SUPPLEMENTARY APPENDIX

Glycemic Efficacy and Safety of the SGLT2 Inhibitor Ertugliflozin in Patients with Type 2 Diabetes and Stage 3 Chronic Kidney Disease: An Analysis from the VERTIS CV Randomized Trial

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Proposed running title: Ertugliflozin Efficacy in T2DM and CKD Stage 3

Journal: *BMJ Open Diabetes Research & Care*

Supplementary Table 1 Baseline demographics and clinical characteristics of VERTIS CV patients with CKD Stage 3A and CKD Stage 3B*

Characteristic†	CKD Stage 3A			CKD Stage 3B		
	Placebo (N=440)	Ertugliflozin 5 mg (N=466)	Ertugliflozin 15 mg (N=413)	Placebo (N=158)	Ertugliflozin 5 mg (N=152)	Ertugliflozin 15 mg (N=147)
Age — years	67.4 (7.6)	68.0 (7.5)	67.8 (7.3)	69.6 (6.9)	69.3 (8.1)	69.0 (8.1)
Male — n (%)	295 (67.0)	303 (65.0)	261 (63.2)	100 (63.3)	93 (61.2)	90 (61.2)
Race — n (%)‡						
White	374 (85.0)	403 (86.5)	369 (89.3)	140 (88.6)	120 (78.9)	124 (84.4)
Black	13 (3.0)	12 (2.6)	7 (1.7)	4 (2.5)	9 (5.9)	2 (1.4)
Asian	34 (7.7)	38 (8.2)	24 (5.8)	9 (5.7)	17 (11.2)	11 (7.5)
Other	19 (4.3)	13 (2.8)	13 (3.1)	5 (3.2)	6 (3.9)	10 (6.8)
Region — n (%)						
North America	132 (30.0)	138 (29.6)	118 (28.6)	59 (37.3)	51 (33.6)	51 (34.7)
South America	37 (8.4)	32 (6.9)	39 (9.4)	9 (5.7)	10 (6.6)	10 (6.8)
Europe	204 (46.4)	230 (49.4)	201 (48.7)	67 (42.4)	60 (39.5)	61 (41.5)
Asia	38 (8.6)	34 (7.3)	23 (5.6)	8 (5.1)	15 (9.9)	9 (6.1)
South Africa	21 (4.8)	24 (5.2)	21 (5.1)	7 (4.4)	13 (8.6)	9 (6.1)

Australia/New Zealand	8 (1.8)	8 (1.7)	11 (2.7)	8 (5.1)	3 (2.0)	7 (4.8)
Body-mass index — kg/m^2	32.4 (5.6)	32.4 (5.4)	32.7 (5.8)	33.0 (5.5)	32.0 (5.0)	31.8 (5.6)
Duration of type 2 diabetes — years	15.9 (9.2)	15.1 (8.5)	14.8 (8.6)	17.8 (9.6)	16.0 (9.4)	16.3 (8.9)
Glycated hemoglobin — %	8.2 (0.9)	8.2 (0.9)	8.2 (1.0)	8.2 (0.9)	8.3 (1.1)	8.3 (0.9)
eGFR — mL/min/1.73 m^2§	52.7 (4.5)	53.0 (4.2)	53.3 (4.2)	38.9 (3.9)	39.0 (4.1)	38.4 (4.1)
Albuminuria — n (%)						
Normal-albuminuria (<30 mg/g)	225 (51.1)	239 (51.3)	216 (52.3)	60 (38.0)	63 (41.4)	52 (35.4)
Micro-albuminuria (≥30 to ≤300 mg/g)	143 (32.5)	158 (33.9)	118 (28.6)	64 (40.5)	51 (33.6)	60 (40.8)
Macro-albuminuria (>300 mg/g)	59 (13.4)	57 (12.2)	62 (15.0)	33 (20.9)	34 (22.4)	33 (22.4)
Unknown	13 (3.0)	12 (2.6)	17 (4.1)	1 (0.6)	4 (2.6)	2 (1.4)
Systolic blood pressure — mm Hg	132.2 (15.0)	134.1 (15.0)	133.4 (13.9)	134.1 (15.7)	136.6 (14.3)	134.2 (16.1)
Hypertension — n (%)	420 (95.5)	443 (95.1)	381 (92.3)	151 (95.6)	146 (96.1)	143 (97.3)
Dyslipidemia — n (%)	352 (80.0)	368 (79.0)	326 (78.9)	137 (86.7)	128 (84.2)	119 (81.0)
Coronary artery disease — n (%)	351 (79.8)	366 (78.5)	317 (76.8)	129 (81.6)	125 (82.2)	119 (81.0)
Cerebrovascular disease — n (%)	105 (23.9)	116 (24.9)	110 (26.6)	33 (20.9)	37 (24.3)	37 (25.2)
Peripheral arterial disease — n (%)	83 (18.9)	78 (16.7)	78 (18.9)	40 (25.3)	35 (23.0)	33 (22.4)
Antihyperglycemic medications — n (%)						

