [-; -]	1.01 [0.86; 1.18]	0.926	
Baseline eGFR (mL/min/1.73 m^2)									
< 60	1,199	220 (18.3)	Not reached [-; -]	608	103 (16.9)	Not reached [-; -]	1.10 [0.87; 1.39]	0.426	0.579
60 to < 90	2,929	380 (13.0)	Not reached [-; -]	1,461	193 (13.2)	Not reached [-; -]	0.97 [0.82; 1.15]	0.739	
≥ 90	1,370	135 (9.9)	Not reached [5.4; -]	678	72 (10.6)	Not reached [-; -]	0.92 [0.69; 1.22]	0.560	
Insulin at Baseline									
No	2,946	350 (11.9)	Not reached [-; -]	1,402	154 (11.0)	Not reached [-; -]	1.10 [0.91; 1.32]	0.343	0.181
Yes	2,553	385 (15.1)	Not reached [-; -]	1,345	214 (15.9)	Not reached [-; -]	0.92 [0.78; 1.09]	0.350	

a: Number of participants: intention-to-treat population
b: From product-limit (Kaplan-Meier) method for censored data
c: Based on Cox regression model With treatment as a covariate using Wald Confidence Interval
d: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)
e: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)
f: The on-study approach included confirmed events that occurred between the randomization date and the on-study censor date, which is defined as the earliest of participants´ end of study date, death date, or last contact date
g: MACE was defined as a composite of confirmed CV death, non-fatal MI or non-fatal stroke
CI: Confidence Interval; CV: Cardiovascular; eGFR: Estimated Glomerular Filtration Rate; MACE: Major Adverse Cardiovascular

Study: VERTIS CV	Ertugliflozin Pooled			Placebo			Ertugliflozin Pooled vs. Placebo		
MACE[f,g]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	Hazard Ratio [95 %-CI][c]	p-Value[c,d]	p-Value for Interaction Test[e]
Events; WHO: World Health Organization									

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

Study: VERTIS CV	Ertugliflozin Pooled			Placebo			Ertugliflozin Pooled vs. Placebo		
MACE-plus[f,g]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	Hazard Ratio [95 %-CI][c]	p-Value[c,d]	p-Value for Interaction Test[e]
Sex									
Female	1,633	190 (11.6)	Not reached [-; -]	844	111 (13.2)	Not reached [-; -]	0.87 [0.69; 1.11]	0.262	0.594
Male	3,866	633 (16.4)	Not reached [-; -]	1,903	328 (17.2)	Not reached [-; -]	0.94 [0.82; 1.07]	0.348	
Age (Years)									
< 65	2,719	337 (12.4)	Not reached [-; -]	1,376	194 (14.1)	Not reached [-; -]	0.85 [0.71; 1.01]	0.070	0.221
≥ 65	2,780	486 (17.5)	Not reached [-; -]	1,371	245 (17.9)	Not reached [-; -]	0.98 [0.84; 1.15]	0.845	
Region									
WHO Stratum A	1,791	316 (17.6)	Not reached [-; -]	890	170 (19.1)	Not reached [-; -]	0.91 [0.75; 1.09]	0.295	0.780
Rest of the World	3,708	507 (13.7)	Not reached [-; -]	1,857	269 (14.5)	Not reached [-; -]	0.94 [0.81; 1.08]	0.377	
Baseline eGFR (mL/min/1.73 m^2)									
< 60	1,199	238 (19.8)	Not reached [-; -]	608	119 (19.6)	Not reached [-; -]	1.02 [0.82; 1.27]	0.861	0.235
60 to < 90	2,929	432 (14.7)	Not reached [-; -]	1,461	224 (15.3)	Not reached [-; -]	0.95 [0.81; 1.12]	0.528	
≥ 90	1,370	153 (11.2)	Not reached [5.4; -]	678	96 (14.2)	Not reached [-; -]	0.77 [0.59; 0.99]	0.041	
Race									
Asian	336	45 (13.4)	Not reached [-; -]	162	24 (14.8)	Not reached [-; -]	0.90 [0.55; 1.48]	0.688	0.814
Black Or African American	166	31 (18.7)	Not reached [-; -]	69	16 (23.2)	Not reached [-; -]	0.80 [0.44; 1.47]	0.468	
Multi-Racial	136	17 (12.5)	Not reached	70	12 (17.1)	Not reached	0.66 [0.31; 1.39]	0.274	

Study: VERTIS CV	Ertugliflozin Pooled			Placebo			Ertugliflozin Pooled vs. Placebo		
MACE-plus[f,g]	**N[a]**	**Participants with Event n (%)**	**Median Time[b] in Years [95 %-CI]**	**N[a]**	**Participants with Event n (%)**	**Median Time[b] in Years [95 %-CI]**	**Hazard Ratio [95 %-CI][c]**	**p-Value[c,d]**	**p-Value for Interaction Test[e]**
			[-; -]			[4.6; -]			
White	4,826	722 (15.0)	Not reached [-; -]	2,414	378 (15.7)	Not reached [-; -]	0.95 [0.84; 1.07]	0.391	
Other	35	8 (22.9)	Not reached [-; -]	32	9 (28.1)	Not reached [4.1; -]	0.77 [0.29; 2.06]	0.599	
Ethnicity									
Hispanic or Latino	700	85 (12.1)	Not reached [-; -]	343	49 (14.3)	Not reached [-; -]	0.85 [0.60; 1.21]	0.358	0.615
Not Hispanic or Latino	4,782	736 (15.4)	Not reached [-; -]	2,399	390 (16.3)	Not reached [-; -]	0.93 [0.82; 1.05]	0.264	
Insulin at Baseline									
No	2,946	393 (13.3)	Not reached [-; -]	1,402	189 (13.5)	Not reached [-; -]	1.00 [0.84; 1.18]	0.961	0.283
Yes	2,553	430 (16.8)	Not reached [-; -]	1,345	250 (18.6)	Not reached [-; -]	0.88 [0.75; 1.02]	0.099	

a: Number of participants: intention-to-treat population
b: From product-limit (Kaplan-Meier) method for censored data
c: Based on Cox regression model with treatment as a covariate using Wald CI
d: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)
e: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)
f: The on-study approach included confirmed events that occurred between the randomization date and the on-study censor date, which is defined as the earliest of participants´ end of study date, death date, or last contact date
g: MACE-plus composite endpoint: CV death, non-fatal MI, non-fatal stroke, hospitalizations for unstable angina
CI: Confidence Interval; CV: Cardiovascular; eGFR: Estimated Glomerular Filtration Rate; MACE: Major Adverse Cardiovascular Events; WHO: World Health Organization

Tabelle 4G-6: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Kardiovaskulärer Tod (Ertugliflozin gepoolt) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS CV	Ertugliflozin Pooled			Placebo			Ertugliflozin Pooled vs. Placebo		
Cardiovascular mortality[f]	**N[a]**	**Participants with Event n (%)**	**Median Time[b] in Years [95 %-CI]**	**N[a]**	**Participants with Event n (%)**	**Median Time[b] in Years [95 %-CI]**	**Hazard Ratio [95 %-CI][c]**	**p-Value[c,d]**	**p-Value for Interaction Test[e]**
Sex									
Female	1,633	78 (4.8)	Not reached [-; -]	844	38 (4.5)	Not reached [-; -]	1.07 [0.72; 1.57]	0.741	0.398
Male	3,866	263 (6.8)	Not reached [-; -]	1,903	146 (7.7)	Not reached [-; -]	0.88 [0.72; 1.08]	0.227	

Study: VERTIS CV	Ertugliflozin Pooled			Placebo			Ertugliflozin Pooled vs. Placebo		
Cardiovascular mortality[f]	**N[a]**	**Participants with Event n (%)**	**Median Time[b] in Years [95 %-CI]**	**N[a]**	**Participants with Event n (%)**	**Median Time[b] in Years [95 %-CI]**	**Hazard Ratio [95 %-CI][c]**	**p-Value[c,d]**	**p-Value for Interaction Test[e]**
Age Group (Years)									
< 65	2,719	123 (4.5)	Not reached [-; -]	1,376	66 (4.8)	Not reached [-; -]	0.93 [0.69; 1.26]	0.657	0.924
≥ 65	2,780	218 (7.8)	Not reached [-; -]	1,371	118 (8.6)	Not reached [-; -]	0.92 [0.73; 1.15]	0.444	
Region									
WHO Stratum A	1,791	111 (6.2)	Not reached [-; -]	890	59 (6.6)	Not reached [-; -]	0.93 [0.68; 1.27]	0.635	0.973
WHO Rest of the World	3,708	230 (6.2)	Not reached [-; -]	1,857	125 (6.7)	Not reached [-; -]	0.92 [0.74; 1.15]	0.467	
Baseline eGFR (mL/min/1.73 m^2)									
< 60	1,199	111 (9.3)	Not reached [-; -]	608	64 (10.5)	Not reached [-; -]	0.88 [0.64; 1.19]	0.397	0.245
60 to < 90	2,929	162 (5.5)	Not reached [-; -]	1,461	94 (6.4)	Not reached [-; -]	0.85 [0.66; 1.10]	0.226	
≥ 90	1,370	68 (5.0)	Not reached [-; -]	678	26 (3.8)	Not reached [-; -]	1.30 [0.83; 2.05]	0.249	
Insulin at Baseline									
No	2,946	156 (5.3)	Not reached [-; -]	1,402	75 (5.3)	Not reached [-; -]	0.99 [0.75; 1.31]	0.964	0.523
Yes	2,553	185 (7.2)	Not reached [-; -]	1,345	109 (8.1)	Not reached [-; -]	0.88 [0.70; 1.12]	0.309	

a: Number of participants: intention-to-treat population
b: From product-limit (Kaplan-Meier) method for censored data
c: Based on Cox regression model With treatment as a covariate using Wald Confidence Interval
d: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)
e: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)
f: The on-study approach included confirmed events that occurred between the randomization date and the on-study censor date, which is defined as the earliest of participants´ end of study date, death date, or last contact date
CI: Confidence Interval; eGFR: Estimated Glomerular Filtration Rate; WHO: World Health Organization

Tabelle 4G-7: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Herzinfarkt (Ertugliflozin gepoolt) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS CV	Ertugliflozin Pooled			Placebo			Ertugliflozin Pooled vs. Placebo		
Fatal or Non Fatal MI[f]	**N[a]**	**Participants with Event n (%)**	**Median Time[b] in Years [95 %-CI]**	**N[a]**	**Participants with Event n (%)**	**Median Time[b] in Years [95 %-CI]**	**Hazard Ratio [95 %-CI][c]**	**p-Value[c,d]**	**p-Value for Interaction Test[e]**
Sex									
Female	1,633	64 (3.9)	Not reached	844	39 (4.6)	Not reached	0.85 [0.57; 1.27]	0.439	0.273

Study: VERTIS CV	Ertugliflozin Pooled			Placebo			Ertugliflozin Pooled vs. Placebo		
Fatal or Non Fatal MI[f]	**N[a]**	**Participants with Event n (%)**	**Median Time[b] in Years [95 %-CI]**	**N[a]**	**Participants with Event n (%)**	**Median Time[b] in Years [95 %-CI]**	**Hazard Ratio [95 %-CI][c]**	**p-Value[c,d]**	**p-Value for Interaction Test[e]**
			[-; -]			[-; -]			
Male	3,866	266 (6.9)	Not reached [-; -]	1,903	119 (6.3)	Not reached [-; -]	1.10 [0.88; 1.36]	0.403	
Age Group (Years)									
< 65	2,719	126 (4.6)	Not reached [-; -]	1,376	72 (5.2)	Not reached [-; -]	0.87 [0.65; 1.16]	0.343	0.119
≥ 65	2,780	204 (7.3)	Not reached [-; -]	1,371	86 (6.3)	Not reached [-; -]	1.18 [0.92; 1.52]	0.191	
Region									
WHO Stratum A	1,791	156 (8.7)	Not reached [-; -]	890	75 (8.4)	Not reached [-; -]	1.03 [0.78; 1.36]	0.826	0.936
WHO Rest of the World	3,708	174 (4.7)	Not reached [-; -]	1,857	83 (4.5)	Not reached [-; -]	1.05 [0.81; 1.36]	0.731	
Baseline eGFR (mL/min/1.73 m^2)									
< 60	1,199	94 (7.8)	Not reached [-; -]	608	37 (6.1)	Not reached [-; -]	1.31 [0.89; 1.91]	0.166	0.115
60 to < 90	2,929	182 (6.2)	Not reached [-; -]	1,461	84 (5.7)	Not reached [-; -]	1.07 [0.83; 1.39]	0.597	
≥ 90	1,370	54 (3.9)	Not reached [-; -]	678	37 (5.5)	Not reached [-; -]	0.72 [0.48; 1.10]	0.131	
Insulin at Baseline									
No	2,946	159 (5.4)	Not reached [-; -]	1,402	61 (4.4)	Not reached [-; -]	1.26 [0.93; 1.69]	0.131	0.104
Yes	2,553	171 (6.7)	Not reached [-; -]	1,345	97 (7.2)	Not reached [-; -]	0.91 [0.71; 1.17]	0.471	

a: Number of participants: intention-to-treat population
b: From product-limit (Kaplan-Meier) method for censored data
c: Based on Cox regression model With treatment as a covariate using Wald Confidence Interval
d: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)
e: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)
f: The on-study approach included confirmed events that occurred between the randomization date and the on-study censor date, which is defined as the earliest of participants´ end of study date, death date, or last contact date
CI: Confidence Interval; eGFR: Estimated Glomerular Filtration Rate; MI: Myocardial Infarction; WHO: World Health Organization

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

Study: VERTIS CV	Ertugliflozin Pooled			Placebo			Ertugliflozin Pooled vs. Placebo		
Fatal or Non Fatal Stroke[f]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	Hazard Ratio [95 %-CI][c]	p-Value[c,d]	p-Value for Interaction Test[e]
Sex									
Female	1,633	43 (2.6)	Not reached [-; -]	844	27 (3.2)	Not reached [-; -]	0.82 [0.51; 1.33]	0.422	0.230
Male	3,866	142 (3.7)	Not reached [-; -]	1,903	60 (3.2)	Not reached [-; -]	1.16 [0.86; 1.57]	0.330	
Age Group (Years)									
< 65	2,719	72 (2.6)	Not reached [-; -]	1,376	39 (2.8)	Not reached [-; -]	0.92 [0.62; 1.36]	0.674	0.357
≥ 65	2,780	113 (4.1)	Not reached [-; -]	1,371	48 (3.5)	Not reached [-; -]	1.17 [0.84; 1.65]	0.352	
Region									
WHO Stratum A	1,791	68 (3.8)	Not reached [-; -]	890	34 (3.8)	Not reached [-; -]	0.99 [0.65; 1.49]	0.949	0.677
WHO Rest of the World	3,708	117 (3.2)	Not reached [-; -]	1,857	53 (2.9)	Not reached [-; -]	1.10 [0.80; 1.53]	0.548	
Baseline eGFR (mL/min/1.73 m^2)									
< 60	1,199	59 (4.9)	Not reached [-; -]	608	20 (3.3)	Not reached [-; -]	1.51 [0.91; 2.51]	0.111	0.215
60 to < 90	2,929	93 (3.2)	Not reached [-; -]	1,461	47 (3.2)	Not reached [-; -]	0.98 [0.69; 1.39]	0.901	
≥ 90	1,370	33 (2.4)	Not reached [-; -]	678	20 (2.9)	Not reached [-; -]	0.81 [0.46; 1.41]	0.447	
Insulin at Baseline									
No	2,946	92 (3.1)	Not reached [-; -]	1,402	41 (2.9)	Not reached [-; -]	1.08 [0.75; 1.56]	0.680	0.908
Yes	2,553	93 (3.6)	Not reached [-; -]	1,345	46 (3.4)	Not reached [-; -]	1.05 [0.74; 1.50]	0.786	

a: Number of participants: intention-to-treat population
b: From product-limit (Kaplan-Meier) method for censored data
c: Based on Cox regression model With treatment as a covariate using Wald Confidence Interval
d: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)
e: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)
f: The on-study approach included confirmed events that occurred between the randomization date and the on-study censor date, which is defined as the earliest of participants´ end of study date, death date, or last contact date
CI: Confidence Interval; eGFR: Estimated Glomerular Filtration Rate; WHO: World Health Organization

Tabelle 4G-9: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Tödlicher Schlaganfall (Ertugliflozin gepoolt) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS CV	Ertugliflozin Pooled			Placebo			Ertugliflozin Pooled vs. Placebo		
Fatal Stroke[f]	**N[a]**	**Participants with Event n (%)**	**Median Time[b] in Years [95 %-CI]**	**N[a]**	**Participants with Event n (%)**	**Median Time[b] in Years [95 %-CI]**	**Hazard Ratio [95 %-CI][c]**	**p-Value[c,d]**	**p-Value for Interaction Test[e]**
Sex									
Female	1,633	7 (0.4)	Not reached [-; -]	844	3 (0.4)	Not reached [-; -]	1.23 [0.32; 4.74]	0.768	0.930
Male	3,866	24 (0.6)	Not reached [-; -]	1,903	9 (0.5)	Not reached [-; -]	1.31 [0.61; 2.81]	0.494	
Age Group (Years)									
< 65	2,719	15 (0.6)	Not reached [-; -]	1,376	5 (0.4)	Not reached [-; -]	1.51 [0.55; 4.16]	0.423	0.677
≥ 65	2,780	16 (0.6)	Not reached [-; -]	1,371	7 (0.5)	Not reached [-; -]	1.14 [0.47; 2.76]	0.778	
Region									
WHO Stratum A	1,791	4 (0.2)	Not reached [-; -]	890	4 (0.4)	Not reached [-; -]	0.50 [0.12; 1.99]	0.324	0.136
WHO Rest of the World	3,708	27 (0.7)	Not reached [-; -]	1,857	8 (0.4)	Not reached [-; -]	1.69 [0.77; 3.72]	0.193	
Baseline eGFR (mL/min/1.73 m^2)									
< 60	1,199	10 (0.8)	Not reached [-; -]	608	2 (0.3)	Not reached [-; -]	2.55 [0.56; 11.62]	0.228	0.538
60 to < 90	2,929	14 (0.5)	Not reached [-; -]	1,461	7 (0.5)	Not reached [-; -]	0.99 [0.40; 2.45]	0.982	
≥ 90	1,370	7 (0.5)	Not reached [-; -]	678	3 (0.4)	Not reached [-; -]	1.17 [0.30; 4.51]	0.825	
Insulin at Baseline									
No	2,946	16 (0.5)	Not reached [-; -]	1,402	9 (0.6)	Not reached [-; -]	0.85 [0.38; 1.92]	0.694	0.120
Yes	2,553	15 (0.6)	Not reached [-; -]	1,345	3 (0.2)	Not reached [-; -]	2.63 [0.76; 9.08]	0.126	

a: Number of participants: intention-to-treat population

b: From product-limit (Kaplan-Meier) method for censored data

c: Based on Cox regression model With treatment as a covariate using Wald Confidence Interval

d: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)

e: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)

f: The on-study approach included confirmed events that occurred between the randomization date and the on-study censor date, which is defined as the earliest of participants´ end of study date, death date, or last contact date

CI: Confidence Interval; eGFR: Estimated Glomerular Filtration Rate; WHO: World Health Organization

Tabelle 4G-10: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Nicht-tödlicher Schlaganfall (Ertugliflozin gepoolt) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS CV	**Ertugliflozin Pooled**			**Placebo**			**Ertugliflozin Pooled vs. Placebo**		
Non-Fatal Stroke[f]	**N[a]**	**Participants with Event n (%)**	**Median Time[b] in Years [95 %-CI]**	**N[a]**	**Participants with Event n (%)**	**Median Time[b] in Years [95 %-CI]**	**Hazard Ratio [95 %-CI][c]**	**p-Value[c,d]**	**p-Value for Interaction Test[e]**
Sex									
Female	1,633	37 (2.3)	Not reached [-; -]	844	24 (2.8)	Not reached [-; -]	0.79 [0.47; 1.33]	0.379	0.302
Male	3,866	120 (3.1)	Not reached [-; -]	1,903	54 (2.8)	Not reached [-; -]	1.09 [0.79; 1.50]	0.594	
Age Group (Years)									
< 65	2,719	59 (2.2)	Not reached [-; -]	1,376	36 (2.6)	Not reached [-; -]	0.81 [0.54; 1.23]	0.333	0.206
≥ 65	2,780	98 (3.5)	Not reached [-; -]	1,371	42 (3.1)	Not reached [-; -]	1.16 [0.81; 1.67]	0.408	
Region									
WHO Stratum A	1,791	64 (3.6)	Not reached [-; -]	890	30 (3.4)	Not reached [-; -]	1.05 [0.68; 1.62]	0.819	0.769
WHO Rest of the World	3,708	93 (2.5)	Not reached [-; -]	1,857	48 (2.6)	Not reached [-; -]	0.97 [0.68; 1.37]	0.864	
Baseline eGFR (mL/min/1.73 m^2)									
< 60	1,199	50 (4.2)	Not reached [-; -]	608	19 (3.1)	Not reached [-; -]	1.35 [0.79; 2.29]	0.268	0.259
60 to < 90	2,929	80 (2.7)	Not reached [-; -]	1,461	40 (2.7)	Not reached [-; -]	0.99 [0.68; 1.45]	0.954	
≥ 90	1,370	27 (2.0)	Not reached [-; -]	678	19 (2.8)	Not reached [-; -]	0.69 [0.38; 1.25]	0.220	
Insulin at Baseline									
No	2,946	78 (2.6)	Not reached [-; -]	1,402	34 (2.4)	Not reached [-; -]	1.11 [0.74; 1.66]	0.620	0.532
Yes	2,553	79 (3.1)	Not reached [-; -]	1,345	44 (3.3)	Not reached [-; -]	0.93 [0.64; 1.35]	0.706	

a: Number of participants: intention-to-treat population

b: From product-limit (Kaplan-Meier) method for censored data

c: Based on Cox regression model With treatment as a covariate using Wald Confidence Interval

d: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)

e: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)

f: The on-study approach included confirmed events that occurred between the randomization date and the on-study censor date, which is defined as the earliest of participants´ end of study date, death date, or last contact date

