EMA/612874/2021
Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Procedure No. EMEA/H/C/WS1953

Medicinal products authorised through the centralised procedure

Invented name:	International non-proprietary name/Common name:	Product-specific application number
Steglatro	ertugliflozin	EMEA/H/C/004315/WS1953/0013
Segluromet	ertugliflozin / metformin hydrochloride	EMEA/H/C/004314/WS1953/0012

Worksharing applicant (WSA): Merck Sharp & Dohme B.V.

This application is in the area of: (Non-)Clinical RMP

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

The PRAC/CHMP Rapporteurs should complete the 'actual' date at each stage of the procedure. This is the date of circulation of the report to CHMP/PRAC members.

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	28 Nov 2020	28 Nov 2020	☐
☐	CHMP Co-Rapporteur Assessment Report	22 Jan 2021	22 Jan 2021	☐
☐	CHMP Rapporteur Assessment Report	22 Jan 2021	22 Jan 2021	☐
☐	PRAC Rapporteur Assessment Report	29 Jan 2021	01 Feb 2021	☐
☐	PRAC members comments	03 Feb 2021	03 Feb 2021	☐
☐	Updated PRAC Rapporteur Assessment Report	04 Feb 2021	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	11 Feb 2021	11 Feb 2021	☐
☐	CHMP members comments	15 Feb 2021	15 Feb 2021	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 Feb 2021	18 Feb 2021	☐
☐	Request for supplementary information	25 Feb 2021	25 Feb 2021	☐
☐	MAH responses by:	23 Apr 2021	23 Apr 2021	☐
☐	Re-Start of procedure	26 Apr 2021	26 Apr 2021	☐
☐	CHMP Rapporteur Assessment Report	31 May 2021	31 May 2021	☐
☐	CHMP members comments	14 Jun 2021	14 Jun 2021	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	17 Jun 2021	17 Jun 2021	☐
☐	2nd Request for supplementary information	24 Jun 2021	24 Jun 2021	☐
☐	MAH responses by:	16 Jul 2021	16 Jul 2021	☐
☐	Re-Start of procedure	19 Jul 2021	19 Jul 2021	☐
☐	CHMP Rapporteur Assessment Report	23 Aug 2021	23 Aug 2021	☐
☐	CHMP members comments	06 Sep 2021	06 Sep 2021	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	09 Sep 2021	09 Sep 2021	☐
☒	Opinion	16 Sep 2021	16 Sep 2021	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Declarations

☒The assessor confirms that reference to ongoing assessments or development plans for other products is not included in this assessment report, including in the Product Information, if any.

Whenever the above box is un-ticked please indicate section and page where confidential information is located here:

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List of abbreviations

Abbreviation	Definition
ACC	American College of Cardiology
ADA	American Diabetes Association
AHA	antihyperglycemic agent
ALT	alanine aminotransferase
APRFU	all post-randomization follow up
ASaT	all Subjects as Treated
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
BW	body weight
CABG	coronary artery bypass grafting
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMQ	custom MedDRA Query
CPH	Cox Proportional Hazard
CSR	clinical study report
CV	cardiovascular
CVMA	cardiovascular meta-analysis
CVOT	cardiovascular outcomes trial
DBP	diastolic blood pressure
DPP-IV	dipeptidyl peptidase-IV
EAC	endpoint adjudication committee
EF	ejection fraction
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
FAS	full analysis set
FDC	fixed-dose combination
FNF	fatal or non-fatal
FPG	fasting plasma glucose
GLP-1	glucagon-like peptide 1

Abbreviation	Definition
GMI	genital mycotic infection
HbA1c	hemoglobin A_{1c}
HF	heart failure
HHF	hospitalization for heart failure
HR	hazard ratio
ITT	intention-to-treat
LDL-C	low-density lipoprotein cholesterol
LS	least squares
MACE	major adverse cardiovascular events
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MRA	mineralocorticoid receptor antagonist
NDA	new drug application
NI	non-inferiority
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
PDLC	predefined limit of change
PT	preferred term
RAAS	renin-angiotensin-aldosterone system
SAP	statistical analysis plan
SBP	systolic blood pressure
SCS	Summary of Clinical Safety
SD	standard deviation
SE	standard error
SGLT2	sodium-glucose co-transporter 2
SMQ	standard MedDRA Query
SOC	system organ class
SU	sulfonylurea
T2DM	type 2 diabetes mellitus
UA	unstable angina
UACR	urinary albumin creatinine ratio
ULN	upper limit of normal
UTI	urinary tract infection

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 5 November 2020 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC of Steglatro and Segluromet in order to modify the indication, update posology recommendations and include efficacy and safety information based on final results from the VERTIS CV study (protocol 8835-004/B1521021) listed as a category 3 study in the RMP. This is a multi-centre, multi-national, randomised, double-blind, placebo-controlled study to evaluate the effect of ertugliflozin on cardiovascular risk in adult patients with type 2 diabetes and established atherosclerotic cardiovascular disease. The Package Leaflet is updated accordingly.

The RMP version 2.0 has also been submitted.

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMA/PDCO/854612/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-001533-PIP01-13-M02 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the WSA did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

Scientific advice related to the VERTIS CV study has been provided by the EMA in procedures EMEA/H/SA/2164/2/2011/III, EMEA/H/SA/2164/2/FU/1/2013/II and EMEA/H/SA/2164/2/FU/2/2016/II.

2. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC of Steglatro and Segluromet in order to modify the indication, update posology recommendations and include efficacy and safety information based on final results from the VERTIS CV study (protocol 8835-004/B1521021) listed as a category 3 study in the RMP. This is a multi-centre, multi-national, randomised, double-blind, placebo-controlled study to evaluate the effect of ertugliflozin on cardiovascular risk in adult patients with type 2 diabetes and established atherosclerotic cardiovascular disease. The Package Leaflet is updated accordingly.

The RMP version 2.0 has also been submitted.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the worksharing procedure, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

3. Scientific discussion

3.1. Introduction

3.1.1. Problem statement

Disease or condition

T2DM is a chronic disease that is a major public healthcare problem globally. The prevalence of diabetes has been growing rapidly in recent decades. Patients with T2DM have a 2- to 4-fold increased risk of CV disease relative to those without T2DM, and CV disease is the leading cause of death and complications in patients with T2DM.

The claimed therapeutic indication

Based on the submitted data on CV safety, the MAH wish to extend the indication as follows:

"Steglatro is indicated for the treatment of ~~in~~ adults ~~aged 18 years and older~~ with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise ~~to improve glycaemic control~~:

- as monotherapy ~~in patients for whom the use of~~ when metformin is considered inappropriate due to intolerance or contraindications.
- in addition to other medicinal products for the treatment of diabetes.

~~(~~For study results with respect to combinations of therapies, ~~and~~ effects on glycaemic control, cardiovascular events, and the populations studied, see sections 4.4, 4.5, and 5.1.~~)~~"

"Segluromet is indicated in adults for the treatment of ~~aged 18 years and older with~~ type 2 diabetes mellitus as an adjunct to diet and exercise ~~to improve glycaemic control~~:

- in patients ~~not adequately~~ insufficiently controlled on their maximally tolerated dose of metformin alone
- in combination with ~~in patients on their maximally tolerated doses of metformin in addition to~~ other medicinal products for the treatment of diabetes in patients insufficiently controlled with metformin and these products
- in patients already being treated with the combination of ertugliflozin and metformin as separate tablets.

~~(~~For study results with respect to combinations of therapies, ~~and~~ effects on glycaemic control, cardiovascular events and the population studied, see sections 4.4, 4.5 and 5.1.~~)~~

Epidemiology

T2DM is a chronic disease and the prevalence of diabetes has been growing rapidly in recent decades. The International Diabetes Federation estimated the global prevalence of diabetes as 151 million in 2000, rising to 382 million in 2013, and is projected to reach 642 million by the year 2040.

Clinical presentation and prognosis

Patients with diabetes are at high risk for adverse outcomes from ASCVD, HF, and CKD. Patients with T2DM have a 2- to 4- fold increased risk of CV disease relative to those without T2DM, and CV disease is the leading cause of death and complications in patients with T2DM.

The lifetime adjusted cumulative hazard for incident HF in patients with T2DM, hypertension, and obesity with an index age of 55 years reaches approximately 60%. Moreover, patients with T2DM represent a substantial proportion of patients hospitalized for HF. In a large global registry, patients with history of atherothrombosis and T2DM had a 30% greater risk of HHF than patients with atherothrombosis but without T2DM. In a large European registry, T2DM was prevalent in approximately one-half of all patients admitted for HF in 1 year at 211 cardiology centers. Compared with those patients without diabetes, patients with diabetes had higher cumulative rates of in hospital and 1-year mortality and 1-year HF re-hospitalization, even when adjusting for multiple clinical risk factors.

T2DM is also the most common cause of CKD and the most common aetiology for patients to progress to dialysis. Moreover, patients with T2DM and CKD have higher risks of death and CV events than progression to ESRD.

Management

In large outcome studies, members of the SGLT2 inhibitor class have been shown to reduce the risk of CV and renal outcomes in subjects with and without T2DM. A consistent finding in all of these studies is a robust effect of SGLT2 inhibitor treatment on reducing the risk of HHF. Preservation of renal function has also been a consistent finding in these studies.

Current diabetes and cardiovascular society guidelines have been significantly impacted by the results of these outcome studies. The 2020 American Diabetes Association Standards of Care recommends that if ASCVD predominates, a GLP-1 receptor agonist or an SGLT2 inhibitor with proven CV disease benefit, if eGFR is adequate, should be used for the treatment of patients with T2DM. However, if HF and/or CKD predominates, the use of a SGLT2 inhibitor with proven benefit in reducing HF and/or CKD progression, if eGFR is adequate, should be used (if tolerated).

3.1.2. About the product

Ertugliflozin is an inhibitor of SGLT2 that possesses a high selectivity over glucose transport via SGLT1 and several other glucose transporters (GLUT1 4). Ertugliflozin inhibits renal glucose reabsorption resulting in urinary glucose excretion and thereby reducing plasma glucose and HbA1c in subjects with T2DM.

Ertugliflozin is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM. Phase 3 studies in adults with T2DM have shown that treatment with ertugliflozin as monotherapy and in combination with other AHAs improves glycaemic control, reduces BW and BP, and is well tolerated.

Ertugliflozin (5 mg and 15 mg) is available as an individual product and in 2 FDCs (ertugliflozin/sitagliptin FDC and ertugliflozin/metformin FDC).

3.1.3. The development programme/compliance with CHMP guidance/scientific advice

The clinical development program supporting the indication for the treatment of adults with T2DM was planned, conducted, and analysed in accordance with the EU regulatory guidance documents that were in effect at the time that the Phase 3 program initiated, i.e. the "Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus" (CPMP/EWP/1080/00 Rev. 1).

VERTIS CV was conducted to satisfy US FDA and EMA guidelines for demonstration of CV safety for novel AHAs in the pre-approval and post-approval periods. At the time of the original submission of the ertugliflozin, ertugliflozin/sitagliptin FDC, and ertugliflozin/metformin FDC dossiers, an assessment of CV safety based on a prespecified CVMA, demonstrated that ertugliflozin was not associated with an increase in CV risk in accordance with US FDA recommendations for T2DM drug development.

The EMA draft reflection paper on assessment of CV risk of medicinal products for the treatment of CV and metabolic diseases (EMA/CHMP/50549/2015) was released during the conduct of the ertugliflozin Phase 3 program. The applicant considers that the approach taken to enable assessment of the CV risk for ertugliflozin is in keeping with this draft reflection paper. This is agreed.

Scientific advice related to the VERTIS CV study has been provided by the EMA:

EMEA/H/SA/2164/2/2011/III (ertugliflozin)

As part of this advice, the design of the CVOT study was discussed by the CHMP. The advice discussed the choice of the endpoint, the HbA1c inclusion criterion and aspects on the interim analysis.

It was stressed that if the purpose of the study is to show reduction of CV risk, only MACE events according to the strict definition will be acceptable as the primary endpoint (see Q 11).

EMEA/H/SA/2164/2/FU/1/2013/II

As part of this advice, the acceptability of the two included 18-week glycaemic sub-studies: add-on to 1) insulin ± metformin, 2) SU monotherapy, was discussed. The CHMP endorsed the applicant's approach but noted that the duration is considered relatively short for efficacy, and that longer follow-up is important. It was also discussed that the population in the CVOT may not be representative for the general population of patients with T2DM, as only patients with CV-disease will be included. With regards to the add-on to insulin sub-study, it was noted that a heterogeneous population with different insulin regimens would be included. Beneficial trend needs to be shown for all regimens.

EMEA/H/SA/2164/2/FU/2/2016/II

The advice discussed the acceptability of the amendment made to the CVOT and the addition of a third glycaemic sub-study: add-on to metformin + SU. The CHMP concluded that the changes from the previous proposal were not considered crucial, but that some comments were deemed necessary. As pointed out in the previous advice, the three 18-week glycaemic efficacy sub-studies (add on to insulin ± metformin, metformin + SU and SU monotherapy) embedded in the CVOT are considered of marginal duration, and a longer observation is still recommended. It was also noted that the fact that ertugliflozin is not a first in class drug, may alleviate some of the concerns with regards to some of the proposed treatment combinations. It was also, again, noted the data in adjunct to insulin might be difficult to interpret because of the inclusion of short-acting/mix/basal insulin, rendering the groups to assess safety and efficacy rather small.

Any potential claim for superiority regarding CV death, CV death/hospitalization for heart failure, and/or chronic kidney disease would be limited to diabetic patients. Although these endpoints are of interest, specific claims may require separate dedicated studies.

The advice given by the CHMP has been followed in all essential aspects.

3.1.4. General comments on compliance with GCP

According to the MAH, VERTIS CV and the three glycaemic sub-studies were conducted following appropriate Good Clinical Practice standards and considerations for the ethical treatment of human participants that were in place at the time the studies were performed.

3.2. Non-clinical aspects

No new clinical data have been submitted in this application, which is considered acceptable.

3.2.1. Ecotoxicity/environmental risk assessment

The applicant has submitted a rationale for not submitting an updated environmental risk assessment. It is agreed that the proposed change of the indication does not significantly increase the extent of use, and the omission of an updated ERA is thus justified.

3.2.2. Conclusion on the non-clinical aspects

Based on the updated data submitted in this application, the new/extended indication does not lead to a significant increase in environmental exposure further to the use of ertugliflozin.

3.3. Clinical aspects

3.3.1. Introduction

This application is supported by one study (VERTIS CV) which includes three sub-studies. In the following the general design of the study is presented. The sub-studies support treatment combinations not investigated at the time of the MAA. Data from the VERTIS CV, on the use of ertugliflozin in patients with renal impairment, is also presented.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the WSA.

The WSA has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1 Overview of the Ertugliflozin Cardiovascular Outcome Study (VERTIS CV)

Study Number (Status) Number of Study Sites (Countries)	Design	Number of Participants Randomized and Treated by Intervention Group	Study Population	Primary Endpoint/Results
MK-8835-004/B1521021 (Main CV Study) (completed) 548 sites‡ (34 countries)	Multicenter, randomized, double-blind, placebo-controlled, event-driven study in subjects on standard of care aged ≥40 years with T2DM, inadequate glycemic control (A1C 7.0% to 10.5%) and established vascular disease involving the coronary, cerebrovascular, or peripheral vascular system.	Ertugliflozin 5 mg qd: 2,746 Ertugliflozin 15 mg qd: 2,747 Placebo: 2,745	Gender: 5,769 males and 2,477 females Mean age (years): 64.4 Percentage aged ≥75 years: 11.0 Mean duration of T2DM (years): 13 Mean BMI (kg/m^2): 32.0 Mean A1C (%): 8.2 Mean eGFR, mL/min/1.73 m^2 (%) 30 to <60: 21.5 60 to <90: 53.2 ≥90: 24.8 Established CV disease (%): 99.3 History of: Coronary Artery Disease (MI and/or coronary revascularization) (%): 75.9 Myocardial infarction (%): 48.0 Coronary revascularization (%): 58.1 Cerebrovascular Disease (%): 22.9 Stroke (%): 21.1 Carotid revascularization (%): 2.6 Peripheral Artery Disease (%): 18.7 Peripheral Revascularization (%:): 4.2 Medical history of Heart Failure N (%): 1,958 (23.7): NYHA in subjects with history of HF NYHA Class I (N): 463 NYHA Class II (N): 1,290 NYHA Class III (N): 139 NYHA Class IV (N): 1 Subjects with EF data available (based on information abstracted from medical history records): • Overall study population: 5,006 out of 8,246 (60.7%) subjects	Time to first occurrence of MACE. Ertugliflozin (5 mg and 15 mg combined) was noninferior to placebo on MACE (HR for all ertugliflozin group versus placebo, 0.97; 95.6% CI, 0.848 to 1.114; p<0.001 for non-inferiority).

Study Number (Status) Number of Study Sites (Countries)	Design	Number of Participants Randomized and Treated by Intervention Group	Study Population	Primary Endpoint/Results
			• Population with history of HF: 1,485 out of 1,958 (75.8%) subjects	

Abbreviations: A1C=glycated hemoglobin; BMI=Body mass index; CABG=coronary artery bypass graft; CV=cardiovascular; EF=ejection fraction; eGFR=estimated glomerular filtration rate; HF=heart failure; MACE=major adverse cardiovascular events (defined as CV death, non-fatal myocardial infarction or non-fatal stroke); MI=myocardial infarction; N=overall number of subjects randomly assigned to study medication; T2DM=type 2 diabetes mellitus

‡This study included subjects in 34 countries at 548 study centers according to subjects' final assigned study center at database lock.

Table 2 Overview of the Glycaemic Sub-Studies in VERTIS CV

Study Number (Status) Number of Study Sites (Countries)	Design	Number of Participants Randomized and Treated by Intervention Group	Study Population	Primary Endpoint/Results
MK-8835-004/B1521021 (Insulin with or without Metformin Sub-study) (completed) 312 sites (29 countries)	Multicenter, double-blind, placebo-controlled, 18-week sub-study in subjects aged ≥40 years with T2DM and inadequate glycemic control (A1C 7.0% to 10.5%) on stable therapy with insulin alone or insulin with metformin‡	Ertugliflozin 5 mg qd: 348 Ertugliflozin 15 mg qd: 370 Placebo: 347	Gender: 726 males and 339 females Mean age (years): 64.8 Percentage aged ≥75 years: 11.0 Mean BMI (kg/m^2): 32.5 Mean duration of T2DM (years): 16.66 Mean A1C (%): 8.41 Mean insulin dose at baseline (units/day): 70.3 Median metformin dose at baseline (mg/day): 2000.0 Percentage on insulin alone (%): 40.6 Percentage on insulin+metformin (%): 59.4	Change from baseline in A1C at Week 18. Reductions from baseline in A1C at Week 18 were significantly greater with ertugliflozin 5 mg and 15 mg relative to placebo (LS mean differences: -0.58% and -0.65%, respectively, $p<0.001$ for both comparisons).

Study Number (Status) Number of Study Sites (Countries)	Design	Number of Participants Randomized and Treated by Intervention Group	Study Population	Primary Endpoint/Results
MK-8835-004/B1521021 (SU Monotherapy Sub-Study) (completed) 68 sites (15 countries)	Multicenter, double-blind, placebo-controlled, 18-week sub-study in subjects aged ≥40 years with T2DM and inadequate glycemic control (A1C 7.0% to 10.5%) on stable monotherapy with an SU[§]	Ertugliflozin 5 mg qd: 55 Ertugliflozin 15 mg qd: 54 Placebo: 48	Gender: 97 males and 60 females Mean age (years): 64.6 Percentage aged ≥75 years: 15.9 Mean BMI (years): 30.7 kg/m2 Mean duration of T2DM (years): 8.48 Mean A1C (%): 8.29 SU used at randomization (N); Median Dose (mg/day): Gliclazide: 75; 60.0 Glimepiride: 60; 4.0 Glipizide: 12; 20.0 Glyburide: 10; 10.3	Change from baseline in A1C at Week 18. Reductions from baseline in A1C at Week 18 were not significantly greater with ertugliflozin 5 mg and 15 mg relative to placebo (LS mean differences: -0.35 % [p=0.063], -0.22% [p=0.247], respectively).
MK-8835-004/B1521021 (Metformin with SU Sub-study) (completed) 164 sites (24 countries)	Multicenter, double-blind, placebo-controlled, 18-week sub-study in subjects aged ≥40 years with T2DM and inadequate glycemic control (A1C 7.0% to 10.5%) on metformin with an SU[¶].	Ertugliflozin 5 mg qd: 100 Ertugliflozin 15 mg qd: 113 Placebo: 117	Gender: 247 males and 83 females Mean age (years): 63.2 Percentage aged ≥75 years: 11.2 Mean BMI (kg/m^2): 31.7 Mean duration of T2DM (years): 11.41 Mean A1C (%): 8.32 Median metformin dose at baseline (mg/day): 2000.0 SU used at randomization (N); Median Dose (mg/day): Gliclazide: 140; 90.0 Glimepiride: 115; 4.0 Glipizide: 38; 15.0 Glyburide: 37; 10.0	Change from baseline in A1C at Week 18. Reductions from baseline A1C at Week 18 were significantly greater with ertugliflozin 5 mg and 15 mg relative to placebo (LS mean differences: -0.66 % and -0.75%, respectively, p<0.001 for both comparisons).

Abbreviations: A1C=glycated hemoglobin; BMI=body mass index; N=overall number of subjects randomly assigned to study medication; SU=sulfonylurea; T2DM=type 2 diabetes mellitus.

[‡]Insulin ≥20 units/day with or without metformin ≥1,500 mg/day, where doses of insulin with or without metformin have been stable for at least 8 weeks prior to the screening visit (V1) and during the period between the screening visit (V1) and randomization.

[§]SU at the V1 at the specified doses: Glyburide (Glibenclamide) ≥10 mg/day, Micronized Glyburide ≥6 mg/day, Glipizide ≥10 mg/day, Gliclazide (immediate-release) ≥160 mg/day, Gliclazide (modified-release) ≥60 mg/day, Glimepiride ≥4 mg/day, The dose of the SU monotherapy must have been stable for at least 8 weeks prior to the time of the V1 and during the period between the V1 and randomization.

Study Number (Status) Number of Study Sites (Countries)	Design	Number of Participants Randomized and Treated by Intervention Group	Study Population	Primary Endpoint/Results
¶Metformin ≥1500 mg/day with an SU at the doses specified above.				

3.4. Clinical efficacy

3.4.1. Main study

Title of Study: Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess Cardiovascular Outcomes Following Treatment With Ertugliflozin (MK-8835/PF-04971729) in Subjects With Type 2 Diabetes Mellitus and Established Vascular Disease, the VERTIS CV Study

Methods

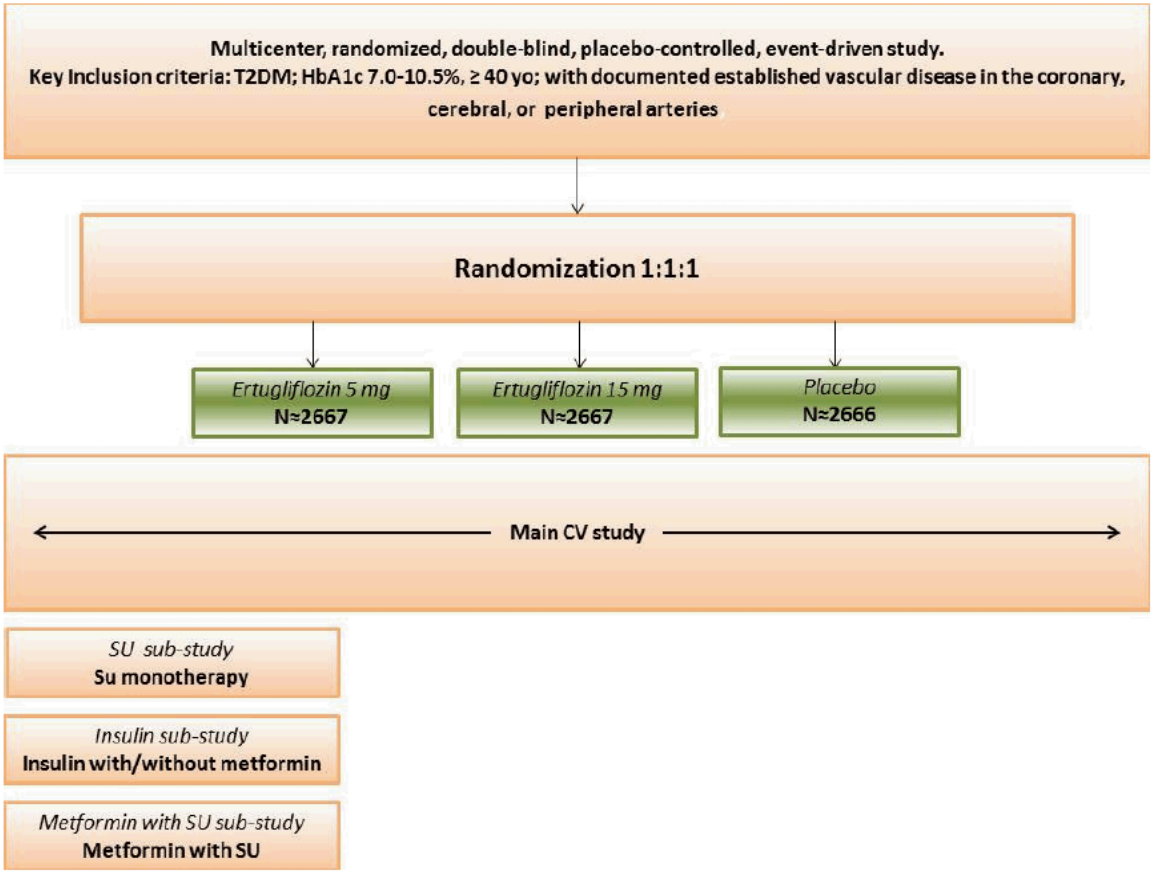
This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, event-driven study that included a main CV study and 3 glycaemic sub-studies in subjects receiving specific background anti-hyperglycaemic treatments.