None	3 (0.7)	4 (0.9)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Metformin	314 (71.4)	319 (68.5)	276 (66.8)	68 (43.0)	66 (43.4)	72 (49.0)
Insulin	245 (55.7)	262 (56.2)	215 (52.1)	112 (70.9)	108 (71.1)	93 (63.3)
Sulfonylurea	174 (39.5)	186 (39.9)	169 (40.9)	53 (33.5)	45 (29.6)	50 (34.0)
Dipeptidyl peptidase-4 inhibitor	58 (13.2)	53 (11.4)	47 (11.4)	14 (8.9)	21 (13.8)	23 (15.6)
Glucagon-like peptide-1 receptor agonist	18 (4.1)	18 (3.9)	14 (3.4)	7 (4.4)	7 (4.6)	5 (3.4)

*CKD stage was based on eGFR calculated using the MDRD equation.

†Values are mean ± standard deviation unless otherwise stated.

‡Race was reported by the participant.

§eGFR was calculated using the MDRD equation.

Abbreviations: CKD, chronic kidney disease; CKD Stage 3A, eGFR 45 to <60 mL/min/1.73 m^2; CKD Stage 3B, eGFR 30 to <45 mL/min/1.73 m^2; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

Supplementary Table 2 Other efficacy outcomes at Week 18 in VERTIS CV patients with CKD Stage 3A and CKD Stage 3B*

Efficacy Outcome	CKD Stage 3A			CKD Stage 3B		
	Placebo	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	Ertugliflozin 5 mg	Ertugliflozin 15 mg
FPG						
n/N†	436/439	464/465	411/413	158/158	152/152	146/146
Baseline mean (SD) — mg/dL	174.7 (54.29)	174.25 (52.83)	176.4 (60.49)	165.75 (48.62)	178.2 (62.375)	163.7 (51.64)
LS-mean change from baseline (95% CI)‡	−22.18 (−26.54, −17.81)	−30.53 (−34.69, −26.38)	−33.52 (−37.80, −29.25)	−25.11 (−32.58, −17.64)	−30.88 (−38.08, −23.68)	−27.46 (−34.86, −20.05)
Difference in LS mean vs. placebo (95% CI)‡	—	−8.36 (−13.43, −3.29)	−11.35 (−16.52, −6.18)	—	−5.77 (−14.52, 2.98)	−2.35 (−11.28, 6.58)
P-value vs. placebo§	—	0.001	<0.001	—	0.195	0.605
Body Weight						
n/N†	439/439	465/465	413/413	158/158	152/152	147/147
Baseline mean (SD) — kg	92.3 (19.12)	92.1 (18.03)	92.5 (19.36)	93.1 (18.85)	90.0 (17.22)	89.1 (19.14)
LS-mean change from baseline (95% CI)‡	−0.52 (−0.80, −0.25)	−1.84 (−2.11, −1.58)	−1.90 (−2.18, −1.62)	−0.08 (−0.55, 0.40)	−1.59 (−2.06, −1.12)	−2.03 (−2.51, −1.55)
Difference in LS mean vs. placebo (95% CI)‡	—	−1.32 (−1.70, −0.94)	−1.38 (−1.77, −0.99)	—	−1.51 (−2.18, −0.84)	−1.95 (−2.63, −1.28)
P-value vs. placebo§	—	<0.001	<0.001	—	<0.001	<0.001
SBP						
n/N†	439/439	464/465	413/413	158/158	151/152	147/147
Baseline mean (SD) — mm Hg	132.2 (15.00)	134.1 (15.00)	133.4 (13.86)	134.1 (15.65)	136.6 (14.26)	134.2 (16.08)
LS-mean change from baseline (95% CI)‡	0.99 (−0.37, 2.35)	−2.03 (−3.35, −0.71)	−2.42 (−3.80, −1.04)	0.59 (−1.89, 3.06)	−1.93 (−4.38, 0.52)	−1.83 (−4.36, 0.69)
Difference in LS mean vs. placebo (95% CI)‡	—	−3.02 (−4.83, −1.21)	−3.41 (−5.26, −1.55)	—	−2.52 (−5.86, 0.82)	−2.42 (−5.81, 0.97)
P-value vs. placebo§	—	0.001	<0.001	—	0.139	0.162

*CKD stage was based on eGFR calculated using the MDRD equation.

†n is the number of patients with non-missing assessments at baseline; N is the number of patients in the cLDA FAS (i.e., randomized patients who took at least 1 dose of study medication and had at least 1 assessment at or after baseline).

‡Calculated using a cLDA model with fixed effects for treatment, time, baseline eGFR (continuous) and the interaction of time (categorical) by treatment.