CI: Confidence Interval; eGFR: Estimated Glomerular Filtration Rate; WHO: World Health Organization

Tabelle 4G-11: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Hospitalisierung wegen Herzinsuffizienz (Ertugliflozin gepoolt) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS CV	Ertugliflozin Pooled			Placebo			Ertugliflozin Pooled vs. Placebo		
Hospitalization for Heart Failure[f]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	Hazard Ratio [95 %-CI][c]	p-Value[c,d]	p-Value for Interaction Test[e]
Sex									
Female	1,633	30 (1.8)	Not reached [-; -]	844	28 (3.3)	Not reached [-; -]	0.55 [0.33; 0.93]	0.025	0.322
Male	3,866	109 (2.8)	Not reached [-; -]	1,903	71 (3.7)	Not reached [-; -]	0.75 [0.56; 1.01]	0.058	
Age Group (Years)									
< 65	2,719	48 (1.8)	Not reached [-; -]	1,376	36 (2.6)	Not reached [-; -]	0.66 [0.43; 1.02]	0.059	0.786
≥ 65	2,780	91 (3.3)	Not reached [-; -]	1,371	63 (4.6)	Not reached [-; -]	0.71 [0.52; 0.98]	0.039	
Region									
WHO Stratum A	1,791	62 (3.5)	Not reached [-; -]	890	42 (4.7)	Not reached [-; -]	0.73 [0.49; 1.08]	0.111	0.778
WHO Rest of the World	3,708	77 (2.1)	Not reached [-; -]	1,857	57 (3.1)	Not reached [-; -]	0.67 [0.48; 0.95]	0.024	
Baseline eGFR (mL/min/1.73 m^2)									
< 60	1,199	45 (3.8)	Not reached [-; -]	608	45 (7.4)	Not reached [-; -]	0.50 [0.33; 0.76]	0.001	0.068
60 to < 90	2,929	75 (2.6)	Not reached [-; -]	1,461	47 (3.2)	Not reached [-; -]	0.79 [0.55; 1.13]	0.200	
≥ 90	1,370	19 (1.4)	Not reached [-; -]	678	7 (1.0)	Not reached [-; -]	1.36 [0.57; 3.23]	0.490	
Insulin at Baseline									
No	2,946	49 (1.7)	Not reached [-; -]	1,402	27 (1.9)	Not reached [-; -]	0.87 [0.54; 1.39]	0.563	0.301
Yes	2,553	90 (3.5)	Not reached [-; -]	1,345	72 (5.4)	Not reached [-; -]	0.65 [0.48; 0.88]	0.006	

a: Number of participants: intention-to-treat population
b: From product-limit (Kaplan-Meier) method for censored data
c: Based on Cox regression model With treatment as a covariate using Wald Confidence Interval
d: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)
e: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)
f: The on-study approach included confirmed events that occurred between the randomization date and the on-study censor date, which is defined as the earliest of participants´ end of study date, death date, or last contact date
CI: Confidence Interval; eGFR: Estimated Glomerular Filtration Rate; WHO: World Health Organization

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

Study: VERTIS CV	Ertugliflozin Pooled			Placebo			Ertugliflozin Pooled vs. Placebo		
SMQ Cardiac Failure[f]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	Hazard Ratio [95 %-CI][c]	p-Value[c,d]	p-Value for Interaction Test[e]
Sex									
Female	1,630	48 (2.9)	Not reached [-; -]	844	46 (5.5)	Not reached [-; -]	0.54 [0.36; 0.81]	0.003	0.192
Male	3,863	181 (4.7)	Not reached [-; -]	1,901	120 (6.3)	Not reached [-; -]	0.73 [0.58; 0.92]	0.008	
Age Group (Years)									
< 65	2,718	80 (2.9)	Not reached [-; -]	1,375	67 (4.9)	Not reached [-; -]	0.59 [0.43; 0.82]	0.002	0.288
≥ 65	2,775	149 (5.4)	Not reached [-; -]	1,370	99 (7.2)	Not reached [-; -]	0.74 [0.57; 0.96]	0.021	
Region									
WHO Stratum A	1,789	96 (5.4)	Not reached [-; -]	890	62 (7.0)	Not reached [-; -]	0.76 [0.55; 1.05]	0.092	0.385
WHO Rest of the World	3,704	133 (3.6)	Not reached [-; -]	1,855	104 (5.6)	Not reached [-; -]	0.63 [0.49; 0.82]	< 0.001	
Baseline eGFR (mL/min/1.73 m^2)									
< 60	1,198	76 (6.3)	Not reached [-; -]	607	68 (11.2)	Not reached [-; -]	0.56 [0.40; 0.77]	< 0.001	0.297
60 to < 90	2,926	124 (4.2)	Not reached [-; -]	1,460	79 (5.4)	Not reached [-; -]	0.77 [0.58; 1.03]	0.075	
≥ 90	1,369	29 (2.1)	Not reached [-; -]	678	19 (2.8)	Not reached [-; -]	0.76 [0.42; 1.35]	0.343	
Insulin at Baseline									
No	2,943	88 (3.0)	Not reached [-; -]	1,400	50 (3.6)	Not reached [-; -]	0.84 [0.59; 1.19]	0.326	0.172
Yes	2,550	141 (5.5)	Not reached [-; -]	1,345	116 (8.6)	Not reached [-; -]	0.63 [0.49; 0.80]	< 0.001	

a: Number of participants: intention-to-treat population

b: From product-limit (Kaplan-Meier) method for censored data

c: Based on Cox regression model With treatment as a covariate using Wald Confidence Interval

d: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)

e: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)

f: The on-study approach included confirmed events that occurred between the randomization date and the on-study censor date, which is defined as the earliest of participants´ end of study date, death date, or last contact date

CI: Confidence Interval; eGFR: Estimated Estimated Glomerular Filtration Rate; SMQ: Standardised MedDRA Query; WHO: World Health Organization

Tabelle 4G-13: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Einzelendpunkt Hospitalisierung wegen instabiler Angina pectoris (Ertugliflozin gepoolt) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS CV	Ertugliflozin Pooled			Placebo			Ertugliflozin Pooled vs. Placebo		
Hospitalization for unstable angina[f]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	Hazard Ratio [95 %-CI][c]	p-Value[c,d]	p-Value for Interaction Test[e]
Sex									
Female	1,633	32 (2.0)	Not reached [-; -]	844	24 (2.8)	Not reached [-; -]	0.69 [0.41; 1.17]	0.167	0.996
Male	3,866	90 (2.3)	Not reached [-; -]	1,903	64 (3.4)	Not reached [-; -]	0.69 [0.50; 0.95]	0.022	
Age Group (Years)									
< 65	2,719	63 (2.3)	Not reached [-; -]	1,376	54 (3.9)	Not reached [-; -]	0.58 [0.40; 0.83]	0.003	0.148
≥ 65	2,780	59 (2.1)	Not reached [-; -]	1,371	34 (2.5)	Not reached [-; -]	0.87 [0.57; 1.32]	0.512	
Region									
WHO Stratum A	1,791	46 (2.6)	Not reached [-; -]	890	28 (3.1)	Not reached [-; -]	0.81 [0.51; 1.30]	0.385	0.394
WHO Rest of the World	3,708	76 (2.0)	Not reached [-; -]	1,857	60 (3.2)	Not reached [-; -]	0.63 [0.45; 0.89]	0.008	
Insulin at Baseline									
No	2,946	53 (1.8)	Not reached [-; -]	1,402	41 (2.9)	Not reached [-; -]	0.62 [0.41; 0.93]	0.022	0.465
Yes	2,553	69 (2.7)	Not reached [-; -]	1,345	47 (3.5)	Not reached [-; -]	0.76 [0.53; 1.10]	0.151	

a: Number of participants: intention-to-treat population
b: From product-limit (Kaplan-Meier) method for censored data
c: Based on Cox regression model With treatment as a covariate using Wald Confidence Interval
d: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)
e: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)
f: The on-study approach included confirmed events that occurred between the randomization date and the on-study censor date, which is defined as the earliest of participants´ end of study date, death date, or last contact date
CI: Confidence Interval; eGFR: Estimated Glomerular Filtration Rate; WHO: World Health Organization

Tabelle 4G-14: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den kombinierten renalen Endpunkt (Kreatinin) (Ertugliflozin gepoolt) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS CV	Ertugliflozin Pooled			Placebo			Ertugliflozin Pooled vs. Placebo		
Renal composite endpoint (creatinine)[f,g]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	Hazard Ratio [95 %-CI][c]	p-Value[c,d]	p-Value for Interaction Test[e]
Sex									
Female	1,633	45 (2.8)	Not reached [-; -]	844	39 (4.6)	Not reached [-; -]	0.60 [0.39; 0.92]	0.020	0.100
Male	3,866	130 (3.4)	Not reached [-; -]	1,903	69 (3.6)	Not reached [-; -]	0.93 [0.69; 1.24]	0.601	
Age Group (Years)									
< 65	2,719	84 (3.1)	Not reached [-; -]	1,376	54 (3.9)	Not reached [-; -]	0.78 [0.55; 1.10]	0.150	0.773
≥ 65	2,780	91 (3.3)	Not reached [-; -]	1,371	54 (3.9)	Not reached [-; -]	0.84 [0.60; 1.17]	0.294	
Region									
WHO Stratum A	1,791	69 (3.9)	Not reached [-; -]	890	37 (4.2)	Not reached [-; -]	0.93 [0.62; 1.38]	0.716	0.387
WHO Rest of the World	3,708	106 (2.9)	Not reached [-; -]	1,857	71 (3.8)	Not reached [-; -]	0.74 [0.55; 1.01]	0.055	
Baseline eGFR (mL/min/1.73 m^2)									
< 60	1,199	58 (4.8)	Not reached [-; -]	608	33 (5.4)	Not reached [-; -]	0.90 [0.59; 1.38]	0.622	0.297
60 to < 90	2,929	71 (2.4)	Not reached [-; -]	1,461	53 (3.6)	Not reached [-; -]	0.66 [0.46; 0.94]	0.023	
≥ 90	1,370	46 (3.4)	Not reached [-; -]	678	22 (3.2)	Not reached [-; -]	1.04 [0.63; 1.73]	0.879	
Insulin at Baseline									
No	2,946	72 (2.4)	Not reached [-; -]	1,402	41 (2.9)	Not reached [-; -]	0.84 [0.57; 1.23]	0.369	0.863
Yes	2,553	103 (4.0)	Not reached [-; -]	1,345	67 (5.0)	Not reached [-; -]	0.80 [0.59; 1.09]	0.161	

a: Number of participants: intention-to-treat population
b: From product-limit (Kaplan-Meier) method for censored data
c: Based on Cox regression model With treatment as a covariate using Wald Confidence Interval
d: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)
e: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)
f: The on-study approach included confirmed events that occurred between the randomization date and the on-study censor date, which is defined as the earliest of participants´ end of study date, death date, or last contact date
g: Renal composite endpoint (creatinine) is defined as renal death, kidney dialysis/transplant, or doubling of serum creatinine from baseline
CI: Confidence Interval; WHO: World Health Organization

Tabelle 4G-15: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den kombinierten renalen Endpunkt (Kreatinin Sensitivität) (Ertugliflozin gepoolt) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS CV	Ertugliflozin Pooled			Placebo			Ertugliflozin Pooled vs. Placebo		
Renal composite endpoint (creatinine, sensitivity)[f,g,h]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	Hazard Ratio [95 %-CI][c]	p-Value[c,d]	p-Value for Interaction Test[e]
Sex									
Female	1,633	11 (0.7)	Not reached [-; -]	844	10 (1.2)	Not reached [-; -]	0.57 [0.24; 1.35]	0.202	0.733
Male	3,866	32 (0.8)	Not reached [-; -]	1,903	23 (1.2)	Not reached [-; -]	0.68 [0.40; 1.16]	0.161	
Age Group (Years)									
< 65	2,719	20 (0.7)	Not reached [-; -]	1,376	21 (1.5)	Not reached [-; -]	0.47 [0.26; 0.87]	0.016	0.131
≥ 65	2,780	23 (0.8)	Not reached [-; -]	1,371	12 (0.9)	Not reached [-; -]	0.96 [0.48; 1.92]	0.903	
Region									
WHO Stratum A	1,791	13 (0.7)	Not reached [-; -]	890	10 (1.1)	Not reached [-; -]	0.65 [0.28; 1.48]	0.302	0.990
WHO Rest of the World	3,708	30 (0.8)	Not reached [-; -]	1,857	23 (1.2)	Not reached [-; -]	0.65 [0.38; 1.12]	0.121	
Baseline eGFR (mL/min/1.73 m^2)									
< 60	1,199	15 (1.3)	Not reached [-; -]	608	10 (1.6)	Not reached [-; -]	0.77 [0.35; 1.71]	0.522	0.445
60 to < 90	2,929	18 (0.6)	Not reached [-; -]	1,461	11 (0.8)	Not reached [-; -]	0.81 [0.38; 1.71]	0.579	
≥ 90	1,370	10 (0.7)	Not reached [-; -]	678	12 (1.8)	Not reached [-; -]	0.41 [0.18; 0.95]	0.039	
Insulin at Baseline									
No	2,946	22 (0.7)	Not reached [-; -]	1,402	11 (0.8)	Not reached [-; -]	0.96 [0.47; 1.99]	0.919	0.157
Yes	2,553	21 (0.8)	Not reached [-; -]	1,345	22 (1.6)	Not reached [-; -]	0.49 [0.27; 0.90]	0.020	

a: Number of participants: intention-to-treat population

b: From product-limit (Kaplan-Meier) method for censored data

c: Based on Cox regression model With treatment as a covariate using Wald Confidence Interval

d: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)

e: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)

f: The on-study approach included confirmed events that occurred between the randomization date and the on-study censor date, which is defined as the earliest of participants´ end of study date, death date, or last contact date

g: Renal composite endpoint (creatinine, sensitivity) is defined as renal death, chronic renal dialysis/transplant, or sustained doubling of serum creatinine from baseline

h: Sustained is defined as the occurrence of a value that meets the cut-off criteria which is followed, more than 30 days later, by a subsequent value that also meets the cut-off criteria

Study: VERTIS CV	Ertugliflozin Pooled			Placebo			Ertugliflozin Pooled vs. Placebo		
Renal composite endpoint (creatinine, sensitivity)[f,g,h]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	Hazard Ratio [95 %-CI][c]	p-Value[c,d]	p-Value for Interaction Test[e]
CI: Confidence Interval; eGFR: Estimated Glomerular Filtration Rate; WHO: World Health Organization									

Tabelle 4G-16: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Tod renaler Ursache (Ertugliflozin gepoolt) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS CV	Ertugliflozin Pooled			Placebo			Ertugliflozin Pooled vs. Placebo		
Renal death[f]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	Hazard Ratio [95 %-CI][c]	p-Value[c,d]	p-Value for Interaction Test[e]
Sex									
Female	1,633	1 (0.1)		844	0 (0.0)		n.c.	n.c.	n.c.
Male	3,866	1 (0.0)		1,903	0 (0.0)		n.c.	n.c.	
Age Group (Years)									
< 65	2,719	1 (0.0)		1,376	0 (0.0)		n.c.	n.c.	n.c.
≥ 65	2,780	1 (0.0)		1,371	0 (0.0)		n.c.	n.c.	
Region									
WHO Stratum A	1,791	1 (0.1)		890	0 (0.0)		n.c.	n.c.	n.c.
WHO Rest of the World	3,708	1 (0.0)		1,857	0 (0.0)		n.c.	n.c.	
Baseline eGFR (mL/min/1.73 m^2)									
< 60	1,199	1 (0.1)		608	0 (0.0)		n.c.	n.c.	n.c.
60 to < 90	2,929	1 (0.0)		1,461	0 (0.0)		n.c.	n.c.	
≥ 90	1,370	0 (0.0)		678	0 (0.0)		n.c.	n.c.	
Insulin at Baseline									
No	2,946	1 (0.0)		1,402	0 (0.0)		n.c.	n.c.	n.c.
Yes	2,553	1 (0.0)		1,345	0 (0.0)		n.c.	n.c.	

a: Number of participants: intention-to-treat population
b: From product-limit (Kaplan-Meier) method for censored data
c: Based on Cox regression model With treatment as a covariate using Wald Confidence Interval
d: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)
e: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)
f: The on-study approach included confirmed events that occurred between the randomization date and the on-study censor date, which is defined as the earliest of participants´ end of study date, death date, or last contact date
CI: Confidence Interval; eGFR: Estimated Glomerular Filtration Rate; 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 ≥ 0,05) für den Endpunkt Nierentrasnplantation/Dialyse (Ertugliflozin gepoolt) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS CV	Ertugliflozin Pooled			Placebo			Ertugliflozin Pooled vs. Placebo		
Kidney dialysis/transplant[f]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	Hazard Ratio [95 %-CI][c]	p-Value[c,d]	p-Value for Interaction Test[e]
Sex									
Female	1,633	3 (0.2)	Not reached [-; -]	844	2 (0.2)	Not reached [-; -]	0.78 [0.13; 4.68]	0.788	0.813
Male	3,866	24 (0.6)	Not reached [-; -]	1,903	12 (0.6)	Not reached [-; -]	0.98 [0.49; 1.96]	0.953	
Age Group (Years)									
< 65	2,719	12 (0.4)	Not reached [-; -]	1,376	9 (0.7)	Not reached [-; -]	0.66 [0.28; 1.56]	0.343	0.214
≥ 65	2,780	15 (0.5)	Not reached [-; -]	1,371	5 (0.4)	Not reached [-; -]	1.51 [0.55; 4.16]	0.423	
Region									
WHO Stratum A	1,791	14 (0.8)	Not reached [-; -]	890	6 (0.7)	Not reached [-; -]	1.16 [0.44; 3.01]	0.764	0.589
WHO Rest of the World	3,708	13 (0.4)	Not reached [-; -]	1,857	8 (0.4)	Not reached [-; -]	0.81 [0.34; 1.96]	0.640	
Baseline eGFR (mL/min/1.73 m^2)									
< 60	1,199	14 (1.2)	Not reached [-; -]	608	8 (1.3)	Not reached [-; -]	0.90 [0.38; 2.14]	0.804	0.963
60 to < 90	2,929	11 (0.4)	Not reached [-; -]	1,461	5 (0.3)	Not reached [-; -]	1.08 [0.37; 3.10]	0.889	
≥ 90	1,370	2 (0.1)	Not reached [-; -]	678	1 (0.1)	Not reached [-; -]	0.99 [0.09; 10.96]	0.996	
Insulin at Baseline									
No	2,946	13 (0.4)	Not reached [-; -]	1,402	4 (0.3)	Not reached [-; -]	1.57 [0.51; 4.83]	0.427	0.256
Yes	2,553	14 (0.5)	Not reached [-; -]	1,345	10 (0.7)	Not reached [-; -]	0.72 [0.32; 1.61]	0.420	

a: Number of participants: intention-to-treat population
b: From product-limit (Kaplan-Meier) method for censored data
c: Based on Cox regression model With treatment as a covariate using Wald Confidence Interval
d: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)
e: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)
f: The on-study approach included confirmed events that occurred between the randomization date and the on-study censor date, which is defined as the earliest of participants´ end of study date, death date, or last contact date
CI: Confidence Interval; eGFR: Estimated Glomerular Filtration Rate; WHO: World Health Organization