This study was intended to address 2 overarching objectives. The first focused on CV safety (non-inferiority) and the second focused on CV and renal efficacy (superiority).

The doses of ertugliflozin evaluated in this study were 5 mg and 15 mg qd.

Subjects were counselled on appropriate dietary and lifestyle guidelines for T2DM at the Day 1 Visit (V2) and were asked to maintain these guidelines throughout participation in the study. Counselling on dietary guidelines was in accordance with local medical standards of care for subjects with T2DM.

Figure 1 Overview of Study Design (Main Cardiovascular Study and add-on Glycaemic Sub-Studies)



Study participants

Key inclusion criteria were:

- Subjects ≥40 years of age with a diagnosis of T2DM in accordance with ADA guidelines.
- A1C at the Screening Visit (V1) of 7.0-10.5% (53-91 mmol/mol) on stable AHA(s) or on no background AHA for at least 8 weeks prior to the Screening Visit (V1). Subjects treated with another SGLT2 inhibitor, rosiglitazone, or chlorpropamide from 8 weeks before the Screening Visit (V1) were not allowed to enrol into the study.
- Body mass index (BMI) ≥18.0 kg/m^2.
- Evidence or a history of atherosclerosis involving the coronary, cerebral or peripheral vascular systems, with the most recent event having occurred at least 3 months (90 days) prior to the Screening Visit (V1).

Key exclusion criteria were:

- Subjects with New York Heart Association (NYHA) Class IV heart failure (HF) at the Screening Visit (V1). Class III or IV HF was exclusionary for subjects in Cohort 1.
- History of type 1 diabetes mellitus or a history of ketoacidosis.
- Screening fasting plasma or finger stick glucose >270 mg/dL (15 mmol/L), confirmed by a single repeat following counselling on exercise and diet.

- Subjects taking blood pressure or lipid altering medications who had not been on a stable dose for at least 4 weeks prior to randomization. Subjects who required a change in blood pressure and/or lipid altering medications to meet the entry criteria related to blood pressure and/or triglycerides had to be on a stable dose of such therapy for at least 4 weeks prior to randomization.
- Subjects who were not weight-stable due to a weight-loss program, a weight-loss medication, other medication associated with weight changes, or had undergone bariatric surgery. Weight-stable was defined as <5% change in body weight in the last 6 months.
- Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 as determined by the 4-variable modification of diet in renal disease (MDRD) equation, confirmed via a single repeat if deemed necessary.
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 × the upper limit of normal (ULN) at the Screening Visit (V1), or a total bilirubin >1.5 × the ULN unless the subject had a history of Gilbert's.

Treatments

Ertugliflozin 5 mg, ertugliflozin 10mg, and matching placebos were supplied as immediate-release tablets for oral administration. On Day 1, each subject was randomly assigned to ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo.

Treatment for Glycaemic Control for Type 2 Diabetes Mellitus

To enable an assessment of the glycaemic effects of ertugliflozin, doses of background AHAs were required to be held constant in all subjects for the initial 18 weeks of the study with 2 exceptions:

- First, subjects were prescribed glycaemic rescue therapy if they met specific, progressively more stringent, glycaemic thresholds (see Table 3) on a repeated, confirmed FPG measured by the central lab.
- Second, a subject experiencing clinically significant hypoglycaemia according to the investigator at any time during the study was permitted to have the dose of appropriate AHA (e.g. insulin, SU, glinide) reduced or discontinued as per the judgment of the investigator or the treating physician.

Choice and dosing of glycaemic rescue was at the discretion of the investigator or the treating physician.

Following the Week 18 visit, the investigator/treating physician was able to make any changes in the subject's AHA treatment regimen to achieve an appropriate A1C level (with exception of prohibited concomitant medications listed in Section 4.2 of the protocol).

Table 3 Glycaemic Rescue Criteria for All Subjects for the First 18 Weeks

Randomization through Week 6	FPG >270 mg/dL (15.0 mmol/L)
After Week 6 through Week 12	FPG >240 mg/dL (13.3 mmol/L)
After Week 12 through Week 18	FPG >200 mg/dL (11.1 mmol/L)

Subjects who received glycaemic rescue therapy continued taking study medication for the duration of the study unless they met withdrawal criteria described in Section 6.7 of the protocol.

Treatment for Secondary Prevention of Cardiovascular Disease

Subjects may have been administered other medications necessary for the treatment of concomitant medical disorders, particularly other disorders that were CV risk factors, including but not limited to hypertension and dyslipidaemia. Attention was to be placed on appropriate use of medications

recommended in local country or national guidelines including anti-platelet therapy, statins, and angiotensin-converting enzyme (ACE) inhibitors. Smokers were to be counselled to quit and received treatment if needed.

The investigator or the treating physician was able to make any changes in the subject's background CV treatment regimen to achieve appropriate targets for secondary disease prevention at any time during the study.

Objectives

Primary Objective:

To demonstrate the non-inferiority of ertugliflozin compared with placebo on the time to first occurrence of the composite endpoint of MACE. (MACE: CV death, non-fatal myocardial infarction [MI] or non-fatal stroke)

Key Secondary Objectives:

To demonstrate the superiority of ertugliflozin compared with placebo on the time to first occurrence of the composite endpoint of CV death or hospitalization for heart failure (HHF).

To demonstrate the superiority of ertugliflozin compared with placebo on the time to CV death.

To demonstrate the superiority of ertugliflozin compared with placebo on the time to first occurrence of the composite endpoint of renal death, renal dialysis/transplant, or ≥2 × increase in baseline serum creatinine.

Outcomes/endpoints

Primary Cardiovascular Evaluation

The primary endpoint was time to first occurrence of the endpoint of MACE, which is a 3-point composite endpoint of CV death, non-fatal MI, or non-fatal stroke.

Key Secondary CV Evaluations

The following were key secondary endpoints corresponding to pre-specified hypothesis tests.

- Time to first occurrence of the composite of CV death or HHF;
- Time to CV death;
- Time to first occurrence of the composite of renal death, renal dialysis/transplant, or ≥2 × increase in baseline serum creatinine.

Other Secondary CV Evaluations

The following were secondary endpoints corresponding to objectives that were not subjected to hypothesis testing.

- Time to first occurrence of:
    - MACE plus;
    - Fatal or non-fatal MI;
    - Fatal or non-fatal stroke;
    - HHF;

- Individual components of MACE (CV death, non-fatal MI, non-fatal stroke).
- All-cause mortality.
- All MACE events (i.e. not censored at the time of the first event).
- All cardiovascular death or hospitalization for heart failure (i.e. not censored at the time of the first event).

Selection of Other Secondary Non-CV Evaluations

- Change from baseline in A1C at Week 18, Week 52 and annually thereafter.
- Proportions of subjects with A1C <7% (53 mmol/mol) and <6.5% (48 mmol/mol) at 12, 24 and 36 months and annually thereafter.
- Change from baseline in FPG at Week 18, Week 52 and annually thereafter.
- Changes from baseline in systolic and diastolic blood pressure at Week 18, Week 52 and annually thereafter.
- Change from baseline in body weight at Week 18, Week 52 and annually thereafter.

Sample size

The cardiovascular safety of ertugliflozin was assessed in two stages.

Stage 1 consists of a meta-analysis of MACE plus events across the Phase 2 and Phase 3 development program with the majority of events expected to come from this trial.

Stage 2 consists of an analysis of MACE and secondary endpoints [e.g. CV death or hospitalization for heart failure (composite), CV death (individual component), and the renal composite] in this trial. The two doses of ertugliflozin (5 and 15 mg) will be pooled for the purpose of all these analyses.

The primary objective for the Stage1 across-program meta-analysis will be addressed by testing the hypotheses H0:HR>=1.8 versus H1:HR<1.8 for the MACE plus endpoint; the primary Stage2 analysis (assessed within this study) will be addressed by testing the hypotheses H0:HR>=1.3 versus H1:HR<1.3 for the MACE endpoint. For these analyses, the HR represents the risk of ertugliflozin relative to a non-ertugliflozin comparator group at Stage 1 and relative to placebo at Stage 2 as measured by the hazard ratio. Stage 1 of the trial uses a group sequential design with up to two analyses: an interim analysis and a final analysis.

For these Stage 1 analyses, using an O'Brien-Fleming type alpha spending function, and analyses at 130 and 173 adjudicated MACE plus events, the meta-analysis will have approximately 95% power to demonstrate non-inferiority of ertugliflozin to a non-ertugliflozin comparator group when there is truly no difference between treatments (HR=1.0) using the non-inferiority margin of 1.8 and testing at the overall one-sided alpha level of 0.025. Stage 2 of the trial uses a group sequential design with up to two analyses: an interim analysis and a final analysis. The Stage 2 interim analysis and the final analysis are planned to occur when approximately 714 and 939 adjudicated MACE events have accrued in this study. These analyses will assess the hazard ratio for the MACE endpoint with respect to the 1.3 non-inferiority margin. If non-inferiority is established for the primary MACE endpoint, then tests of superiority on the secondary endpoints of CV death or hospitalization for heart failure (composite), CV death (individual component), and the renal composite will also be performed in a sequential manner. If any of the first three tests in this four-step testing sequence are unsuccessful at the interim analysis, the study may be continued to the final analysis (depending on the result of futility assessment). For the primary Stage 2 analyses, using an O'Brien-Fleming type alpha spending function and analyses at approximately 714 and

939 adjudicated MACE events, the study will have approximately 96% power to demonstrate non-inferiority of ertugliflozin to placebo when there is truly no difference between treatments (HR=1.0) using the non-inferiority margin of 1.3 and testing at the overall one-sided alpha level of 0.025. The accrual of 714 MACE events (i.e. an information fraction of about 76%) was selected as the time point for interim assessment as the power to demonstrate non-inferiority at the interim with this number of events is >80% and the estimated corresponding number of CV deaths and heart failure hospitalizations(i.e. 442 events) provides approximately 70% power to detect a 25% risk reduction in this secondary endpoint at the interim. With two enrolment periods of 19 months each and assuming an event rate of 3.5% per annum for MACE, a total of approximately 8000 subjects (about 4000 per enrolment cohort) randomized in a 1:1:1 ratio to ertugliflozin 5mg, ertugliflozin 15 mg or placebo will be sufficient to accrue approximately 714 MACE events within approximately 5.0 years and approximately 939 MACE events within approximately 6.1 years from the start of this study. These calculations assume that subjects will withdraw from the study at a rate of 5% per annum.

Power for Secondary Hypotheses For the Stage2 analyses of secondary endpoints, using an O'Brien-Fleming alpha-spending approach and assuming accrual of at least 442 and 582 composite events of cardiovascular death or hospitalization for heart failure at the interim and final analysis respectively, the study will have approximately 90% power to demonstrate superiority of ertugliflozin to placebo on the composite of cardiovascular death or hospitalization for heart failure when the true HR=0.75. Moreover, assuming accrual of at least 287 and 377 cardiovascular death events at the interim and final analysis respectively, the study will have approximately 83% power to demonstrate superiority of ertugliflozin to placebo on cardiovascular death when the true HR=0.725. With accrual of at least 144 and 190 renal composite events at the interim and final analysis respectively, the study will have approximately 79% power to demonstrate superiority of ertugliflozin to placebo on the renal composite endpoint when the true HR=0.65.

Sample Size for Insulin with or without Metformin Add-on Glycemic Sub-Study: The sub-study is powered to demonstrate superiority of ertugliflozin compared with placebo in reducing HbA1c from Baseline to Week18. It is estimated that a minimum of 450 subjects will be enrolled into the sub-study. The sub-study enrollment will not be allowed to exceed 50% of the overall trial sample size. The final determination of inclusion in the sub-study will be based on a programmatic assessment of the sub-study criteria. Assuming a standard deviation of 1.0% and a lost to follow up rate of 10%, a sample size of 450 subjects (150per arm) will provide approximately 98% power to detect a difference of 0.5% in the reduction of HbA1c from Baseline to Week18 between ertugliflozin and placebo using a 2-sided 0.05 alpha level test.

Sample Size for SU Monotherapy Add-on Glycemic Sub-Study: The primary endpoint for the sub-study is the HbA1c change from Baseline to Week18. It is estimated that approximately 170 subjects will be enrolled into the sub-study. The final determination of inclusion in the sub-study will be based on a programmatic assessment of the sub-study criteria. Assuming a standard deviation of 1.0%, a lost to follow up rate of 10%, and a sample size of 170 subjects (~56 per arm), the power to detect a between treatment difference of 0.6% will be approximately 85% using a 2-sided alpha level of 0.05.

Sample Size for Metformin with SU Add-on Glycemic Sub-Study: The primary endpoint is the HbA1c change from Baseline to Week18. It is estimated that at least 260 subjects will satisfy the criteria for inclusion in this sub-study. Assuming a standard deviation of 1.0% and a lost to follow up rate of 10%, a sample size of 260 subjects (~86 per arm) will provide approximately 96% power to detect a difference of 0.6% between ertugliflozin and placebo using a 2-sided 0.05 alpha level test. As there is no separate randomization stratum for the metformin with SU sub-study, this sub-study will consist of a sub-group of subjects from the "main cardiovascular study". The determination of inclusion in the sub-study was based on a programmatic assessment of the sub-study criteria.

Randomisation

Approximately 8000 subjects were to be randomized in a 1:1:1 ratio to receive 5mg ertugliflozin once daily, ertugliflozin 15 mg once daily or matching placebo. Allocation of subjects to treatment groups proceeded through the use of a randomization system (IVRS or equivalent). Subjects were enrolled in two distinct cohorts. Cohort 1 refers to subjects randomized under the original protocol prior to Amendment 1, and Cohort 2 refers to subjects randomized under Amendment 1. Each cohort has a targeted enrolment of approximately 4000 subjects. The randomization was stratified by cohort (i.e. Cohort 2 have a separate randomization list). Subjects in Cohort1 were stratified into the main cardiovascular study, the insulin (with or with metformin) sub-study or the SU monotherapy sub- study, according to their background anti-hyperglycaemic treatment. Subject information was entered into the system starting at the Screening visit(V1) when the subject was assigned to a unique identifier which was retained throughout the duration of participation in the trial. On the Day1 visit (V2), once the inclusion, exclusion and randomization criteria have been verified, each subject was provided with a subject randomization number.

Blinding (masking)

The study utilized a double-dummy approach to maintain double-blinding, with a placebo tablet matching the ertugliflozin 5mg tablet and another placebo tablet matching the ertugliflozin 10mg tablet. Subjects were instructed to take 1 ertugliflozin 5 mg tablet (or matching placebo) and 1 ertugliflozin 10 mg tablet (or matching placebo) daily, according to their assigned treatment (ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo). Thus, all subjects were to take 2 tablets each day of ertugliflozin/placebo.

The trial was subject-, investigator- and sponsor-blinded. At the initiation of the trial, the sites were instructed on the method for breaking the blind. The method was an electronic process via IVRS. Blinding codes should only be broken in emergency situations for reasons of subject safety. Whenever possible, the investigator or sub-investigator should consult with a member of the sponsor trial team prior to breaking the blind. When the blinding code was broken, the reason must be fully documented and entered in the source documents.

Statistical methods

Analysis sets

The primary analysis set (CV FAS) for the analysis of cardiovascular safety in Study B1521021 includes all subjects who were randomized into the study and who received at least one dose of blinded study medication. In addition, for Stage 2 superiority analyses, an intention-to-treat (ITT) analysis set was defined to include all randomized subjects in Study B1521021 and will be referred to as the CV ITT set.

The data to be included from subjects in these analysis sets varied based on the analysis ascertainment window.

Statistical analysis methods

The two doses of ertugliflozin were to be pooled for the analysis of cardiovascular endpoints.

The time-to-first-event endpoints was analyzed using a stratified Cox proportional hazards (CPH) model including treatment group (pooled ertugliflozin doses or placebo) as a covariate. For Stage 2 analyses of Study B1521021, Cohort was included as a stratification factor. For the MACE, CV death/HHF, CV death, and renal composite (Stage 2) endpoints, a point estimate and alpha-adjusted (ie, adjusted for multiple looks) two-sided confidence interval for the hazard ratio was provided for testing hypotheses. An O'Brien-

Fleming type alpha-spending function was utilized. P-values to assess the significance of the hazard ratio was also reported for these endpoints.

For other CV endpoints not included in the formal testing sequence, a point estimate and nominal (ie, unadjusted for multiple looks) two-sided 95% confidence interval for the hazard ratio was calculated based on the Cox proportional hazards model.

Graphical summaries included Kaplan-Meier curves for each treatment group in the analysis (pooled ertugliflozin doses vs. non-ertugliflozin comparator or placebo) and separately by dose (ertugliflozin 5 mg, ertugliflozin 15 mg).

Table 4 Summary of Stage 2 Primary and Secondary Model Based Analyses

Endpoint	Analysis Set	Statistical Method	Ascertainment Window (Days)	Description
MACE	CV FAS	CPH	365	Primary NI analysis
	CV ITT		No limit	On-study analysis
	CV FAS		14	On-treatment analysis
			30	On-treatment analysis
		Min Risk	365	Sensitivity analysis
		MI-RD	365	Sensitivity analysis
		Tipping Point	365	Sensitivity analysis
CV death/HHF	CV ITT	CPH	No limit	Secondary superiority analysis
	CV FAS		14	On-treatment analysis
			30	On-treatment analysis
	CV ITT	MI-RD	No limit	Sensitivity analysis
CV death	CV ITT	CPH	No limit	Secondary superiority analysis
	CV FAS		14	On-treatment analysis
			30	On-treatment analysis
	CV ITT	MI-RD	No limit	Sensitivity analysis
Renal composite	CV ITT	CPH	No limit	Secondary superiority analysis
	CV FAS		14	On-treatment analysis
			30	On-treatment analysis
	CV ITT	MI-RD	No limit	Sensitivity analysis
MACE plus	CV ITT	CPH	No limit	Secondary analysis
	CV FAS		14	On-treatment analysis
FNF MI	CV ITT	CPH	No limit	Secondary analysis
	CV FAS		14	On-treatment analysis
FNF stroke	CV ITT	CPH	No limit	Secondary analysis
	CV FAS		14	On-treatment analysis
Hospitalization for HF	CV ITT	CPH	No limit	Secondary analysis
	CV FAS		14	On-treatment analysis
All-cause mortality	CV ITT	CPH	No limit	Secondary analysis
	CV FAS		14	On-treatment analysis
	CV ITT	MI-RD	No limit	Sensitivity analysis
Total MACE	CV ITT	Andersen-Gill	No limit	Exploratory analysis
Total CV death/HHF	CV ITT	Andersen-Gill	No limit	Exploratory analysis

CV=cardiovascular; CPH=Cox Proportional Hazards; FAS=Full Analysis Set; FNF=fatal or non-fatal; HF=heart failure; HHF=hospitalization for heart failure; ITT=Intention-to-Treat;

MACE=major adverse cardiovascular event; MI=myocardial infarction;
MI-RD=multiple imputation with retrieved dropout; NI=non-inferiority.

Ascertainment windows refer to the number of days after the last dose of the study medication.

Sensitivity analyses

The stratified CPH model utilized in the primary analyses assumes a constant hazard across strata. An alternative approach was utilized as a sensitivity analysis. The (log) HR is estimated separately for each stratum using an unstratified Cox model, and the stratum-specific estimates were combined for overall inference using "minimum risk" stratum weights. This sensitivity analysis is referred to as the minimum risk method.

For time-to-event analyses, such as those required for the primary and secondary CV endpoints, subjects who are lost to follow-up will be censored. A subject was considered lost to follow-up if it is not possible to determine whether or not that subject had an event during the study period based on available data. Such subjects will be censored at the date of last contact except in the case of mortality analyses where the vital status is known or where a vital status death contributes to the outcome of interest. Identifying the reasons for missing data is an important step in assessing the appropriateness of the models used in the statistical analyses. An accounting of missingness (amount of missing data and associated reasons) were to be provided for the primary endpoint.

To address the robustness of the primary and key secondary endpoint analyses to the impact of missing data, sensitivity analyses will be performed using a multiple imputation with retrieved dropout (MI-RD) approach. These sensitivity analyses imputed event status and event time for each subject with missing data conditional on censoring time and vital status. The imputation is based on a parametric survival distribution (eg, Weibull distribution) fit to the available data from subjects who discontinued study medication but remained in the trial for follow-up (ie, retrieved dropouts). The parameters of the distribution are estimated separately for each treatment group. Time on treatment is included as a covariate in the imputation model. Each dataset completed by imputation is analysed using the same Cox model from the primary analysis, and the results from 100 imputations is combined based on Rubin's rule.

An accounting of vital status will also be provided, and subjects with unknown vital status will form the basis for sensitivity analyses on both the CV death and all-cause mortality endpoints. These sensitivity analyses will utilize a similar MI-RD approach as that described for the primary endpoint with the parametric distribution being fit to data from subjects in each treatment group who discontinued study medication but had known vital status at end of study.

Tipping point analyses was also conducted with imputation of missing data based on the Weibull distribution. For the tipping point analysis, subjects in the Ertugliflozin group who discontinued the trial without an event are assumed to have the same or a higher hazard ($\delta \geq 1$) compared to those in the same treatment group who remained in the trial. The same hazard ($\delta = 1$) is assumed for subjects in the placebo group who discontinued the trial without an event compared to those in the placebo group who remained in the trial. Given a value of δ, the primary Cox model is applied to the imputed dataset, and a p-value is obtained. These steps are repeated with values of δ ranging from 1 to a pre-specified upper limit. The smallest value of δ under which the significance disappears (ie, p-value >0.05) is taken as the tipping point.

Multiplicity

The overall Type I error rate in Stage 2 was strongly controlled (at 2.5% one-sided) based on repeated hypothesis testing using a sequentially rejective graphical procedure. The following chart summarizes the fixed testing sequence and the alpha levels that were utilized for each endpoint at each analysis time

point in Stage 2 (assuming the planned information fraction of 0.76 at the interim). Note that alpha allocated to the secondary superiority tests at the interim will be considered to be consumed even if the test is not conducted due to the hierarchical testing sequence. Also note that any hypotheses that are rejected at the interim will not be formally retested at the final analysis, although supportive analyses based on all available data at the end of study will be provided.

Sequence Number*	Endpoint (test)	Alpha for adjusted confidence interval	
		Interim Analysis	Final Analysis
1	MACE (non-inferiority)	1% (one-sided)	2.2% (one-sided); if test not successful at interim
2	Cardiovascular death/hospitalization for heart failure (superiority)	2% (two-sided)	4.4% (two-sided); if test not successful at interim
3	CV death (superiority)	2% (two-sided)	4.4% (two-sided)
4	Renal composite (superiority)	2% (two-sided)	4.4% (two-sided)
*Note: If the result of the test at any step of the sequence is not statistically significant, then testing will stop so that tests further down in the sequence will not be conducted (and therefore not considered successful).			

As a single interim analysis and a final analysis are planned, an O'Brien-Fleming (OBF) alpha spending function are used to construct group sequential boundaries to control the type I error rate. The actual boundary and the alpha to be spent is determined from the actual number of events observed at the time of the interim analysis using the OBF alpha spending function. The boundaries for the final analysis were adjusted according to the actual alpha spent at the interim analysis and the actual numbers of events observed at the interim and final analyses. The example boundaries (on the p-values) given below assume the planned information fraction of 0.76 at the interim.

Testing at the interim will proceed sequentially by comparing the interim p-values to the OBF levels, e.g. 0.01. If the primary hypothesis cannot be rejected, then no hypothesis will be rejected, and the trial will proceed to the final analysis.

For the final analysis, the nominal levels at which the remaining hypotheses can be sequentially tested are the OBF levels, e.g. 0.022. Sequential testing at the final analysis will proceed starting with the first remaining hypothesis and updating the graph with each sequential rejection until either a hypothesis fails to be rejected or all hypotheses are rejected.

Subgroup analyses

For Stage 2, analyses of MACE and the secondary CV endpoints included in the formal testing sequence were performed in subgroups based on region, gender, age (<65 and ≥65 years), race, ethnicity, category of chronic kidney disease (CKD; based on baseline eGFR: <60, 60 to <90, and ≥90 mL/min/1.73 m2), history of heart failure, baseline HbA1c (<8.5 and ≥8.5%), baseline BMI (<30 and ≥30 kg/m2), and use of the following concomitant medications at baseline: statins, ezetimibe, ASA/anti-platelets, diuretics, beta blockers, calcium channel blockers, mineralocorticoid receptor antagonists, renin- angiotensin-aldosterone system (RAAS) blockers, insulin, DPP-IV inhibitors, metformin, sulfonylureas, and GLP-1 agonists. Selected subgroups (to be specified in the list of tables) was also analysed for the renal composite endpoint. These subgroup analyses are considered exploratory and are not adjusted for multiple comparisons. The same model used for the primary analysis is run within each subgroup. The data is also summarized descriptively by treatment group within each subgroup.

In order to provide model-based point and interval estimates of the hazard ratios for MACE and the endpoints in the formal testing sequence for each dose of ertugliflozin (5 mg and 15 mg), an analysis of Study B1521021 was conducted using the individual dose groups.