§Nominal P-values.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CKD Stage 3A, eGFR 45 to <60 mL/min/1.73 m^2; CKD Stage 3B, eGFR 30 to <45 mL/min/1.73 m^2; cLDA, constrained longitudinal data analysis; eGFR, estimated glomerular filtration rate; FAS, full analysis set; FPG, fasting plasma glucose; LS, least squares; MDRD, Modification of Diet in Renal Disease; SBP, systolic blood pressure; SD, standard deviation.

Supplementary Table 3 Adverse events in VERTIS CV patients with CKD Stage 3A and CKD Stage 3B*

Adverse Event†	CKD Stage 3A			CKD Stage 3B		
	Placebo (N=439)‡	Ertugliflozin 5 mg (N=465)‡	Ertugliflozin 15 mg (N=413)‡	Placebo (N=158)‡	Ertugliflozin 5 mg (N=152)‡	Ertugliflozin 15 mg (N=147)‡
Any AE — n (%)	394 (89.7)	422 (90.8)	372 (90.1)	141 (89.2)	139 (91.4)	129 (87.8)
Serious AEs — n (%)	180 (41.0)	191 (41.1)	151 (36.6)	70 (44.3)	61 (40.1)	71 (48.3)
AEs leading to discontinuation of study drug— n (%)	29 (6.6)	51 (11.0)	34 (8.2)	22 (13.9)	15 (9.9)	20 (13.6)
Deaths — n (%)	17 (3.9)	26 (5.6)	18 (4.4)	11 (7.0)	8 (5.3)	12 (8.2)
Pre-specified AEs of interest — n (%)						
Urinary tract infection	58 (13.2)	70 (15.1)	56 (13.6)	19 (12.0)	15 (9.9)	23 (15.6)
Genital mycotic infection — women§	5 (3.4)	8 (4.9)	11 (7.2)	3 (5.2)	1 (1.7)	6 (10.5)
Genital mycotic infection — men¶	1 (0.3)	10 (3.3)	12 (4.6)	0 (0.0)	2 (2.2)	1 (1.1)
Symptomatic hypoglycemia‖	161 (36.7)	172 (37.0)	144 (34.9)	63 (39.9)	60 (39.5)	49 (33.3)
Hypovolemia	27 (6.2)	35 (7.5)	18 (4.4)	12 (7.6)	9 (5.9)	15 (10.2)
Kidney-related AEs — n (%)						
Any kidney-related AE	36 (8.2)	41 (8.8)	33 (8.0)	25 (15.8)	19 (12.5)	23 (15.6)
Acute kidney injury	20 (4.6)	16 (3.4)	16 (3.9)	12 (7.6)	7 (4.6)	14 (9.5)
Kidney failure	11 (2.5)	4 (0.9)	8 (1.9)	6 (3.8)	10 (6.6)	3 (2.0)
Kidney impairment	11 (2.5)	22 (4.7)	11 (2.7)	7 (4.4)	6 (3.9)	6 (4.1)

Adjudicated kidney events — n (%)						
Any adjudicated kidney event	13	7	14	11	9	7
Causality						
Very likely	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Probable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Possible	3 (23.1)	0 (0.0)	2 (14.3)	1 (9.1)	0 (0.0)	1 (14.3)
Doubtful	5 (38.5)	4 (57.1)	6 (42.9)	2 (18.2)	6 (66.7)	2 (28.6)
Not related	5 (38.5)	3 (42.9)	6 (42.9)	8 (72.7)	3 (33.3)	4 (57.1)

*CKD stage was based on eGFR calculated using the MDRD equation.

†All events occurring within 14 days of final dose of treatment and including events after initiation of glycemic rescue medication, except for those related to hypoglycemia.

‡N is the number of patients in the safety analysis population (i.e., patients who took at least 1 dose of study medication).

§Number of women with CKD Stage 3A: placebo, n=145; ertugliflozin 5 mg, n=163; ertugliflozin 15 mg, n=152. Number of women with CKD Stage 3B: placebo, n=58; ertugliflozin 5 mg, n=59; ertugliflozin 15 mg, n=57.

¶Number of men with CKD Stage 3A: placebo, n=294; ertugliflozin 5 mg, n=302; ertugliflozin 15 mg, n=261. Number of men with CKD Stage 3B: placebo, n=100; ertugliflozin 5 mg, n=93; ertugliflozin 15 mg, n=90.

‖Symptomatic hypoglycemia was defined as an event with clinical symptoms reported by the investigator as hypoglycemia (biochemical documentation not required).

Abbreviations: AE, adverse event; CKD, chronic kidney disease; CKD Stage 3A, eGFR 45 to <60 mL/min/1.73 m^2; CKD Stage 3B, eGFR 30 to <45 mL/min/1.73 m^2; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.