Tabelle 4G-18: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Nierentrasnplantation/Dialyse mind. 90 Tage (Ertugliflozin gepoolt) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS CV	Ertugliflozin Pooled			Placebo			Ertugliflozin Pooled vs. Placebo		
Chronic kidney dialysis/transplant[f]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	Hazard Ratio [95 %-CI][c]	p-Value[c,d]	p-Value for Interaction Test[e]
Sex									
Female	1,633	0 (0.0)	Not reached [-; -]	844	1 (0.1)	Not reached [-; -]	n.a. [n.a.; n.a.]	0.164	0.129
Male	3,866	8 (0.2)	Not reached [-; -]	1,903	3 (0.2)	Not reached [-; -]	1.30 [0.34; 4.90]	0.698	
Age Group (Years)									
< 65	2,719	4 (0.1)		1,376	4 (0.3)		n.c.	n.c.	n.c.
≥ 65	2,780	4 (0.1)		1,371	0 (0.0)		n.c.	n.c.	
Region									
WHO Stratum A	1,791	4 (0.2)		890	1 (0.1)		n.c.	n.c.	n.c.
WHO Rest of the World	3,708	4 (0.1)		1,857	3 (0.2)		n.c.	n.c.	
Baseline eGFR (mL/min/1.73 m^2)									
< 60	1,199	4 (0.3)		608	2 (0.3)		n.c.	n.c.	n.c.
60 to < 90	2,929	4 (0.1)		1,461	2 (0.1)		n.c.	n.c.	
≥ 90	1,370	0 (0.0)		678	0 (0.0)		n.c.	n.c.	
Insulin at Baseline									
No	2,946	4 (0.1)		1,402	1 (0.1)		n.c.	n.c.	n.c.
Yes	2,553	4 (0.2)		1,345	3 (0.2)		n.c.	n.c.	

a: Number of participants: intention-to-treat population

b: From product-limit (Kaplan-Meier) method for censored data

c: Based on Cox regression model With treatment as a covariate using Wald Confidence Interval

d: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)

e: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)

f: The on-study approach included confirmed events that occurred between the randomization date and the on-study censor date, which is defined as the earliest of participants´ end of study date, death date, or last contact date

CI: Confidence Interval; eGFR: Estimated Glomerular Filtration Rate; 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-19: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Verdopplung des Serum-Kreatinin-Spiegels (Ertugliflozin gepoolt) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS CV	**Ertugliflozin Pooled**			**Placebo**			**Ertugliflozin Pooled vs. Placebo**		
Doubling of serum creatinine from baseline[f,g]	**N[a]**	**Participants with Event n (%)**	**Median Time[b] in Years [95 %-CI]**	**N[a]**	**Participants with Event n (%)**	**Median Time[b] in Years [95 %-CI]**	**Hazard Ratio [95 %-CI][c]**	**p-Value[c,d]**	**p-Value for Interaction Test[e]**
Sex									
Female	1,633	44 (2.7)	Not reached [-; -]	844	38 (4.5)	Not reached [-; -]	0.60 [0.39; 0.93]	0.022	0.129
Male	3,866	125 (3.2)	Not reached [-; -]	1,903	68 (3.6)	Not reached [-; -]	0.90 [0.67; 1.21]	0.496	
Age Group (Years)									
< 65	2,719	83 (3.1)	Not reached [-; -]	1,376	54 (3.9)	Not reached [-; -]	0.77 [0.55; 1.08]	0.133	0.798
≥ 65	2,780	86 (3.1)	Not reached [-; -]	1,371	52 (3.8)	Not reached [-; -]	0.82 [0.58; 1.16]	0.258	
Region									
WHO Stratum A	1,791	66 (3.7)	Not reached [-; -]	890	35 (3.9)	Not reached [-; -]	0.94 [0.62; 1.42]	0.765	0.315
WHO Rest of the World	3,708	103 (2.8)	Not reached [-; -]	1,857	71 (3.8)	Not reached [-; -]	0.72 [0.53; 0.98]	0.036	
Baseline eGFR (mL/min/1.73 m^2)									
< 60	1,199	55 (4.6)	Not reached [-; -]	608	31 (5.1)	Not reached [-; -]	0.91 [0.58; 1.41]	0.664	0.319
60 to < 90	2,929	70 (2.4)	Not reached [-; -]	1,461	53 (3.6)	Not reached [-; -]	0.65 [0.46; 0.93]	0.019	
≥ 90	1,370	44 (3.2)	Not reached [-; -]	678	22 (3.2)	Not reached [-; -]	1.00 [0.60; 1.66]	0.986	
Insulin at Baseline									
No	2,946	70 (2.4)	Not reached [-; -]	1,402	41 (2.9)	Not reached [-; -]	0.82 [0.55; 1.20]	0.299	0.929
Yes	2,553	99 (3.9)	Not reached [-; -]	1,345	65 (4.8)	Not reached [-; -]	0.80 [0.58; 1.09]	0.154	

a: Number of participants: intention-to-treat population

b: From product-limit (Kaplan-Meier) method for censored data

c: Based on Cox regression model With treatment as a covariate using Wald Confidence Interval

d: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)

e: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)

f: The on-study approach included confirmed events that occurred between the randomization date and the on-study censor date, which is defined as the earliest of participants´ end of study date, death date, or last contact date

g: Sustained is defined as the occurrence of a value that meets the cut-off criteria which is followed, more than 30 days later, by a subsequent value that also meets the cut-off criteria

CI: Confidence Interval; eGFR: Estimated Glomerular Filtration Rate; WHO: World Health Organization

Tabelle 4G-20: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Bestätigte Verdopplung des Serum-Kreatinin-Spiegels (Ertugliflozin gepoolt) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS CV	**Ertugliflozin Pooled**			**Placebo**			**Ertugliflozin Pooled vs. Placebo**		
Sustained doubling of serum creatinine from baseline[f,g]	**N[a]**	**Participants with Event n (%)**	**Median Time[b] in Years [95 %-CI]**	**N[a]**	**Participants with Event n (%)**	**Median Time[b] in Years [95 %-CI]**	**Hazard Ratio [95 %-CI][c]**	**p-Value[c,d]**	**p-Value for Interaction Test[e]**
Sex									
Female	1,633	10 (0.6)	Not reached [-; -]	844	10 (1.2)	Not reached [-; -]	0.52 [0.22; 1.25]	0.144	0.590
Male	3,866	31 (0.8)	Not reached [-; -]	1,903	22 (1.2)	Not reached [-; -]	0.69 [0.40; 1.19]	0.184	
Age Group (Years)									
< 65	2,719	19 (0.7)	Not reached [-; -]	1,376	20 (1.5)	Not reached [-; -]	0.47 [0.25; 0.88]	0.019	0.164
≥ 65	2,780	22 (0.8)	Not reached [-; -]	1,371	12 (0.9)	Not reached [-; -]	0.92 [0.45; 1.85]	0.805	
Region									
WHO Stratum A	1,791	13 (0.7)	Not reached [-; -]	890	10 (1.1)	Not reached [-; -]	0.65 [0.28; 1.48]	0.302	0.971
WHO Rest of the World	3,708	28 (0.8)	Not reached [-; -]	1,857	22 (1.2)	Not reached [-; -]	0.64 [0.36; 1.11]	0.111	
Baseline eGFR (mL/min/1.73 m^2)									
< 60	1,199	14 (1.2)	Not reached [-; -]	608	9 (1.5)	Not reached [-; -]	0.80 [0.35; 1.85]	0.601	0.468
60 to < 90	2,929	17 (0.6)	Not reached [-; -]	1,461	11 (0.8)	Not reached [-; -]	0.76 [0.36; 1.63]	0.485	
≥ 90	1,370	10 (0.7)	Not reached [-; -]	678	12 (1.8)	Not reached [-; -]	0.41 [0.18; 0.95]	0.039	
Insulin at Baseline									
No	2,946	20 (0.7)	Not reached [-; -]	1,402	11 (0.8)	Not reached [-; -]	0.87 [0.42; 1.82]	0.720	0.274
Yes	2,553	21 (0.8)	Not reached [-; -]	1,345	21 (1.6)	Not reached [-; -]	0.52 [0.28; 0.95]	0.032	

a: Number of participants: intention-to-treat population

b: From product-limit (Kaplan-Meier) method for censored data

c: Based on Cox regression model With treatment as a covariate using Wald Confidence Interval

d: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)

e: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)

f: The on-study approach included confirmed events that occurred between the randomization date and the on-study censor date, which is defined as the earliest of participants´ end of study date, death date, or last contact date

g: Sustained is defined as the occurrence of a value that meets the cut-off criteria which is followed, more than 30 days later, by a subsequent value that also meets the cut-off criteria

CI: Confidence Interval; eGFR: Estimated Glomerular Filtration Rate; WHO: World Health Organization

Tabelle 4G-21: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Bestätigte Verdopplung des Serum-Kreatinin-Spiegels und eGFR <=45ml/min/1,73m^2 (Ertugliflozin gepoolt) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS CV	**Ertugliflozin Pooled**			**Placebo**			**Ertugliflozin Pooled vs. Placebo**		
Sustained doubling of serum creatinine from baseline and eGFR ≤ 45 ml/min/1.73m^2 [f,g]	**N[a]**	**Participants with Event n (%)**	**Median Time[b] in Years [95 %-CI]**	**N[a]**	**Participants with Event n (%)**	**Median Time[b] in Years [95 %-CI]**	**Hazard Ratio [95 %-CI][c]**	**p-Value[c,d]**	**p-Value for Interaction Test[e]**
Sex									
Female	1,633	7 (0.4)	Not reached [-; -]	844	7 (0.8)	Not reached [-; -]	0.52 [0.18; 1.49]	0.223	0.864
Male	3,866	19 (0.5)	Not reached [-; -]	1,903	16 (0.8)	Not reached [-; -]	0.58 [0.30; 1.13]	0.110	
Age Group (Years)									
< 65	2,719	14 (0.5)	Not reached [-; -]	1,376	15 (1.1)	Not reached [-; -]	0.46 [0.22; 0.96]	0.038	0.412
≥ 65	2,780	12 (0.4)	Not reached [-; -]	1,371	8 (0.6)	Not reached [-; -]	0.75 [0.31; 1.83]	0.524	
Region									
WHO Stratum A	1,791	6 (0.3)	Not reached [-; -]	890	7 (0.8)	Not reached [-; -]	0.43 [0.14; 1.27]	0.125	0.555
WHO Rest of the World	3,708	20 (0.5)	Not reached [-; -]	1,857	16 (0.9)	Not reached [-; -]	0.62 [0.32; 1.20]	0.160	
Baseline eGFR (mL/min/1.73 m^2)									
< 60	1,199	8 (0.7)	Not reached [-; -]	608	5 (0.8)	Not reached [-; -]	0.82 [0.27; 2.52]	0.734	0.710
60 to < 90	2,929	11 (0.4)	Not reached [-; -]	1,461	10 (0.7)	Not reached [-; -]	0.54 [0.23; 1.28]	0.162	
≥ 90	1,370	7 (0.5)	Not reached [-; -]	678	8 (1.2)	Not reached [-; -]	0.44 [0.16; 1.20]	0.108	
Insulin at Baseline									
No	2,946	15 (0.5)	Not reached [-; -]	1,402	9 (0.6)	Not reached [-; -]	0.80 [0.35; 1.83]	0.602	0.237
Yes	2,553	11 (0.4)	Not reached [-; -]	1,345	14 (1.0)	Not reached [-; -]	0.41 [0.18; 0.89]	0.025	

a: Number of participants: intention-to-treat population

b: From product-limit (Kaplan-Meier) method for censored data

c: Based on Cox regression model With treatment as a covariate using Wald Confidence Interval

d: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)

e: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)

f: The on-study approach included confirmed events that occurred between the randomization date and the on-study censor date, which is defined as the earliest of participants´ end of study date, death date, or last contact date

g: Sustained is defined as the occurrence of a value that meets the cut-off criteria which is followed, more than 30 days later, by a subsequent value that also meets the cut-off criteria

CI: Confidence Interval; eGFR: Estimated Estimated Glomerular Filtration Rate; WHO: World Health Organization

Tabelle 4G-22: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den kombinierten renalen Endpunkt (eGFR) (Ertugliflozin gepoolt) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS CV	Ertugliflozin Pooled			Placebo			Ertugliflozin Pooled vs. Placebo		p-Value for Interaction Test[e]
Renal composite endpoint (eGFR)[f,g,h]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	Hazard Ratio [95 %-CI][c]	p-Value[c,d]	
Sex									
Female	1,633	30 (1.8)	Not reached [-; -]	844	33 (3.9)	Not reached [-; -]	0.47 [0.29; 0.78]	0.003	0.146
Male	3,866	73 (1.9)	Not reached [-; -]	1,903	48 (2.5)	Not reached [-; -]	0.74 [0.52; 1.07]	0.109	
Age Group (Years)									
< 65	2,719	53 (1.9)	Not reached [-; -]	1,376	48 (3.5)	Not reached [-; -]	0.54 [0.37; 0.80]	0.002	0.269
≥ 65	2,780	50 (1.8)	Not reached [-; -]	1,371	33 (2.4)	Not reached [-; -]	0.76 [0.49; 1.17]	0.213	
Region									
WHO Stratum A	1,791	33 (1.8)	Not reached [-; -]	890	23 (2.6)	Not reached [-; -]	0.71 [0.42; 1.21]	0.205	0.623
WHO Rest of the World	3,708	70 (1.9)	Not reached [-; -]	1,857	58 (3.1)	Not reached [-; -]	0.60 [0.43; 0.85]	0.004	
Baseline eGFR (mL/min/1.73 m^2)									
< 60	1,199	33 (2.8)	Not reached [-; -]	608	20 (3.3)	Not reached [-; -]	0.85 [0.49; 1.48]	0.557	0.440
60 to < 90	2,929	44 (1.5)	Not reached [-; -]	1,461	40 (2.7)	Not reached [-; -]	0.54 [0.35; 0.83]	0.005	
≥ 90	1,370	26 (1.9)	Not reached [-; -]	678	21 (3.1)	Not reached [-; -]	0.62 [0.35; 1.09]	0.098	
Insulin at Baseline									
No	2,946	52 (1.8)	Not reached [-; -]	1,402	32 (2.3)	Not reached [-; -]	0.78 [0.50; 1.22]	0.276	0.208
Yes	2,553	51 (2.0)	Not reached [-; -]	1,345	49 (3.6)	Not reached [-; -]	0.53 [0.36; 0.79]	0.002	

a: Number of participants: intention-to-treat population

b: From product-limit (Kaplan-Meier) method for censored data

c: Based on Cox regression model With treatment as a covariate using Wald Confidence Interval

d: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)

e: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)

f: The on-study approach included confirmed events that occurred between the randomization date and the on-study censor date, which is defined as the earliest of participants´ end of study date, death date, or last contact date

g: Renal composite endpoint (eGFR) is defined as sustained 40% reduction in eGFR, chronic kidney dialysis/transplant or renal death

h: Sustained is defined as the occurrence of a value that meets the cut-off criteria which is followed, more than 30 days later, by a subsequent value that also meets the cut-off criteria

CI: Confidence Interval; eGFR: Estimated Estimated Glomerular Filtration Rate; WHO: World Health Organization

Tabelle 4G-23: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Anhaltende Reduktion der eGFR um 40% (Ertugliflozin gepoolt) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS CV	Ertugliflozin Pooled			Placebo			Ertugliflozin Pooled vs. Placebo		
Sustained 40% reduction in eGFR[f,g]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	Hazard Ratio [95 %-CI][c]	p-Value[c,d]	p-Value for Interaction Test[e]
Sex									
Female	1,633	29 (1.8)	Not reached [-; -]	844	33 (3.9)	Not reached [-; -]	0.46 [0.28; 0.75]	0.002	0.116
Male	3,866	72 (1.9)	Not reached [-; -]	1,903	47 (2.5)	Not reached [-; -]	0.75 [0.52; 1.08]	0.121	
Age Group (Years)									
< 65	2,719	51 (1.9)	Not reached [-; -]	1,376	47 (3.4)	Not reached [-; -]	0.53 [0.36; 0.79]	0.002	0.249
≥ 65	2,780	50 (1.8)	Not reached [-; -]	1,371	33 (2.4)	Not reached [-; -]	0.76 [0.49; 1.17]	0.213	
Region									
WHO Stratum A	1,791	32 (1.8)	Not reached [-; -]	890	23 (2.6)	Not reached [-; -]	0.69 [0.40; 1.17]	0.170	0.701
WHO Rest of the World	3,708	69 (1.9)	Not reached [-; -]	1,857	57 (3.1)	Not reached [-; -]	0.60 [0.43; 0.86]	0.005	
Baseline eGFR (mL/min/1.73 m^2)									
< 60	1,199	33 (2.8)	Not reached [-; -]	608	19 (3.1)	Not reached [-; -]	0.89 [0.51; 1.57]	0.692	0.307
60 to < 90	2,929	42 (1.4)	Not reached [-; -]	1,461	40 (2.7)	Not reached [-; -]	0.51 [0.33; 0.79]	0.003	
≥ 90	1,370	26 (1.9)	Not reached [-; -]	678	21 (3.1)	Not reached [-; -]	0.62 [0.35; 1.09]	0.098	
Insulin at Baseline									
No	2,946	51 (1.7)	Not reached [-; -]	1,402	32 (2.3)	Not reached [-; -]	0.77 [0.49; 1.19]	0.240	0.237
Yes	2,553	50 (2.0)	Not reached [-; -]	1,345	48 (3.6)	Not reached [-; -]	0.54 [0.36; 0.80]	0.002	

a: Number of participants: intention-to-treat population
b: From product-limit (Kaplan-Meier) method for censored data
c: Based on Cox regression model With treatment as a covariate using Wald Confidence Interval
d: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)
e: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)
f: The on-study approach included confirmed events that occurred between the randomization date and the on-study censor date, which is defined as the earliest of participants´ end of study date, death date, or last contact date
g: Sustained is defined as the occurrence of a value that meets the cut-off criteria which is followed, more than 30 days later, by a subsequent value that also meets the cut-off criteria

Study: VERTIS CV	Ertugliflozin Pooled			Placebo			Ertugliflozin Pooled vs. Placebo		
Sustained 40% reduction in eGFR[f,g]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	Hazard Ratio [95 %-CI][c]	p-Value[c,d]	p-Value for Interaction Test[e]
CI: Confidence Interval; eGFR: Estimated Glomerular Filtration Rate; WHO: World Health Organization									

Tabelle 4G-24: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Anhaltende Reduktion der eGFR um 40% auf <60 ml/min/1,73 m² (Ertugliflozin gepoolt) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS CV	Ertugliflozin Pooled			Placebo			Ertugliflozin Pooled vs. Placebo		
Sustained 40% reduction in eGFR to <60ml/min/1.73m² [f,g]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	Hazard Ratio [95 %-CI][c]	p-Value[c,d]	p-Value for Interaction Test[e]
Sex									
Female	1,633	25 (1.5)	Not reached [-; -]	844	31 (3.7)	Not reached [-; -]	0.42 [0.25; 0.71]	0.001	0.090
Male	3,866	66 (1.7)	Not reached [-; -]	1,903	44 (2.3)	Not reached [-; -]	0.73 [0.50; 1.07]	0.109	
Age Group (Years)									
< 65	2,719	44 (1.6)	Not reached [-; -]	1,376	44 (3.2)	Not reached [-; -]	0.49 [0.32; 0.75]	< 0.001	0.170
≥ 65	2,780	47 (1.7)	Not reached [-; -]	1,371	31 (2.3)	Not reached [-; -]	0.76 [0.48; 1.19]	0.233	
Region									
WHO Stratum A	1,791	30 (1.7)	Not reached [-; -]	890	22 (2.5)	Not reached [-; -]	0.67 [0.39; 1.17]	0.160	0.646
WHO Rest of the World	3,708	61 (1.6)	Not reached [-; -]	1,857	53 (2.9)	Not reached [-; -]	0.58 [0.40; 0.83]	0.003	
Baseline eGFR (mL/min/1.73 m²)									
< 60	1,199	33 (2.8)	Not reached [-; -]	608	19 (3.1)	Not reached [-; -]	0.89 [0.51; 1.57]	0.692	0.256
60 to < 90	2,929	42 (1.4)	Not reached [-; -]	1,461	40 (2.7)	Not reached [-; -]	0.51 [0.33; 0.79]	0.003	
≥ 90	1,370	16 (1.2)	Not reached [-; -]	678	16 (2.4)	Not reached [-; -]	0.50 [0.25; 0.99]	0.048	
Insulin at Baseline									
No	2,946	45 (1.5)	Not reached [-; -]	1,402	29 (2.1)	Not reached [-; -]	0.75 [0.47; 1.19]	0.223	0.241
Yes	2,553	46 (1.8)	Not reached [-; -]	1,345	46 (3.4)	Not reached [-; -]	0.51 [0.34; 0.77]	0.001	
a: Number of participants: intention-to-treat population b: From product-limit (Kaplan-Meier) method for censored data									