Sub-studies

The primary analysis population for each sub-study was the sub-study Full Analysis Set defined as all subjects randomized receiving those specific background treatments at baseline, who met all sub-study inclusion criteria, who had received at least one dose of investigational product and had at least one observation of HbA1c during the time of the sub-study, including baseline and post-baseline time points up to Week18 inclusive. If subjects received glycemic rescue therapy, the observations post rescue therapy was excluded from efficacy analyses of the primary and secondary endpoints. The primary endpoint of HbA1c was analyzed using a constrained longitudinal data analysis (cLDA) model with the following fixed effects: Treatment (categorical); Visit (categorical); Treatment by visit interaction; Baseline eGFR; Metformin use (yes/no; applicable for insulin (with or without metformin) sub-study only). This model assumed a common mean across treatment groups at baseline and a different mean for each treatment at each of the post-baseline time points. In this model, the response vector consisted of baseline and the values observed at each post-baseline time point. Time was treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. No explicit imputation of missing assessments was performed. The treatment difference in terms of mean change from baseline to the primary time point of Week18 was be estimated and tested from this model using least-squares means and 95% confidence intervals. The two-sided p-value was provided for testing the significance of the difference between treatment groups. Sensitivity analyses were planned to assess the robustness of the primary model. The two primary hypotheses, comparisons of each ertugliflozin dose to placebo, was tested sequentially to control the overall Type I error rate at 0.05. The 15 mg dose was tested first, and the 5mg dose was tested if and only if a statistically significant result is achieved for 15mg.

Results

Participant flow

Figure 2 Subject Disposition

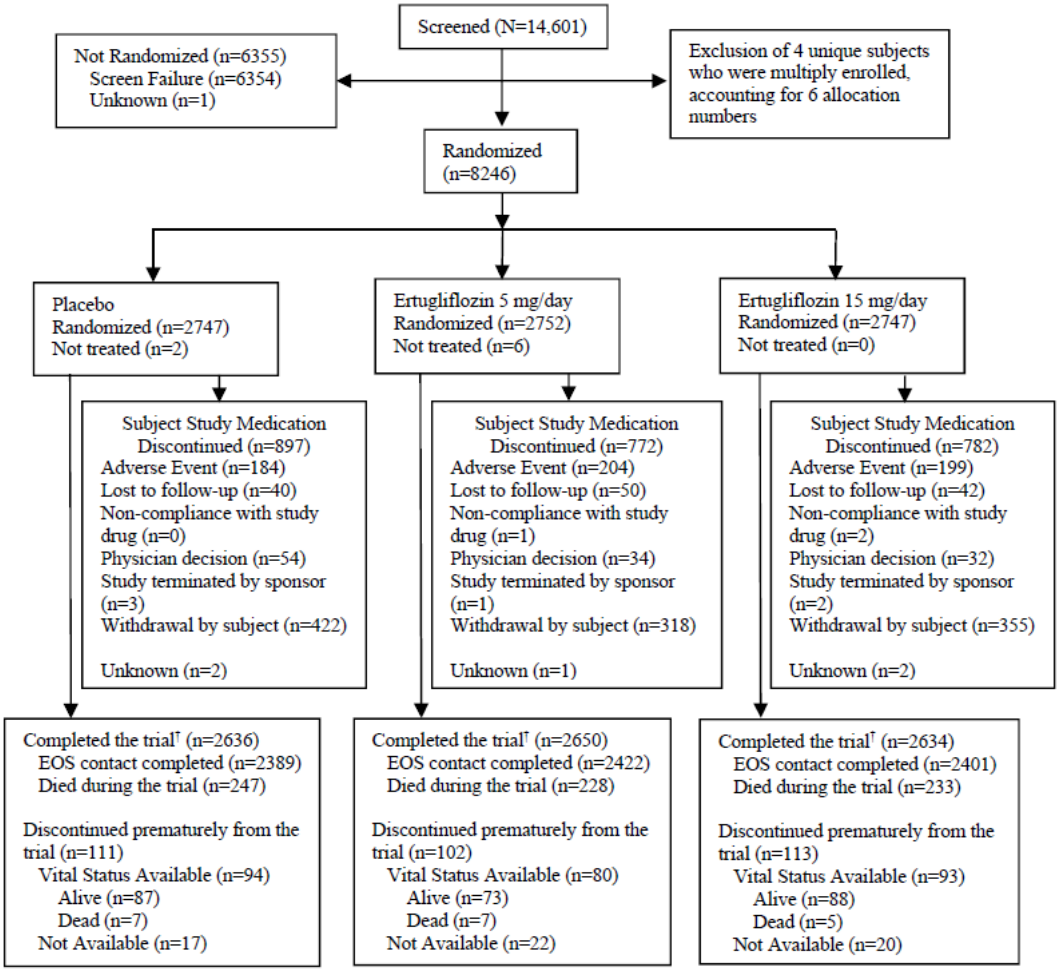


Table 5 Disposition of Subjects – Study Medication

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Entered Screening							14601	
Not Randomized							6355	
Subjects Randomized	2747		2752		2747		8246	
Subject Study Medication Disposition								
Completed	1846	(67.2)	1973	(71.7)	1963	(71.5)	5782	(70.1)
Did Not Take Study Medication	2	(0.1)	6	(0.2)	0	(0.0)	8	(0.1)
Discontinued	897	(32.7)	772	(28.1)	782	(28.5)	2451	(29.7)
Adverse Event	184	(6.7)	204	(7.4)	199	(7.2)	587	(7.1)
Creatinine/eGFR	1	(0.0)	0	(0.0)	0	(0.0)	1	(0.0)
Death	130	(4.7)	137	(5.0)	126	(4.6)	393	(4.8)
Excluded Medication	38	(1.4)	10	(0.4)	10	(0.4)	58	(0.7)
Lost To Follow-Up	40	(1.5)	50	(1.8)	42	(1.5)	132	(1.6)
Non-Compliance with Study Drug	0	(0.0)	1	(0.0)	2	(0.1)	3	(0.0)
Physician Decision	54	(2.0)	34	(1.2)	32	(1.2)	120	(1.5)
Pregnancy	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Study Terminated By Sponsor	3	(0.1)	1	(0.0)	2	(0.1)	6	(0.1)
Subject Moved	25	(0.9)	16	(0.6)	14	(0.5)	55	(0.7)
Withdrawal By Subject	422	(15.4)	318	(11.6)	355	(12.9)	1095	(13.3)
Unknown	2	(0.1)	1	(0.0)	2	(0.1)	5	(0.1)

Source: Table 14.1.1.7

Each subject was counted once for Subject Study Medication Disposition.

For the calculation of percentage, the denominator was the number of randomized subjects.

The Study Terminated By Sponsor category includes any subject who was discontinued from study drug because the site was closed by Pfizer.

Unknown: Study medication disposition was not reported.

Recruitment

The study included subjects in 34 countries at 548 study centers. 56.2% of subjects were recruited by European centers and 22.0% by centers in North America.

First Subject First Visit (FSFV): 13 November 2013
Primary Completion Date:27 December 2019
Last Subject Last Visit (LSLV): 27 December 2019
Data cut date: 16MAR2020 (Final)
Date of Reporting Dataset Creation: 21MAR2020
CSR date: 13 August 2020

Cohort1 includes subjects randomized between December 2013 and July 2015 and Cohort2 subjects randomized in 2016 and beyond.

Conduct of the study

Changes in the Conduct of the Study

Major changes in study conduct are described in Table 6.

Table 6 Protocol amendment

Document	Version Date	Summary of Major Changes
Amendment 1	11 March 2016	Added a superiority analysis on the newly added secondary endpoints of cardiovascular death or hospitalization for heart failure (composite) and cardiovascular death (individual component).

Document	Version Date	Summary of Major Changes
		Increased the overall sample size to approximately 8000 subjects. Updated assumptions to indicate that the rate of withdrawal from the study will be 5% per year. Added secondary end point of: Change in insulin dose from Baseline at Week 18, Week 52 and annually thereafter to the overall study and to the insulin with or without metformin sub-study (at Week18 only for the sub-study). Added a glycaemic sub-study in subjects receiving metformin plus sulfonylurea (SU) at the doses specified and clarification regarding inclusion into this sub-study which will be done programmatically at the time of the analyses for all the sub-studies without changing the randomization scheme (only applicable to subjects enrolled prior to amendment). Modified the exclusion criterion to remove Class III heart failure as exclusionary. Added a superiority analysis for the composite endpoint of renal death, renal dialysis/transplant or ≥2x increase in baseline serum creatinine.

All changes to the protocol were implemented prior to database lock and unblinding.

Changes in the Planned Analyses

The changes in the analysis plan made prior to database lock and unblinding were of minor importance for the conclusions drawn from the study.

The statistical methods for subgroup analyses of A1C and FPG in subjects with Stage 3A CKD are not specified in the Non-CV SAP. The subgroup analyses were performed using 3 methods: cLDA, MI-RD, and return to baseline (RTB). The FAS and ER approach were used for the cLDA analysis, while the FASbase, defined as the FAS restricted to subjects with a baseline measurement, and IR approach were used for the MI-RD and RTB analyses.

Protocol Deviations

A total of 1148 (13.9%) of randomized subjects had at least 1 major protocol deviation. The occurrence of major protocol deviations was balanced across treatment groups, with 378 (13.8%) subjects in the ertugliflozin 5 mg group, 359 (13.1%) subjects in the ertugliflozin 15 mg group, and 411 (15.0%) subjects in the placebo group reporting major protocol deviations. None of the observed protocol deviations were considered to have impacted the conclusions of this report.

The most common major protocol deviation category across treatment groups was failure to conduct major/significant evaluations (424 [5.1%] subjects). Other common major protocol deviation categories were eligibility criteria not met (315 [3.8%] subjects), which was balanced across treatment groups, and SAEs/AEs were not reported or were not reported in timeframe per protocol (244 [3.0%] subjects). The inclusion of subjects that did not satisfy all entry criteria did not impact the interpretation of study results.

During the conduct of the study, 2 subjects were found to have simultaneously enrolled at more than 1 site in this study and 2 subjects were found to have simultaneously enrolled in more than 1 study in the ertugliflozin Phase 3 program. These cases of multiple enrolments were recorded as major protocol deviations.

One subject, in the ertugliflozin 5 mg group, did not adhere to protocol-required guidance on contraception and became pregnant. This subject was discontinued from study medication. The outcome was reported as a healthy birth.

A formal acknowledgment by the study team was made that deviations were reviewed and GCP compliance was maintained.

Baseline data

Demographic and Other Baseline Characteristics

Demographic and Baseline Characteristics

Demographic and baseline characteristics were balanced across treatment groups (Table 1). The overall mean age was 64.4 years, and 11.0% of subjects were ≥ 75 years old at baseline. The majority of subjects (70.0%) were male, most subjects were White (87.8%), and most subjects were not Hispanic or Latino (87.1%). The mean BMI was 32.0 kg/m^2.

Baseline Disease Characteristics

In total, the mean duration of T2DM was 13.0 years and was similar across treatment groups (Table 1). Background AHA therapy at screening was balanced across treatment groups with a large proportion of subjects receiving metformin (76.3%), insulin (47.3%), or SU (41.1%).

Baseline A1C and FPG were similar across treatment groups with mean A1C of 8.2% and mean FPG of 174.8 mg/dL in the total population.

In total, mean eGFR at baseline was 76.0 mL/min/1.73 m^2 and was similar across treatment groups. Overall, 21.5% of subjects had moderate renal impairment (eGFR 30 to <60 mL/min/1.73 m^2). Micro-albuminuria (≥ 30 to ≤ 300 mg/g) was present in 30.2% of subjects and macro-albuminuria (>300 mg/g) in 9.2%.

Baseline history of CV disease and CV risk factors were balanced across treatment groups. A total of 8187 (99.3%) subjects had established CV disease at baseline (Table 1).

A total of 75.9% of subjects had a history of coronary artery disease (Table 1), defined as presence of MI (48.0%) and/or coronary revascularization (58.1%) by CABG (22.1%), PCI (42.3%), or other (2.2%). A total of 22.9% of subjects had a history of cerebrovascular disease and 18.7% of subjects had a history of peripheral artery disease. CV risk factors were present in a majority of the population, with a history of hypertension in 91.2% of subjects, dyslipidaemia in 74.9% of subjects, and current or history of past tobacco use in 53.8% of subjects.

A total of 21.1% of subjects had a history of stroke, and 23.7% of subjects had a history of HF. In the 1958 subjects with HF at baseline, NYHA functional classification was collected for 1942 subjects in which the majority were in NYHA Functional Class I or II.

EF data that were available prior to randomization were collected regardless of presence or absence of history of HF. Sites were instructed to report the EF measurement data collected closest to the date of randomization. EF history was collected for 5006 (60.7%) subjects: 542 (6.6%) subjects had reduced EF ≤ 40% and 4464 (54.1%) subjects had preserved EF >40%. EF data were available for 1485 (75.8%)

subjects with a history of HF. In the HF population, 288 (14.7%) subjects had reduced EF ≤ 40% and 1197 (61.1%) subjects had preserved EF >40%.

Baseline lipids and blood pressure were balanced across treatment groups. The mean baseline LDL-C was 89.1 mg/dL and the mean baseline LDL/HDL ratio was 2.1. Mean sitting systolic and diastolic blood pressures were 133.3 mmHg and 76.6 mmHg, respectively.

There were no meaningful differences in the prevalence of baseline microvascular or macrovascular conditions across treatment groups. At baseline, neuropathy, nephropathy, and retinopathy were present in 28.1%, 9.3%, and 17.0% of subjects, respectively.

History of non-traumatic amputation was present in 3.7% of subjects, in which the majority of subjects (2.5%) experienced toe amputation, with no meaningful differences across treatment groups. History of peripheral revascularization and carotid revascularization was present in 4.2% and 2.6% of subjects, respectively, with no meaningful differences across treatment groups.

Other Medical Conditions at Baseline

The most common medical history conditions by SOC were Vascular disorders (94.3%), Cardiac disorders (80.5%), and Metabolism and nutrition disorders (79.8%). The most common medical history conditions by PT were Hypertension (89.4%), Uncircumcised (49.0%), and Myocardial infarction (40.1%). There were no meaningful differences among treatment groups in the frequency or type of medical history conditions.

Prior and Concomitant Medications

Anti-Hyperglycaemic Medications

At baseline, 8,134 (98.7%) subjects were on background AHA therapy with 50.4% of subjects taking 2 or more background AHAs. A total of 76.3% of subjects were taking metformin, 41.1% were taking an SU, 47.3% were taking insulin, 11.0% were taking DPP-4, 3.4% were taking GLP-1 receptor agonists, and 1.9% were taking thiazolidinediones. A total of 16.1% of subjects were taking 3 or more medications at baseline.

Use of DPP-4 increased from baseline in the ertugliflozin 5 and 15 mg groups and the placebo group (3.2%, 1.9%, and 3.7%, respectively). Use of GLP-1 receptor agonists increased from baseline in the ertugliflozin and placebo groups, although increases were slightly smaller in the ertugliflozin 5 mg and 15 mg groups compared to the placebo group (1.1%, 1.7%, and 2.5%, respectively). Use of SGLT2 inhibitors was low (total of 1 subject, in the placebo group) at baseline and increased across the treatment groups by the final visit, although increases were slightly smaller in the ertugliflozin 5 mg and 15 mg groups compared to the placebo group (2.2%, 1.8%, and 3.0%, respectively). Use of insulin increased from baseline in the ertugliflozin and placebo groups, although increases were smaller in the ertugliflozin 5 mg and 15 mg groups compared to the placebo group (4.4%, 2.6%, and 6.2%, respectively). Use of thiazolidinediones was similar relative to baseline in the ertugliflozin 5 mg and 15 mg groups and there was a small increase from baseline in the placebo group (0.2%, 0.2%, and 1.3%, respectively). Use of metformin, SU, alpha glucosidase inhibitors, and meglitinides from baseline compared to the final visit was similar across treatment groups. Use of 3 or more medications increased from baseline in the ertugliflozin and placebo groups, although increases were smaller in the ertugliflozin 5 mg and 15 mg groups compared to the placebo group (4.1%, 2.2%, and 6.6%, respectively).

Cardiovascular Medications

This trial was designed to enrol subjects on stable guideline-directed therapy. Use of therapies for secondary prevention at baseline was balanced across treatment groups. At baseline, 81.8% of subjects

were on statins, 84.6% were on platelet aggregation inhibitors, 81.1% were on agents acting on the renin-angiotensin system, and 43.0% were on diuretics, including 15.2% on a loop diuretic.

Compared to baseline, the use of calcium channel blockers, loop diuretics, and mineralocorticoid receptor antagonists had increased by the final visit in both treatment groups, although increases were slightly smaller in all ertugliflozin group versus placebo group: calcium channel blockers (2.1% vs 2.8%), loop diuretics (3.3% vs 4.6%), and mineralocorticoid receptor antagonists (1.7% vs 2.6%).

Compared to baseline, the use of non-loop diuretics had decreased by the final visit in all ertugliflozin group (1.8% decrease) and increased in the placebo group (0.7% increase).

Other Medications

Use of other specific prior medications was balanced across treatment groups. The most common prior medication categories were drugs used in diabetes (98.9%), lipid modifying agents (84.7%), agents acting on the renin-angiotensin system (81.5%), and aspirin (69.5%) in the Analgesics category.

Use of other specific concomitant medications (i.e. individual medications taken by ≥ 5% of subjects in 1 or more treatment groups during the study) was also balanced across treatment groups, the most common categories being drugs used in diabetes (99.3%), lipid modifying agents (89.3%), and agents acting on the renin-angiotensin system (85.7%).

Measurements of Treatment Compliance

Overall mean compliance with study medication was 96.2% and was similar across treatment groups.

Numbers analysed

Table 7 Analysis Population Summary

	Placebo n	Ertugliflozin 5 mg n	Ertugliflozin 15 mg n	All Ertugliflozin n	Total n
Entered Screening					14601
Not Randomized					6355
Randomized (CV ITT)	2747	2752	2747	5499	8246
Randomized But Not Treated	2	6	0	6	8
Randomized and Treated	2745	2746	2747	5493	8238
Randomized but Took Incorrect Treatment†	0	0	0	0	0
Treated (CV FAS)	2745	2746	2747	5493	8238
Treated But Not Randomized	0	0	0	0	0

Source: Table 14.1.2.16

† Subjects who had taken incorrect treatment throughout the study.

Outcomes and estimation

Primary Endpoint

MACE

The success criterion for the primary hypothesis test was met. The upper confidence limit for the MACE HR comparing all ertugliflozin and placebo was 1.114 (Table 8), which was below the non-inferiority margin of 1.3. MACE occurred in a similar percentage of subjects in all ertugliflozin group (11.89%) compared with the placebo group (11.91%) (HR for all ertugliflozin group vs placebo, 0.97; 95.6% CI, 0.848 to 1.114; p<0.001 for non-inferiority).

For the individual ertugliflozin 5 mg and 15 mg groups versus placebo group, the 95.6% CIs overlapped (HR for the ertugliflozin 5 mg group vs placebo, 0.91; 95.6% CI, 0.773 to 1.065 and HR for the ertugliflozin 15 mg group vs placebo, 1.04; 95.6% CI, 0.887 to 1.211).

Table 8 Cox Proportional Hazards Model for Time to First MACE (CV FAS: On-Treatment + 365-Day Approach)

Treatment	N	Number of Subjects with an Event (%)	Person-Years[†]	Rate/100 Person-Years	Hazard Ratio[‡] (95.6% CI)	p-value[‡]
Ertugliflozin 5 mg	2746	307 (11.18)	8441.29	3.64	0.91 (0.773, 1.065)	<.001
Ertugliflozin 15 mg	2747	346 (12.60)	8321.22	4.16	1.04 (0.887, 1.211)	0.002
All Ertugliflozin	5493	653 (11.89)	16762.51	3.90	0.97 (0.848, 1.114)	<.001
Placebo	2745	327 (11.91)	8147.06	4.01		

[†] Person-years is calculated as the sum of subjects´ time to first event or time to censoring (the earliest of subjects´ end of study date, death date, last contact date, or 365 days after the last dose).

[‡] Hazard ratio, CI, and one-sided p-value for non-inferiority of Ertugliflozin vs Placebo, based on the stratified Cox proportional hazards model that includes treatment as an explanatory factor and cohort category as a stratification factor.

MACE is defined as a composite of confirmed CV death, non-fatal MI, or non-fatal stroke.

The on-treatment approach includes confirmed events that occurred between the date of the first dose of study medication and the on-treatment censor date.

Individual components of first MACE are presented in Table 9.

Table 9 Composite of MACE (CV FAS: On-Treatment + 365-Day Approach)

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in Population	2745		2746		2747		5493		8238	
MACE	327	(11.91)	307	(11.18)	346	(12.60)	653	(11.89)	980	(11.90)
Component of First MACE										
CV death	126	(4.59)	121	(4.41)	120	(4.37)	241	(4.39)	367	(4.45)
Non-fatal MI	131	(4.77)	125	(4.55)	153	(5.57)	278	(5.06)	409	(4.96)
Non-fatal stroke	70	(2.55)	61	(2.22)	73	(2.66)	134	(2.44)	204	(2.48)

Source: Table 14.2.12.4.1

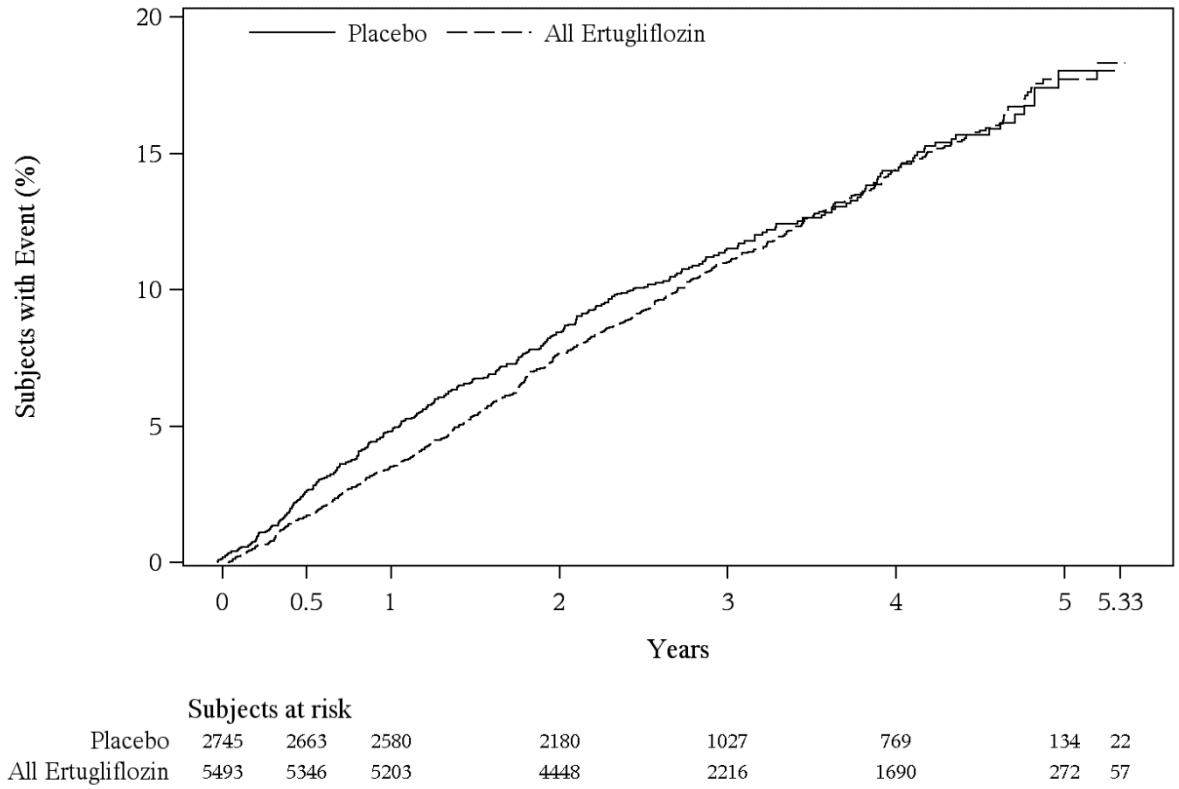
MACE was defined as a composite of confirmed CV death, non-fatal MI, or non-fatal stroke.

n = Number of subjects with a first event that contributed to the composite of MACE. For example, if a subject had a non-fatal MI and subsequent non-fatal stroke, only the non-fatal MI contributed to the MACE composite and was recorded within the non-fatal MI category.

The on-treatment approach included confirmed events that occurred between the date of first dose of study medication and the on-treatment censor date.

The Kaplan-Meier curves for MACE demonstrate initial separation between the all ertugliflozin and placebo curves, after which the lines converged for the remainder of the study (Figure 3).

Figure 3 Kaplan-Meier Curves of Time to First MACE (CV FAS: On-Treatment + 365-Day Approach)



MACE is defined as a composite of confirmed CV death, non-fatal MI, or non-fatal stroke. Year 0 = Baseline.
All Ertugliflozin - includes Ertugliflozin 5 mg and 15 mg.
The on-treatment approach includes confirmed events that occurred between the date of the first dose of study medication and the on-treatment censor date.

The results for the ertugliflozin 5 mg and 15 mg groups were consistent with those of the all ertugliflozin group, with comparable Kaplan-Meier curves, and the 95.6% CIs for the individual ertugliflozin groups versus placebo group overlapped (Table 8).

Results from sensitivity analyses for MACE were consistent with those from the primary analysis approach, indicating that the primary analysis results are robust.

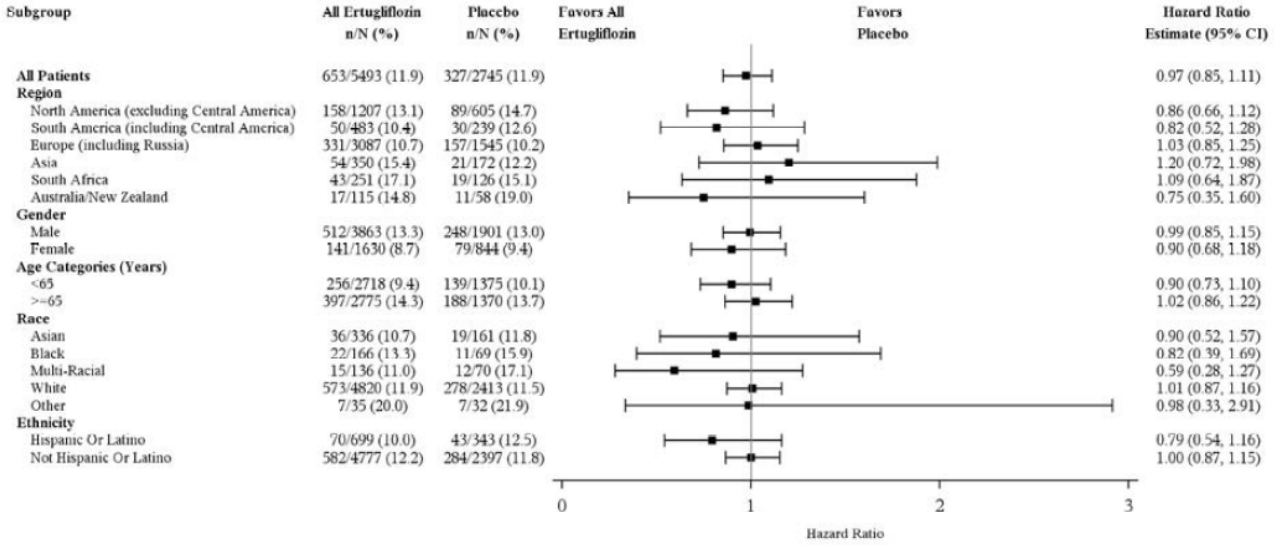
Analyses of the Composite of All-Cause Death, Non-Fatal Stroke, or Non-Fatal MI

In the CV ITT population, results from post hoc analyses of MACE in which the CV death component was replaced by all-cause death (all-cause death MACE) were consistent with those using the primary definition of MACE. The HR for all ertugliflozin group versus the placebo group was 0.97; 95% CI; 0.867 to 1.093. Kaplan-Meier curves and Kaplan-Meier estimates for all cause death MACE were consistent with those for MACE.

Subgroup Analyses for MACE

The subgroup analyses for MACE showed generally consistent results across all pre-specified subgroups as exemplified in Figure 4 and Figure 5.

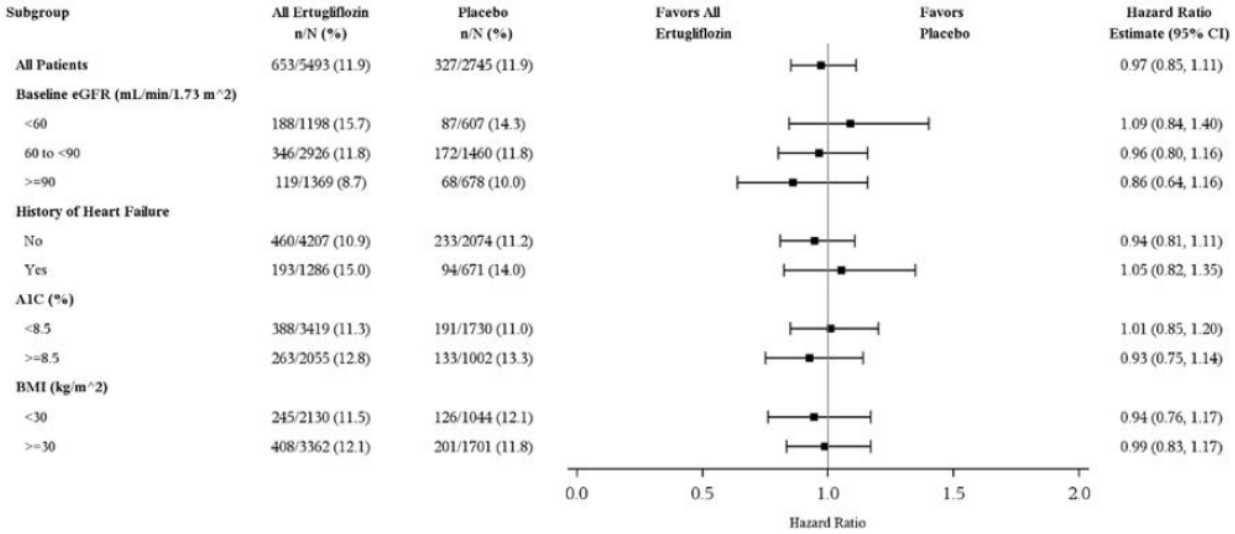
Figure 4 Forest Plot of Hazard Ratio for MACE by Region, Gender, Age, Race, and Ethnicity (CV FAS: On-Treatment + 365-Day Approach)



PFIZER CONFIDENTIAL Date of Reporting Dataset Creation: 21MAR2020 Date of Table Creation: 13APR2020(21:36) Source: [P004MK8835: adam-adsl; adcvtte]

Source: Figure 14.2.12.14.1
MACE was defined as a composite of CV death, non-fatal MI, or non-fatal stroke. CV FAS population with on-treatment approach was used - Included confirmed CV events that occurred between the date of first dose of study medication and the on-treatment censor date.
The analysis was only performed for subgroups with at least 20 subjects in all of the treatment groups in each subgroup category. For the race subgroup analysis, if the sample size was not at least 20 subjects in all of the treatment groups in a certain race category, then that race was combined with the "Other" race category.
CI = 2-sided 95% CI.

Figure 5 Forest Plot of Hazard Ratio for MACE by Baseline eGFR, HF, A1C (< or ⩾ 8.5%), and BMI (< or ⩾ 30) (CV FAS: On-Treatment + 365-Day Approach)



PFIZER CONFIDENTIAL Date of Reporting Dataset Creation: 21MAR2020 Date of Table Creation: 17APR2020(17:44) Source: [P004MK8835: adam-adsl; adcvtte]

Source: Figure 14.2.12.14.2
MACE was defined as a composite of confirmed CV death, non-fatal MI, or non-fatal stroke. CV FAS population with on-treatment approach was used - Included confirmed CV events that occurred between the date of the first dose of study medication and the on-treatment censor date.
For subgroups that had only 2 categories, if the sample size was not at least 20 subjects in all of the treatment groups in each subgroup category, then that subgroup analysis was not performed.
CI = 2-sided 95% CI.

Secondary Endpoints (Superiority)

Composite of CV Death or HHF

In the CV ITT population, an estimated 12% risk reduction for all ertugliflozin group relative to the placebo group was observed for the composite of CV death or HHF. However, the success criterion for the first secondary hypothesis test for the composite of CV death or HHF was not met (HR 0.88; 95.8% CI: 0.750 to 1.034; p=0.108) (Table 10). Hypothesis testing within the ordered testing procedure was therefore stopped at this step, and the remaining secondary hypotheses were not formally tested. P-values provided for subsequent endpoints should be considered descriptive only.

Table 10 Cox Proportional Hazards Model for Time to First CV Death or HHF (CV ITT: On-Study Approach)

Treatment	N	Number of Subjects with an Event (%)	Person-Years[†]	Rate/100 Person-Years	Hazard Ratio[‡] (95.8% CI)	p-value[‡]
Ertugliflozin 5 mg	2752	224 (8.14)	9506.96	2.36	0.89 (0.735, 1.068)	0.188
Ertugliflozin 15 mg	2747	220 (8.01)	9455.52	2.33	0.88 (0.725, 1.057)	0.150
All Ertugliflozin	5499	444 (8.07)	18962.48	2.34	0.88 (0.750, 1.034)	0.108
Placebo	2747	250 (9.10)	9413.97	2.66		

[†] Person-years is calculated as the sum of subjects´ time to first event or time to censoring (the earliest of subjects´ end of study date, death date, or last contact date).

[‡] Hazard ratio, CI, and two-sided p-value for superiority of Ertugliflozin vs Placebo, based on the stratified Cox proportional hazards model that includes treatment as an explanatory factor and cohort category as a stratification factor.

CV = Cardiovascular; HHF = Hospitalization for heart failure.

The on-study approach includes confirmed events that occurred between the randomization date and the on-study censor date.

Within the composite endpoint of CV death or HHF, the evaluation of the individual components of this composite showed that the incidences of CV death were very similar in the ertugliflozin 5 mg (5.56%), 15 mg (5.53%), and placebo (5.50%) (Table 11); however, a notable difference in the incidence of HHF was observed in the ertugliflozin groups relative to the placebo group.

Table 11 Composite of CV Death or HHF (CV ITT: On-Study Approach)

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in Population	2747		2752		2747		5499		8246	
CV Death or HHF	250	(9.10)	224	(8.14)	220	(8.01)	444	(8.07)	694	(8.42)
Component of First CV Death or HHF										
CV death	151	(5.50)	153	(5.56)	152	(5.53)	305	(5.55)	456	(5.53)
HHF	99	(3.60)	71	(2.58)	68	(2.48)	139	(2.53)	238	(2.89)

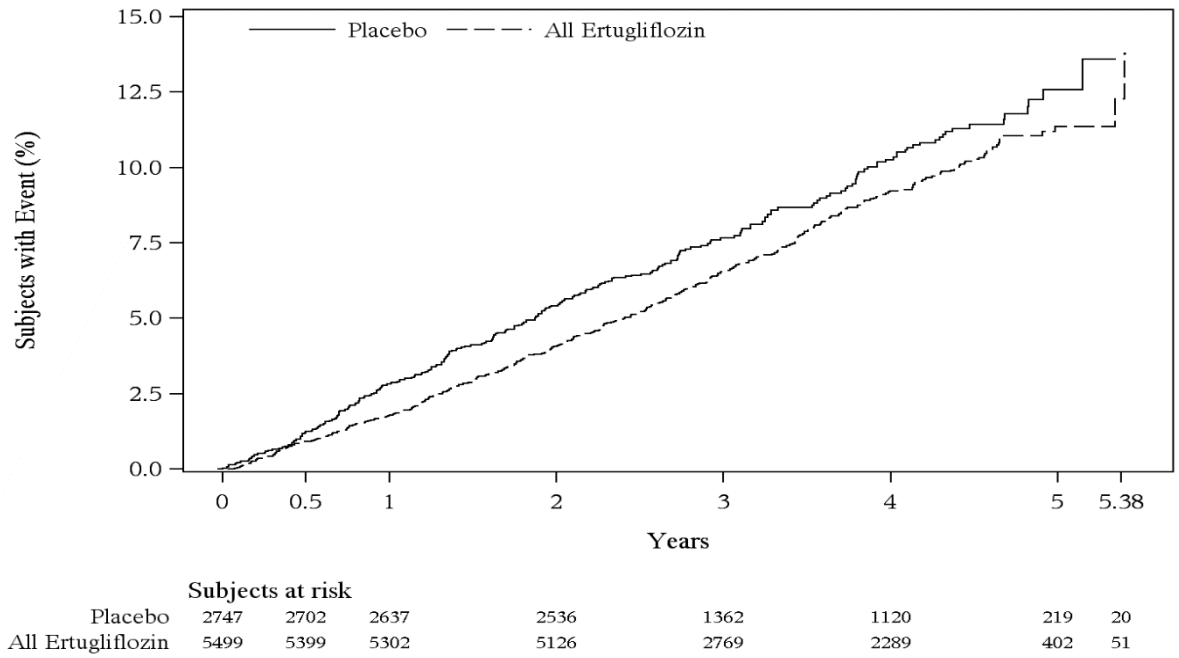
Source: Table 14.2.13.4.2

n = Number of subjects with a first event that contributed to the composite of CV death or HHF. For example, if a subject had HHF and subsequently another HHF before CV death, only the first HHF contributed to the CV death or HHF composite and was recorded within the HHF component.

The on-study approach included confirmed events that occurred between the randomization date and the on-study censor date.

Kaplan-Meier curves for the composite of CV death or HHF showed a separation between the all ertugliflozin and placebo curves starting after approximately 0.5 years that was maintained for the duration of the study (Figure 6).

Figure 6 Kaplan-Meier Curves of Time to First CV Death or HHF (CV ITT: On-Study Approach)



CV=Cardiovascular; HHF=Hospitalization for heart failure. Year 0=Baseline.
All Ertugliflozin - includes Ertugliflozin 5 mg and 15 mg.
The on-study approach includes confirmed events that occurred between the randomization date and the on-study censor date.

The results for the analysis of the composite of CV death or HHF, individual components of CV death and HHF, and Kaplan-Meier curves for the composite of CV death or HHF were similar for the individual ertugliflozin 5 mg and 15 mg groups.

Composite of All-Cause Death or HHF

In the CV ITT population, results from post hoc analyses of the composite of all-cause death or HHF were consistent with those from the analyses of the composite of CV death or HHF.

- The HR for all ertugliflozin group versus the placebo group was 0.90; 95.8% CI; 0.776 to 1.032.
- Kaplan-Meier curves and Kaplan-Meier estimates for the composite of all cause death or HHF were consistent with those from the composite of CV death or HHF.
- The results for the analysis of the composite of all-cause death or HHF, individual components of all-cause death and HHF, and Kaplan-Meier curves for the composite of all-cause death or HHF were similar for the individual ertugliflozin 5 mg and 15 mg groups.

Subgroup Analyses for the Composite of CV Death or HHF

In the CV ITT population, subgroup analyses for the composite of CV death or HHF showed generally similar results across the prespecified subgroups.

CV Death

In the CV ITT population, the risk of CV death was not notably different between the all ertugliflozin group and the placebo group (Table 12).

Table 12 Cox Proportional Hazards Model for Time to CV Death (CV ITT: On-Study Approach)

Treatment	N	Number of Subjects with an Event (%)	Person-Years[†]	Rate/100 Person-Years	Hazard Ratio[‡] (95.8% CI)	p-value[‡]
Ertugliflozin 5 mg	2752	172 (6.25)	9723.39	1.77	0.93 (0.750, 1.154)	0.494
Ertugliflozin 15 mg	2747	169 (6.15)	9692.92	1.74	0.92 (0.739, 1.139)	0.417
All Ertugliflozin	5499	341 (6.20)	19416.31	1.76	0.92 (0.767, 1.113)	0.385
Placebo	2747	184 (6.70)	9686.36	1.90		

[†] Person-years is calculated as the sum of subjects´ time to CV death or time to censoring (the earliest of subjects´ end of study date or date last known to be alive).

[‡] Hazard ratio, CI, and two-sided p-value for superiority of Ertugliflozin vs Placebo, based on the stratified Cox proportional hazards model that includes treatment as an explanatory factor and cohort category as a stratification factor.

CV=Cardiovascular.

The on-study approach includes confirmed events that occurred between the randomization date and the on-study censor date.

Kaplan-Meier curves for time to CV death showed separation of the all ertugliflozin and placebo curves after approximately 1 year, which briefly converged after approximately 3.5 years, and then separated again after approximately 4 years.

The most common adjudication-confirmed categories of CV death across treatment groups were sudden cardiac death (214 subjects [2.60%]), HF (40 subjects [0.49%]), and acute MI (35 subjects [0.42%]). Among these categories, the incidences of sudden cardiac death and HF death were lower in all ertugliflozin group (134 subjects [2.44%] and 21 subjects [0.38%], respectively) than in the placebo group (80 subjects [2.91%] and 19 subjects [0.69%], respectively); incidences of acute MI death were similar in all ertugliflozin group (25 subjects [0.45%]) and the placebo group (10 subjects [0.36%]). Unexplained death (ie, cause of death was undetermined) was classified as CV death and the incidences were similar in all ertugliflozin group (106 [1.93%] subjects) and the placebo group (52 [1.89%] subjects).

The results for the analysis of CV death and Kaplan-Meier curves for CV death were similar for the individual ertugliflozin 5 mg and 15 mg groups.

Results from the pre-specified sensitivity analyses for CV death addressing the impact of different ascertainment windows as well as the impact of missing data were consistent with those from the primary analysis approach.

Subgroup Analyses for CV Death

In the CV ITT population, subgroup analyses for time to CV death showed similar results across all prespecified subgroups.

Renal Composite

In the CV ITT population, an estimated 19% risk reduction for all ertugliflozin group relative to the placebo group was observed for the renal composite endpoint; the 95.8% CI for the between-group difference included 1 (HR for all ertugliflozin group versus placebo was 0.81; 95.8% CI, 0.630 to 1.036) (Table 13).

Table 13 Cox Proportional Hazards Model for Time to First Renal Composite Event (CV ITT: On-Study Approach)

Treatment	N	Number of Subjects with an Event (%)	Person-Years[†]	Rate/100 Person-Years	Hazard Ratio[‡] (95.8% CI)	p-value[‡]
Ertugliflozin 5 mg	2752	83 (3.02)	9485.94	0.87	0.76 (0.568, 1.028)	0.065
Ertugliflozin 15 mg	2747	92 (3.35)	9427.87	0.98	0.85 (0.638, 1.137)	0.258
All Ertugliflozin	5499	175 (3.18)	18913.81	0.93	0.81 (0.630, 1.036)	0.081
Placebo	2747	108 (3.93)	9431.13	1.15		

[†] Person-years is calculated as the sum of subjects´ time to first event or time to censoring (the earliest of subjects´ end of study date, death date, or last contact date).

[‡] Hazard ratio, CI, and two-sided p-value for superiority of Ertugliflozin vs Placebo, based on the stratified Cox proportional hazards model that includes treatment as an explanatory factor and cohort category as a stratification factor.

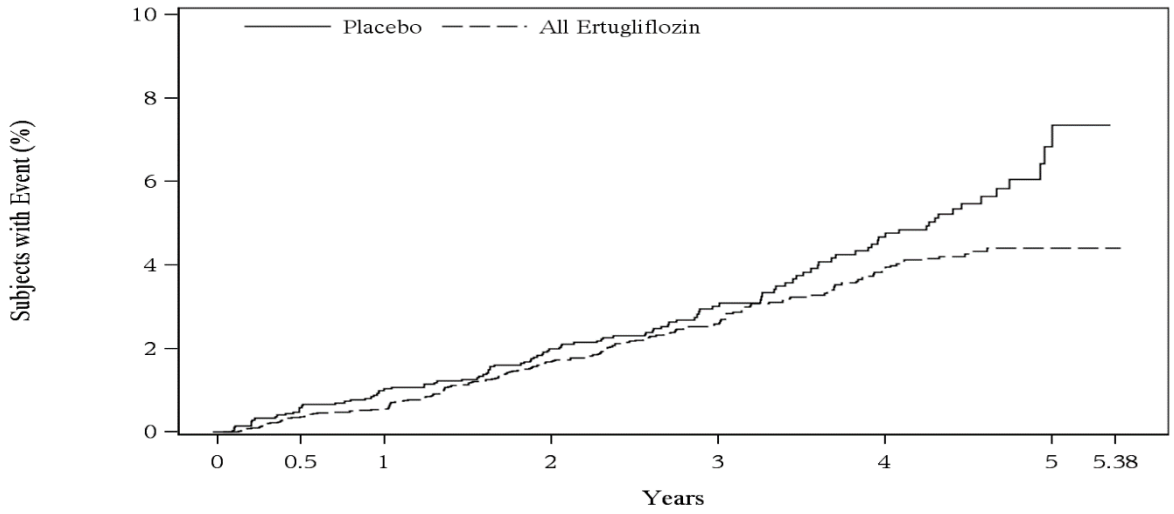
Renal composite endpoint is defined as a composite of renal death, renal dialysis/transplant, or doubling of serum creatinine from baseline.

The on-study approach includes events that occurred between the randomization date and the on-study censor date.)

The observed risk reduction in the primary analysis of the renal composite endpoint was primarily due to the lower proportion of subjects in all ertugliflozin group (3.06%) than in the placebo group (3.82%) with doubling of serum creatinine. In the time to first event analysis, renal dialysis/transplant occurred in a small percentage of subjects in all ertugliflozin group (0.13%) and placebo group (0.11%); there were no events of renal death.

Kaplan-Meier curves for the renal composite endpoint showed a separation of the all ertugliflozin and placebo curves after approximately 3.5 years that continued for the duration of the study (Figure 7).

Figure 7 Kaplan-Meier Curves of Time to First Renal Composite Event (CV ITT: On Study Approach)



Subjects at risk

Placebo	2747	2703	2643	2543	1371	1116	215	20
All Ertugliflozin	5499	5394	5299	5110	2756	2271	406	55

Renal composite endpoint is defined as a composite of renal death, renal dialysis/transplant, or doubling of serum creatinine from baseline. Year 0=Baseline.
All Ertugliflozin - includes Ertugliflozin 5 mg and 15 mg.
The on-study approach includes events that occurred between the randomization date and the on-study censor date.

The results for the primary analysis of the renal composite endpoint, the individual components of the renal composite endpoint (Table 14), and Kaplan-Meier curves for the renal composite endpoint were similar for the individual ertugliflozin 5 mg and 15 mg groups.

Table 14 Composite of Renal Events: Renal Death, Chronic Renal Dialysis/Transplant, or Sustained Doubling of SCr From Baseline (CV ITT: On-Study Approach)

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in Population	2747		2752		2747		5499		8246	
Renal Composite	33	(1.20)	23	(0.84)	20	(0.73)	43	(0.78)	76	(0.92)
Component of First Renal Composite										
Renal death	0	(0.00)	1	(0.04)	0	(0.00)	1	(0.02)	1	(0.01)
Chronic Renal Dialysis/Transplant	1	(0.04)	0	(0.00)	1	(0.04)	1	(0.02)	2	(0.02)
Sustained Doubling of Serum Creatinine From Baseline	32	(1.16)	22	(0.80)	19	(0.69)	41	(0.75)	73	(0.89)

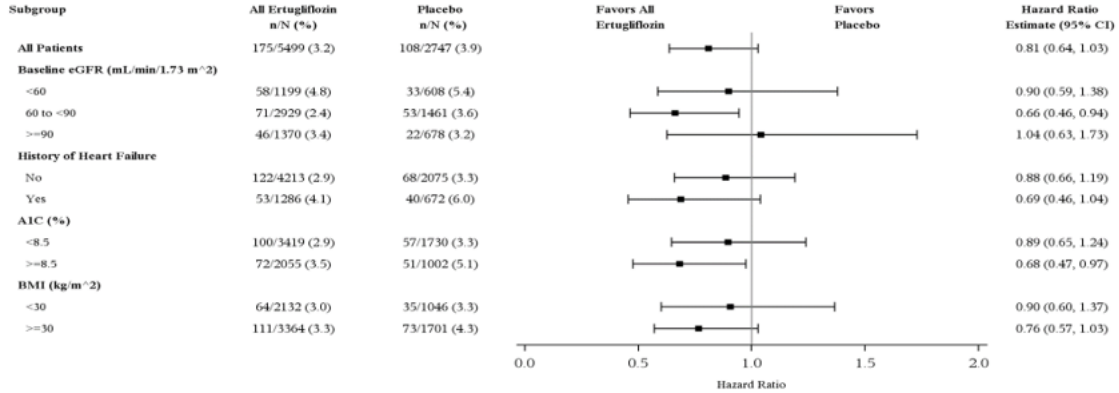
Source: Table 14.2.15.4.2.1
Renal composite endpoint was defined as a composite of renal death, chronic renal dialysis/transplant, or sustained doubling of serum creatinine from baseline.
Sustained doubling of serum creatinine was defined as a doubling value obtained, via central or local lab, at least 30 days following the initial observation. The baseline serum creatinine was the average of serum creatinine values obtained at Screening and Day 1.
Chronic renal dialysis was defined as subjects requiring dialysis for at least 90 days.
n = Number of subjects with a first event that contributed to the composite of renal composite events. For example, if a subject sustained doubling of serum creatinine from baseline and subsequent renal transplant, only the first sustained doubling of serum creatinine from baseline contributed to the renal composite and was recorded within the sustained doubling of serum creatinine from baseline component.
The on-study approach included events that occurred between the randomization date and the on-study censor date.

Results from the sensitivity analyses for the renal composite endpoint addressing the impact of different ascertainment windows as well as the impact of missing data were consistent with those from the primary analysis approach.

Subgroup Analyses for the Renal Composite

In the CV ITT population, subgroup analyses for the renal composite endpoint showed similar results across subgroups as exemplified in Figure 8.

Figure 8 Forest Plot of Hazard Ratio for Renal Composite Event by Baseline eGFR, HF, A1C (< or >= 8.5%), and BMI (< or >=30) (CV ITT: On-Study Approach)



CI = Confidence interval.
Renal composite endpoint is defined as a composite of renal death, renal dialysis/transplant, or doubling of serum creatinine from baseline.
The on-study approach includes events that occurred between the randomization date and the on-study censor date.
For subgroups that have only 2 categories, if the sample size is not at least 20 subjects in all of the treatment groups in each subgroup category, then that subgroup analysis will not be performed.
CI = 2-sided 95% CI.