Study: VERTIS CV	Ertugliflozin Pooled			Placebo			Ertugliflozin Pooled vs. Placebo		
Sustained 40% reduction in eGFR to <60ml/min/1.73m^{2} [f,g]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	Hazard Ratio [95 %-CI][c]	p-Value[c,d]	p-Value for Interaction Test[e]
c: Based on Cox regression model With treatment as a covariate using Wald Confidence Interval									
d: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)									
e: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)									
f: The on-study approach included confirmed events that occurred between the randomization date and the on-study censor date, which is defined as the earliest of participants´ end of study date, death date, or last contact date									
g: Sustained is defined as the occurrence of a value that meets the cut-off criteria which is followed, more than 30 days later, by a subsequent value that also meets the cut-off criteria									
CI: Confidence Interval; eGFR: Estimated Estimated Glomerular Filtration Rate; WHO: World Health Organization									

Tabelle 4G-25: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Veränderung des HbA1c-Wertes (Ertugliflozin gepoolt) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS CV Hemoglobin A1C (%)	N[a]	N[b]	Mean at Baseline of Study (SD)	Mean at Week 52 (SD)	Mean Change from Baseline to Week 52 (SE)[c]	Ertugliflozin Pooled vs. Placebo			p-Value for Interaction Test[e]
						Mean Difference[c] [95 %-CI]	p-Value[c]	Standardized Mean Difference[d] [95 %-CI]	
Sex									
Female									
Ertugliflozin Pooled	1,633	1,630	8.30 (0.963)	7.64 (0.995)	-0.64 (0.026)	-0.52	< 0.0001	-0.48	0.1009
Placebo	844	844	8.26 (0.952)	8.14 (1.224)	-0.11 (0.036)	[-0.61; -0.44]		[-0.56; -0.41]	
Male									
Ertugliflozin Pooled	3,866	3,863	8.22 (0.960)	7.51 (1.007)	-0.70 (0.017)	-0.48	< 0.0001	-0.44	
Placebo	1,903	1,901	8.19 (0.941)	7.97 (1.190)	-0.22 (0.024)	[-0.53; -0.42]		[-0.49; -0.39]	
Insulin at Baseline									
Yes									
Ertugliflozin Pooled	2,553	2,550	8.39 (0.936)	7.73 (1.009)	-0.65 (0.021)	-0.53	< 0.0001	-0.49	0.0690
Placebo	1,345	1,345	8.37 (0.935)	8.24 (1.215)	-0.11 (0.028)	[-0.60; -0.47]		[-0.55; -0.43]	
No									
Ertugliflozin Pooled	2,946	2,943	8.12 (0.966)	7.39 (0.976)	-0.70 (0.020)	-0.44	< 0.0001	-0.42	
Placebo	1,402	1,400	8.06 (0.930)	7.81 (1.155)	-0.26 (0.027)	[-0.50; -0.38]		[-0.48; -0.36]	

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

b: Number of patients with data available for the analysis

c: Based on constrained longitudinal data analysis model that include fixed effects for treatment, time, baseline eGFR (continuous) and the interaction of time by treatment, where time was treated as categorical variable

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

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

CI: Confidence Interval; eGFR: Estimated Glomerular Filtration Rate; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

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

Study: VERTIS CV Weight (kg)	N[a]	N[b]	Mean at Baseline of Study (SD)	Mean at Week 52 (SD)	Mean Change from Baseline to Week 52 (SE)[c]	Ertugliflozin Pooled vs. Placebo			p-Value for Interaction Test[e]
						Mean Difference[c] [95 %-CI]	p-Value[c]	Standardized Mean Difference[d] [95 %-CI]	
Age Group (Years)									
< 65									
Ertugliflozin Pooled	2,719	2,717	94.73 (19.299)	91.97 (18.664)	-2.58 (0.081)	-2.32	< 0.0001	-0.12	0.1943
Placebo	1,376	1,375	94.64 (19.316)	93.70 (19.011)	-0.26 (0.114)	[-2.59; -2.04]		[-0.14; -0.11]	
≥ 65									
Ertugliflozin Pooled	2,780	2,775	88.81 (17.228)	86.02 (16.731)	-2.72 (0.074)	-2.20	< 0.0001	-0.13	
Placebo	1,371	1,370	89.12 (16.729)	88.42 (16.825)	-0.52 (0.104)	[-2.45; -1.95]		[-0.15; -0.12]	
Insulin at Baseline									
Yes									
Ertugliflozin Pooled	2,553	2,549	93.34 (18.903)	90.69 (18.616)	-2.66 (0.085)	-2.73	< 0.0001	-0.15	0.8103
Placebo	1,345	1,345	94.17 (18.355)	93.55 (18.280)	0.07 (0.116)	[-3.01; -2.45]		[-0.16; -0.13]	
No									
Ertugliflozin Pooled	2,946	2,943	90.34 (18.066)	87.71 (17.344)	-2.64 (0.071)	-1.82	< 0.0001	-0.10	
Placebo	1,402	1,400	89.69 (17.936)	88.84 (17.768)	-0.83 (0.103)	[-2.06; -1.57]		[-0.12; -0.09]	

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

b: Number of patients with data available for the analysis

c: Based on constrained longitudinal data analysis model that include fixed effects for treatment, time, baseline eGFR (continuous) and the interaction of time by treatment, where time was treated as categorical variable

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

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

CI: Confidence Interval; eGFR: Estimated Glomerular Filtration Rate; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

Tabelle 4G-27: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Veränderung des systolischen Blutdrucks (Ertugliflozin gepoolt) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS CV **Sitting Systolic Blood Pressure (mmHg)**	**N[a]**	**N[b]**	**Mean at Baseline of Study (SD)**	**Mean at Week 52 (SD)**	**Mean Change from Baseline to Week 52 (SE)[c]**	**Ertugliflozin Pooled vs. Placebo**			**p-Value for Interaction Test[e]**
						Mean Difference[c] [95 %-CI]	**p-Value[c]**	**Standardized Mean Difference[d] [95 %-CI]**	
Insulin at Baseline									
Yes									
Ertugliflozin Pooled	2,553	2,550	134.13 (14.265)	131.79 (14.596)	-2.10 (0.298)	-2.93	< 0.0001	-0.20	0.8427
Placebo	1,345	1,345	133.53 (14.516)	134.29 (14.801)	0.83 (0.397)	[-3.85; -2.01]		[-0.26; -0.14]	
No									
Ertugliflozin Pooled	2,946	2,943	132.91 (13.218)	130.67 (13.539)	-2.13 (0.251)	-2.78	< 0.0001	-0.20	
Placebo	1,402	1,400	132.69 (13.367)	133.25 (13.572)	0.65 (0.351)	[-3.58; -1.98]		[-0.26; -0.14]	

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

b: Number of patients with data available for the analysis

c: Based on constrained longitudinal data analysis model that include fixed effects for treatment, time, baseline eGFR (continuous) and the interaction of time by treatment, where time was treated as categorical variable

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

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

CI: Confidence Interval; eGFR: Estimated Glomerular Filtration Rate; SD: Standard Deviation; SE: Standard Error; WHO: World Health Organization

Tabelle 4G-28: Subgruppenanalysen mit nicht signifikantem Interaktionstest ($p \geq 0,05$) für den Endpunkt Zeit bis zum Beginn einer Insulintherapie (Ertugliflozin gepoolt) aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS CV	Ertugliflozin Pooled			Placebo			Ertugliflozin Pooled vs. Placebo		
Time to initiation of insulin[f]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	N[a]	Participants with Event n (%)	Median Time[b] in Years [95 %-CI]	Hazard Ratio [95 %-CI][c]	p-Value[c,d]	p-Value for Interaction Test[e]
Sex									
Female	843	98 (11.6)	Not reached [-; -]	398	61 (15.3)	Not reached [-; -]	0.74 [0.54; 1.03]	0.071	0.460
Male	2,104	260 (12.4)	Not reached [-; -]	1,004	184 (18.3)	Not reached [-; -]	0.65 [0.54; 0.78]	< 0.001	
Region									
WHO Stratum A	852	157 (18.4)	Not reached [-; -]	401	89 (22.2)	Not reached [-; -]	0.80 [0.61; 1.03]	0.087	0.090
WHO Rest of the World	2,095	201 (9.6)	Not reached [-; -]	1,001	156 (15.6)	Not reached [-; -]	0.60 [0.48; 0.73]	< 0.001	
Baseline eGFR (mL/min/1.73 m^2)									
< 60	508	95 (18.7)	Not reached [-; -]	241	57 (23.7)	Not reached [-; -]	0.78 [0.56; 1.09]	0.145	0.460
60 to < 90	1,595	171 (10.7)	Not reached [-; -]	770	128 (16.6)	Not reached [-; -]	0.61 [0.49; 0.77]	< 0.001	
≥ 90	843	92 (10.9)	Not reached [-; -]	391	60 (15.3)	Not reached [-; -]	0.70 [0.51; 0.97]	0.033	
Insulin at Baseline									
No	2,942	356 (12.1)		1,401	244 (17.4)		n.c.	n.c.	n.c.
Yes	5	2 (40.0)		1	1 (100.0)		n.c.	n.c.	

a: Number of participants: intention-to-treat population

b: From product-limit (Kaplan-Meier) method for censored data

c: Based on Cox regression model With treatment as a covariate using Wald Confidence Interval

d: Two-sided p-Value using Wald test (Score test in case of zero event in one treatment group)

e: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-Value of likelihood ratio test for interaction term)

f: The on-study approach included confirmed events that occurred between the randomization date and the on-study censor date, which is defined as the earliest of participants´ end of study date, death date, or last contact date

CI: Confidence Interval; eGFR: Estimated Glomerular Filtration Rate; 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-G4.3: Unerwünschte Ereignisse

Unerwünschte Ereignisse

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

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
Sex							
Female	1,630	1,391 (85.3)	844	713 (84.5)	1.01 [0.98; 1.05]	0.570	0.335
Male	3,863	3,291 (85.2)	1,901	1,636 (86.1)	0.99 [0.97; 1.01]	0.380	
Age Group (Years)							
< 65	2,718	2,251 (82.8)	1,375	1,159 (84.3)	0.98 [0.95; 1.01]	0.233	0.192
≥ 65	2,775	2,431 (87.6)	1,370	1,190 (86.9)	1.01 [0.98; 1.03]	0.499	
Region							
WHO Stratum A	1,789	1,617 (90.4)	890	803 (90.2)	1.00 [0.98; 1.03]	0.894	0.701
WHO Rest of the World	3,704	3,065 (82.7)	1,855	1,546 (83.3)	0.99 [0.97; 1.02]	0.579	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	1,080 (90.2)	607	545 (89.8)	1.00 [0.97; 1.04]	0.807	0.447
60 to < 90	2,926	2,480 (84.8)	1,460	1,233 (84.5)	1.00 [0.98; 1.03]	0.792	
≥ 90	1,369	1,122 (82.0)	678	571 (84.2)	0.97 [0.93; 1.01]	0.203	

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

b: 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.'.

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

d: 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; eGFR: Estimated Glomerular Filtration Rate; 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 Schwerwiegende unerwünschte Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Serious Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
Sex							
Female	1,630	478 (29.3)	844	268 (31.8)	0.92 [0.82; 1.05]	0.212	0.587
Male	3,863	1,417 (36.7)	1,901	722 (38.0)	0.97 [0.90; 1.04]	0.337	

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Serious Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
Age Group (Years)							
< 65	2,718	815 (30.0)	1,375	461 (33.5)	0.89 [0.81; 0.98]	0.021	0.072
≥ 65	2,775	1,080 (38.9)	1,370	529 (38.6)	1.01 [0.93; 1.09]	0.849	
Region							
WHO Stratum A	1,789	725 (40.5)	890	383 (43.0)	0.94 [0.86; 1.03]	0.214	0.620
WHO Rest of the World	3,704	1,170 (31.6)	1,855	607 (32.7)	0.97 [0.89; 1.05]	0.392	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	486 (40.6)	607	256 (42.2)	0.96 [0.86; 1.08]	0.512	0.400
60 to < 90	2,926	1,014 (34.7)	1,460	512 (35.1)	0.99 [0.91; 1.08]	0.786	
≥ 90	1,369	395 (28.9)	678	222 (32.7)	0.88 [0.77; 1.01]	0.071	
Insulin at Baseline							
No	2,943	889 (30.2)	1,400	432 (30.9)	0.98 [0.89; 1.08]	0.664	0.584
Yes	2,550	1,006 (39.5)	1,345	558 (41.5)	0.95 [0.88; 1.03]	0.218	

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

b: 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.'.

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

d: 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; eGFR: Estimated Glomerular Filtration Rate; 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 ≥ 0,05) für den Endpunkt Nicht-schwere unerwünschte Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Non-Severe Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
Sex							
Female	1,630	1,350 (82.8)	844	704 (83.4)	0.99 [0.96; 1.03]	0.711	0.903
Male	3,863	3,153 (81.6)	1,901	1,568 (82.5)	0.99 [0.96; 1.02]	0.424	
Age Group (Years)							
< 65	2,718	2,161 (79.5)	1,375	1,125 (81.8)	0.97 [0.94; 1.00]	0.079	0.108
≥ 65	2,775	2,342 (84.4)	1,370	1,147 (83.7)	1.01 [0.98; 1.04]	0.576	
Region							
WHO Stratum A	1,789	1,570 (87.8)	890	778 (87.4)	1.00 [0.97; 1.03]	0.800	0.419

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Non-Severe Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
WHO Rest of the World	3,704	2,933 (79.2)	1,855	1,494 (80.5)	0.98 [0.96; 1.01]	0.237	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	1,044 (87.1)	607	532 (87.6)	0.99 [0.96; 1.03]	0.764	0.070
60 to < 90	2,926	2,391 (81.7)	1,460	1,181 (80.9)	1.01 [0.98; 1.04]	0.508	
≥ 90	1,369	1,068 (78.0)	678	559 (82.4)	0.95 [0.90; 0.99]	0.019	
Insulin at Baseline							
No	2,943	2,303 (78.3)	1,400	1,126 (80.4)	0.97 [0.94; 1.00]	0.100	0.079
Yes	2,550	2,200 (86.3)	1,345	1,146 (85.2)	1.01 [0.99; 1.04]	0.362	

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

b: 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.'.

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

d: 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; eGFR: Estimated Glomerular Filtration Rate; 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 Schwere unerwünschte Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Severe Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
Sex							
Female	1,630	439 (26.9)	844	240 (28.4)	0.95 [0.83; 1.08]	0.427	0.677
Male	3,863	1,272 (32.9)	1,901	638 (33.6)	0.98 [0.91; 1.06]	0.631	
Age Group (Years)							
< 65	2,718	758 (27.9)	1,375	407 (29.6)	0.94 [0.85; 1.04]	0.252	0.416
≥ 65	2,775	953 (34.3)	1,370	471 (34.4)	1.00 [0.91; 1.09]	0.981	
Region							
WHO Stratum A	1,789	663 (37.1)	890	354 (39.8)	0.93 [0.84; 1.03]	0.173	0.266
WHO Rest of the World	3,704	1,048 (28.3)	1,855	524 (28.2)	1.00 [0.92; 1.09]	0.972	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	448 (37.4)	607	235 (38.7)	0.97 [0.85; 1.09]	0.585	0.690
60 to < 90	2,926	898 (30.7)	1,460	448 (30.7)	1.00 [0.91; 1.10]	0.997	
≥ 90	1,369	365 (26.7)	678	195 (28.8)	0.93 [0.80; 1.07]	0.316	
Insulin at Baseline							
No	2,943	805 (27.4)	1,400	379 (27.1)	1.01 [0.91; 1.12]	0.846	0.417

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Severe Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
Yes	2,550	906 (35.5)	1,345	499 (37.1)	0.96 [0.88; 1.04]	0.332	

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

b: 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.'.

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

d: 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; eGFR: Estimated Glomerular Filtration Rate; 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-33: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Therapieabbruch wegen unerwünschter Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
AE Leading to Treatment Discontinuation	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
Sex							
Female	1,630	114 (7.0)	844	46 (5.5)	1.28 [0.92; 1.79]	0.139	0.240
Male	3,863	294 (7.6)	1,901	142 (7.5)	1.02 [0.84; 1.24]	0.849	
Age Group (Years)							
< 65	2,718	146 (5.4)	1,375	76 (5.5)	0.97 [0.74; 1.27]	0.835	0.315
≥ 65	2,775	262 (9.4)	1,370	112 (8.2)	1.15 [0.93; 1.43]	0.181	
Region							
WHO Stratum A	1,789	209 (11.7)	890	102 (11.5)	1.02 [0.82; 1.27]	0.866	0.469
WHO Rest of the World	3,704	199 (5.4)	1,855	86 (4.6)	1.16 [0.91; 1.48]	0.240	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	124 (10.4)	607	52 (8.6)	1.21 [0.89; 1.65]	0.228	0.455
60 to < 90	2,926	218 (7.5)	1,460	99 (6.8)	1.10 [0.87; 1.38]	0.420	
≥ 90	1,369	66 (4.8)	678	37 (5.5)	0.88 [0.60; 1.31]	0.536	
Insulin at Baseline							
No	2,943	187 (6.4)	1,400	92 (6.6)	0.97 [0.76; 1.23]	0.785	0.178
Yes	2,550	221 (8.7)	1,345	96 (7.1)	1.21 [0.96; 1.53]	0.097	

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

b: 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.'.

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

d: 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

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
AE Leading to Treatment Discontinuation	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
participant with event, p-value of interaction test is reported as 'n.a.'							
AE: Adverse Events; CI: Confidence Interval; eGFR: Estimated Glomerular Filtration Rate; 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-34: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschter Ereignisse ohne krankheitsbezogene Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
AE Without Disease Related Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
Sex							
Female	1,630	1,371 (84.1)	844	704 (83.4)	1.01 [0.97; 1.05]	0.655	0.419
Male	3,863	3,224 (83.5)	1,901	1,602 (84.3)	0.99 [0.97; 1.01]	0.432	
Age Group (Years)							
< 65	2,718	2,212 (81.4)	1,375	1,139 (82.8)	0.98 [0.95; 1.01]	0.254	0.225
≥ 65	2,775	2,383 (85.9)	1,370	1,167 (85.2)	1.01 [0.98; 1.04]	0.550	
Region							
WHO Stratum A	1,789	1,596 (89.2)	890	793 (89.1)	1.00 [0.97; 1.03]	0.931	0.737
WHO Rest of the World	3,704	2,999 (81.0)	1,855	1,513 (81.6)	0.99 [0.97; 1.02]	0.592	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	1,064 (88.8)	607	537 (88.5)	1.00 [0.97; 1.04]	0.826	0.271
60 to < 90	2,926	2,438 (83.3)	1,460	1,208 (82.7)	1.01 [0.98; 1.04]	0.628	
≥ 90	1,369	1,093 (79.8)	678	561 (82.7)	0.96 [0.92; 1.01]	0.116	
a: Number of participants: all-participants-as-treated population							
b: 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.'.							
c: Based on Cochran-Mantel-Haenszel test with no stratification factor. In case zero participant with event in both treatment groups, report 'n.a.'							
d: 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.'							
AE: Adverse Events; CI: Confidence Interval; eGFR: Estimated Glomerular Filtration Rate; 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-35: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwerwiegende unerwünschter Ereignisse ohne krankheitsbezogene Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Serious AE Without Disease Related Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
Sex							
Female	1,630	396 (24.3)	844	219 (25.9)	0.94 [0.81; 1.08]	0.367	0.571
Male	3,863	1,158 (30.0)	1,901	579 (30.5)	0.98 [0.91; 1.07]	0.708	
Age Group (Years)							
< 65	2,718	662 (24.4)	1,375	363 (26.4)	0.92 [0.83; 1.03]	0.154	0.224
≥ 65	2,775	892 (32.1)	1,370	435 (31.8)	1.01 [0.92; 1.11]	0.799	
Region							
WHO Stratum A	1,789	643 (35.9)	890	328 (36.9)	0.98 [0.88; 1.08]	0.644	0.998
WHO Rest of the World	3,704	911 (24.6)	1,855	470 (25.3)	0.97 [0.88; 1.07]	0.546	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	410 (34.2)	607	209 (34.4)	0.99 [0.87; 1.14]	0.930	0.636
60 to < 90	2,926	827 (28.3)	1,460	416 (28.5)	0.99 [0.90; 1.10]	0.874	
≥ 90	1,369	317 (23.2)	678	173 (25.5)	0.91 [0.77; 1.07]	0.239	
Insulin at Baseline							
No	2,943	705 (24.0)	1,400	346 (24.7)	0.97 [0.87; 1.08]	0.585	0.793
Yes	2,550	849 (33.3)	1,345	452 (33.6)	0.99 [0.90; 1.09]	0.844	

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

b: 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.'.

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

d: 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.'