Other Secondary CV Endpoints

Time to First HHF

In the CV ITT population, the risk of HHF was lower in all ertugliflozin group than in the placebo group (Table 15). The results for the individual ertugliflozin 5 mg and 15 mg groups were similar.

Table 15 Cox Proportional Hazards Model for Time to First HHF (CV ITT: On-Study Approach)

Treatment	N	Number of Subjects with an Event (%)	Person-Years[†]	Rate/100 Person-Years	Hazard Ratio[‡] (95% CI)	p-value[‡]
Ertugliflozin 5 mg	2752	71 (2.58)	9497.82	0.75	0.71 (0.524, 0.964)	0.028
Ertugliflozin 15 mg	2747	68 (2.48)	9445.60	0.72	0.68 (0.502, 0.932)	0.016
All Ertugliflozin	5499	139 (2.53)	18943.42	0.73	0.70 (0.539, 0.902)	0.006
Placebo	2747	99 (3.60)	9408.30	1.05		

[†] Person-years is calculated as the sum of subjects´ time to first event or time to censoring (the earliest of subjects´ end of study date, death date, or last contact date).

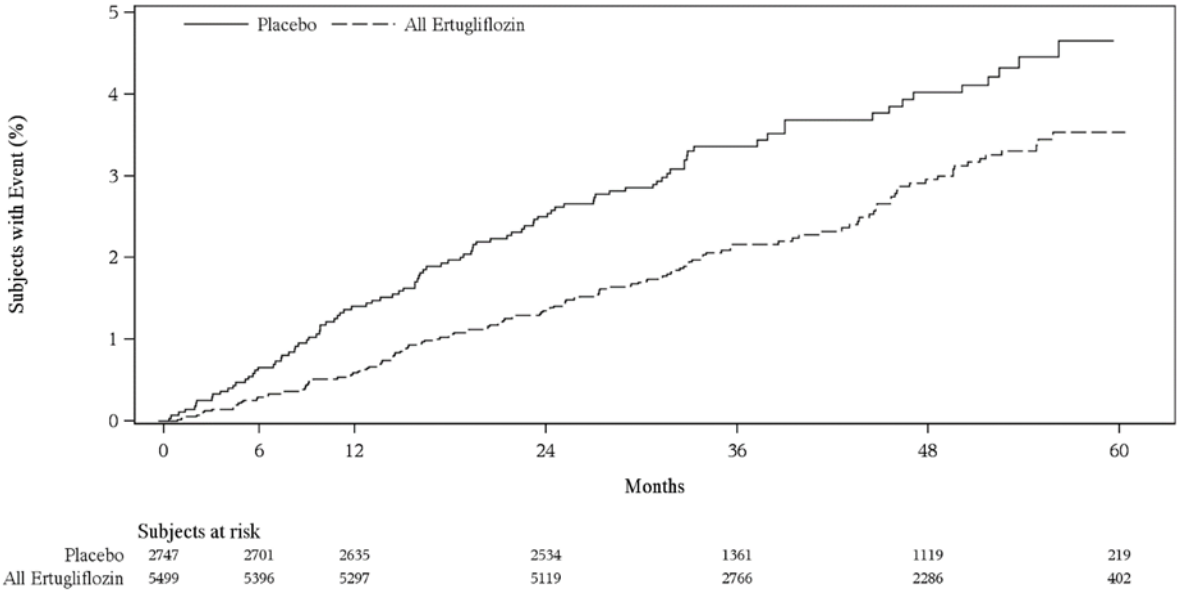
[‡] Hazard ratio, CI, and two-sided p-value comparing Ertugliflozin vs Placebo, based on the stratified Cox proportional hazards model that includes treatment as an explanatory factor and cohort category as a stratification factor.

HHF=Hospitalization for heart failure.

The on-study approach includes confirmed events that occurred between the randomization date and the on-study censor date.

Kaplan-Meier curves for HHF in the CV ITT population showed an early separation of the all ertugliflozin and placebo curves that continued for the duration of the study (Figure 9). The results for the individual ertugliflozin 5 mg and 15 mg groups were similar.

Figure 9 Kaplan-Meier Curves of Time to First HHF (CV ITT: On Study Approach)



All Ertugliflozin – included Ertugliflozin 5 mg and 15 mg.
The on-study approach included confirmed events that occurred between the randomization date and the on-study censor date.

Sensitivity analyses were consistent with those from the primary analysis approach, including an analysis accounting for the competing risk of all cause mortality.

Subgroup Analyses for Time to First HHF

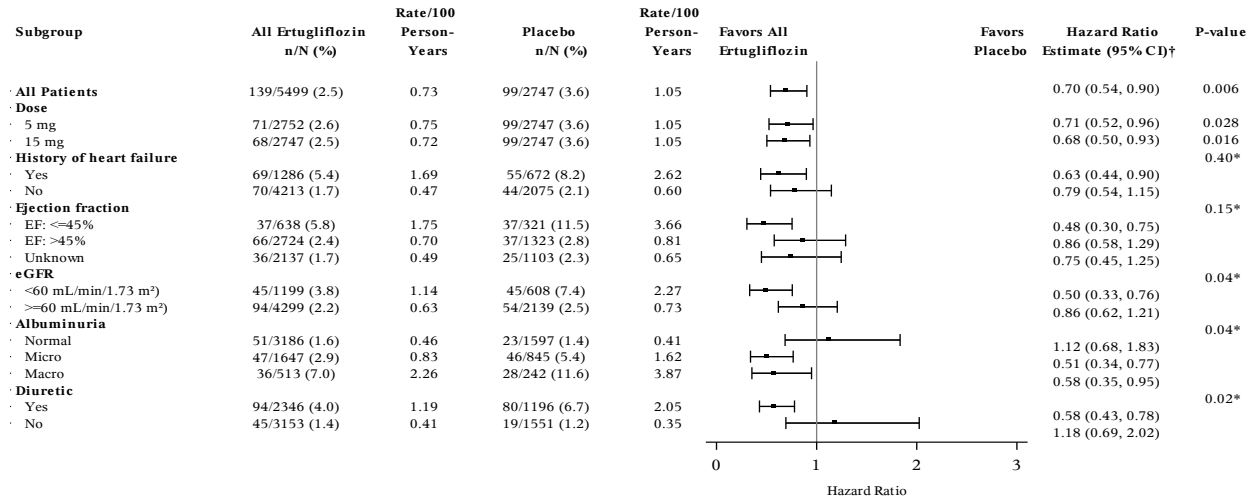
In a post hoc analysis, the effect of ertugliflozin on time to first HHF was consistent between the 2 cohorts (Cohort 1 [HR 0.68; 95% CI, 0.482 to 0.949] versus Cohort 2: [HR 0.73; 95% CI, 0.489 to 1.083]).

In a post hoc analysis of time to first HHF by baseline NYHA Class, the HR for all ertugliflozin group versus the placebo group was 0.48; 95% CI, 0.224 to 1.047 for NYHA Class I, 0.57; 95% CI, 0.355 to 0.927 for NYHA Class II, and 0.89; 95% CI, 0.350 to 2.287 for NYHA Class III.

Results in subjects with HF at baseline and reduced EF ≤45% (rEF), preserved EF >45% (pEF), and unknown EF were similar. The HR for all ertugliflozin group compared with the placebo group in subjects with HF was 0.60; 95% CI, 0.356 to 0.996 for reduced EF ≤45%, 0.70, 95% CI; 0.391 to 1.255 for preserved EF >45%, and 0.52; 95% CI, 0.205 to 1.314 for unknown EF.

Additional subgroup analyses for time to first HHF showed generally similar results across subgroups, with the exception of the following subgroups. Results suggested greater benefit of ertugliflozin in (1) those with albuminuria versus those without albuminuria at baseline, (2) those with eGFR <60 mL/min/1.73 m^2 versus those with eGFR ≥60 mL/min/1.73 m^2 at baseline, and (3) those taking diuretics versus those not taking diuretics at baseline.

Figure 10 Forest Plot of Hazard Ratio for HHF: Overall and by Dose of Ertugliflozin, History of HF, EF, Baseline eGFR, Albuminuria, and Diuretic Use CV ITT: On-Study Approach



CI=2-sided 95% Confidence interval; HHF=Hospitalization for heart failure.
The on-study approach includes confirmed events that occurred between the randomization date and the on-study censor date.
For subgroups that have only 2 categories, if the sample size is not at least 20 subjects in all of the treatment groups in each subgroup category, then that subgroup analysis will not be performed.
† For history of heart failure, based on the stratified Cox proportional hazards model that includes terms for treatment, subgroup, treatment-by-subgroup interaction, ASCVD risk factors, and region as the stratification factor.
* P-value for interaction

Post hoc Analysis of Time to First HHF

Analyses in the CV ITT population in which potential effect modifiers of eGFR, albuminuria, and diuretic use at baseline were added to the primary model provided results that were similar to the primary analysis approach. In this expanded model, the risk of HHF was lower in all ertugliflozin group compared with the placebo group (HR: 0.68; 95% CI, 0.524 to 0.877).

Total CV Death/HHF Composite and Total HHF

The analysis of total CV death/HHF events (i.e. not censored at the time of the first event) showed a reduction in total events in all ertugliflozin groups compared with the placebo group (Table 16).

Table 16 Andersen-Gill Model for Total CV Death or HHF (CV ITT: On-Study Approach)

Treatment	N	Number of Events	Event-Years†	Rate/100 Event-Years	Hazard Ratio‡ (95% CI)
Ertugliflozin 5 mg	2752	280	9603.47	2.92	0.85 (0.725, 1.001)
Ertugliflozin 15 mg	2747	259	9540.35	2.71	0.79 (0.673, 0.935)
All Ertugliflozin	5499	539	19143.82	2.82	0.82 (0.716, 0.945)
Placebo	2747	327	9568.95	3.42	

† The sum of time from the randomization to the end of follow-up.
‡ Ertugliflozin vs Placebo, based on the Andersen-Gill model for the recurrent events at the end of study.
CV = Cardiovascular; HHF = Hospitalization for Heart Failure.
The on-study approach includes confirmed events that occurred between the randomization date and the on-study censor date.
Data cut date: 16MAR2020 (Final)
PFIZER CONFIDENTIAL Date of Reporting Dataset Creation: 19APR2020 Date of Table Creation: 20APR2020 (18:51)

A lower rate of total HHF events was observed in the ertugliflozin group compared with the placebo group (HR: 0.70; 95% CI, 0.561 to 0.868).

Recurrent HF Hospital Admission and Mortality in Subjects with a First HHF Event

Recurrent hospital admission for HHF and subsequent mortality in subjects with a first HHF event were lower in subjects treated with ertugliflozin compared with placebo. The percentage of subjects with hospital readmissions for HF in all ertugliflozin group was 28.78% versus 33.33% in the placebo group. The percentage of subjects with subsequent CV deaths among subjects with a first HHF event in all ertugliflozin group was 25.90% versus 33.33 % in the placebo group.

All-Cause Mortality

The risk of death from any cause was not notably different between the all ertugliflozin and placebo groups (HR: 0.93; 95% CI, 0.797 to 1.081). Results for the individual ertugliflozin 5 mg and 15 mg groups were similar.

The Kaplan-Meier curves for all-cause mortality showed a separation of the all ertugliflozin and placebo curves during the study, consistent with the observed HR of 0.93.

Results of the sensitivity analyses were consistent with those from the primary analysis approach.

Other Adjudicated Efficacy Endpoints

Other CV efficacy endpoints analyzed in VERTIS CV were time to first MACE plus, fatal or non-fatal MI, fatal or non-fatal stroke, HHF, and the individual components of MACE (CV death, non-fatal myocardial infarction, non-fatal stroke).

For each of these adjudicated efficacy endpoints, with exception of HHF, the risk was not notably different in all ertugliflozin group relative to the placebo group (Table 17).

Table 17 Cox Proportional Hazards Model for Other Secondary Endpoints (CV ITT: On-Study Approach)

Endpoint	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin		Hazard ratio† (95% CI)	p-value†
	n (%)	Rate/ 100 Person-years	n (%)	Rate/ 100 Person-years	n (%)	Rate/ 100 Person-years	n (%)	Rate/ 100 Person-years		
MACE plus‡	439 (15.98)	4.92	402 (14.61)	4.42	421 (15.33)	4.67	823 (14.97)	4.54	0.92 (0.823, 1.038)	0.183
Fatal or non-fatal MI	158 (5.75)	1.70	145 (5.27)	1.55	185 (6.73)	2.00	330 (6.00)	1.77	1.04 (0.861, 1.259)	0.676
Non-fatal MI	148 (5.39)	1.60	135 (4.91)	1.44	175 (6.37)	1.89	310 (5.64)	1.67	1.04 (0.859, 1.270)	0.664
Fatal or non-fatal stroke	87 (3.17)	0.93	87 (3.16)	0.92	98 (3.57)	1.04	185 (3.36)	0.98	1.06 (0.820, 1.365)	0.663
Non-fatal stroke	78 (2.84)	0.83	73 (2.65)	0.77	84 (3.06)	0.90	157 (2.86)	0.83	1.00 (0.764, 1.315)	0.986
Hospitalization for heart failure	99 (3.60)	1.05	71 (2.58)	0.75	68 (2.48)	0.72	139 (2.53)	0.73	0.70 (0.539, 0.902)	0.006

† Hazard ratio, CI, and 2-sided p-value comparing All Ertugliflozin versus Placebo, based on the stratified Cox proportional hazards model that included treatment as an explanatory factor and cohort category as a stratification factor.
‡ MACE plus was defined as a composite of confirmed CV death, non-fatal MI, or non-fatal stroke, or hospitalization for unstable angina.
The on-study approach included confirmed events that occurred between the randomization date and the on-study censor date

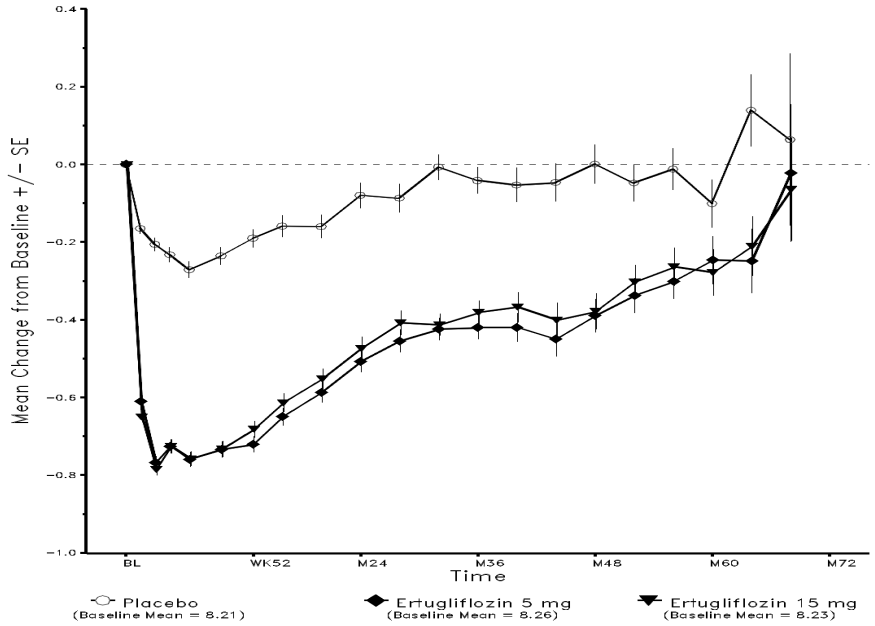
Glycemic Control and Cardiometabolic Endpoints

Data summarized in this section are for the overall FAS population in VERTIS CV. Of note, investigators or treating physicians were permitted to make changes in subjects' AHA regimens after Week 18 and blood pressure medications at any time to maximize glucose and blood pressure control, respectively.

Glycemic Endpoints: Reductions from baseline in A1C were greater in the ertugliflozin 5 mg and 15 mg groups relative to the placebo group at Week 18 and Week 52. The mean changes from baseline in A1C over time showed greater reductions in the ertugliflozin groups compared with the placebo group, with

the reductions beginning at Week 6. Subsequent to Week 12, all treatment groups showed a gradual increase in A1C over time (Figure 11). The proportions of subjects with A1C <7.0% (53 mmol/mol) were greater in the ertugliflozin 5 mg and 15 mg groups compared with the placebo group from Week 6 through Month 48.

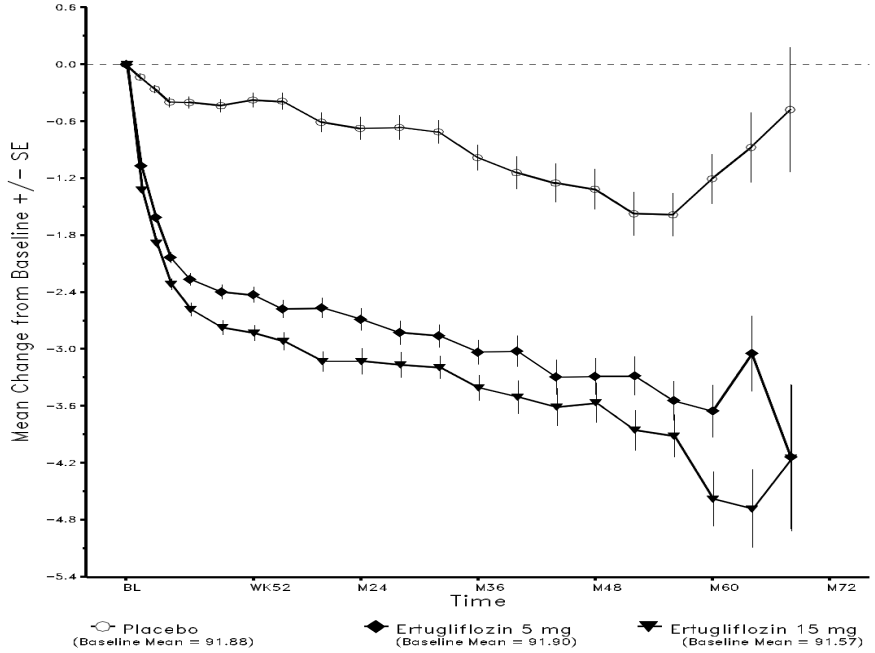
Figure 11 A1C (%): Mean Change from Baseline Over Time (Mean ± SE) Full Analysis Set



Treatments with less than 30 samples at a timepoint are excluded from the plot.
Data cut date: 16MAR2020 (Final)

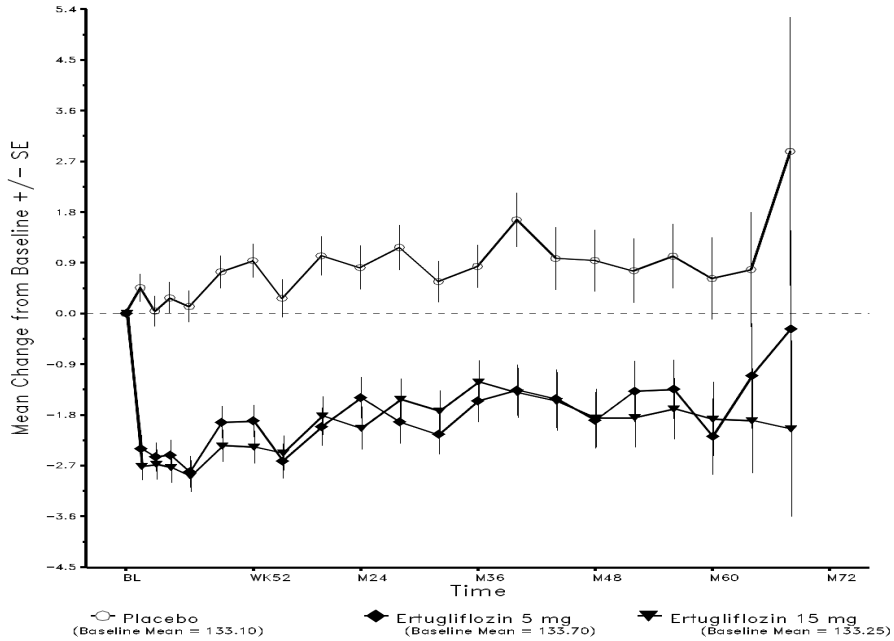
Cardiometabolic Endpoints: Reductions from baseline in BW, SBP, and DBP were greater in the ertugliflozin groups compared to the placebo group at Week 52. The mean changes from baseline in BW, SBP, and DBP over time showed greater reductions in the ertugliflozin groups compared to the placebo group, with the reductions beginning at Week 6 and persisting for the duration of the study (Figure 12, Figure **13**, Figure 14).

Figure 12 Body Weight (kg): Mean Change from Baseline Over Time (Mean ± SE) Full Analysis Set



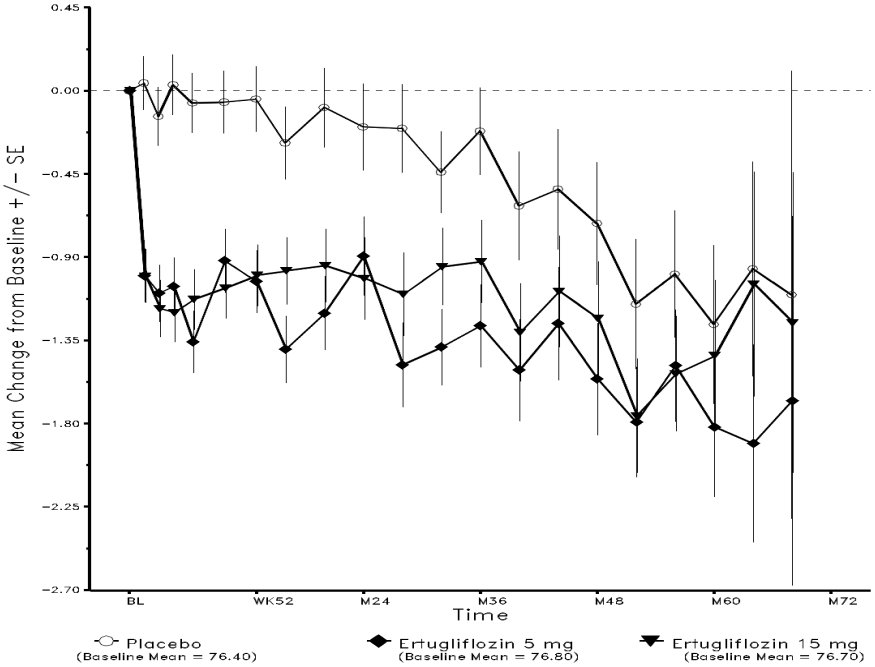
Treatments with less than 30 samples at a timepoint are excluded from the plot.

Figure 13 Sitting Systolic Blood Pressure (mm Hg): Mean Change from Baseline Over Time (Mean ± SE) Full Analysis Set



Treatments with less than 30 samples at a timepoint are excluded from the plot.

Figure 14 Sitting Diastolic Blood Pressure (mm Hg): LS Mean Change from Baseline Over Time (Mean ± SE) Full Analysis Set



Treatments with less than 30 samples at a timepoint are excluded from the plot.

Glycemic Control and Cardiometabolic Endpoints in Subjects with Stage 3 Chronic Kidney Disease (eGFR 30 to <60 mL/min/1.73m^2)

Demographic and Baseline Characteristics

Of the 8,246 randomized subjects in VERTIS CV, 1,776 (21.5%) had Stage 3 CKD (eGFR 30 and <60 mL/min/1.73m^2). The demographic and baseline characteristics of subjects with Stage 3 CKD were balanced across treatment groups. The mean age was 68.1 years and 21.2% of subjects were ≥75 years old at baseline. The mean A1C was 8.2% and the mean eGFR was 49.3 mL/min/1.73 m^2. Other diabetes characteristics, use of AHA therapies, and CV risk factors at baseline were balanced across treatment groups.

Within the Stage 3 CKD population, 1,319 subjects had Stage 3A CKD (eGFR ≥45 to <60 mL/min/1.73 m^2) and 457 had Stage 3B CKD (eGFR ≥30 to <45 mL/min/1.73 m^2). Demographic and baseline characteristics were generally balanced across treatment groups within the Stage 3A CKD and 3B CKD subgroups. In Stage 3A CKD subgroup, the mean age was 67.7 years and 19.6% of subjects were ≥75 years old at baseline. Mean A1C and eGFR were 8.2% and 53.0 mL/min/1.73 m^2, respectively. Other diabetes characteristics, use of AHA therapies, and CV risk factors at baseline were balanced across treatment groups. In CKD stage 3B subgroup, the mean age was 69.3 years and 25.8% of subjects were ≥75 years old at baseline. Mean A1C and eGFR were 8.3% and 38.8 mL/min/1.73 m^2, respectively. Other diabetes characteristics, use of AHA therapies, and CV risk factors at baseline were balanced across treatment groups.

Glycemic Control

Glycemic Control in Subjects with Stage 3 CKD (eGFR 30 to <60 mL/min/1.73 m^2)

In subjects with Stage 3 CKD, post hoc analyses showed that glycemic control was greater with ertugliflozin treatment than with placebo treatment.

- *A1C*

Reductions from baseline in A1C were greater in the ertugliflozin 5 mg and 15 mg groups relative to the placebo group at Week 18 (Table 18). Results from missing data sensitivity analyses using the MI-RD and RTB approaches were consistent with those using the cLDA approach.