AE: Adverse Events; CI: Confidence Interval; eGFR: Estimated Glomerular Filtration Rate; 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-36: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Schwere unerwünschter Ereignisse ohne krankheitsbezogene Ereignisse aus RCT mit dem zu bewertenden Arzneimittel

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Severe AE Without Disease Related Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
Sex							
Female	1,630	356 (21.8)	844	196 (23.2)	0.94 [0.81; 1.10]	0.434	0.560
Male	3,863	1,029 (26.6)	1,901	510 (26.8)	0.99 [0.91; 1.09]	0.878	
Age Group (Years)							

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Severe AE Without Disease Related Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
< 65	2,718	614 (22.6)	1,375	317 (23.1)	0.98 [0.87; 1.10]	0.738	0.971
≥ 65	2,775	771 (27.8)	1,370	389 (28.4)	0.98 [0.88; 1.08]	0.681	
Region							
WHO Stratum A	1,789	585 (32.7)	890	313 (35.2)	0.93 [0.83; 1.04]	0.202	0.224
WHO Rest of the World	3,704	800 (21.6)	1,855	393 (21.2)	1.02 [0.92; 1.13]	0.724	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	376 (31.4)	607	192 (31.6)	0.99 [0.86; 1.15]	0.916	0.894
60 to < 90	2,926	721 (24.6)	1,460	363 (24.9)	0.99 [0.89; 1.11]	0.872	
≥ 90	1,369	288 (21.0)	678	151 (22.3)	0.94 [0.79; 1.12]	0.522	
Insulin at Baseline							
No	2,943	629 (21.4)	1,400	305 (21.8)	0.98 [0.87; 1.11]	0.757	0.879
Yes	2,550	756 (29.6)	1,345	401 (29.8)	0.99 [0.90; 1.10]	0.914	

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

b: 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.'.

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

d: 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.'

AE: Adverse Events; CI: Confidence Interval; eGFR: Estimated Glomerular Filtration Rate; 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-37: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Unerwünschte Ereignisse gesamt (SOC)

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
SOC: Cardiac disorders							
Sex							
Female	1,630	315 (19.3)	844	182 (21.6)	0.90 [0.76; 1.05]	0.188	0.892
Male	3,863	928 (24.0)	1,901	500 (26.3)	0.91 [0.83; 1.00]	0.060	
Age Group (Years)							
< 65	2,718	564 (20.8)	1,375	307 (22.3)	0.93 [0.82; 1.05]	0.244	0.597
≥ 65	2,775	679 (24.5)	1,370	375 (27.4)	0.89 [0.80; 1.00]	0.043	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	300 (25.0)	607	184 (30.3)	0.83 [0.71; 0.96]	0.017	0.157
60 to < 90	2,926	684 (23.4)	1,460	348 (23.8)	0.98 [0.88; 1.10]	0.736	
≥ 90	1,369	259 (18.9)	678	150 (22.1)	0.86 [0.72; 1.02]	0.088	

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Adverse Events	**N[a]**	**Participants with Event n (%)**	**N[a]**	**Participants with Event n (%)**	**Relative Risk [95 %-CI][b]**	**Treatment Effect p-Value[c]**	**Interaction Test p-Value[d]**
Insulin at Baseline							
No	2,943	591 (20.1)	1,400	302 (21.6)	0.93 [0.82; 1.05]	0.256	0.674
Yes	2,550	652 (25.6)	1,345	380 (28.3)	0.90 [0.81; 1.01]	0.071	
SOC: Congenital, familial and genetic disorders							
Sex							
Female	1,630	12 (0.7)	844	4 (0.5)	1.55 [0.50; 4.80]	0.440	0.670
Male	3,863	50 (1.3)	1,901	12 (0.6)	2.05 [1.09; 3.84]	0.022	
Region							
WHO Stratum A	1,789	18 (1.0)	890	5 (0.6)	1.79 [0.67; 4.81]	0.240	0.852
WHO Rest of the World	3,704	44 (1.2)	1,855	11 (0.6)	2.00 [1.04; 3.87]	0.035	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	11 (0.9)	607	6 (1.0)	0.93 [0.35; 2.50]	0.884	0.203
60 to < 90	2,926	30 (1.0)	1,460	7 (0.5)	2.14 [0.94; 4.86]	0.063	
≥ 90	1,369	21 (1.5)	678	3 (0.4)	3.47 [1.04; 11.58]	0.031	
Insulin at Baseline							
No	2,943	27 (0.9)	1,400	7 (0.5)	1.83 [0.80; 4.20]	0.145	0.840
Yes	2,550	35 (1.4)	1,345	9 (0.7)	2.05 [0.99; 4.25]	0.048	
SOC: Infections and infestations							
Sex							
Female	1,630	789 (48.4)	844	369 (43.7)	1.11 [1.01; 1.21]	0.027	0.204
Male	3,863	1,609 (41.7)	1,901	765 (40.2)	1.04 [0.97; 1.11]	0.307	
Age Group (Years)							
< 65	2,718	1,107 (40.7)	1,375	536 (39.0)	1.04 [0.96; 1.13]	0.282	0.649
≥ 65	2,775	1,291 (46.5)	1,370	598 (43.6)	1.07 [0.99; 1.15]	0.081	
Region							
WHO Stratum A	1,789	974 (54.4)	890	478 (53.7)	1.01 [0.94; 1.09]	0.719	0.311
WHO Rest of the World	3,704	1,424 (38.4)	1,855	656 (35.4)	1.09 [1.01; 1.17]	0.025	
Insulin at Baseline							
No	2,943	1,189 (40.4)	1,400	541 (38.6)	1.05 [0.97; 1.13]	0.269	0.525
Yes	2,550	1,209 (47.4)	1,345	593 (44.1)	1.08 [1.00; 1.16]	0.048	
SOC: Metabolism and nutrition disorders							
Sex							
Female	1,630	737 (45.2)	844	402 (47.6)	0.95 [0.87; 1.04]	0.253	0.916
Male	3,863	1,667 (43.2)	1,901	871 (45.8)	0.94 [0.89; 1.00]	0.055	
Age Group (Years)							
< 65	2,718	1,134 (41.7)	1,375	631 (45.9)	0.91 [0.85; 0.98]	0.011	0.182
≥ 65	2,775	1,270 (45.8)	1,370	642 (46.9)	0.98 [0.91; 1.05]	0.506	
Region							
WHO Stratum A	1,789	915 (51.1)	890	460 (51.7)	0.99 [0.92; 1.07]	0.792	0.204
WHO Rest of the World	3,704	1,489 (40.2)	1,855	813 (43.8)	0.92 [0.86; 0.98]	0.010	
Baseline eGFR (mL/min/1.73 m^2)							

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
< 60	1,198	633 (52.8)	607	324 (53.4)	0.99 [0.90; 1.08]	0.828	0.078
60 to < 90	2,926	1,271 (43.4)	1,460	654 (44.8)	0.97 [0.90; 1.04]	0.394	
≥ 90	1,369	500 (36.5)	678	295 (43.5)	0.84 [0.75; 0.94]	0.002	
Insulin at Baseline							
No	2,943	969 (32.9)	1,400	512 (36.6)	0.90 [0.83; 0.98]	0.018	0.122
Yes	2,550	1,435 (56.3)	1,345	761 (56.6)	0.99 [0.94; 1.05]	0.855	
SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps)							
Sex							
Female	1,630	84 (5.2)	844	35 (4.1)	1.24 [0.85; 1.83]	0.267	0.854
Male	3,863	280 (7.2)	1,901	116 (6.1)	1.19 [0.96; 1.46]	0.106	
Age Group (Years)							
< 65	2,718	129 (4.7)	1,375	59 (4.3)	1.11 [0.82; 1.49]	0.511	0.479
≥ 65	2,775	235 (8.5)	1,370	92 (6.7)	1.26 [1.00; 1.59]	0.049	
Region							
WHO Stratum A	1,789	169 (9.4)	890	74 (8.3)	1.14 [0.88; 1.48]	0.337	0.586
WHO Rest of the World	3,704	195 (5.3)	1,855	77 (4.2)	1.27 [0.98; 1.64]	0.070	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	83 (6.9)	607	38 (6.3)	1.11 [0.76; 1.60]	0.592	0.480
60 to < 90	2,926	193 (6.6)	1,460	84 (5.8)	1.15 [0.89; 1.47]	0.280	
≥ 90	1,369	88 (6.4)	678	29 (4.3)	1.50 [1.00; 2.26]	0.049	
Insulin at Baseline							
No	2,943	191 (6.5)	1,400	72 (5.1)	1.26 [0.97; 1.64]	0.082	0.641
Yes	2,550	173 (6.8)	1,345	79 (5.9)	1.16 [0.89; 1.49]	0.272	
SOC: Reproductive system and breast disorders							
Age Group (Years)							
< 65	2,718	190 (7.0)	1,375	47 (3.4)	2.05 [1.50; 2.80]	< 0.001	0.285
≥ 65	2,775	257 (9.3)	1,370	78 (5.7)	1.63 [1.27; 2.08]	< 0.001	
Region							
WHO Stratum A	1,789	177 (9.9)	890	52 (5.8)	1.69 [1.26; 2.28]	< 0.001	0.701
WHO Rest of the World	3,704	270 (7.3)	1,855	73 (3.9)	1.85 [1.44; 2.38]	< 0.001	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	98 (8.2)	607	22 (3.6)	2.26 [1.44; 3.55]	< 0.001	0.473
60 to < 90	2,926	249 (8.5)	1,460	76 (5.2)	1.63 [1.27; 2.10]	< 0.001	
≥ 90	1,369	100 (7.3)	678	27 (4.0)	1.83 [1.21; 2.78]	0.003	
Insulin at Baseline							
No	2,943	238 (8.1)	1,400	68 (4.9)	1.66 [1.28; 2.16]	< 0.001	0.450
Yes	2,550	209 (8.2)	1,345	57 (4.2)	1.93 [1.45; 2.57]	< 0.001	
SOC: Skin and subcutaneous tissue disorders							
Sex							
Female	1,630	185 (11.3)	844	69 (8.2)	1.39 [1.07; 1.81]	0.014	0.222
Male	3,863	416 (10.8)	1,901	179 (9.4)	1.14 [0.97; 1.35]	0.113	
Age Group (Years)							

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
< 65	2,718	256 (9.4)	1,375	114 (8.3)	1.14 [0.92; 1.40]	0.235	0.416
≥ 65	2,775	345 (12.4)	1,370	134 (9.8)	1.27 [1.05; 1.54]	0.012	
Region							
WHO Stratum A	1,789	282 (15.8)	890	114 (12.8)	1.23 [1.01; 1.51]	0.042	0.750
WHO Rest of the World	3,704	319 (8.6)	1,855	134 (7.2)	1.19 [0.98; 1.45]	0.074	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	167 (13.9)	607	63 (10.4)	1.34 [1.02; 1.76]	0.032	0.331
60 to < 90	2,926	323 (11.0)	1,460	130 (8.9)	1.24 [1.02; 1.50]	0.029	
≥ 90	1,369	111 (8.1)	678	55 (8.1)	1.00 [0.73; 1.36]	0.998	
Insulin at Baseline							
No	2,943	268 (9.1)	1,400	96 (6.9)	1.33 [1.06; 1.66]	0.012	0.375
Yes	2,550	333 (13.1)	1,345	152 (11.3)	1.16 [0.97; 1.38]	0.114	
SOC: Vascular disorders							
Sex							
Female	1,630	258 (15.8)	844	145 (17.2)	0.92 [0.77; 1.11]	0.388	0.580
Male	3,863	518 (13.4)	1,901	296 (15.6)	0.86 [0.75; 0.98]	0.027	
Age Group (Years)							
< 65	2,718	342 (12.6)	1,375	191 (13.9)	0.91 [0.77; 1.07]	0.240	0.583
≥ 65	2,775	434 (15.6)	1,370	250 (18.2)	0.86 [0.74; 0.99]	0.033	
Region							
WHO Stratum A	1,789	248 (13.9)	890	149 (16.7)	0.83 [0.69; 1.00]	0.048	0.442
WHO Rest of the World	3,704	528 (14.3)	1,855	292 (15.7)	0.91 [0.79; 1.03]	0.141	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	204 (17.0)	607	102 (16.8)	1.01 [0.82; 1.26]	0.904	0.352
60 to < 90	2,926	405 (13.8)	1,460	240 (16.4)	0.84 [0.73; 0.98]	0.022	
≥ 90	1,369	167 (12.2)	678	99 (14.6)	0.84 [0.66; 1.05]	0.128	
Insulin at Baseline							
No	2,943	367 (12.5)	1,400	219 (15.6)	0.80 [0.68; 0.93]	0.004	0.077
Yes	2,550	409 (16.0)	1,345	222 (16.5)	0.97 [0.84; 1.13]	0.707	

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

b: 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.'.

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

d: 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.'

e: 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; eGFR: Estimated Glomerular Filtration Rate; 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)

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
SOC: Cardiac disorders PT: Angina pectoris							
Sex							
Female	1,630	56 (3.4)	844	33 (3.9)	0.88 [0.58; 1.34]	0.548	0.511
Male	3,863	119 (3.1)	1,901	79 (4.2)	0.74 [0.56; 0.98]	0.035	
Age Group (Years)							
< 65	2,718	74 (2.7)	1,375	55 (4.0)	0.68 [0.48; 0.96]	0.027	0.296
≥ 65	2,775	101 (3.6)	1,370	57 (4.2)	0.87 [0.64; 1.20]	0.410	
Region							
WHO Stratum A	1,789	80 (4.5)	890	47 (5.3)	0.85 [0.60; 1.20]	0.353	0.556
WHO Rest of the World	3,704	95 (2.6)	1,855	65 (3.5)	0.73 [0.54; 1.00]	0.048	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	51 (4.3)	607	28 (4.6)	0.92 [0.59; 1.45]	0.727	0.627
60 to < 90	2,926	95 (3.2)	1,460	62 (4.2)	0.76 [0.56; 1.05]	0.093	
≥ 90	1,369	29 (2.1)	678	22 (3.2)	0.65 [0.38; 1.13]	0.124	
Insulin at Baseline							
No	2,943	75 (2.5)	1,400	46 (3.3)	0.78 [0.54; 1.11]	0.168	0.913
Yes	2,550	100 (3.9)	1,345	66 (4.9)	0.80 [0.59; 1.08]	0.148	
SOC: Cardiac disorders PT: Cardiac failure congestive							
Sex							
Female	1,630	17 (1.0)	844	11 (1.3)	0.80 [0.38; 1.70]	0.562	0.456
Male	3,863	47 (1.2)	1,901	40 (2.1)	0.58 [0.38; 0.88]	0.009	
Age Group (Years)							
< 65	2,718	20 (0.7)	1,375	17 (1.2)	0.60 [0.31; 1.13]	0.110	0.869
≥ 65	2,775	44 (1.6)	1,370	34 (2.5)	0.64 [0.41; 0.99]	0.046	
Region							
WHO Stratum A	1,789	39 (2.2)	890	36 (4.0)	0.54 [0.35; 0.84]	0.006	0.258
WHO Rest of the World	3,704	25 (0.7)	1,855	15 (0.8)	0.83 [0.44; 1.58]	0.578	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	23 (1.9)	607	23 (3.8)	0.51 [0.29; 0.90]	0.017	0.590
60 to < 90	2,926	34 (1.2)	1,460	24 (1.6)	0.71 [0.42; 1.19]	0.188	
≥ 90	1,369	7 (0.5)	678	4 (0.6)	0.87 [0.25; 2.95]	0.819	
Insulin at Baseline							
No	2,943	24 (0.8)	1,400	13 (0.9)	0.88 [0.45; 1.72]	0.705	0.255
Yes	2,550	40 (1.6)	1,345	38 (2.8)	0.56 [0.36; 0.86]	0.008	
SOC: Eye disorders PT: Diabetic retinopathy							
Sex							
Female	1,630	20 (1.2)	844	21 (2.5)	0.49 [0.27; 0.90]	0.020	0.211
Male	3,863	65 (1.7)	1,901	41 (2.2)	0.78 [0.53; 1.15]	0.208	
Region							
WHO Stratum A	1,789	30 (1.7)	890	15 (1.7)	0.99 [0.54; 1.84]	0.987	0.150

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
WHO Rest of the World	3,704	55 (1.5)	1,855	47 (2.5)	0.59 [0.40; 0.86]	0.006	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	19 (1.6)	607	12 (2.0)	0.80 [0.39; 1.64]	0.546	0.233
60 to < 90	2,926	50 (1.7)	1,460	31 (2.1)	0.80 [0.52; 1.25]	0.337	
≥ 90	1,369	16 (1.2)	678	19 (2.8)	0.42 [0.22; 0.81]	0.007	
Insulin at Baseline							
No	2,943	34 (1.2)	1,400	24 (1.7)	0.67 [0.40; 1.13]	0.134	0.893
Yes	2,550	51 (2.0)	1,345	38 (2.8)	0.71 [0.47; 1.07]	0.101	
SOC: Gastrointestinal disorders PT: Constipation							
Sex							
Female	1,630	49 (3.0)	844	21 (2.5)	1.21 [0.73; 2.00]	0.461	0.687
Male	3,863	144 (3.7)	1,901	52 (2.7)	1.36 [1.00; 1.86]	0.051	
Age Group (Years)							
< 65	2,718	71 (2.6)	1,375	30 (2.2)	1.20 [0.79; 1.83]	0.402	0.561
≥ 65	2,775	122 (4.4)	1,370	43 (3.1)	1.40 [1.00; 1.97]	0.051	
Region							
WHO Stratum A	1,789	111 (6.2)	890	38 (4.3)	1.45 [1.01; 2.08]	0.040	0.410
WHO Rest of the World	3,704	82 (2.2)	1,855	35 (1.9)	1.17 [0.79; 1.74]	0.423	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	54 (4.5)	607	16 (2.6)	1.71 [0.99; 2.96]	0.052	0.427
60 to < 90	2,926	111 (3.8)	1,460	43 (2.9)	1.29 [0.91; 1.82]	0.150	
≥ 90	1,369	28 (2.0)	678	14 (2.1)	0.99 [0.52; 1.87]	0.977	
Insulin at Baseline							
No	2,943	93 (3.2)	1,400	28 (2.0)	1.58 [1.04; 2.40]	0.030	0.284
Yes	2,550	100 (3.9)	1,345	45 (3.3)	1.17 [0.83; 1.66]	0.367	
SOC: General disorders and administration site conditions PT: Oedema peripheral							
Sex							
Female	1,630	26 (1.6)	844	27 (3.2)	0.50 [0.29; 0.85]	0.009	0.912
Male	3,863	44 (1.1)	1,901	42 (2.2)	0.52 [0.34; 0.78]	0.002	
Age Group (Years)							
< 65	2,718	23 (0.8)	1,375	22 (1.6)	0.53 [0.30; 0.95]	0.029	0.829
≥ 65	2,775	47 (1.7)	1,370	47 (3.4)	0.49 [0.33; 0.74]	< 0.001	
Region							
WHO Stratum A	1,789	37 (2.1)	890	46 (5.2)	0.40 [0.26; 0.61]	< 0.001	0.081
WHO Rest of the World	3,704	33 (0.9)	1,855	23 (1.2)	0.72 [0.42; 1.22]	0.219	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	24 (2.0)	607	25 (4.1)	0.49 [0.28; 0.84]	0.009	0.971
60 to < 90	2,926	38 (1.3)	1,460	36 (2.5)	0.53 [0.34; 0.83]	0.005	
≥ 90	1,369	8 (0.6)	678	8 (1.2)	0.50 [0.19; 1.31]	0.150	
Insulin at Baseline							
No	2,943	29 (1.0)	1,400	19 (1.4)	0.73 [0.41; 1.29]	0.273	0.141