Table 18 A1C (%): Change from Baseline at Week 18 (cLDA; Full Analysis Set: Excluding Rescue Approach) in Subjects with Baseline eGFR 30 to <60 mL/min/1.73m²

	Baseline		Week 18		Change from Baseline at Week 18		
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)†
Placebo	597	8.23 (0.883)	467	7.89 (1.054)	597	-0.30 (0.912)	-0.26 (-0.33, -0.18)
Ertugliflozin 5 mg	615	8.21 (0.923)	497	7.62 (0.944)	617	-0.55 (0.837)	-0.52 (-0.60, -0.45)
Ertugliflozin 15 mg	557	8.23 (0.931)	457	7.68 (0.941)	559	-0.55 (0.924)	-0.53 (-0.61, -0.46)
Pairwise Comparison					Difference in LS Means (95% CI)†		p-Value
Ertugliflozin 5 mg vs. Placebo					-0.27 (-0.37, -0.17)		<0.001
Ertugliflozin 15 mg vs. Placebo					-0.28 (-0.38, -0.17)		<0.001
Conditional Pooled SD of Change from Baseline					0.83		

For baseline and Week 18, N is the number of subjects with non-missing assessments at the specific timepoint; for Change from Baseline at Week 18, N is the number of subjects in the FAS (i.e., randomized subjects who took at least 1 dose of study medication and had at least one assessment at or after baseline). The Mean and SD for the change from baseline are based on non-missing values.

† Based on cLDA model with fixed effects for treatment, time, baseline eGFR (continuous) and the interaction of time by treatment. Time was treated as a categorical variable.

CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation.

The reductions from baseline in A1C were greater in the ertugliflozin 5 mg and 15 mg groups than in the placebo group at all time points through Week 18.

The model-based odds of having A1C <7.0% (<53 mmol/mol) at Week 18, using multiple imputation for subjects with missing Week 18 data, were greater in the ertugliflozin 5 mg group (20.7%) and ertugliflozin 15 mg group (17.0%) compared with the placebo group (12.9%). These results from the analysis of subjects with A1C <7.0% at Week 18 in which missing values were imputed as not at goal were consistent with the results of the primary analysis.

- *FPG*

At Week 18, the placebo-adjusted LS mean (95% CI) change from baseline in FPG (mg/dL) was -7.85 (-12.23, -3.47) for the ertugliflozin 5 mg group and -9.21 (-13.67, -4.74) for the 15 mg group. Results from missing data sensitivity analyses using the MI-RD and RTB approaches were consistent with those using the cLDA approach.

Glycemic Control in Subjects with Stage 3A CKD (eGFR 45 to <60 mL/min/1.73 m²)

In subjects with Stage 3A CKD, glycemic control was greater with ertugliflozin treatment than with placebo treatment.

- *A1C*

Reductions from baseline in A1C were greater in the ertugliflozin 5 mg and 15 mg groups relative to the placebo group at Week 18 (Table 19). Results from analyses using the MI-RD approach were consistent with those using the cLDA approach.

Table 19 A1C (%): Change from Baseline at Week 18 (cLDA; Full Analysis Set: Excluding Rescue Approach) in Subjects with Baseline eGFR 45 to <60 mL/min/1.73m²

	Baseline	Week 18	Change from Baseline at Week 18

Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)†
Placebo	439	8.23 (0.860)	346	7.86 (1.068)	439	-0.31 (0.915)	-0.27 (-0.36, -0.18)
Ertugliflozin 5 mg	463	8.18 (0.876)	377	7.58 (0.914)	465	-0.57 (0.824)	-0.54 (-0.62, -0.45)
Ertugliflozin 15 mg	411	8.22 (0.950)	346	7.62 (0.913)	413	-0.61 (0.975)	-0.58 (-0.67, -0.49)

Pairwise Comparison	Difference in LS Means (95% CI)†	p-Value
Ertugliflozin 5 mg vs. Placebo	-0.27 (-0.38, -0.15)	<0.001
Ertugliflozin 15 mg vs. Placebo	-0.31 (-0.43, -0.19)	<0.001
Conditional Pooled SD of Change from Baseline	0.83	

For baseline and Week 18, N is the number of subjects with non-missing assessments at the specific timepoint; for Change from Baseline at Week 18, N is the number of subjects in the FAS (i.e., randomized subjects who took at least 1 dose of study medication and had at least one assessment at or after baseline). The Mean and SD for the change from baseline are based on non-missing values.

† Based on cLDA model with fixed effects for treatment, time, baseline eGFR (continuous) and the interaction of time by treatment. Time was treated as a categorical variable.

CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation.

The reductions from baseline in A1C were greater in the ertugliflozin 5 mg and 15 mg groups than in the placebo group at all time points through Week 18.

The model-based odds of having A1C <7.0% (<53 mmol/mol) at Week 18, using multiple imputation for subjects with missing Week 18 data, were greater in the ertugliflozin 5 mg group (21.9%) and ertugliflozin 15 mg group (18.4%) compared with the placebo group (14.1%). Results from the analysis of subjects with A1C <7.0% at Week 18 in which missing values were imputed as not at goal were consistent with those using multiple imputation for missing Week 18 data.

- *FPG*

At Week 18, the placebo-adjusted LS mean change (95% CI) from baseline in FPG (mg/dL) was -8.36 (-13.43, -3.29) for the ertugliflozin 5 mg group and -11.35 (-16.52, -6.18) for the ertugliflozin 15 mg group. Results from missing data sensitivity analyses using the MI-RD approach were consistent with those using the cLDA approach.

Glycemic Control in Subjects with Stage 3B CKD (eGFR 30 to <45 mL/min/1.73 m^2)

In subjects with CKD stage 3B, post hoc analyses showed that there was a small improvement in glycemic control with ertugliflozin treatment compared with placebo treatment.

- *A1C*

The reduction from baseline in A1C at Week 18 was greater in the ertugliflozin 5 mg group than in the placebo group; for the ertugliflozin 15 mg group, the 95% CI included 0 (Table 20). Results from the missing data sensitivity analysis using the RTB approach were consistent with those using the cLDA approach. The MI-RD including rescue approach was not performed as the retrieved data were insufficient to support the analysis.

Table 20 A1C (%): Change from Baseline at Week 18 (cLDA; Full Analysis Set: Excluding Rescue Approach) in Subjects with Baseline eGFR 30 to <45 mL/min/1.73m^2

	Baseline		Week 18		Change from Baseline at Week 18		
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)†
Placebo	158	8.24 (0.948)	121	7.98 (1.012)	158	-0.25 (0.904)	-0.21 (-0.35, -0.07)
Ertugliflozin 5 mg	152	8.32 (1.052)	120	7.76 (1.024)	152	-0.48 (0.876)	-0.49 (-0.63, -0.35)
Ertugliflozin 15 mg	146	8.27 (0.877)	111	7.85 (1.010)	146	-0.38 (0.725)	-0.40 (-0.54, -0.25)

Pairwise Comparison	Difference in LS Means	p-Value

	(95% CI)[†]	
Ertugliflozin 5 mg vs. Placebo	-0.28 (-0.47, -0.08)	0.006
Ertugliflozin 15 mg vs. Placebo	-0.19 (-0.39, 0.01)	0.064
Conditional Pooled SD of Change from Baseline	0.80	

For baseline and Week 18, N is the number of subjects with non-missing assessments at the specific timepoint; for Change from Baseline at Week 18, N is the number of subjects in the FAS (i.e., randomized subjects who took at least 1 dose of study medication and had at least one assessment at or after baseline). The Mean and SD for the change from baseline are based on non-missing values.

[†] Based on cLDA model with fixed effects for treatment, time, baseline eGFR (continuous) and the interaction of time by treatment. Time was treated as a categorical variable.

CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation.

The reductions from baseline in A1C were greater in the ertugliflozin 5 mg and 15 mg groups than in the placebo group at all time points through Week 18.

- *FPG*

At Week 18, the placebo-adjusted LS mean (95% CI) change from baseline in FPG (mg/dL) was -5.77 mg/dL (-14.52, 2.98) for the ertugliflozin 5 mg group and -2.35 mg/dL (-11.28, 6.58) for the ertugliflozin 15 mg group. Results from the missing data sensitivity analysis using the RTB approach were consistent with those using the cLDA approach. The MI-RD including rescue approach was not performed as the retrieved data were insufficient to support the analysis.

Cardiometabolic Endpoints (post-hoc analysis)

Body Weight and Systolic Blood Pressure in Subjects with Stage 3 CKD (eGFR 30 to <60 mL/min/1.73 m^2)

The placebo-adjusted LS mean (95% CI) change from baseline in BW (kg) at Week 18 was -1.37 (-1.70, -1.04) for the ertugliflozin 5 mg group and -1.53 (-1.86, -1.19) for the ertugliflozin 15 mg group].

The placebo-adjusted LS mean (95% CI) change from baseline in SBP (mm Hg) at Week 18 was -2.89 (-4.48, -1.30) for the ertugliflozin 5 mg and -3.19 (-4.81, -1.56) for the ertugliflozin 15 mg group.

Body Weight and Systolic Blood Pressure in Subjects with Stage 3A CKD (eGFR 45 to <60 mL/min/1.73 m^2)

The placebo-adjusted LS mean (95% CI) change from baseline in BW (kg) at Week 18 was -1.32 (-1.70, -0.94) for the ertugliflozin 5 mg group and -1.38 (-1.77, -0.99) for the ertugliflozin 15 mg group.

The placebo-adjusted LS mean (95% CI) change from baseline in SBP (mm Hg) at Week 18 was -3.02 (-4.83, -1.21) for the ertugliflozin 5 mg group and -3.41 (-5.26, -1.55) for the ertugliflozin 15 mg group.

Body Weight and Systolic Blood Pressure in Subjects with Stage 3B CKD (eGFR 30 to <45 mL/min/1.73 m^2)

The placebo-adjusted LS mean (95% CI) change from baseline in BW (kg) at Week 18 was -1.51 (-2.18, -0.84) for the ertugliflozin 5 mg group and -1.95 (-2.63, -1.28) for the ertugliflozin 15 mg group.

The placebo-adjusted LS mean (95% CI) change from baseline in SBP (mm Hg) at Week 18 was -2.52 (-5.86, 0.82) for the ertugliflozin 5 mg group and -2.42 (-5.81, 0.97) for the ertugliflozin 15 mg group.

Glycemic Sub-Studies

Insulin With or Without Metformin Add-on Glycemic Sub-Study

A minimum of 450 subjects were expected to be enrolled in the insulin with or without metformin sub-study. The actual sample size was 1,065.

Of the 1,065 subjects included in the insulin with or without metformin sub-study, 1045 (98.1%) completed the 18-week treatment period, and 979 (91.9%) completed this period on study medication. The proportion of subjects who discontinued study medication prior to Week 18 was generally similar across treatment groups.

Baseline demographic and anthropometric characteristics were balanced across treatment groups. The mean age was 64.8 years, 31.8% were female, and 52.3% were ≥65 years old. At baseline, mean A1C and eGFR were 8.41% and 73.7 mL/min/1.73 m2, respectively. The mean duration of diabetes was 16.66 years. The median insulin dose at baseline was 58.0 units/day (Table 2: Overview of the Glycaemic Sub-Studies in VERTIS CV).

After 18 weeks, treatment with ertugliflozin at doses of 5 mg or 15 mg provided significant reductions from baseline relative to placebo in A1C and FPG (Figure 15,

Table 21). The proportions of subjects with an A1C <7.0% in the ertugliflozin 5 mg group (20.7%) and the 15 mg group (21.1%) were approximately 2-times greater than in the placebo group (10.7%). The model-based odds of having A1C <7.0% (<53 mmol/mol) at Week 18 using multiple imputation for subjects with missing Week 18 data were significantly greater with both doses of ertugliflozin compared with placebo (

Table 21)

Figure 15 (Insulin +/- Metformin) A1C (%): LS Mean Change from Baseline Over Time (cLDA; Full Analysis Set: Week 18, Excluding Rescue Approach)

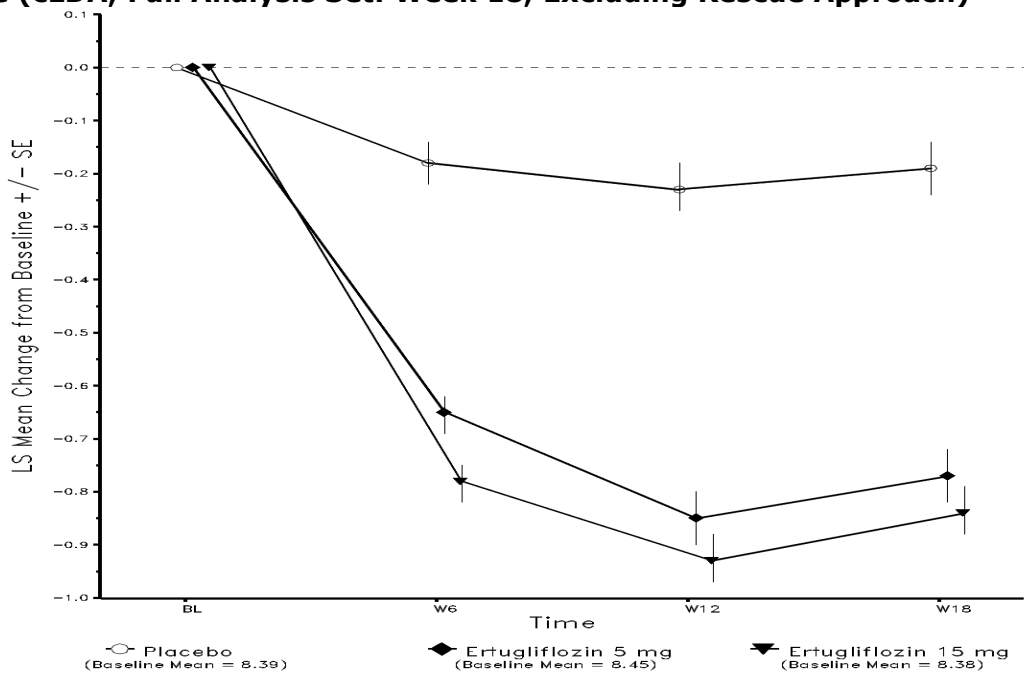


Table 21 (Insulin +/- Metformin) Key Efficacy Endpoints Full Analysis Set: Week 18, Excluding Rescue Approach

Treatment	N	LS Mean (95% CI)	Pairwise Comparisons	
			Difference in LS Means (95% CI) vs. Placebo†	p-Value
Change from Baseline in A1C (%) at Week 18: cLDA				
Placebo	347	-0.19 (-0.29, -0.09)		
Ertugliflozin 5 mg	348	-0.77 (-0.86, -0.67)	-0.58 (-0.71, -0.44)	<0.001
Ertugliflozin 15 mg	370	-0.84 (-0.93, -0.74)	-0.65 (-0.78, -0.51)	<0.001
Change from Baseline in FPG (mg/dL) at Week 18: cLDA				

Placebo	347	-7.74 (-13.67, -1.81)		
Ertugliflozin 5 mg	348	-26.98 (-32.80, -21.17)	-19.24 (-26.80, -11.68)	<0.001
Ertugliflozin 15 mg	370	-33.15 (-38.81, -27.48)	-25.40 (-32.84, -17.96)	<0.001
Change from Baseline in Body Weight (kg) at Week 18: cLDA				
Placebo	347	-0.25 (-0.60, 0.11)		
Ertugliflozin 5 mg	348	-1.87 (-2.22, -1.52)	-1.62 (-2.12, -1.13)	<0.001
Ertugliflozin 15 mg	370	-2.13 (-2.47, -1.79)	-1.88 (-2.37, -1.40)	<0.001
Change from Baseline in Sitting Systolic Blood Pressure (mmHg) at Week 18: cLDA				
Placebo	347	0.20 (-1.33, 1.74)		
Ertugliflozin 5 mg	348	-2.67 (-4.17, -1.18)	-2.88 (-4.94, -0.82)	0.006
Ertugliflozin 15 mg	370	-2.12 (-3.57, -0.67)	-2.32 (-4.35, -0.30)	0.025
Change from Baseline in Sitting Diastolic Blood Pressure (mmHg) at Week 18: cLDA				
Placebo	347	-0.26 (-1.14, 0.62)		
Ertugliflozin 5 mg	348	-0.86 (-1.72, -0.00)	-0.60 (-1.81, 0.60)	0.326
Ertugliflozin 15 mg	370	-0.64 (-1.47, 0.20)	-0.38 (-1.56, 0.81)	0.533
Treatment	N	n (%)	Odds Ratio (95% CI) vs. Placebo	p-Value
A1C < 7.0% at Week 18 (logistic regression with multiple imputation based on cLDA model)[§]				
Placebo	347	37 (10.7)		
Ertugliflozin 5 mg	348	72 (20.7)	2.60 (1.64, 4.12)	<0.001
Ertugliflozin 15 mg	370	78 (21.1)	2.49 (1.61, 3.83)	<0.001
A1C < 7.0% at Week 18 (logistic regression with missing Values Imputed as Not at Goal)[§]				
Placebo	347	37 (10.7)		
Ertugliflozin 5 mg	348	72 (20.7)	2.44 (1.55, 3.85)	<0.001
Ertugliflozin 15 mg	370	78 (21.1)	2.28 (1.46, 3.56)	<0.001

N is the number of subjects in the analysis population.

n is the number of subjects with the event of interest.

[†] cLDA model is fitted with fixed effects for treatment, time, interaction of time by treatment. Time was treated as a categorical variable.

[§] Logistic regression model fitted with terms for treatment and baseline A1C. For the analyses with multiple imputation, missing data imputed using the cLDA model fitted.

All model based analyses fitted with terms for baseline eGFR (continuous), stratum for insulin substudy (insulin alone or insulin + metformin).

CI=Confidence Interval; LS =Least Squares.

After 18 weeks, treatment with both doses of ertugliflozin relative to placebo provided significant reductions from baseline in BW and SBP. The reductions from baseline in DBP at Week 18 were not significantly greater in the ertugliflozin 5 mg and 15 mg groups relative to the placebo group (

Table 21).

There were not enough retrieved dropouts to perform the MI-RD imputation, hence RTB was used instead of MI-RD for supportive analyses. Results from missing data sensitivity analysis using the RTB approach for change from baseline in A1C and FPG were consistent with the primary analysis results. Results from an analysis of subjects with A1C <7.0 % (<53 mmol/mol) at Week 18 with missing values imputed as 'not at goal' were consistent with the primary analysis results. The results from missing data sensitivity analyses using the RTB approach for change from baseline in BW, SBP, and DBP were consistent with the primary analysis results.

SU Monotherapy Add-on Glycemic Sub-Study

The planned sample size for this sub-study was 170 subjects; however, the actual sample size was 157.

Of the 157 subjects included in the SU monotherapy sub-study, 155 (98.7%) completed the 18-week treatment period, and 148 (94.3%) completed this period on study medication. The proportion of

subjects who discontinued study medication prior to Week 18 was low with a higher number in the ertugliflozin 15 mg group.

Baseline demographic and anthropometric characteristics were balanced across treatment groups for most categories. A majority of subjects for the total population (61.8%) were male, although the proportion was lower within the ertugliflozin 15 mg group (44.4% male). The mean age was 64.6 years, and 49.7% were ≥65 years old. At baseline, mean A1C and eGFR were 8.29% and 77.7 mL/min/1.73 m^2, respectively. The mean duration of diabetes was 8.48 years. The most commonly used SU was gliclazide with a median dose of 60.0 mg/day at randomization (Table 2).

After 18 weeks, reductions from baseline in A1C were not significantly different between the ertugliflozin and placebo groups (Figure 16,

Table 22). Hence, all p-values for the comparison of ertugliflozin 5 mg compared to placebo for A1C, and for both 5 mg and 15 mg ertugliflozin groups compared to the placebo group for FPG, BW, proportion of subjects with A1C <7.0% (<53 mmol/mol), SBP and DBP were considered descriptive only (

Table 22). The reductions from baseline in FPG at Week 18 were greater with both doses of ertugliflozin relative to placebo. The proportion of subjects with an A1C <7.0% (<53 mmol/mol) at Week 18 was not notably different across the treatment groups (ertugliflozin 5 mg: 32.7%, ertugliflozin 15 mg: 27.8 %, placebo: 25 %) (

Table 22).

Figure 16 (SU Monotherapy) A1C (%): LS Mean Change from Baseline Over Time (cLDA; Full Analysis Set: Week 18, Excluding Rescue Approach)

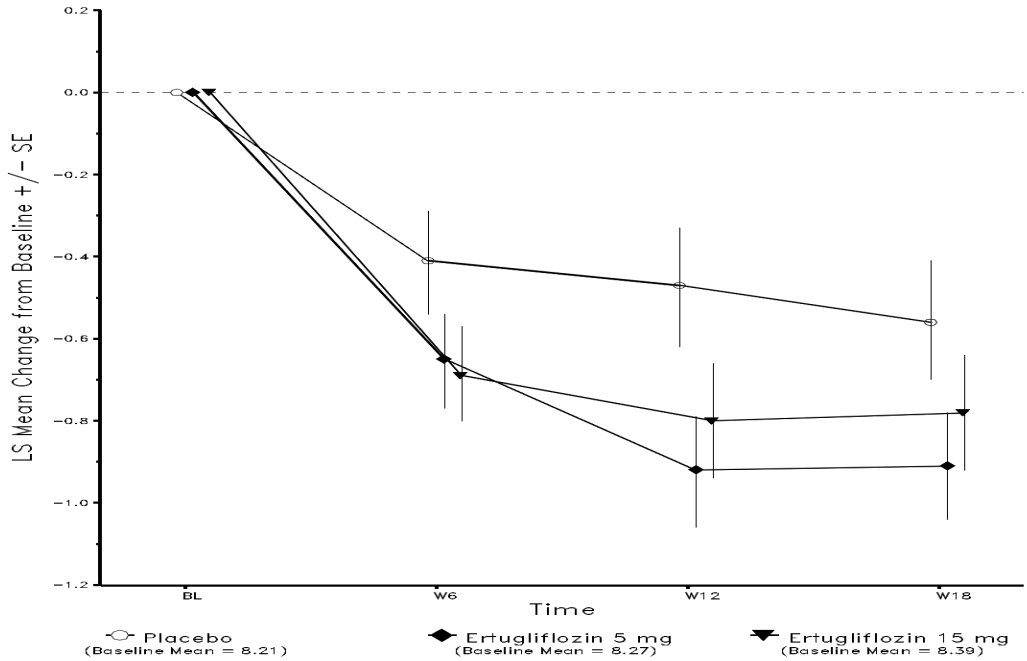


Table 22 (SU Monotherapy) Key Efficacy Endpoints (Full Analysis Set: Week 18, Excluding Rescue Approach)

Treatment	N	LS Mean (95% CI)	Pairwise Comparisons	
			Difference in LS Means (95% CI) vs. Placebo†	p-Value
Change from Baseline in A1C (%) at Week 18: cLDA				
Placebo	48	-0.56 (-0.84, -0.27)		

Ertugliflozin 5 mg	55	-0.91 (-1.17, -0.65)	-0.35 (-0.72, 0.02)	0.063
Ertugliflozin 15 mg	54	-0.78 (-1.06, -0.51)	-0.22 (-0.60, 0.16)	0.247
Change from Baseline in FPG (mg/dL) at Week 18: cLDA				
Placebo	48	-14.76 (-26.43, -3.08)		
Ertugliflozin 5 mg	55	-28.28 (-39.44, -17.12)	-13.53 (-28.06, 1.00)	0.068
Ertugliflozin 15 mg	54	-26.97 (-38.51, -15.44)	-12.22 (-27.03, 2.60)	0.105
Change from Baseline in Body Weight (kg) at Week 18: cLDA				
Placebo	48	-0.68 (-1.60, 0.25)		
Ertugliflozin 5 mg	55	-1.75 (-2.61, -0.89)	-1.07 (-2.32, 0.18)	0.092
Ertugliflozin 15 mg	54	-1.20 (-2.09, -0.31)	-0.52 (-1.79, 0.75)	0.418
Change from Baseline in Sitting Systolic Blood Pressure (mmHg) at Week 18: cLDA				
Placebo	48	-3.53 (-7.03, -0.02)		
Ertugliflozin 5 mg	55	-0.72 (-4.06, 2.63)	2.81 (-1.85, 7.48)	0.235
Ertugliflozin 15 mg	54	-0.80 (-4.23, 2.63)	2.73 (-2.00, 7.45)	0.255
Change from Baseline in Sitting Diastolic Blood Pressure (mmHg) at Week 18: cLDA				
Placebo	48	-2.91 (-5.06, -0.76)		
Ertugliflozin 5 mg	55	-1.18 (-3.24, 0.88)	1.73 (-1.11, 4.58)	0.230
Ertugliflozin 15 mg	54	-0.93 (-3.05, 1.18)	1.98 (-0.91, 4.86)	0.178
Treatment	N	n (%)	Odds Ratio (95% CI) vs. Placebo	p-Value
A1C < 7.0% at Week 18 (logistic regression with multiple imputation based on cLDA model)[§]				
Placebo	48	12 (25.0)		
Ertugliflozin 5 mg	55	18 (32.7)	1.62 (0.61, 4.35)	0.335
Ertugliflozin 15 mg	54	15 (27.8)	1.48 (0.52, 4.17)	0.460
A1C < 7.0% at Week 18 (logistic regression with missing Values Imputed as Not at Goal)[§]				
Placebo	48	12 (25.0)		
Ertugliflozin 5 mg	55	18 (32.7)	1.62 (0.63, 4.15)	0.317
Ertugliflozin 15 mg	54	15 (27.8)	1.38 (0.52, 3.62)	0.517

N is the number of subjects in the analysis population.

n is the number of subjects with the event of interest.

[†] cLDA model is fitted with fixed effects for treatment, time, interaction of time by treatment. Time was treated as a categorical variable.

[§] Logistic regression model fitted with terms for treatment and baseline A1C. For the analyses with multiple imputation, missing data imputed using the cLDA model fitted.

All model based analyses fitted with terms for baseline eGFR (continuous).

CI=Confidence Interval; LS =Least Squares.

After 18 weeks, reductions from baseline in BW were observed in all groups, including placebo, and reductions from baseline in SBP and DBP at Week 18 were not notably different between the treatment groups (

Table 22).

Metformin with SU Add-on Glycemic Sub-Study

It was expected that a minimum of 260 subjects would be enrolled into the sub-study. The actual sample size was 330 subjects.

Among the 330 subjects, 328 (99.4%) completed the 18-week treatment period, and 313 (94.8%) completed this period on study medication. The proportion of subjects who discontinued study medication prior to Week 18 was generally similar across treatment groups.

Baseline demographic and anthropometric characteristics were balanced across treatment groups. The mean age was 63.2 years, 25.2% were female, and 44.5% were ≥65 years old. At baseline, mean A1C and eGFR were 8.32% and 83.5 mL/min/1.73 m^2, respectively. The mean duration of diabetes was 11.41

years. The median metformin dose at baseline was 2000.0 mg/day. The most commonly used SU was gliclazide with a median dose of 90.0 mg/day at randomization (Table 2).

After 18 weeks, treatment with both doses of ertugliflozin relative to placebo provided significant reductions from baseline in A1C and FPG (Figure 17,

Table 23). The proportions of subjects with an A1C <7.0% at Week 18 in the ertugliflozin 5 mg group (37.0%) and the ertugliflozin 15 mg group (32.7%) were almost 3 times greater than in the placebo group (12.8%). The model-based odds of having A1C <7.0% (<53 mmol/mol) at Week 18 using multiple imputation for subjects with missing Week 18 data were significantly greater in both ertugliflozin groups compared with the placebo group (

Table 23).

Figure 17 (Metformin + SU) A1C (%): LS Means Over Time (cLDA; Full Analysis Set: Week 18, Excluding Rescue Approach)

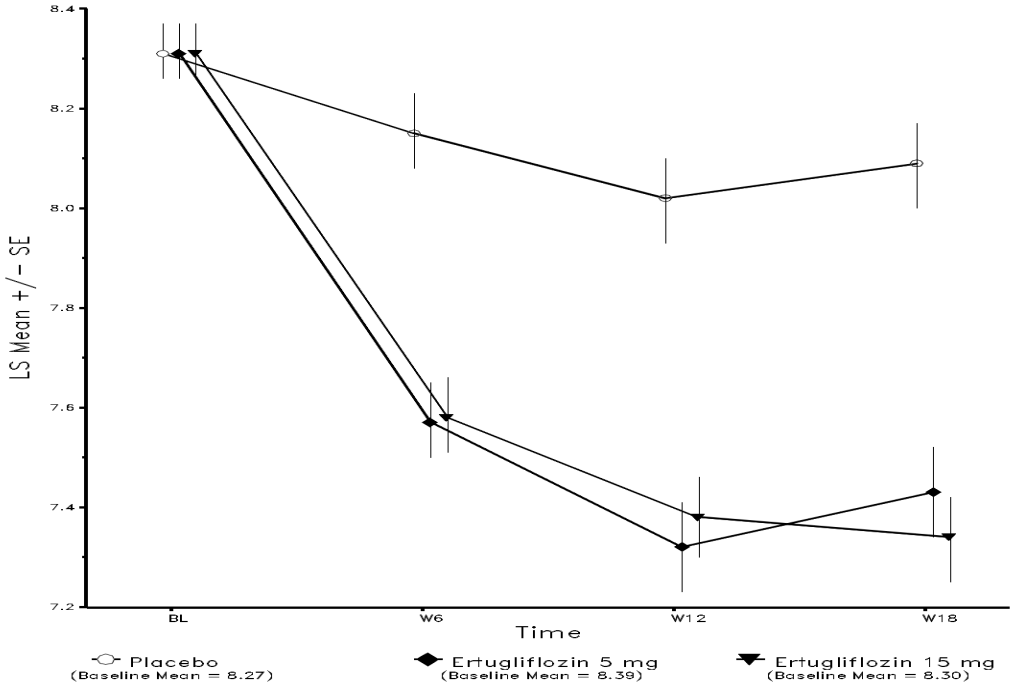


Table 23 (Metformin + SU) Key Efficacy Endpoints (Full Analysis Set: Week 18, Excluding Rescue Approach)

Treatment	N	LS Mean (95% CI)	Pairwise Comparisons	
			Difference in LS Means (95% CI) vs. Placebo†	p-Value
Change from Baseline in A1C (%) at Week 18: cLDA				
Placebo	117	-0.23 (-0.39, -0.06)		
Ertugliflozin 5 mg	100	-0.89 (-1.06, -0.71)	-0.66 (-0.89, -0.43)	<0.001
Ertugliflozin 15 mg	113	-0.98 (-1.14, -0.82)	-0.75 (-0.98, -0.53)	<0.001
Change from Baseline in FPG (mg/dL) at Week 18: cLDA				
Placebo	117	-4.81 (-12.10, 2.49)		
Ertugliflozin 5 mg	100	-35.28 (-43.05, -27.50)	-30.47 (-40.23, -20.72)	<0.001
Ertugliflozin 15 mg	113	-36.18 (-43.36, -28.99)	-31.37 (-40.68, -22.07)	<0.001
Change from Baseline in Body Weight (kg) at Week 18: cLDA				
Placebo	117	-0.47 (-0.97, 0.03)		
Ertugliflozin 5 mg	100	-2.04 (-2.58, -1.50)	-1.57 (-2.30, -0.84)	<0.001

Ertugliflozin 15 mg	113	-2.41 (-2.91, -1.91)	-1.94 (-2.65, -1.24)	<0.001
Change from Baseline in Sitting Systolic Blood Pressure (mmHg) at Week 18: cLDA				
Placebo	117	-0.70 (-3.04, 1.64)		
Ertugliflozin 5 mg	100	-2.26 (-4.78, 0.25)	-1.57 (-4.87, 1.73)	0.351
Ertugliflozin 15 mg	113	-1.54 (-3.85, 0.77)	-0.85 (-4.00, 2.30)	0.597
Change from Baseline in Sitting Diastolic Blood Pressure (mmHg) at Week 18: cLDA				
Placebo	117	-0.24 (-1.64, 1.15)		
Ertugliflozin 5 mg	100	-0.30 (-1.80, 1.21)	-0.05 (-2.07, 1.96)	0.958
Ertugliflozin 15 mg	113	-0.92 (-2.30, 0.46)	-0.68 (-2.60, 1.25)	0.490
Treatment	N	n (%)	Odds Ratio (95% CI) vs. Placebo	p-Value
A1C < 7.0% at Week 18 (logistic regression with multiple imputation based on cLDA model)[§]				
Placebo	117	15 (12.8)		
Ertugliflozin 5 mg	100	37 (37.0)	5.97 (2.86, 12.49)	<0.001
Ertugliflozin 15 mg	113	37 (32.7)	4.10 (2.00, 8.42)	<0.001
A1C < 7.0% at Week 18 (logistic regression with missing Values Imputed as Not at Goal)[§]				
Placebo	117	15 (12.8)		
Ertugliflozin 5 mg	100	37 (37.0)	5.57 (2.67, 11.61)	<0.001
Ertugliflozin 15 mg	113	37 (32.7)	3.95 (1.92, 8.12)	<0.001

N is the number of subjects in the analysis population.

n is the number of subjects with the event of interest.

[†] cLDA model is fitted with fixed effects for treatment, time, interaction of time by treatment. Time was treated as a categorical variable.

[§] Logistic regression model fitted with terms for treatment and baseline A1C. For the analyses with multiple imputation, missing data imputed using the cLDA model fitted.

All model based analyses fitted with terms for baseline eGFR (continuous).

CI=Confidence Interval; LS =Least Squares.

After 18 weeks, treatment with both doses of ertugliflozin relative to placebo provided significant reductions from baseline in BW. The reduction from baseline in SBP at Week 18 was not significantly greater in the ertugliflozin 15 mg group relative to the placebo group (

Table 23). Hypothesis testing within the ordered testing procedure was therefore stopped at this step, and the remaining secondary hypotheses were not formally tested. P-values provided for subsequent endpoints are descriptive and should not be interpreted as formal hypothesis tests. The reductions from baseline in SBP at Week 18 in the ertugliflozin 5 mg group and in DBP at Week 18 for both ertugliflozin groups were not greater relative to the placebo group (

Table 23).

There were not enough retrieved dropouts to perform the MI-RD imputation, so RTB was used instead of MI-RD for all secondary analysis. Results from missing data sensitivity analyses using the RTB approach for change from baseline in A1C and FPG were consistent with the primary analysis results. Results from an analysis of subjects with A1C <7.0% (<53 mmol/mol) at Week 18 with missing values imputed as 'not at goal' were consistent with the primary analysis results. Additionally, the results from missing data sensitivity analyses using the RTB approach for change from baseline in BW, SBP, and DBP were consistent with the primary analysis results.

Ancillary analyses

N/A

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 24 Summary of Efficacy for trial MK-8835-004/B1521021

Title: Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess Cardiovascular Outcomes Following Treatment With Ertugliflozin (MK-8835/PF-04971729) in Subjects With Type 2 Diabetes Mellitus and Established Vascular Disease, the VERTIS CV Study			
Study identifier	MK-8835-004/B1521021		
Design	Multicenter, randomized, double-blind, placebo-controlled, event-driven study in subjects on standard of care aged ⩾40 years with T2DM, inadequate glycaemic control (A1C 7.0% to 10.5%) and established vascular disease involving the coronary, cerebrovascular, or peripheral vascular system.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		mean duration in study: 3.5 years not applicable not applicable
Hypothesis	Non-inferiority (primary endpoint) Superiority (secondary endpoints)		
Treatments groups	Ertugliflozin 5 mg		number randomized=2,752
	Ertugliflozin 15 mg		number randomized=2,747
	Placebo		number randomized=2,747
Endpoints and definitions	Primary endpoint	MACE	Time to first occurrence of the endpoint of MACE, which is a 3-point composite endpoint of CV death, non-fatal MI, or non-fatal stroke.
	Secondary endpoint	CV death or HHF	Time to first occurrence of the composite of CV death or HHF.
	Secondary endpoint	CV death	Time to CV death.
	Secondary endpoint	Renal events	Time to first occurrence of the composite of renal death, renal dialysis/transplant, or ≥2 × increase in baseline serum creatinine.
	Secondary endpoint	HHF	Time to first HHF.
Database lock	16MAR2020		

Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Intent to treat				
Descriptive statistics and estimate variability	Treatment group	All Ertugliflozin	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo
	Number of subjects	5 493	2 746	2 747	2 745
	MACE (rate/100 P-Y)	3.90	3.64	4.16	4.01
	CV death or HHF (rate/100 P-Y)	2.34	2.36	2.33	2.66
	CV death (rate/100 P-Y)	1.76	1.77	1.74	1.90
	Renal events (rate/100 P-Y)	0.93	0.97	0.98	1.15

	HHF (rate/100 P-Y)	0.73	0.75	0.72	1.05

Effect estimate per comparison	Primary endpoint MACE	Comparison groups	All Ertugliflozin vs Placebo
		HR	0.97
		95% CI	0.848, 1.114
		P-value (non-inferiority)	<0.001
	Secondary endpoint CV death or HHF	Comparison groups	All Ertugliflozin vs Placebo
		HR	0.88
		95% CI	0.750, 1.034
		P-value	
	Secondary endpoint CV death	Comparison groups	All Ertugliflozin vs Placebo
		HR	0.92
		95% CI	0.767, 1.113
		P-value	0.385
	Secondary endpoint Renal events	Comparison groups	All Ertugliflozin vs Placebo
		HR	0.81
		95% CI	0.630, 1.036
		P-value	0.081
	Secondary endpoint HHF	Comparison groups	All Ertugliflozin vs Placebo
		HR	0.70
		95% CI	0.539, 0.902
		P-value	0.006
Notes			
Analysis description			

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

Data in patients with renal impairment are presented in relation to the main study.

3.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The VERTIS CV study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, event-driven study that included a main CV study. This study was intended to address two overarching objectives: 1) CV safety (non-inferiority) and 2) CV and renal efficacy (superiority).

The study included three glycaemic sub-studies, investigating treatment combinations not previously studied in the clinical development programme, add-on to: 1) insulin with or without metformin, 2) SU monotherapy and 3) metformin with SU.

The general study design is adequate. The doses of ertugliflozin evaluated in this study were 5 mg and 15 mg qd. At the time of the initiation of the study, ertugliflozin was not yet approved, and the doses used in the study were selected based on Phase 1 and Phase 2 study data. Thus, as opposed to the current posology, which states that treatment should be initiated with ertugliflozin 5 mg, one group was assigned to a starting dose of 15 mg. Anti-hyperglycaemic background treatment was to be kept unchanged for the first 18 weeks of the study to allow assessment of the anti-hyperglycaemic effect of ertugliflozin in the three glycaemic sub-studies. To safeguard the patients, rescue medication was allowed, and rescue

criteria were in place. Background medications for secondary prevention of CV disease was to be provided in line with applicable treatment guidelines and could be changed as needed during the study.

The study duration of the glycaemic sub-studies was 18 weeks which, as pointed out in the scientific advice (SA) given, is somewhat short for the assessment of efficacy. No further data has been provided on the sub-studies.

Inclusion criteria were adequate for patients at high CV risk and in need for additional anti-hyperglycaemic treatment. Treatment with rosiglitazone, which may have a potentially negative effect on CV safety was not allowed. After the amendment of the protocol (see below), patients with HF, NYHA Class III could be included in the study. Other exclusion criteria were adequate for patients where assessment may be affected by unstable disease, or where treatment with ertugliflozin may not be safe.

The primary endpoint (MACE) includes CV death, non-fatal MI, non-fatal stroke, which is adequate for assessing the primary objective. With the amendment, the key secondary endpoints were changed to include time to first occurrence of the composite of CV death or HHF. The key secondary endpoints also include renal outcomes in terms of renal death, renal dialysis/transplant, or ≥2 × increase in baseline serum creatinine. In addition, secondary endpoints related to glycaemic control and renal function were included.

The statistical analysis plan for the study was acceptable. The primary endpoint was evaluated, according to plan in SAP, using the pooled data from the two active treatment arms. The Stage 2 assessment of CV data for ertugliflozin included an interim analysis and a final analysis. The Stage 2 interim analysis was performed after the requisite number of adjudicated MACE and CV death events accrued in the study. The study continued after the interim analysis because early stopping criteria were not met. The type 1-error was controlled for the interim analysis, the primary non-inferiority analysis and 3 secondary analyses. Several sensitivity analyses were planned and performed for the analysis of primary and secondary endpoints, these included multiple imputation methods based on retrieved drop-outs within treatment group and a tipping point analysis. All sensitivity analyses were consistent with the primary analysis.

Only one amendment of the protocol was made, due to the publication of CV outcome data for another SGLT2-inhibitor, empagliflozin. With this amendment the superiority analysis of the new secondary endpoint of CV death or hospitalisation for heart failure was included and the overall sample size was increased to 8,000 subjects. A superiority analysis for the composite renal endpoint was also added. In addition, the third glycaemic sub-study in subjects receiving metformin plus sulfonylurea (SU) was added. With this amendment, patients with NYHA Class III heart failure could be enrolled in the study.

The study appears to have been well conducted. Protocol deviations were recorded for 13.9% of patients, and the reporting was balanced between groups. The observed protocol deviations are not considered to have impacted the outcome and conclusions of the study. Overall, only eight patients (2 in the placebo treated group and 6 in the ertugliflozin 5 mg group) were excluded from the CV ITT population.

Baseline data

In total 8,246 patients were randomised in the study with 2,752 subjects in the ertugliflozin 5 mg group, 2,747 in the ertugliflozin 15 mg group, and 2,747 subjects in the placebo group. The number of patients who discontinued the study was low (4%) and evenly distributed between the treatment groups. In addition, vital status was available for the majority of discontinued patients. About 30% of patients discontinued study treatment, the proportion being somewhat higher in the placebo treated group (placebo 32.7% and 28.1/28.5% for ertugliflozin 5/15 mg). The reasons for treatment discontinuation were largely balanced between groups.

Baseline demographic and disease characteristics were balanced between groups. The majority of patients (56.2%) were recruited in Europe. The characteristics were as expected in a T2DM population at

high cardiovascular risk. The study managed to include 139 patients in NYHA Class III after the amendment. Notably, 76.3% of subjects were taking metformin, whereas only 11% were taking DPP-4 inhibitors. Thus, the data are relevant for both Steglatro (ertugliflozin) and Segluromet (ertugliflozin + metformin). The use of DPP-4, GLP-1 RA, SGLT2i, insulin, thiazolidinediones increased from baseline but less in the ertugliflozin treated groups compared to placebo. Use of metformin, SU, alpha glucosidase inhibitors, and meglitinides remained stable throughout the study.

The patients were to be treated according to current treatment guidelines with regards to cardiovascular medications. The use of statins, platelets aggregation inhibitors and agents acting on the renin-angiotensin system was high (>80% of patients). About 40% were on diuretics including 15% who were on loop diuretics. The treatment compliance was high (96.2%) and similar across treatment groups.

In conclusion, the study population is considered representative for the target population of T2DM patients.

Efficacy data and additional analyses

Cardiovascular safety

The study met its primary endpoint as non-inferiority for MACE was shown for the "All ertugliflozin" group (HR 0.97; 95% CI: 0.848, 1.114). Non-inferiority was also shown for each of the two doses (5 mg and 15 mg) but it is noted that the HR for the higher dose was 1.04 compared to 0.91 for the lower dose. No meaningful differences were observed for the components of MACE compared to placebo. Notably, MACE and the components non-fatal MI and non-fatal stroke was reported at numerically higher rates in the ertugliflozin 15 mg treated group compared to ertugliflozin 5 mg and placebo. The Kaplan-Meier curves separated slightly after about 6 months but converged again after about three years.

A post-hoc analysis was conducted, where the CV death component of MACE was replaced by "All-cause death", which showed a comparable HR (0.97; 95% CI: 0.867 to 1.093) as for the primary analysis.

The subgroup analysis generally showed consistent findings across the subgroups. Although point estimates for the HR varied somewhat, the 95% CI was within the non-inferiority margin also for all large subgroups. The most notable exceptions are in patients with eGFR < 60 (HR 1.09; 95% CI: 0.84, 1.40) and history of heart failure (HR 1.05; 95% CI: 0.82, 1.35).

Superiority was however not shown for the key secondary endpoint "CV death or HHF" (HR 0.88; 95% CI: 0.750, 1.034). Hypothesis testing was therefore stopped at this step. The outcome was comparable when "CV death" was exchanged by "All-cause death or HHF" (HR: 0.90; 95.8% CI; 0.776 to 1.032). The findings were consistent across subgroups, the only subgroups where the point estimate was higher than 1 were patients with GFR >90 and patients on diuretics. The secondary endpoint "total CV death/HHF events" (i.e. not censored at the time of the first event), showed a reduction in the total number of events (HR 0.82 95% CI 0.716, 0945) which is lower than for the endpoint "CV death or HHF".

"CV death" was analysed separately as a secondary endpoint. There was no noticeable difference between treatment groups (HR 0.92; 95% CI: 0.767, 1.113). Only small differences in the pattern of the cause of death were observed, with slightly lower reporting of "sudden cardiac death" and "HF death" in the ertugliflozin groups, whereas "acute MI death" and "unexplained death" were reported at similar rates in all groups. A comparable outcome was observed for the secondary endpoint "All-cause death" (HR: 0.93; 95% CI, 0.797 to 1.081).

The secondary endpoint "time to first HHF" was not subject to hypothesis testing but the analysis showed a 30% reduction of the risk with a CI excluding 1 (HR 0.70; 95% CI:0.539, 0.902). Comparable outcomes were observed for both doses (HR 0.71 and 0.68 for the 5 mg and 15 mg dose, respectively).

Sensitivity analyses were consistent with the primary analysis. The Kaplan-Meier curves separated early and the separation continued for the duration of the study. The subgroup analysis indicated that patients with albuminuria, patients with lower GFR and patients not using diuretics may have a greater benefit. The data was further supported by the analysis of recurrent HF hospital admissions and mortality in subjects with a first HHF event, which was lower in the ertugliflozin treated groups compared to placebo. Although this endpoint was not subject to formal hypothesis testing, these data are considered of interest for the prescriber, and are included in section 5.1 of the SmPC.

Other CV efficacy endpoints analyzed in VERTIS CV were time to first MACE+, fatal or non-fatal MI, fatal or non-fatal stroke and HHF. Apart from a reduction of the risk of HHF, no differences were observed between the ertugliflozin treated groups and placebo. It is noted that the observed rates for these endpoints were numerically higher in the ertugliflozin 15 mg treated group compared to both ertugliflozin 5 mg and placebo. However, none of these outcomes are statistically different to placebo.

In summary, the data on CV safety and efficacy show that treatment with ertugliflozin does not carry an increased risk of CV events and there appears to be a beneficial effect in reducing the risk of HHF. These findings are in line with the outcome of other CV outcome trials conducted with some other SGLT2 inhibitors. The data is considered sufficient to allow an update of the indication. The outcome, including the data on HHF, is reflected in section 5.1 of the SmPC.

Composite of renal events

No formal testing of the composite "renal events" was performed, but it is noted that the 19% reduction of events in the ertugliflozin treated groups was not statistically significant since the CI includes 1 (HR 0.81; 95% CI: 0.630, 1.036). The Kaplan-Meier curve show a separation of the curves over time. The potentially reduced risk is mainly driven by an effect on GFR, whereas other components of the composite endpoint were rare and balanced between groups. The MAH argues that sustained 40% decrease from baseline in eGFR is a more relevant endpoint than doubling of serum creatinine from baseline and points out that this endpoint has been used in studies with other SGLT2i. This is acknowledged.

The MAH has conducted a pre-specified exploratory analysis using the endpoint "sustained 40% decrease from baseline in eGFR" instead of "doubling of creatinine" which shows a lower event rate (events per 100 person-years) in the ertugliflozin group compared with placebo (0.60 vs 0.90), with an HR (95% CI) of 0.66 (0.50, 0.88), with consistent findings across baseline kidney function subgroups. This is in line with data for other SGLT2-inhibitors in studies where this endpoint was applied.

Thus, the data are reassuring with regards to the effects of ertugliflozin on renal function, but no claims regarding this effect can yet be made.

Glycaemic control and cardiometabolic endpoints

In the study, beneficial effects on HbA1c, body weight and blood pressure were observed with ertugliflozin treatment. The changes observed at week 18, after which the anti-hyperglycaemic treatment could be adjusted, were of comparable magnitude as observed in previous clinical studies with ertugliflozin.

Use in patients with renal impairment

The efficacy of ertugliflozin was investigated in order to provide support for a lowering of the limits for treatment initiation and discontinuation. In the VERTIS CV study, 21.5% of the subjects (1 776 patients) had an eGFR 30 – 60 mL/min/1.73 m^2 at baseline (Stage 3 CKD). This subgroup was older than the overall population (68.1 years vs 64.4 years), but with comparable metabolic control. Of these patients, 1 319 were in Stage 3A (eGFR 45-60) and 457 were in Stage 3B (eGFR 30-45).

In the overall Stage 3 CKD population, ertugliflozin treatment resulted in a modest decrease in HbA1c of 0.27% (5 mg dose) and 0.28% (15 mg dose), in line with the data from the dedicated study in patients with Stage 3 CKD assessed in the MAA. In contrast to the previous study, no increase is observed with increasing dose. The calculated odds of achieving HbA1c <7.0% was higher with ertugliflozin (20.7% and 17.0% for the 5 mg and 15 mg dose, respectively) compared to placebo (12.9%), but still modest. Statistically significant reductions of FPG were observed for both doses.

Comparable results were observed for the Stage 3A CKD subgroup (GFR 45-60), where a reduction of 0.27% (5 mg dose) and 0.31% (15 mg dose) was observed, whereas the effect on HbA1c was further attenuated in the subgroup with Stage 3B CKD subgroup (GFR 30-45) with no statistically significant difference observed with the 15 mg dose compared to placebo.

A similar pattern was observed with regards to the effect on body weight and SBP. In the overall Stage 3 CKD subgroup (GFR 30-60), reductions in BW and SBP were more pronounced with ertugliflozin treatment than with placebo treatment but the effect on body weight appears attenuated compared to the overall study population. The outcome in the Stage 3A CKD subgroup (GFR 45-60) compared well with the outcome in the overall Stage 3 CKD population but the effect (especially on SBP) was attenuated in the Stage 3B CKD subgroup (GFR 30-45).

The MAH proposes to lower the limit for initiation of ertugliflozin treatment to eGFR 45 mL/min/1.73 m^2 and to allow treatment down to an eGFR of 30 mL/min/1.73 m^2. The MAH has summarised the data for the stage 3 CKD subgroup with eGFR 30-60 mL/min/1.73m^2. The data indicate that eGFR is maintained with long-term treatment. Apart from any potential beneficial effect of maintained eGFR per se, this indicates that treatment could be maintained for a relevant period of time also in the population with eGFR 30-45. The data presented indicate that the potential beneficial effects observed on renal function and HHF are present also in the stage 3 CKD subgroup. It should however be noted that these data are descriptive since formal testing was not performed for these endpoints. However, the data for ertugliflozin is well in line with outcomes observed for other SGLT2i, which indicates that the observed benefits are due to class effects on renal function and on HHF.