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
Yes	2,550	41 (1.6)	1,345	50 (3.7)	0.43 [0.29; 0.65]	< 0.001	
SOC: Infections and infestations PT: Genital infection fungal							
Sex							
Female	1,630	24 (1.5)	844	2 (0.2)	6.21 [1.47; 26.23]	0.004	0.491
Male	3,863	50 (1.3)	1,901	7 (0.4)	3.52 [1.60; 7.74]	< 0.001	
Age Group (Years)							
< 65	2,718	43 (1.6)	1,375	3 (0.2)	7.25 [2.25; 23.33]	< 0.001	0.146
≥ 65	2,775	31 (1.1)	1,370	6 (0.4)	2.55 [1.07; 6.10]	0.029	
Region							
WHO Stratum A	1,789	40 (2.2)	890	6 (0.7)	3.32 [1.41; 7.79]	0.003	0.475
WHO Rest of the World	3,704	34 (0.9)	1,855	3 (0.2)	5.68 [1.75; 18.46]	0.001	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	8 (0.7)	607	1 (0.2)	4.05 [0.51; 32.33]	0.152	0.977
60 to < 90	2,926	47 (1.6)	1,460	6 (0.4)	3.91 [1.68; 9.12]	< 0.001	
≥ 90	1,369	19 (1.4)	678	2 (0.3)	4.70 [1.10; 20.14]	0.021	
Insulin at Baseline							
No	2,943	42 (1.4)	1,400	7 (0.5)	2.85 [1.29; 6.34]	0.007	0.179
Yes	2,550	32 (1.3)	1,345	2 (0.1)	8.44 [2.03; 35.16]	< 0.001	
SOC: Infections and infestations PT: Urinary tract infection							
Sex							
Female	1,630	262 (16.1)	844	123 (14.6)	1.10 [0.91; 1.34]	0.329	0.212
Male	3,863	276 (7.1)	1,901	100 (5.3)	1.36 [1.09; 1.70]	0.006	
Age Group (Years)							
< 65	2,718	217 (8.0)	1,375	91 (6.6)	1.21 [0.95; 1.53]	0.118	0.990
≥ 65	2,775	321 (11.6)	1,370	132 (9.6)	1.20 [0.99; 1.45]	0.061	
Region							
WHO Stratum A	1,789	211 (11.8)	890	94 (10.6)	1.12 [0.89; 1.40]	0.344	0.428
WHO Rest of the World	3,704	327 (8.8)	1,855	129 (7.0)	1.27 [1.04; 1.54]	0.016	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	140 (11.7)	607	71 (11.7)	1.00 [0.76; 1.31]	0.995	0.286
60 to < 90	2,926	285 (9.7)	1,460	110 (7.5)	1.29 [1.05; 1.60]	0.016	
≥ 90	1,369	113 (8.3)	678	42 (6.2)	1.33 [0.95; 1.88]	0.097	
Insulin at Baseline							
No	2,943	249 (8.5)	1,400	97 (6.9)	1.22 [0.97; 1.53]	0.081	0.981
Yes	2,550	289 (11.3)	1,345	126 (9.4)	1.21 [0.99; 1.48]	0.059	
SOC: Injury, poisoning and procedural complications PT: Limb injury							
Sex							
Female	1,630	19 (1.2)	844	11 (1.3)	0.89 [0.43; 1.87]	0.767	0.158
Male	3,863	93 (2.4)	1,901	28 (1.5)	1.63 [1.08; 2.48]	0.020	
Age Group (Years)							
< 65	2,718	55 (2.0)	1,375	18 (1.3)	1.55 [0.91; 2.62]	0.103	0.700
≥ 65	2,775	57 (2.1)	1,370	21 (1.5)	1.34 [0.82; 2.20]	0.245	

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
Region							
WHO Stratum A	1,789	55 (3.1)	890	20 (2.2)	1.37 [0.83; 2.27]	0.222	0.810
WHO Rest of the World	3,704	57 (1.5)	1,855	19 (1.0)	1.50 [0.90; 2.52]	0.119	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	25 (2.1)	607	8 (1.3)	1.58 [0.72; 3.49]	0.249	0.803
60 to < 90	2,926	61 (2.1)	1,460	20 (1.4)	1.52 [0.92; 2.51]	0.098	
≥ 90	1,369	26 (1.9)	678	11 (1.6)	1.17 [0.58; 2.35]	0.658	
Insulin at Baseline							
No	2,943	46 (1.6)	1,400	13 (0.9)	1.68 [0.91; 3.11]	0.091	0.560
Yes	2,550	66 (2.6)	1,345	26 (1.9)	1.34 [0.85; 2.10]	0.201	
SOC: Investigations PT: Blood glucose increased							
Sex							
Female	1,630	14 (0.9)	844	21 (2.5)	0.35 [0.18; 0.68]	0.001	0.077
Male	3,863	54 (1.4)	1,901	38 (2.0)	0.70 [0.46; 1.06]	0.087	
Age Group (Years)							
< 65	2,718	36 (1.3)	1,375	33 (2.4)	0.55 [0.35; 0.88]	0.012	0.782
≥ 65	2,775	32 (1.2)	1,370	26 (1.9)	0.61 [0.36; 1.02]	0.055	
Region							
WHO Stratum A	1,789	13 (0.7)	890	9 (1.0)	0.72 [0.31; 1.67]	0.442	0.564
WHO Rest of the World	3,704	55 (1.5)	1,855	50 (2.7)	0.55 [0.38; 0.80]	0.002	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	14 (1.2)	607	13 (2.1)	0.55 [0.26; 1.15]	0.108	0.413
60 to < 90	2,926	35 (1.2)	1,460	24 (1.6)	0.73 [0.43; 1.22]	0.225	
≥ 90	1,369	19 (1.4)	678	22 (3.2)	0.43 [0.23; 0.78]	0.005	
Insulin at Baseline							
No	2,943	41 (1.4)	1,400	32 (2.3)	0.61 [0.39; 0.96]	0.032	0.689
Yes	2,550	27 (1.1)	1,345	27 (2.0)	0.53 [0.31; 0.90]	0.016	
SOC: Investigations PT: Glycosylated haemoglobin increased							
Sex							
Female	1,630	14 (0.9)	844	9 (1.1)	0.81 [0.35; 1.85]	0.610	0.181
Male	3,863	15 (0.4)	1,901	19 (1.0)	0.39 [0.20; 0.76]	0.004	
Age Group (Years)							
< 65	2,718	14 (0.5)	1,375	19 (1.4)	0.37 [0.19; 0.74]	0.003	0.144
≥ 65	2,775	15 (0.5)	1,370	9 (0.7)	0.82 [0.36; 1.88]	0.642	
Region							
WHO Stratum A	1,789	7 (0.4)	890	10 (1.1)	0.35 [0.13; 0.91]	0.025	0.332
WHO Rest of the World	3,704	22 (0.6)	1,855	18 (1.0)	0.61 [0.33; 1.14]	0.117	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	9 (0.8)	607	11 (1.8)	0.41 [0.17; 0.99]	0.042	0.458
60 to < 90	2,926	14 (0.5)	1,460	9 (0.6)	0.78 [0.34; 1.79]	0.551	
≥ 90	1,369	6 (0.4)	678	8 (1.2)	0.37 [0.13; 1.07]	0.055	

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
Insulin at Baseline							
No	2,943	12 (0.4)	1,400	14 (1.0)	0.41 [0.19; 0.88]	0.018	0.396
Yes	2,550	17 (0.7)	1,345	14 (1.0)	0.64 [0.32; 1.30]	0.211	
SOC: Investigations PT: Weight decreased							
Sex							
Female	1,630	29 (1.8)	844	12 (1.4)	1.25 [0.64; 2.44]	0.509	0.503
Male	3,863	93 (2.4)	1,901	28 (1.5)	1.63 [1.08; 2.48]	0.020	
Age Group (Years)							
< 65	2,718	44 (1.6)	1,375	17 (1.2)	1.31 [0.75; 2.28]	0.340	0.498
≥ 65	2,775	78 (2.8)	1,370	23 (1.7)	1.67 [1.06; 2.65]	0.026	
Region							
WHO Stratum A	1,789	31 (1.7)	890	10 (1.1)	1.54 [0.76; 3.13]	0.226	0.976
WHO Rest of the World	3,704	91 (2.5)	1,855	30 (1.6)	1.52 [1.01; 2.29]	0.043	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	33 (2.8)	607	7 (1.2)	2.39 [1.06; 5.37]	0.029	0.442
60 to < 90	2,926	58 (2.0)	1,460	22 (1.5)	1.32 [0.81; 2.14]	0.268	
≥ 90	1,369	31 (2.3)	678	11 (1.6)	1.40 [0.71; 2.76]	0.335	
Insulin at Baseline							
No	2,943	72 (2.4)	1,400	26 (1.9)	1.32 [0.85; 2.05]	0.222	0.344
Yes	2,550	50 (2.0)	1,345	14 (1.0)	1.88 [1.05; 3.39]	0.032	
SOC: Metabolism and nutrition disorders PT: Diabetes mellitus							
Sex							
Female	1,630	36 (2.2)	844	30 (3.6)	0.62 [0.39; 1.00]	0.049	0.659
Male	3,863	88 (2.3)	1,901	79 (4.2)	0.55 [0.41; 0.74]	< 0.001	
Age Group (Years)							
< 65	2,718	61 (2.2)	1,375	60 (4.4)	0.51 [0.36; 0.73]	< 0.001	0.413
≥ 65	2,775	63 (2.3)	1,370	49 (3.6)	0.63 [0.44; 0.92]	0.015	
Region							
WHO Stratum A	1,789	48 (2.7)	890	31 (3.5)	0.77 [0.49; 1.20]	0.249	0.099
WHO Rest of the World	3,704	76 (2.1)	1,855	78 (4.2)	0.49 [0.36; 0.67]	< 0.001	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	39 (3.3)	607	22 (3.6)	0.90 [0.54; 1.50]	0.682	0.123
60 to < 90	2,926	59 (2.0)	1,460	62 (4.2)	0.47 [0.33; 0.67]	< 0.001	
≥ 90	1,369	26 (1.9)	678	25 (3.7)	0.52 [0.30; 0.88]	0.015	
Insulin at Baseline							
No	2,943	54 (1.8)	1,400	48 (3.4)	0.54 [0.36; 0.79]	0.001	0.653
Yes	2,550	70 (2.7)	1,345	61 (4.5)	0.61 [0.43; 0.85]	0.003	
SOC: Metabolism and nutrition disorders PT: Hyperglycaemia							
Sex							
Female	1,630	66 (4.0)	844	65 (7.7)	0.53 [0.38; 0.73]	< 0.001	0.580
Male	3,863	142 (3.7)	1,901	119 (6.3)	0.59 [0.46; 0.74]	< 0.001	
Age Group (Years)							

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
< 65	2,718	106 (3.9)	1,375	92 (6.7)	0.58 [0.44; 0.76]	< 0.001	0.753
≥ 65	2,775	102 (3.7)	1,370	92 (6.7)	0.55 [0.42; 0.72]	< 0.001	
Region							
WHO Stratum A	1,789	49 (2.7)	890	44 (4.9)	0.55 [0.37; 0.83]	0.003	0.952
WHO Rest of the World	3,704	159 (4.3)	1,855	140 (7.5)	0.57 [0.46; 0.71]	< 0.001	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	59 (4.9)	607	47 (7.7)	0.64 [0.44; 0.92]	0.016	0.744
60 to < 90	2,926	107 (3.7)	1,460	96 (6.6)	0.56 [0.43; 0.73]	< 0.001	
≥ 90	1,369	42 (3.1)	678	41 (6.0)	0.51 [0.33; 0.77]	0.001	
Insulin at Baseline							
No	2,943	88 (3.0)	1,400	88 (6.3)	0.48 [0.36; 0.63]	< 0.001	0.109
Yes	2,550	120 (4.7)	1,345	96 (7.1)	0.66 [0.51; 0.86]	0.002	
SOC: Metabolism and nutrition disorders PT: Hyperuricaemia							
Sex							
Female	1,630	24 (1.5)	844	20 (2.4)	0.62 [0.35; 1.12]	0.109	0.735
Male	3,863	43 (1.1)	1,901	30 (1.6)	0.71 [0.44; 1.12]	0.138	
Age Group (Years)							
< 65	2,718	33 (1.2)	1,375	28 (2.0)	0.60 [0.36; 0.98]	0.040	0.507
≥ 65	2,775	34 (1.2)	1,370	22 (1.6)	0.76 [0.45; 1.30]	0.318	
Region							
WHO Stratum A	1,789	3 (0.2)	890	6 (0.7)	0.25 [0.06; 0.99]	0.033	0.130
WHO Rest of the World	3,704	64 (1.7)	1,855	44 (2.4)	0.73 [0.50; 1.06]	0.101	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	29 (2.4)	607	14 (2.3)	1.05 [0.56; 1.97]	0.880	0.216
60 to < 90	2,926	31 (1.1)	1,460	29 (2.0)	0.53 [0.32; 0.88]	0.013	
≥ 90	1,369	7 (0.5)	678	7 (1.0)	0.50 [0.17; 1.41]	0.178	
Insulin at Baseline							
No	2,943	31 (1.1)	1,400	22 (1.6)	0.67 [0.39; 1.15]	0.146	0.979
Yes	2,550	36 (1.4)	1,345	28 (2.1)	0.68 [0.42; 1.11]	0.118	
SOC: Metabolism and nutrition disorders PT: Hypomagnesaemia							
Sex							
Female	1,630	7 (0.4)	844	20 (2.4)	0.18 [0.08; 0.43]	< 0.001	0.825
Male	3,863	12 (0.3)	1,901	29 (1.5)	0.20 [0.10; 0.40]	< 0.001	
Age Group (Years)							
< 65	2,718	9 (0.3)	1,375	20 (1.5)	0.23 [0.10; 0.50]	< 0.001	0.586
≥ 65	2,775	10 (0.4)	1,370	29 (2.1)	0.17 [0.08; 0.35]	< 0.001	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	4 (0.3)	607	8 (1.3)	0.25 [0.08; 0.84]	0.015	0.363
60 to < 90	2,926	11 (0.4)	1,460	22 (1.5)	0.25 [0.12; 0.51]	< 0.001	
≥ 90	1,369	4 (0.3)	678	19 (2.8)	0.10 [0.04; 0.31]	< 0.001	
Insulin at Baseline							
No	2,943	10 (0.3)	1,400	26 (1.9)	0.18 [0.09; 0.38]	< 0.001	0.822

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
Yes	2,550	9 (0.4)	1,345	23 (1.7)	0.21 [0.10; 0.44]	< 0.001	
SOC: Metabolism and nutrition disorders PT: Type 2 diabetes mellitus							
Age Group (Years)							
< 65	2,718	34 (1.3)	1,375	29 (2.1)	0.59 [0.36; 0.97]	0.035	0.452
≥ 65	2,775	23 (0.8)	1,370	14 (1.0)	0.81 [0.42; 1.57]	0.534	
Region							
WHO Stratum A	1,789	30 (1.7)	890	19 (2.1)	0.79 [0.44; 1.39]	0.405	0.414
WHO Rest of the World	3,704	27 (0.7)	1,855	24 (1.3)	0.56 [0.33; 0.97]	0.037	
Insulin at Baseline							
No	2,943	32 (1.1)	1,400	18 (1.3)	0.85 [0.48; 1.50]	0.567	0.243
Yes	2,550	25 (1.0)	1,345	25 (1.9)	0.53 [0.30; 0.91]	0.021	
SOC: Nervous system disorders PT: Dizziness							
Sex							
Female	1,630	96 (5.9)	844	32 (3.8)	1.55 [1.05; 2.30]	0.026	0.911
Male	3,863	188 (4.9)	1,901	61 (3.2)	1.52 [1.14; 2.01]	0.004	
Region							
WHO Stratum A	1,789	152 (8.5)	890	44 (4.9)	1.72 [1.24; 2.38]	< 0.001	0.268
WHO Rest of the World	3,704	132 (3.6)	1,855	49 (2.6)	1.35 [0.98; 1.86]	0.068	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	77 (6.4)	607	31 (5.1)	1.26 [0.84; 1.89]	0.264	0.248
60 to < 90	2,926	146 (5.0)	1,460	49 (3.4)	1.49 [1.08; 2.04]	0.013	
≥ 90	1,369	61 (4.5)	678	13 (1.9)	2.32 [1.29; 4.20]	0.004	
Insulin at Baseline							
No	2,943	153 (5.2)	1,400	45 (3.2)	1.62 [1.17; 2.24]	0.003	0.620
Yes	2,550	131 (5.1)	1,345	48 (3.6)	1.44 [1.04; 1.99]	0.026	
SOC: Renal and urinary disorders PT: Pollakiuria							
Sex							
Female	1,630	16 (1.0)	844	6 (0.7)	1.38 [0.54; 3.52]	0.497	0.247
Male	3,863	98 (2.5)	1,901	19 (1.0)	2.54 [1.56; 4.14]	< 0.001	
Age Group (Years)							
< 65	2,718	44 (1.6)	1,375	6 (0.4)	3.71 [1.58; 8.68]	0.001	0.155
≥ 65	2,775	70 (2.5)	1,370	19 (1.4)	1.82 [1.10; 3.01]	0.018	
Region							
WHO Stratum A	1,789	68 (3.8)	890	13 (1.5)	2.60 [1.45; 4.68]	< 0.001	0.469
WHO Rest of the World	3,704	46 (1.2)	1,855	12 (0.6)	1.92 [1.02; 3.61]	0.040	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	17 (1.4)	607	5 (0.8)	1.72 [0.64; 4.65]	0.276	0.821
60 to < 90	2,926	71 (2.4)	1,460	15 (1.0)	2.36 [1.36; 4.11]	0.002	
≥ 90	1,369	26 (1.9)	678	5 (0.7)	2.58 [0.99; 6.68]	0.043	
Insulin at Baseline							
No	2,943	64 (2.2)	1,400	13 (0.9)	2.34 [1.29; 4.24]	0.004	0.883

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
Yes	2,550	50 (2.0)	1,345	12 (0.9)	2.20 [1.17; 4.11]	0.011	
SOC: Renal and urinary disorders PT: Polyuria							
Sex							
Female	1,630	12 (0.7)	844	1 (0.1)	6.21 [0.81; 47.70]	0.044	0.557
Male	3,863	53 (1.4)	1,901	8 (0.4)	3.26 [1.55; 6.84]	< 0.001	
Age Group (Years)							
< 65	2,718	33 (1.2)	1,375	3 (0.2)	5.56 [1.71; 18.11]	0.001	0.309
≥ 65	2,775	32 (1.2)	1,370	6 (0.4)	2.63 [1.10; 6.28]	0.023	
Region							
WHO Stratum A	1,789	42 (2.3)	890	5 (0.6)	4.18 [1.66; 10.53]	< 0.001	0.591
WHO Rest of the World	3,704	23 (0.6)	1,855	4 (0.2)	2.88 [1.00; 8.31]	0.040	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	5 (0.4)	607	1 (0.2)	2.53 [0.30; 21.64]	0.378	0.857
60 to < 90	2,926	42 (1.4)	1,460	5 (0.3)	4.19 [1.66; 10.57]	< 0.001	
≥ 90	1,369	18 (1.3)	678	3 (0.4)	2.97 [0.88; 10.05]	0.065	
Insulin at Baseline							
No	2,943	31 (1.1)	1,400	4 (0.3)	3.69 [1.30; 10.42]	0.008	0.972
Yes	2,550	34 (1.3)	1,345	5 (0.4)	3.59 [1.41; 9.15]	0.004	
SOC: Reproductive system and breast disorders PT: Balanoposthitis							
Sex							
Female	1,630	0 (0.0)	844	0 (0.0)	n.a.	n.a.	n.a.
Male	3,863	95 (2.5)	1,901	8 (0.4)	5.84 [2.85; 12.00]	< 0.001	
Age Group (Years)							
< 65	2,718	46 (1.7)	1,375	4 (0.3)	5.82 [2.10; 16.13]	< 0.001	0.957
≥ 65	2,775	49 (1.8)	1,370	4 (0.3)	6.05 [2.19; 16.72]	< 0.001	
Region							
WHO Stratum A	1,789	35 (2.0)	890	5 (0.6)	3.48 [1.37; 8.86]	0.005	0.151
WHO Rest of the World	3,704	60 (1.6)	1,855	3 (0.2)	10.02 [3.15; 31.89]	< 0.001	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	11 (0.9)	607	0 (0.0)	n.a.	n.a.	0.555
60 to < 90	2,926	58 (2.0)	1,460	6 (0.4)	4.82 [2.09; 11.15]	< 0.001	
≥ 90	1,369	26 (1.9)	678	2 (0.3)	6.44 [1.53; 27.05]	0.003	
Insulin at Baseline							
No	2,943	52 (1.8)	1,400	5 (0.4)	4.95 [1.98; 12.36]	< 0.001	0.575
Yes	2,550	43 (1.7)	1,345	3 (0.2)	7.56 [2.35; 24.32]	< 0.001	
SOC: Skin and subcutaneous tissue disorders PT: Skin ulcer							
Sex							
Female	1,630	21 (1.3)	844	8 (0.9)	1.36 [0.60; 3.06]	0.456	0.748
Male	3,863	77 (2.0)	1,901	24 (1.3)	1.58 [1.00; 2.49]	0.047	
Age Group (Years)							
< 65	2,718	42 (1.5)	1,375	12 (0.9)	1.77 [0.94; 3.35]	0.075	0.554
≥ 65	2,775	56 (2.0)	1,370	20 (1.5)	1.38 [0.83; 2.29]	0.208	

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
Region							
WHO Stratum A	1,789	53 (3.0)	890	11 (1.2)	2.40 [1.26; 4.57]	0.006	0.052
WHO Rest of the World	3,704	45 (1.2)	1,855	21 (1.1)	1.07 [0.64; 1.80]	0.788	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	22 (1.8)	607	5 (0.8)	2.23 [0.85; 5.86]	0.094	0.559
60 to < 90	2,926	58 (2.0)	1,460	19 (1.3)	1.52 [0.91; 2.55]	0.106	
≥ 90	1,369	18 (1.3)	678	8 (1.2)	1.11 [0.49; 2.55]	0.798	
Insulin at Baseline							
No	2,943	29 (1.0)	1,400	8 (0.6)	1.72 [0.79; 3.76]	0.165	0.792
Yes	2,550	69 (2.7)	1,345	24 (1.8)	1.52 [0.96; 2.40]	0.073	
SOC: Vascular disorders PT: Hypertension							
Sex							
Female	1,630	123 (7.5)	844	72 (8.5)	0.88 [0.67; 1.17]	0.389	0.577
Male	3,863	164 (4.2)	1,901	102 (5.4)	0.79 [0.62; 1.01]	0.057	
Region							
WHO Stratum A	1,789	61 (3.4)	890	45 (5.1)	0.67 [0.46; 0.98]	0.040	0.240
WHO Rest of the World	3,704	226 (6.1)	1,855	129 (7.0)	0.88 [0.71; 1.08]	0.220	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	66 (5.5)	607	39 (6.4)	0.86 [0.58; 1.26]	0.432	0.791
60 to < 90	2,926	154 (5.3)	1,460	90 (6.2)	0.85 [0.66; 1.10]	0.220	
≥ 90	1,369	67 (4.9)	678	45 (6.6)	0.74 [0.51; 1.06]	0.103	
Insulin at Baseline							
No	2,943	147 (5.0)	1,400	100 (7.1)	0.70 [0.55; 0.89]	0.004	0.057
Yes	2,550	140 (5.5)	1,345	74 (5.5)	1.00 [0.76; 1.31]	0.988	

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

b: 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.'.

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

d: 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.'

e: A specific adverse event 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; eGFR: Estimated Glomerular Filtration Rate; 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 Schwerwiegende unerwünschte Ereignisse (SOC)

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Serious Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
SOC: Cardiac disorders							
Sex							
Female	1,630	164 (10.1)	844	113 (13.4)	0.75 [0.60; 0.94]	0.013	0.213
Male	3,863	582 (15.1)	1,901	321 (16.9)	0.89 [0.79; 1.01]	0.074	
Age Group (Years)							
< 65	2,718	334 (12.3)	1,375	199 (14.5)	0.85 [0.72; 1.00]	0.050[f]	0.897
≥ 65	2,775	412 (14.8)	1,370	235 (17.2)	0.87 [0.75; 1.00]	0.054	
Region							
WHO Stratum A	1,789	258 (14.4)	890	159 (17.9)	0.81 [0.67; 0.97]	0.021	0.389
WHO Rest of the World	3,704	488 (13.2)	1,855	275 (14.8)	0.89 [0.78; 1.02]	0.092	
Insulin at Baseline							
No	2,943	357 (12.1)	1,400	175 (12.5)	0.97 [0.82; 1.15]	0.729	0.062
Yes	2,550	389 (15.3)	1,345	259 (19.3)	0.79 [0.69; 0.91]	0.001	
SOC: Gastrointestinal disorders							
Sex							
Female	1,630	33 (2.0)	844	14 (1.7)	1.22 [0.66; 2.27]	0.528	0.680
Male	3,863	129 (3.3)	1,901	45 (2.4)	1.41 [1.01; 1.97]	0.043	
Age Group (Years)							
< 65	2,718	60 (2.2)	1,375	28 (2.0)	1.08 [0.70; 1.69]	0.721	0.178
≥ 65	2,775	102 (3.7)	1,370	31 (2.3)	1.62 [1.09; 2.42]	0.015	
Region							
WHO Stratum A	1,789	67 (3.7)	890	33 (3.7)	1.01 [0.67; 1.52]	0.962	0.050[f]
WHO Rest of the World	3,704	95 (2.6)	1,855	26 (1.4)	1.83 [1.19; 2.81]	0.005	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	53 (4.4)	607	15 (2.5)	1.79 [1.02; 3.15]	0.040	0.534
60 to < 90	2,926	82 (2.8)	1,460	33 (2.3)	1.24 [0.83; 1.85]	0.290	
≥ 90	1,369	27 (2.0)	678	11 (1.6)	1.22 [0.61; 2.44]	0.581	
Insulin at Baseline							
No	2,943	76 (2.6)	1,400	30 (2.1)	1.21 [0.79; 1.83]	0.380	0.382
Yes	2,550	86 (3.4)	1,345	29 (2.2)	1.56 [1.03; 2.37]	0.033	

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

b: 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.'.

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

d: 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.'

e: A system organ class appears on this report only if its incidence ≥ 5% 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

f: Unrounded p-value > 0.050.

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Serious Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
CI: Confidence Interval; eGFR: Estimated Glomerular Filtration Rate; 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 Schwere unerwünschte Ereignisse (SOC)

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Severe Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps)							
Sex							
Female	1,630	44 (2.7)	844	10 (1.2)	2.28 [1.15; 4.50]	0.015	0.110
Male	3,863	152 (3.9)	1,901	60 (3.2)	1.25 [0.93; 1.67]	0.140	
Age Group (Years)							
< 65	2,718	70 (2.6)	1,375	26 (1.9)	1.36 [0.87; 2.13]	0.172	0.880
≥ 65	2,775	126 (4.5)	1,370	44 (3.2)	1.41 [1.01; 1.98]	0.042	
Region							
WHO Stratum A	1,789	79 (4.4)	890	29 (3.3)	1.36 [0.89; 2.06]	0.151	0.860
WHO Rest of the World	3,704	117 (3.2)	1,855	41 (2.2)	1.43 [1.01; 2.03]	0.045	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	44 (3.7)	607	16 (2.6)	1.39 [0.79; 2.45]	0.246	0.880
60 to < 90	2,926	104 (3.6)	1,460	39 (2.7)	1.33 [0.93; 1.91]	0.121	
≥ 90	1,369	48 (3.5)	678	15 (2.2)	1.58 [0.89; 2.81]	0.111	
Insulin at Baseline							
No	2,943	97 (3.3)	1,400	35 (2.5)	1.32 [0.90; 1.93]	0.153	0.649
Yes	2,550	99 (3.9)	1,345	35 (2.6)	1.49 [1.02; 2.18]	0.037	
SOC: Vascular disorders							
Sex							
Female	1,630	35 (2.1)	844	26 (3.1)	0.70 [0.42; 1.15]	0.156	0.877
Male	3,863	107 (2.8)	1,901	72 (3.8)	0.73 [0.55; 0.98]	0.036	
Age Group (Years)							
< 65	2,718	64 (2.4)	1,375	38 (2.8)	0.85 [0.57; 1.27]	0.428	0.276
≥ 65	2,775	78 (2.8)	1,370	60 (4.4)	0.64 [0.46; 0.89]	0.008	
Region							
WHO Stratum A	1,789	45 (2.5)	890	37 (4.2)	0.61 [0.39; 0.93]	0.020	0.309
WHO Rest of the World	3,704	97 (2.6)	1,855	61 (3.3)	0.80 [0.58; 1.09]	0.157	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	44 (3.7)	607	32 (5.3)	0.70 [0.45; 1.09]	0.110	0.938
60 to < 90	2,926	73 (2.5)	1,460	48 (3.3)	0.76 [0.53; 1.09]	0.131	

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Severe Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
≥ 90	1,369	25 (1.8)	678	18 (2.7)	0.69 [0.38; 1.25]	0.219	
Insulin at Baseline							
No	2,943	66 (2.2)	1,400	40 (2.9)	0.78 [0.53; 1.16]	0.220	0.617
Yes	2,550	76 (3.0)	1,345	58 (4.3)	0.69 [0.49; 0.97]	0.030	

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

b: 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.'.

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

d: 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.'

e: A system organ class appears on this report only if its incidence ≥ 5% 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; eGFR: Estimated Glomerular Filtration Rate; 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-41: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Nicht-schwere unerwünschte Ereignisse (SOC)

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Non-Severe Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
SOC: Congenital, familial and genetic disorders							
Sex							
Female	1,630	12 (0.7)	844	3 (0.4)	2.07 [0.59; 7.32]	0.248	0.854
Male	3,863	48 (1.2)	1,901	10 (0.5)	2.36 [1.20; 4.66]	0.010	
Region							
WHO Stratum A	1,789	18 (1.0)	890	4 (0.4)	2.24 [0.76; 6.59]	0.133	0.947
WHO Rest of the World	3,704	42 (1.1)	1,855	9 (0.5)	2.34 [1.14; 4.79]	0.017	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	11 (0.9)	607	4 (0.7)	1.39 [0.45; 4.36]	0.567	0.571
60 to < 90	2,926	29 (1.0)	1,460	6 (0.4)	2.41 [1.00; 5.80]	0.042	
≥ 90	1,369	20 (1.5)	678	3 (0.4)	3.30 [0.98; 11.07]	0.040	
Insulin at Baseline							
No	2,943	27 (0.9)	1,400	6 (0.4)	2.14 [0.89; 5.17]	0.083	0.804
Yes	2,550	33 (1.3)	1,345	7 (0.5)	2.49 [1.10; 5.61]	0.023	
SOC: Infections and infestations							
Sex							
Female	1,630	761 (46.7)	844	353 (41.8)	1.12 [1.02; 1.23]	0.021	0.216
Male	3,863	1,502 (38.9)	1,901	708 (37.2)	1.04 [0.97; 1.12]	0.229	

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Non-Severe Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
Age Group (Years)							
< 65	2,718	1,047 (38.5)	1,375	499 (36.3)	1.06 [0.98; 1.16]	0.165	0.840
≥ 65	2,775	1,216 (43.8)	1,370	562 (41.0)	1.07 [0.99; 1.15]	0.087	
Region							
WHO Stratum A	1,789	929 (51.9)	890	448 (50.3)	1.03 [0.95; 1.12]	0.438	0.506
WHO Rest of the World	3,704	1,334 (36.0)	1,855	613 (33.0)	1.09 [1.01; 1.18]	0.029	
Insulin at Baseline							
No	2,943	1,135 (38.6)	1,400	509 (36.4)	1.06 [0.98; 1.15]	0.161	0.704
Yes	2,550	1,128 (44.2)	1,345	552 (41.0)	1.08 [1.00; 1.16]	0.056	
SOC: Metabolism and nutrition disorders							
Sex							
Female	1,630	726 (44.5)	844	399 (47.3)	0.94 [0.86; 1.03]	0.195	0.999
Male	3,863	1,645 (42.6)	1,901	861 (45.3)	0.94 [0.88; 1.00]	0.051	
Age Group (Years)							
< 65	2,718	1,122 (41.3)	1,375	623 (45.3)	0.91 [0.85; 0.98]	0.014	0.267
≥ 65	2,775	1,249 (45.0)	1,370	637 (46.5)	0.97 [0.90; 1.04]	0.366	
Region							
WHO Stratum A	1,789	905 (50.6)	890	455 (51.1)	0.99 [0.91; 1.07]	0.794	0.175
WHO Rest of the World	3,704	1,466 (39.6)	1,855	805 (43.4)	0.91 [0.85; 0.97]	0.006	
Insulin at Baseline							
No	2,943	957 (32.5)	1,400	510 (36.4)	0.89 [0.82; 0.97]	0.011	0.095
Yes	2,550	1,414 (55.5)	1,345	750 (55.8)	0.99 [0.94; 1.05]	0.853	
SOC: Nervous system disorders							
Sex							
Female	1,630	343 (21.0)	844	175 (20.7)	1.01 [0.86; 1.19]	0.858	0.228
Male	3,863	749 (19.4)	1,901	320 (16.8)	1.15 [1.02; 1.30]	0.019	
Age Group (Years)							
< 65	2,718	452 (16.6)	1,375	203 (14.8)	1.13 [0.97; 1.31]	0.124	0.744
≥ 65	2,775	640 (23.1)	1,370	292 (21.3)	1.08 [0.96; 1.22]	0.205	
Region							
WHO Stratum A	1,789	468 (26.2)	890	202 (22.7)	1.15 [1.00; 1.33]	0.051	0.370
WHO Rest of the World	3,704	624 (16.8)	1,855	293 (15.8)	1.07 [0.94; 1.21]	0.319	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	274 (22.9)	607	136 (22.4)	1.02 [0.85; 1.22]	0.823	0.544
60 to < 90	2,926	582 (19.9)	1,460	262 (17.9)	1.11 [0.97; 1.26]	0.124	
≥ 90	1,369	236 (17.2)	678	97 (14.3)	1.20 [0.97; 1.50]	0.091	
Insulin at Baseline							
No	2,943	555 (18.9)	1,400	238 (17.0)	1.11 [0.97; 1.27]	0.139	0.969
Yes	2,550	537 (21.1)	1,345	257 (19.1)	1.10 [0.96; 1.26]	0.151	
SOC: Reproductive system and breast disorders							
Age Group (Years)							

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Non-Severe Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
< 65	2,718	181 (6.7)	1,375	42 (3.1)	2.18 [1.57; 3.03]	< 0.001	0.172
≥ 65	2,775	242 (8.7)	1,370	74 (5.4)	1.61 [1.25; 2.08]	< 0.001	
Region							
WHO Stratum A	1,789	168 (9.4)	890	48 (5.4)	1.74 [1.28; 2.38]	< 0.001	0.762
WHO Rest of the World	3,704	255 (6.9)	1,855	68 (3.7)	1.88 [1.45; 2.44]	< 0.001	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	96 (8.0)	607	22 (3.6)	2.21 [1.41; 3.48]	< 0.001	0.580
60 to < 90	2,926	232 (7.9)	1,460	69 (4.7)	1.68 [1.29; 2.18]	< 0.001	
≥ 90	1,369	95 (6.9)	678	25 (3.7)	1.88 [1.22; 2.90]	0.003	
Insulin at Baseline							
No	2,943	227 (7.7)	1,400	64 (4.6)	1.69 [1.29; 2.21]	< 0.001	0.428
Yes	2,550	196 (7.7)	1,345	52 (3.9)	1.99 [1.47; 2.68]	< 0.001	
SOC: Skin and subcutaneous tissue disorders							
Sex							
Female	1,630	182 (11.2)	844	67 (7.9)	1.41 [1.08; 1.84]	0.011	0.206
Male	3,863	401 (10.4)	1,901	172 (9.0)	1.15 [0.97; 1.36]	0.112	
Age Group (Years)							
< 65	2,718	247 (9.1)	1,375	110 (8.0)	1.14 [0.92; 1.41]	0.244	0.380
≥ 65	2,775	336 (12.1)	1,370	129 (9.4)	1.29 [1.06; 1.56]	0.010	
Region							
WHO Stratum A	1,789	276 (15.4)	890	110 (12.4)	1.25 [1.02; 1.53]	0.033	0.679
WHO Rest of the World	3,704	307 (8.3)	1,855	129 (7.0)	1.19 [0.98; 1.45]	0.081	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	158 (13.2)	607	60 (9.9)	1.33 [1.01; 1.77]	0.042	0.259
60 to < 90	2,926	319 (10.9)	1,460	125 (8.6)	1.27 [1.05; 1.55]	0.015	
≥ 90	1,369	106 (7.7)	678	54 (8.0)	0.97 [0.71; 1.33]	0.860	
Insulin at Baseline							
No	2,943	264 (9.0)	1,400	92 (6.6)	1.37 [1.09; 1.72]	0.007	0.262
Yes	2,550	319 (12.5)	1,345	147 (10.9)	1.14 [0.95; 1.38]	0.148	

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

b: 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.'.

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

d: 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.'

e: 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; eGFR: Estimated Glomerular Filtration Rate; 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-42: Subgruppenanalysen mit nicht signifikantem Interaktionstest (p ≥ 0,05) für den Endpunkt Nicht-schwere unerwünschte Ereignisse (PT)

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Non-Severe Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
SOC: Cardiac disorders PT: Angina pectoris							
Sex							
Female	1,630	35 (2.1)	844	28 (3.3)	0.65 [0.40; 1.06]	0.080	0.708
Male	3,863	81 (2.1)	1,901	55 (2.9)	0.72 [0.52; 1.02]	0.061	
Age Group (Years)							
< 65	2,718	48 (1.8)	1,375	38 (2.8)	0.64 [0.42; 0.97]	0.036	0.594
≥ 65	2,775	68 (2.5)	1,370	45 (3.3)	0.75 [0.51; 1.08]	0.121	
Region							
WHO Stratum A	1,789	57 (3.2)	890	36 (4.0)	0.79 [0.52; 1.19]	0.253	0.441
WHO Rest of the World	3,704	59 (1.6)	1,855	47 (2.5)	0.63 [0.43; 0.92]	0.016	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	39 (3.3)	607	23 (3.8)	0.86 [0.52; 1.42]	0.557	0.456
60 to < 90	2,926	57 (1.9)	1,460	48 (3.3)	0.59 [0.41; 0.87]	0.006	
≥ 90	1,369	20 (1.5)	678	12 (1.8)	0.83 [0.41; 1.68]	0.596	
Insulin at Baseline							
No	2,943	51 (1.7)	1,400	37 (2.6)	0.66 [0.43; 1.00]	0.047	0.661
Yes	2,550	65 (2.5)	1,345	46 (3.4)	0.75 [0.51; 1.08]	0.120	
SOC: Eye disorders PT: Diabetic retinopathy							
Sex							
Female	1,630	18 (1.1)	844	20 (2.4)	0.47 [0.25; 0.88]	0.015	0.119
Male	3,863	65 (1.7)	1,901	38 (2.0)	0.84 [0.57; 1.25]	0.394	
Age Group (Years)							
< 65	2,718	39 (1.4)	1,375	37 (2.7)	0.53 [0.34; 0.83]	0.005	0.055
≥ 65	2,775	44 (1.6)	1,370	21 (1.5)	1.03 [0.62; 1.73]	0.898	
Region							
WHO Stratum A	1,789	29 (1.6)	890	15 (1.7)	0.96 [0.52; 1.78]	0.902	0.255
WHO Rest of the World	3,704	54 (1.5)	1,855	43 (2.3)	0.63 [0.42; 0.94]	0.021	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	18 (1.5)	607	11 (1.8)	0.83 [0.39; 1.74]	0.621	0.362
60 to < 90	2,926	49 (1.7)	1,460	30 (2.1)	0.81 [0.52; 1.28]	0.372	
≥ 90	1,369	16 (1.2)	678	17 (2.5)	0.47 [0.24; 0.92]	0.024	
Insulin at Baseline							
No	2,943	33 (1.1)	1,400	21 (1.5)	0.75 [0.43; 1.29]	0.293	0.884
Yes	2,550	50 (2.0)	1,345	37 (2.8)	0.71 [0.47; 1.08]	0.113	
SOC: General disorders and administration site conditions PT: Oedema peripheral							
Sex							
Female	1,630	25 (1.5)	844	27 (3.2)	0.48 [0.28; 0.82]	0.006	0.876
Male	3,863	43 (1.1)	1,901	42 (2.2)	0.50 [0.33; 0.77]	0.001	
Age Group (Years)							
< 65	2,718	21 (0.8)	1,375	22 (1.6)	0.48 [0.27; 0.87]	0.014	0.973

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Non-Severe Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
≥ 65	2,775	47 (1.7)	1,370	47 (3.4)	0.49 [0.33; 0.74]	< 0.001	
Region							
WHO Stratum A	1,789	36 (2.0)	890	46 (5.2)	0.39 [0.25; 0.60]	< 0.001	0.085
WHO Rest of the World	3,704	32 (0.9)	1,855	23 (1.2)	0.70 [0.41; 1.19]	0.182	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	24 (2.0)	607	25 (4.1)	0.49 [0.28; 0.84]	0.009	0.995
60 to < 90	2,926	36 (1.2)	1,460	36 (2.5)	0.50 [0.32; 0.79]	0.002	
≥ 90	1,369	8 (0.6)	678	8 (1.2)	0.50 [0.19; 1.31]	0.150	
Insulin at Baseline							
No	2,943	29 (1.0)	1,400	19 (1.4)	0.73 [0.41; 1.29]	0.273	0.109
Yes	2,550	39 (1.5)	1,345	50 (3.7)	0.41 [0.27; 0.62]	< 0.001	
SOC: Infections and infestations PT: Genital infection fungal							
Sex							
Female	1,630	24 (1.5)	844	2 (0.2)	6.21 [1.47; 26.23]	0.004	0.491
Male	3,863	50 (1.3)	1,901	7 (0.4)	3.52 [1.60; 7.74]	< 0.001	
Age Group (Years)							
< 65	2,718	43 (1.6)	1,375	3 (0.2)	7.25 [2.25; 23.33]	< 0.001	0.146
≥ 65	2,775	31 (1.1)	1,370	6 (0.4)	2.55 [1.07; 6.10]	0.029	
Region							
WHO Stratum A	1,789	40 (2.2)	890	6 (0.7)	3.32 [1.41; 7.79]	0.003	0.475
WHO Rest of the World	3,704	34 (0.9)	1,855	3 (0.2)	5.68 [1.75; 18.46]	0.001	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	8 (0.7)	607	1 (0.2)	4.05 [0.51; 32.33]	0.152	0.977
60 to < 90	2,926	47 (1.6)	1,460	6 (0.4)	3.91 [1.68; 9.12]	< 0.001	
≥ 90	1,369	19 (1.4)	678	2 (0.3)	4.70 [1.10; 20.14]	0.021	
Insulin at Baseline							
No	2,943	42 (1.4)	1,400	7 (0.5)	2.85 [1.29; 6.34]	0.007	0.179
Yes	2,550	32 (1.3)	1,345	2 (0.1)	8.44 [2.03; 35.16]	< 0.001	
SOC: Infections and infestations PT: Respiratory tract infection							
Sex							
Female	1,630	36 (2.2)	844	30 (3.6)	0.62 [0.39; 1.00]	0.049	0.468
Male	3,863	42 (1.1)	1,901	26 (1.4)	0.79 [0.49; 1.29]	0.354	
Age Group (Years)							
< 65	2,718	40 (1.5)	1,375	33 (2.4)	0.61 [0.39; 0.97]	0.034	0.413
≥ 65	2,775	38 (1.4)	1,370	23 (1.7)	0.82 [0.49; 1.36]	0.436	
Region							
WHO Stratum A	1,789	12 (0.7)	890	8 (0.9)	0.75 [0.31; 1.82]	0.518	0.862
WHO Rest of the World	3,704	66 (1.8)	1,855	48 (2.6)	0.69 [0.48; 0.99]	0.046	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	14 (1.2)	607	9 (1.5)	0.79 [0.34; 1.81]	0.574	0.093
60 to < 90	2,926	50 (1.7)	1,460	28 (1.9)	0.89 [0.56; 1.41]	0.622	

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Non-Severe Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
≥ 90	1,369	14 (1.0)	678	19 (2.8)	0.36 [0.18; 0.72]	0.003	
Insulin at Baseline							
No	2,943	45 (1.5)	1,400	29 (2.1)	0.74 [0.46; 1.17]	0.197	0.699
Yes	2,550	33 (1.3)	1,345	27 (2.0)	0.64 [0.39; 1.07]	0.086	
SOC: Infections and infestations PT: Urinary tract infection							
Sex							
Female	1,630	255 (15.6)	844	118 (14.0)	1.12 [0.91; 1.37]	0.273	0.173
Male	3,863	267 (6.9)	1,901	93 (4.9)	1.41 [1.12; 1.78]	0.003	
Age Group (Years)							
< 65	2,718	211 (7.8)	1,375	87 (6.3)	1.23 [0.96; 1.56]	0.095	0.918
≥ 65	2,775	311 (11.2)	1,370	124 (9.1)	1.24 [1.02; 1.51]	0.033	
Region							
WHO Stratum A	1,789	203 (11.3)	890	90 (10.1)	1.12 [0.89; 1.42]	0.335	0.324
WHO Rest of the World	3,704	319 (8.6)	1,855	121 (6.5)	1.32 [1.08; 1.62]	0.007	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	135 (11.3)	607	66 (10.9)	1.04 [0.79; 1.37]	0.801	0.352
60 to < 90	2,926	278 (9.5)	1,460	103 (7.1)	1.35 [1.08; 1.67]	0.007	
≥ 90	1,369	109 (8.0)	678	42 (6.2)	1.29 [0.91; 1.81]	0.150	
Insulin at Baseline							
No	2,943	242 (8.2)	1,400	94 (6.7)	1.22 [0.97; 1.54]	0.082	0.819
Yes	2,550	280 (11.0)	1,345	117 (8.7)	1.26 [1.03; 1.55]	0.025	
SOC: Investigations PT: Blood glucose increased							
Sex							
Female	1,630	14 (0.9)	844	21 (2.5)	0.35 [0.18; 0.68]	0.001	0.085
Male	3,863	53 (1.4)	1,901	38 (2.0)	0.69 [0.45; 1.04]	0.073	
Age Group (Years)							
< 65	2,718	35 (1.3)	1,375	33 (2.4)	0.54 [0.33; 0.86]	0.009	0.723
≥ 65	2,775	32 (1.2)	1,370	26 (1.9)	0.61 [0.36; 1.02]	0.055	
Region							
WHO Stratum A	1,789	12 (0.7)	890	9 (1.0)	0.66 [0.28; 1.57]	0.347	0.688
WHO Rest of the World	3,704	55 (1.5)	1,855	50 (2.7)	0.55 [0.38; 0.80]	0.002	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	14 (1.2)	607	13 (2.1)	0.55 [0.26; 1.15]	0.108	0.457
60 to < 90	2,926	34 (1.2)	1,460	24 (1.6)	0.71 [0.42; 1.19]	0.188	
≥ 90	1,369	19 (1.4)	678	22 (3.2)	0.43 [0.23; 0.78]	0.005	
Insulin at Baseline							
No	2,943	41 (1.4)	1,400	32 (2.3)	0.61 [0.39; 0.96]	0.032	0.616
Yes	2,550	26 (1.0)	1,345	27 (2.0)	0.51 [0.30; 0.87]	0.011	
SOC: Investigations PT: Weight decreased							
Sex							
Female	1,630	29 (1.8)	844	12 (1.4)	1.25 [0.64; 2.44]	0.509	0.577
Male	3,863	89 (2.3)	1,901	28 (1.5)	1.56 [1.03; 2.38]	0.035	

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Non-Severe Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
Age Group (Years)							
< 65	2,718	41 (1.5)	1,375	17 (1.2)	1.22 [0.70; 2.14]	0.487	0.407
≥ 65	2,775	77 (2.8)	1,370	23 (1.7)	1.65 [1.04; 2.62]	0.031	
Region							
WHO Stratum A	1,789	29 (1.6)	890	10 (1.1)	1.44 [0.71; 2.95]	0.311	0.939
WHO Rest of the World	3,704	89 (2.4)	1,855	30 (1.6)	1.49 [0.99; 2.24]	0.056	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	32 (2.7)	607	7 (1.2)	2.32 [1.03; 5.22]	0.036	0.445
60 to < 90	2,926	57 (1.9)	1,460	22 (1.5)	1.29 [0.79; 2.11]	0.301	
≥ 90	1,369	29 (2.1)	678	11 (1.6)	1.31 [0.66; 2.60]	0.446	
Insulin at Baseline							
No	2,943	70 (2.4)	1,400	26 (1.9)	1.28 [0.82; 2.00]	0.275	0.363
Yes	2,550	48 (1.9)	1,345	14 (1.0)	1.81 [1.00; 3.27]	0.046	
SOC: Metabolism and nutrition disorders PT: Diabetes mellitus							
Sex							
Female	1,630	34 (2.1)	844	30 (3.6)	0.59 [0.36; 0.95]	0.029	0.813
Male	3,863	87 (2.3)	1,901	78 (4.1)	0.55 [0.41; 0.74]	< 0.001	
Age Group (Years)							
< 65	2,718	60 (2.2)	1,375	59 (4.3)	0.51 [0.36; 0.73]	< 0.001	0.492
≥ 65	2,775	61 (2.2)	1,370	49 (3.6)	0.61 [0.42; 0.89]	0.009	
Region							
WHO Stratum A	1,789	47 (2.6)	890	31 (3.5)	0.75 [0.48; 1.18]	0.215	0.107
WHO Rest of the World	3,704	74 (2.0)	1,855	77 (4.2)	0.48 [0.35; 0.66]	< 0.001	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	39 (3.3)	607	22 (3.6)	0.90 [0.54; 1.50]	0.682	0.094
60 to < 90	2,926	56 (1.9)	1,460	62 (4.2)	0.45 [0.32; 0.64]	< 0.001	
≥ 90	1,369	26 (1.9)	678	24 (3.5)	0.54 [0.31; 0.93]	0.024	
Insulin at Baseline							
No	2,943	54 (1.8)	1,400	48 (3.4)	0.54 [0.36; 0.79]	0.001	0.731
Yes	2,550	67 (2.6)	1,345	60 (4.5)	0.59 [0.42; 0.83]	0.002	
SOC: Metabolism and nutrition disorders PT: Hyperglycaemia							
Sex							
Female	1,630	63 (3.9)	844	64 (7.6)	0.51 [0.36; 0.71]	< 0.001	0.373
Male	3,863	137 (3.5)	1,901	110 (5.8)	0.61 [0.48; 0.78]	< 0.001	
Age Group (Years)							
< 65	2,718	102 (3.8)	1,375	85 (6.2)	0.61 [0.46; 0.80]	< 0.001	0.586
≥ 65	2,775	98 (3.5)	1,370	89 (6.5)	0.54 [0.41; 0.72]	< 0.001	
Region							
WHO Stratum A	1,789	45 (2.5)	890	38 (4.3)	0.59 [0.39; 0.90]	0.014	0.854
WHO Rest of the World	3,704	155 (4.2)	1,855	136 (7.3)	0.57 [0.46; 0.71]	< 0.001	
Baseline eGFR (mL/min/1.73 m^2)							

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Non-Severe Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
< 60	1,198	55 (4.6)	607	43 (7.1)	0.65 [0.44; 0.95]	0.027	0.728
60 to < 90	2,926	105 (3.6)	1,460	92 (6.3)	0.57 [0.43; 0.75]	< 0.001	
≥ 90	1,369	40 (2.9)	678	39 (5.8)	0.51 [0.33; 0.78]	0.002	
Insulin at Baseline							
No	2,943	85 (2.9)	1,400	85 (6.1)	0.48 [0.35; 0.64]	< 0.001	0.083
Yes	2,550	115 (4.5)	1,345	89 (6.6)	0.68 [0.52; 0.89]	0.005	
SOC: Metabolism and nutrition disorders PT: Hyperuricaemia							
Sex							
Female	1,630	24 (1.5)	844	20 (2.4)	0.62 [0.35; 1.12]	0.109	0.735
Male	3,863	43 (1.1)	1,901	30 (1.6)	0.71 [0.44; 1.12]	0.138	
Age Group (Years)							
< 65	2,718	33 (1.2)	1,375	28 (2.0)	0.60 [0.36; 0.98]	0.040	0.507
≥ 65	2,775	34 (1.2)	1,370	22 (1.6)	0.76 [0.45; 1.30]	0.318	
Region							
WHO Stratum A	1,789	3 (0.2)	890	6 (0.7)	0.25 [0.06; 0.99]	0.033	0.130
WHO Rest of the World	3,704	64 (1.7)	1,855	44 (2.4)	0.73 [0.50; 1.06]	0.101	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	29 (2.4)	607	14 (2.3)	1.05 [0.56; 1.97]	0.880	0.216
60 to < 90	2,926	31 (1.1)	1,460	29 (2.0)	0.53 [0.32; 0.88]	0.013	
≥ 90	1,369	7 (0.5)	678	7 (1.0)	0.50 [0.17; 1.41]	0.178	
Insulin at Baseline							
No	2,943	31 (1.1)	1,400	22 (1.6)	0.67 [0.39; 1.15]	0.146	0.979
Yes	2,550	36 (1.4)	1,345	28 (2.1)	0.68 [0.42; 1.11]	0.118	
SOC: Metabolism and nutrition disorders PT: Hypomagnesaemia							
Sex							
Female	1,630	7 (0.4)	844	20 (2.4)	0.18 [0.08; 0.43]	< 0.001	0.825
Male	3,863	12 (0.3)	1,901	29 (1.5)	0.20 [0.10; 0.40]	< 0.001	
Age Group (Years)							
< 65	2,718	9 (0.3)	1,375	20 (1.5)	0.23 [0.10; 0.50]	< 0.001	0.586
≥ 65	2,775	10 (0.4)	1,370	29 (2.1)	0.17 [0.08; 0.35]	< 0.001	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	4 (0.3)	607	8 (1.3)	0.25 [0.08; 0.84]	0.015	0.363
60 to < 90	2,926	11 (0.4)	1,460	22 (1.5)	0.25 [0.12; 0.51]	< 0.001	
≥ 90	1,369	4 (0.3)	678	19 (2.8)	0.10 [0.04; 0.31]	< 0.001	
Insulin at Baseline							
No	2,943	10 (0.3)	1,400	26 (1.9)	0.18 [0.09; 0.38]	< 0.001	0.822
Yes	2,550	9 (0.4)	1,345	23 (1.7)	0.21 [0.10; 0.44]	< 0.001	
SOC: Metabolism and nutrition disorders PT: Type 2 diabetes mellitus							
Age Group (Years)							
< 65	2,718	33 (1.2)	1,375	28 (2.0)	0.60 [0.36; 0.98]	0.040	0.462
≥ 65	2,775	23 (0.8)	1,370	14 (1.0)	0.81 [0.42; 1.57]	0.534	
Region							
WHO Stratum A	1,789	30 (1.7)	890	19 (2.1)	0.79 [0.44; 1.39]	0.405	0.426

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Non-Severe Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
WHO Rest of the World	3,704	26 (0.7)	1,855	23 (1.2)	0.57 [0.32; 0.99]	0.043	
Insulin at Baseline							
No	2,943	32 (1.1)	1,400	18 (1.3)	0.85 [0.48; 1.50]	0.567	0.248
Yes	2,550	24 (0.9)	1,345	24 (1.8)	0.53 [0.30; 0.93]	0.023	
SOC: Nervous system disorders PT: Dizziness							
Sex							
Female	1,630	95 (5.8)	844	32 (3.8)	1.54 [1.04; 2.27]	0.030	0.874
Male	3,863	186 (4.8)	1,901	57 (3.0)	1.61 [1.20; 2.15]	0.001	
Region							
WHO Stratum A	1,789	151 (8.4)	890	40 (4.5)	1.88 [1.34; 2.64]	< 0.001	0.128
WHO Rest of the World	3,704	130 (3.5)	1,855	49 (2.6)	1.33 [0.96; 1.84]	0.084	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	76 (6.3)	607	31 (5.1)	1.24 [0.83; 1.86]	0.293	0.267
60 to < 90	2,926	146 (5.0)	1,460	45 (3.1)	1.62 [1.17; 2.25]	0.004	
≥ 90	1,369	59 (4.3)	678	13 (1.9)	2.25 [1.24; 4.07]	0.006	
Insulin at Baseline							
No	2,943	152 (5.2)	1,400	44 (3.1)	1.64 [1.18; 2.28]	0.003	0.727
Yes	2,550	129 (5.1)	1,345	45 (3.3)	1.51 [1.08; 2.11]	0.014	
SOC: Renal and urinary disorders PT: Pollakiuria							
Sex							
Female	1,630	15 (0.9)	844	6 (0.7)	1.29 [0.50; 3.32]	0.591	0.234
Male	3,863	94 (2.4)	1,901	19 (1.0)	2.43 [1.49; 3.97]	< 0.001	
Age Group (Years)							
< 65	2,718	41 (1.5)	1,375	6 (0.4)	3.46 [1.47; 8.12]	0.002	0.183
≥ 65	2,775	68 (2.5)	1,370	19 (1.4)	1.77 [1.07; 2.93]	0.025	
Region							
WHO Stratum A	1,789	64 (3.6)	890	13 (1.5)	2.45 [1.36; 4.42]	0.002	0.529
WHO Rest of the World	3,704	45 (1.2)	1,855	12 (0.6)	1.88 [1.00; 3.54]	0.047	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	16 (1.3)	607	5 (0.8)	1.62 [0.60; 4.40]	0.338	0.806
60 to < 90	2,926	68 (2.3)	1,460	15 (1.0)	2.26 [1.30; 3.94]	0.003	
≥ 90	1,369	25 (1.8)	678	5 (0.7)	2.48 [0.95; 6.44]	0.054	
Insulin at Baseline							
No	2,943	62 (2.1)	1,400	13 (0.9)	2.27 [1.25; 4.11]	0.005	0.830
Yes	2,550	47 (1.8)	1,345	12 (0.9)	2.07 [1.10; 3.88]	0.021	
SOC: Renal and urinary disorders PT: Polyuria							
Sex							
Female	1,630	12 (0.7)	844	1 (0.1)	6.21 [0.81; 47.70]	0.044	0.545
Male	3,863	52 (1.3)	1,901	8 (0.4)	3.20 [1.52; 6.72]	0.001	
Age Group (Years)							
< 65	2,718	33 (1.2)	1,375	3 (0.2)	5.56 [1.71; 18.11]	0.001	0.289

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Non-Severe Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
≥ 65	2,775	31 (1.1)	1,370	6 (0.4)	2.55 [1.07; 6.10]	0.029	
Region							
WHO Stratum A	1,789	41 (2.3)	890	5 (0.6)	4.08 [1.62; 10.29]	0.001	0.615
WHO Rest of the World	3,704	23 (0.6)	1,855	4 (0.2)	2.88 [1.00; 8.31]	0.040	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	5 (0.4)	607	1 (0.2)	2.53 [0.30; 21.64]	0.378	0.832
60 to < 90	2,926	42 (1.4)	1,460	5 (0.3)	4.19 [1.66; 10.57]	< 0.001	
≥ 90	1,369	17 (1.2)	678	3 (0.4)	2.81 [0.83; 9.54]	0.084	
Insulin at Baseline							
No	2,943	30 (1.0)	1,400	4 (0.3)	3.57 [1.26; 10.11]	0.010	0.992
Yes	2,550	34 (1.3)	1,345	5 (0.4)	3.59 [1.41; 9.15]	0.004	
SOC: Reproductive system and breast disorders PT: Balanoposthitis							
Sex							
Female	1,630	0 (0.0)	844	0 (0.0)	n.a.	n.a.	n.a.
Male	3,863	94 (2.4)	1,901	8 (0.4)	5.78 [2.82; 11.88]	< 0.001	
Age Group (Years)							
< 65	2,718	45 (1.7)	1,375	4 (0.3)	5.69 [2.05; 15.79]	< 0.001	0.933
≥ 65	2,775	49 (1.8)	1,370	4 (0.3)	6.05 [2.19; 16.72]	< 0.001	
Region							
WHO Stratum A	1,789	35 (2.0)	890	5 (0.6)	3.48 [1.37; 8.86]	0.005	0.158
WHO Rest of the World	3,704	59 (1.6)	1,855	3 (0.2)	9.85 [3.09; 31.38]	< 0.001	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	11 (0.9)	607	0 (0.0)	n.a.	n.a.	0.547
60 to < 90	2,926	57 (1.9)	1,460	6 (0.4)	4.74 [2.05; 10.97]	< 0.001	
≥ 90	1,369	26 (1.9)	678	2 (0.3)	6.44 [1.53; 27.05]	0.003	
Insulin at Baseline							
No	2,943	51 (1.7)	1,400	5 (0.4)	4.85 [1.94; 12.13]	< 0.001	0.557
Yes	2,550	43 (1.7)	1,345	3 (0.2)	7.56 [2.35; 24.32]	< 0.001	
SOC: Skin and subcutaneous tissue disorders PT: Skin ulcer							
Sex							
Female	1,630	19 (1.2)	844	7 (0.8)	1.41 [0.59; 3.33]	0.437	0.783
Male	3,863	72 (1.9)	1,901	22 (1.2)	1.61 [1.00; 2.59]	0.046	
Age Group (Years)							
< 65	2,718	38 (1.4)	1,375	10 (0.7)	1.92 [0.96; 3.85]	0.060	0.453
≥ 65	2,775	53 (1.9)	1,370	19 (1.4)	1.38 [0.82; 2.32]	0.225	
Region							
WHO Stratum A	1,789	50 (2.8)	890	10 (1.1)	2.49 [1.27; 4.88]	0.006	0.054
WHO Rest of the World	3,704	41 (1.1)	1,855	19 (1.0)	1.08 [0.63; 1.86]	0.779	
Baseline eGFR (mL/min/1.73 m^2)							
< 60	1,198	19 (1.6)	607	5 (0.8)	1.93 [0.72; 5.13]	0.182	0.614
60 to < 90	2,926	57 (1.9)	1,460	17 (1.2)	1.67 [0.98; 2.87]	0.058	

Study: VERTIS CV	Ertugliflozin Pooled		Placebo		Ertugliflozin Pooled vs. Placebo		
Non-Severe Adverse Events	N[a]	Participants with Event n (%)	N[a]	Participants with Event n (%)	Relative Risk [95 %-CI][b]	Treatment Effect p-Value[c]	Interaction Test p-Value[d]
≥ 90	1,369	15 (1.1)	678	7 (1.0)	1.06 [0.43; 2.59]	0.896	
Insulin at Baseline							
No	2,943	29 (1.0)	1,400	7 (0.5)	1.97 [0.87; 4.49]	0.099	0.569
Yes	2,550	62 (2.4)	1,345	22 (1.6)	1.49 [0.92; 2.41]	0.104	

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

b: 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.'.

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

d: 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.'

e: A specific adverse event 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; eGFR: Estimated Glomerular Filtration Rate; 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