The effects of ertugliflozin on SBP and body weight were largely comparable for patients with stage 3 CKD and the overall population whereas the effect on glycaemic control in patients with eGFR 30-45 is clearly attenuated (about -0.2% to -0.3%, placebo adjusted).

In summary, the MAH has provided sufficient data supporting that patients with eGFR 30-60 have additional benefits in terms of preservation of renal function and a reduced risk of HHF with ertugliflozin treatment, which outweigh the loss of glycaemic effects in this population. The findings are line with the observations made for other products in the class of SGLT2i. No safety concerns arise from the data presented for patients with eGFR 30-60. Therefore, initiation of treatment with Steglatro in patients with eGFR<45 and continuation of ertugliflozin treatment in patients with eGFR>30 is accepted. The proposed wording for section 4.2 is accepted.

Glycaemic sub-studies

The MAH has provided data on three sub-studies included in the VERTIS CV study, in order to support wording on combinations with ertugliflozin not previously studied to be included in section 5.1 of the SmPC. The studies have been discussed in previous CHMP SA and the main issue raised was the short duration of the sub-studies (18 weeks). Concerns were also raised that the population included in the VERTIS CV study may not be representative for the target population. It is noted that the population in the sub-studies are older, had a longer duration of T2DM and a lower eGFR than the patients included in the studies supporting the MAA but had comparable HbA1c and BMI at inclusion. The lower eGFR could affect the glycaemic outcome, but it is still considered possible to generalise the findings to the target population of T2DM.

Add-on to insulin with or without metformin

The study included 348 patients on ertugliflozin 5 mg, 370 patients on ertugliflozin 15 mg and 347 patients on placebo. When added to a background therapy of insulin with or without metformin, ertugliflozin resulted in a clinically relevant and statistically significant decrease in HbA1c of -0.58% with the 5 mg dose and -0.65% with the 15 mg dose (placebo-adjusted). Statistically significant decreases in FPG were also observed and the proportion of patients achieving the target of HbA1c <7.0% were twice as high (20.7% and 21.1% for ertugliflozin 5 mg and 15 mg respectively, vs 10.7% for placebo). A placebo-adjusted decrease in body weight of -1.62 kg (5 mg dose) and -1.88 kg (15 mg dose) was also observed. A statistically significant reduction of SBP vs placebo was observed whereas the decrease in DBP did not reach statistical significance.

The duration of the study was however considered too short. The MAH has therefore conducted a post-hoc analysis, including data on all patients in the VERTIS CV study who were taking insulin at baseline, irrespective of the insulin dose as opposed to the sub-study in which only patients with an insulin dose of ≥20 U/day. The new analysis includes a larger number of patients (placebo=1337, ertugliflozin 5 mg=1298, and ertugliflozin 15 mg=1243) compared to 1065 patients in the sub study.

The data show that the additive effect on glycaemic control is maintained at least up to month 48. Insulin doses remained essentially stable in the ertugliflozin treated groups whereas the insulin dose slowly increased in placebo treated patients. Slightly more patients in the ertugliflozin treated groups discontinued insulin treatment during the study and more patients in the placebo treated group received additional treatment with other AHAs.

Considering that a clinically relevant effect on glycaemic endpoints is shown, which is of the same magnitude as observed with other products in the class with this combination, it is acceptable to include this information in section 5.1 of the SmPC.

Add-on to SU monotherapy

Monotherapy with SU in longstanding T2DM is uncommon and the study failed to recruit more than 157 patients, i.e. less than the target of 170 patients. The primary endpoint of the study was not met as the placebo-adjusted change in HbA1c was only -0.35% with the 5 mg dose and -0.22% with the 15 mg dose. This is explained by a higher than expected effect in the placebo treated group of -0.56% reduction in HbA1c, as compared to a HbA1c reduction of about -0.2% in the overall placebo treated group. The effect on body weight was also modest (placebo-adjusted: -1.07 kg and -0.52 kg for the 5 mg and 15 mg dose, respectively), and SBP and DBP increased compared to placebo. The MAH has not proposed to include these data in section 5.1 of the SmPC, which is endorsed.

Add-on to metformin and SU

This sub-study included 100 patients on ertugliflozin 5 mg, 113 patients on ertugliflozin 15 mg and 117 patients on placebo. When added to metformin and SU, ertugliflozin resulted in a clinically relevant and statistically significant decrease in HbA1c of -0.66% with the 5 mg dose and -0.75% with the 15 mg dose (placebo-adjusted). Statistically significant decreases in FPG were also observed and the proportion of patients achieving the target of HbA1c <7.0% were almost three times as high (37.0% and 32.7% for ertugliflozin 5 mg and 15 mg respectively, vs 12.8% for placebo). A placebo-adjusted decrease in body weight of -1.57 kg (5 mg dose) and -1.94 kg (15 mg dose) was also observed. Only modest reductions of SBP and DBP vs placebo were observed, none of which reached statistical significance.

The study duration of 18 weeks was however considered too short. Therefore, the MAH has provided a post-hoc analysis of the efficacy of ertugliflozin over 52 weeks (when added to metformin and SU), The data show that the HbA1c-lowering effect is maintained up to 52 weeks.

Again, considering that a clinically relevant effect on glycaemic endpoints is shown, which is of the same magnitude as observed with other products in the class with this combination, it is acceptable to include this information in section 5.1 of the SmPC.

3.4.3. Conclusions on the clinical efficacy

The CV outcome data from the VERTIS CV study showed that ertugliflozin is not associated with an unacceptable increase in CV risk, as non-inferiority to placebo has been demonstrated. A reduction of hospitalization due to heart failure was observed. These data are reflected in the SmPC. These data are also deemed sufficient to allow an update of the wording of the indication for both Steglatro and Segluromet.

Also, the data provided in patients with Stage 3 CKD is deemed sufficient to allow the proposed changes to the recommendations on treatment initiation and discontinuations based on eGFR.

In addition, the data on add-on to 1) insulin with or without metformin, and 2) metformin with SU, showed clinically relevant effects with ertugliflozin treatment and these data should be reflected in the SmPC.

3.5. Clinical safety

Introduction

The current safety evaluation is based on data from the completed VERTIS CV study. The VERTIS CV also included three glycaemic sub-studies defined by background AHA therapy (insulin with or without metformin, SU monotherapy, and metformin with SU) and a prespecified assessment of glycaemic efficacy in the subgroup of subjects with Stage 3A CKD (eGFR 45 to <60 mL/min/1.73 m^2).

The target population were patients with T2DM and established CV disease.

Patient exposure

The VERTIS CV safety population included 8,238 patients, 2,746 on ertugliflozin 5 mg, 2,747 on ertugliflozin 15 mg and 2,745 on placebo.

Duration of exposure

The mean duration on treatment was 150.94 weeks: 152.96 weeks in all ertugliflozin group and 146.91 weeks in the placebo group (Table 25). The mean duration on study was 181.77 weeks and was similar across treatment groups.

Table 25 Duration of Treatment and Follow-up All Subjects as Treated

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin		Total	
	n (%)		n (%)		n (%)		n (%)		n (%)	
Subjects in population	2745		2746		2747		5493		8238	
Number of Weeks on Treatment										
0 to ≤26	248	(9.03)	227	(8.27)	248	(9.03)	475	(8.65)	723	(8.78)
>26 to 52	152	(5.54)	130	(4.73)	125	(4.55)	255	(4.64)	407	(4.94)
>52 to 104	253	(9.22)	191	(6.96)	204	(7.43)	395	(7.19)	648	(7.87)
>104 to 156	1107	(40.33)	1136	(41.37)	1099	(40.01)	2235	(40.69)	3342	(40.57)

>156 to 208	217	(7.91)	187	(6.81)	219	(7.97)	406	(7.39)	623	(7.56)
>208 to 260	655	(23.86)	747	(27.20)	725	(26.39)	1472	(26.80)	2127	(25.82)
>260	113	(4.12)	128	(4.66)	127	(4.62)	255	(4.64)	368	(4.47)
Subjects with data	2745		2746		2747		5493		8238	
Mean	146.91		153.59		152.32		152.96		150.94	
SD	74.37		73.68		74.41		74.04		74.20	
Median	140.00		143.14		143.14		143.14		142.00	
Range	0.1 to 294.7		0.1 to 293.7		0.1 to 301.0		0.1 to 301.0		0.1 to 301.0	
Number of Weeks in Study										
0 to ≤26	31	(1.13)	38	(1.38)	48	(1.75)	86	(1.57)	117	(1.42)
>26 to 52	49	(1.79)	42	(1.53)	42	(1.53)	84	(1.53)	133	(1.61)
>52 to 104	80	(2.91)	73	(2.66)	77	(2.80)	150	(2.73)	230	(2.79)
>104 to 156	1164	(42.40)	1174	(42.75)	1160	(42.23)	2334	(42.49)	3498	(42.46)
>156 to 208	270	(9.84)	244	(8.89)	256	(9.32)	500	(9.10)	770	(9.35)
>208 to 260	913	(33.26)	951	(34.63)	937	(34.11)	1888	(34.37)	2801	(34.00)
>260	238	(8.67)	224	(8.16)	227	(8.26)	451	(8.21)	689	(8.36)
Subjects with data	2745		2746		2747		5493		8238	
Mean	181.85		182.25		181.23		181.74		181.77	
SD	59.54		59.87		60.81		60.34		60.07	
Median	157.86		157.71		157.86		157.86		157.86	
Range	1.7 to 296.9		0.1 to 304.3		2.4 to 303.1		0.1 to 304.3		0.1 to 304.3	

Demographic and baseline characteristics

VERTIS CV study patients with T2DM and established CV disease.

Adverse events

Adverse events and adverse events leading to discontinuation of study medication in the ertugliflozin 5 mg and 15 mg groups compared with the placebo group in Table 26.

Table 26 Adverse Event Summary All Subjects as Treated

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg	
	n	(%)	n	(%)	n	(%)
Subjects in population	2,745		2,746		2,747	
with one or more adverse events	2,349	(85.6)	2,357	(85.8)	2,325	(84.6)
with no adverse event	396	(14.4)	389	(14.2)	422	(15.4)
with drug-related[†] adverse events	601	(21.9)	710	(25.9)	730	(26.6)
with serious adverse events	990	(36.1)	958	(34.9)	937	(34.1)
with serious drug-related adverse events	41	(1.5)	40	(1.5)	33	(1.2)
who died	117	(4.3)	131	(4.8)	134	(4.9)
discontinued due to an adverse event	188	(6.8)	207	(7.5)	201	(7.3)
discontinued due to a drug-related adverse event	51	(1.9)	91	(3.3)	89	(3.2)
discontinued due to a serious adverse event	102	(3.7)	91	(3.3)	90	(3.3)
discontinued due to a serious drug-related adverse event	7	(0.3)	12	(0.4)	12	(0.4)

Table 27 Subjects with Adverse Events Incidence ≥2% in One or More Treatment Groups All Subjects as Treated

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg	
	n	(%)	n	(%)	n	(%)
Subjects in population	2,745		2,746		2,747	
with one or more	2,349	(85.6)	2,357	(85.8)	2,325	(84.6)

adverse events						
with no adverse events	396	(14.4)	389	(14.2)	422	(15.4)
Blood and lymphatic system disorders	**162**	**(5.9)**	**170**	**(6.2)**	**145**	**(5.3)**
Anaemia	90	(3.3)	83	(3.0)	68	(2.5)
Cardiac disorders	**682**	**(24.8)**	**630**	**(22.9)**	**613**	**(22.3)**
Acute myocardial infarction	73	(2.7)	52	(1.9)	78	(2.8)
Angina pectoris	112	(4.1)	85	(3.1)	90	(3.3)
Angina unstable	94	(3.4)	77	(2.8)	76	(2.8)
Atrial fibrillation	118	(4.3)	112	(4.1)	106	(3.9)
Cardiac failure	60	(2.2)	53	(1.9)	48	(1.7)
Myocardial infarction	39	(1.4)	46	(1.7)	54	(2.0)
Ear and labyrinth disorders	**100**	**(3.6)**	**112**	**(4.1)**	**89**	**(3.2)**
Eye disorders	**276**	**(10.1)**	**255**	**(9.3)**	**237**	**(8.6)**
Cataract	113	(4.1)	98	(3.6)	101	(3.7)
Diabetic retinopathy	62	(2.3)	52	(1.9)	33	(1.2)
Gastrointestinal disorders	**585**	**(21.3)**	**610**	**(22.2)**	**626**	**(22.8)**
Abdominal pain	57	(2.1)	51	(1.9)	55	(2.0)
Constipation	73	(2.7)	90	(3.3)	103	(3.7)
Diarrhoea	126	(4.6)	135	(4.9)	138	(5.0)
Nausea	72	(2.6)	64	(2.3)	74	(2.7)
Vomiting	43	(1.6)	42	(1.5)	59	(2.1)
General disorders and administration site conditions	**373**	**(13.6)**	**395**	**(14.4)**	**352**	**(12.8)**
Asthenia	36	(1.3)	54	(2.0)	44	(1.6)
Chest pain	37	(1.3)	54	(2.0)	35	(1.3)
Fatigue	59	(2.1)	46	(1.7)	55	(2.0)
Oedema peripheral	69	(2.5)	43	(1.6)	27	(1.0)
Hepatobiliary disorders	**143**	**(5.2)**	**126**	**(4.6)**	**131**	**(4.8)**
Infections and infestations	**1,134**	**(41.3)**	**1,194**	**(43.5)**	**1,204**	**(43.8)**
Bronchitis	137	(5.0)	114	(4.2)	133	(4.8)
Cellulitis	52	(1.9)	63	(2.3)	75	(2.7)
Gastroenteritis	45	(1.6)	56	(2.0)	51	(1.9)
Influenza	96	(3.5)	131	(4.8)	106	(3.9)
Lower respiratory tract infection	45	(1.6)	55	(2.0)	55	(2.0)
Nasopharyngitis	186	(6.8)	178	(6.5)	204	(7.4)
Pneumonia	96	(3.5)	99	(3.6)	104	(3.8)
Respiratory tract infection	56	(2.0)	34	(1.2)	48	(1.7)
Upper respiratory tract infection	205	(7.5)	197	(7.2)	177	(6.4)
Urinary tract infection	223	(8.1)	267	(9.7)	271	(9.9)
Injury, poisoning and procedural complications	**366**	**(13.3)**	**386**	**(14.1)**	**390**	**(14.2)**
Fall	45	(1.6)	54	(2.0)	54	(2.0)
Limb injury	39	(1.4)	54	(2.0)	58	(2.1)
Investigations	**467**	**(17.0)**	**414**	**(15.1)**	**466**	**(17.0)**
Blood glucose increased	59	(2.1)	38	(1.4)	30	(1.1)
Glomerular filtration rate decreased	46	(1.7)	38	(1.4)	67	(2.4)
Weight decreased	40	(1.5)	52	(1.9)	70	(2.5)

Metabolism and nutrition disorders	**1,273**	**(46.4)**	**1,212**	**(44.1)**	**1,192**	**(43.4)**
Diabetes mellitus	109	(4.0)	67	(2.4)	57	(2.1)
Diabetes mellitus inadequate control	71	(2.6)	53	(1.9)	53	(1.9)
Dyslipidaemia	76	(2.8)	60	(2.2)	98	(3.6)
Hyperglycaemia	184	(6.7)	108	(3.9)	100	(3.6)
Hyperkalaemia	97	(3.5)	85	(3.1)	82	(3.0)
Hypoglycaemia	890	(32.4)	883	(32.2)	857	(31.2)
Musculoskeletal and connective tissue disorders	**614**	**(22.4)**	**625**	**(22.8)**	**625**	**(22.8)**
Arthralgia	120	(4.4)	130	(4.7)	116	(4.2)
Back pain	143	(5.2)	135	(4.9)	139	(5.1)
Musculoskeletal and connective tissue disorders	**614**	**(22.4)**	**625**	**(22.8)**	**625**	**(22.8)**
Musculoskeletal pain	58	(2.1)	61	(2.2)	75	(2.7)
Osteoarthritis	100	(3.6)	98	(3.6)	91	(3.3)
Pain in extremity	91	(3.3)	89	(3.2)	111	(4.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**151**	**(5.5)**	**178**	**(6.5)**	**186**	**(6.8)**
Nervous system disorders	**578**	**(21.1)**	**639**	**(23.3)**	**613**	**(22.3)**
Diabetic neuropathy	49	(1.8)	61	(2.2)	55	(2.0)
Dizziness	93	(3.4)	141	(5.1)	143	(5.2)
Headache	105	(3.8)	113	(4.1)	105	(3.8)
Psychiatric disorders	**147**	**(5.4)**	**127**	**(4.6)**	**150**	**(5.5)**
Renal and urinary disorders	**458**	**(16.7)**	**461**	**(16.8)**	**465**	**(16.9)**
Acute kidney injury	60	(2.2)	48	(1.7)	53	(1.9)
Chronic kidney disease	62	(2.3)	40	(1.5)	64	(2.3)
Pollakiuria	25	(0.9)	50	(1.8)	64	(2.3)
Reproductive system and breast disorders	**125**	**(4.6)**	**227**	**(8.3)**	**220**	**(8.0)**
Benign prostatic hyperplasia	56	(2.0)	72	(2.6)	67	(2.4)
Respiratory, thoracic and mediastinal disorders	**387**	**(14.1)**	**374**	**(13.6)**	**327**	**(11.9)**
Cough	78	(2.8)	90	(3.3)	56	(2.0)
Dyspnoea	54	(2.0)	40	(1.5)	48	(1.7)
Skin and subcutaneous tissue disorders	**248**	**(9.0)**	**281**	**(10.2)**	**320**	**(11.6)**
Vascular disorders	**441**	**(16.1)**	**380**	**(13.8)**	**396**	**(14.4)**
Vascular disorders	**441**	**(16.1)**	**380**	**(13.8)**	**396**	**(14.4)**
Hypertension	174	(6.3)	134	(4.9)	153	(5.6)

Serious adverse event/deaths/other significant events

Deaths

The incidences of AEs resulting in death, based on events occurring during the treatment Period, were: 4.3% (n=117), 4.8% (n=131) and 4,9% (n=134) for placebo, ertugliflozin 5 mg and ertugliflozin 15 mg (Table 28).

Table 28 Subjects with Adverse Events Resulting in Death Incidence >0% in One or More Treatment Groups All Subjects as Treated

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg	
	n	(%)	n	(%)	n	(%)
Subjects in population	2,745		2,746		2,747	
with one or more adverse events resulting in death	117	(4.3)	131	(4.8)	134	(4.9)
with no adverse events resulting in death	2,628	(95.7)	2,615	(95.2)	2,613	(95.1)
Cardiac disorders	**36**	**(1.3)**	**34**	**(1.2)**	**46**	**(1.7)**
Acute myocardial infarction	6	(0.2)	4	(0.1)	7	(0.3)
Angina pectoris	0	(0.0)	0	(0.0)	1	(0.0)
Angina unstable	0	(0.0)	0	(0.0)	1	(0.0)
Cardiac arrest	9	(0.3)	5	(0.2)	7	(0.3)
Cardiac failure	1	(0.0)	4	(0.1)	4	(0.1)
Cardiac failure acute	0	(0.0)	5	(0.2)	1	(0.0)
Cardiac failure chronic	0	(0.0)	0	(0.0)	1	(0.0)
Cardiac failure congestive	4	(0.1)	1	(0.0)	3	(0.1)
Cardio-respiratory arrest	1	(0.0)	3	(0.1)	5	(0.2)
Cardiogenic shock	5	(0.2)	3	(0.1)	1	(0.0)
Cardiomyopathy	0	(0.0)	1	(0.0)	1	(0.0)
Cardiopulmonary failure	1	(0.0)	0	(0.0)	0	(0.0)
Cardiovascular insufficiency	1	(0.0)	0	(0.0)	1	(0.0)
Coronary artery disease	0	(0.0)	0	(0.0)	2	(0.1)
Coronary artery insufficiency	1	(0.0)	1	(0.0)	0	(0.0)
Hypertensive cardiomyopathy	0	(0.0)	0	(0.0)	1	(0.0)
Ischaemic cardiomyopathy	0	(0.0)	0	(0.0)	1	(0.0)
Myocardial infarction	6	(0.2)	5	(0.2)	6	(0.2)
Myocardial ischaemia	1	(0.0)	1	(0.0)	1	(0.0)
Silent myocardial infarction	0	(0.0)	0	(0.0)	1	(0.0)
Ventricular arrhythmia	0	(0.0)	0	(0.0)	1	(0.0)
Ventricular fibrillation	0	(0.0)	1	(0.0)	1	(0.0)
General disorders and administration site conditions	**34**	**(1.2)**	**45**	**(1.6)**	**26**	**(0.9)**
Accidental death	0	(0.0)	1	(0.0)	0	(0.0)
Death	25	(0.9)	35	(1.3)	22	(0.8)
Hanging	0	(0.0)	1	(0.0)	0	(0.0)
Multiple organ dysfunction syndrome	2	(0.1)	2	(0.1)	1	(0.0)
Sudden death	4	(0.1)	2	(0.1)	0	(0.0)

Serious adverse events

The incidences of SAEs (including fatal and non-fatal SAEs) are presented in Table 29.

Table 29 Subjects with Serious Adverse Events Incidence >1% in One or More Treatment Groups All Subjects as Treated

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg	
	n	(%)	n	(%)	n	(%)
Subjects in population	2,745		2,746		2,747	
with one or more serious adverse events	990	(36.1)	958	(34.9)	937	(34.1)
with no serious adverse events	1,755	(63.9)	1,788	(65.1)	1,810	(65.9)
Cardiac disorders	**434**	**(15.8)**	**362**	**(13.2)**	**384**	**(14.0)**
Acute myocardial infarction	73	(2.7)	52	(1.9)	76	(2.8)
Angina pectoris	49	(1.8)	38	(1.4)	42	(1.5)
Angina unstable	89	(3.2)	74	(2.7)	71	(2.6)
Atrial fibrillation	37	(1.3)	30	(1.1)	31	(1.1)
Cardiac failure	43	(1.6)	35	(1.3)	34	(1.2)
Cardiac failure congestive	35	(1.3)	19	(0.7)	28	(1.0)
Coronary artery disease	38	(1.4)	35	(1.3)	34	(1.2)
Myocardial infarction	37	(1.3)	39	(1.4)	49	(1.8)
Eye disorders	**31**	**(1.1)**	**19**	**(0.7)**	**21**	**(0.8)**
Gastrointestinal disorders	**59**	**(2.1)**	**78**	**(2.8)**	**84**	**(3.1)**
General disorders and administration site conditions	**75**	**(2.7)**	**95**	**(3.5)**	**58**	**(2.1)**
Death	25	(0.9)	35	(1.3)	22	(0.8)
Hepatobiliary disorders	**35**	**(1.3)**	**30**	**(1.1)**	**24**	**(0.9)**
Infections and infestations	**176**	**(6.4)**	**197**	**(7.2)**	**179**	**(6.5)**
Cellulitis	21	(0.8)	21	(0.8)	31	(1.1)
Pneumonia	45	(1.6)	51	(1.9)	46	(1.7)
Injury, poisoning and procedural complications	**80**	**(2.9)**	**78**	**(2.8)**	**69**	**(2.5)**
Metabolism and nutrition disorders	**62**	**(2.3)**	**54**	**(2.0)**	**40**	**(1.5)**
Musculoskeletal and connective tissue disorders	**58**	**(2.1)**	**65**	**(2.4)**	**54**	**(2.0)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**118**	**(4.3)**	**141**	**(5.1)**	**135**	**(4.9)**
Nervous system disorders	**145**	**(5.3)**	**150**	**(5.5)**	**155**	**(5.6)**
Ischaemic stroke	41	(1.5)	29	(1.1)	40	(1.5)
Renal and urinary disorders	**55**	**(2.0)**	**49**	**(1.8)**	**39**	**(1.4)**
Respiratory, thoracic and mediastinal disorders	**66**	**(2.4)**	**59**	**(2.1)**	**48**	**(1.7)**
Vascular disorders	**99**	**(3.6)**	**84**	**(3.1)**	**74**	**(2.7)**

Adverse events of special interest

Hypovolemia

The incidences of AEs of hypovolemia are presented in Table 30.

AEs of hypovolemia led to discontinuation of study medication in 7 (0.3%) subjects in the ertugliflozin 5 mg group, 2 (0.1%) in the ertugliflozin 15 mg group, and 1 (0.0%) in the placebo group. Twenty-seven (1.0%) subjects in the ertugliflozin 5 mg group, 24 (0.9%) in the ertugliflozin 15 mg group, and 28 (1.0%) in the placebo group had an SAE of hypovolemia. Hypovolemia AEs led to death in 3 (0.3%)

subjects in the ertugliflozin 5 mg group, 3 (0.3%) in the ertugliflozin 15 mg group, and none in the placebo group. Three of these 6 subjects died from cardiac events leading to circulatory collapse. Two of these subjects had a fatal gastrointestinal haemorrhage, and 1 subject died of hypovolemic shock in the context of "cardiac events" per investigator. None of these events were assessed as related to study medication by the investigator.

Table 30 Subjects with Adverse Events (Hypovolemia) by SOC and PT All Subjects as Treated

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg	
	n	(%)	n	(%)	n	(%)
Subjects in population	2,745		2,746		2,747	
with one or more adverse events	106	(3.9)	118	(4.3)	118	(4.3)
with no adverse events	2,639	(96.1)	2,628	(95.7)	2,629	(95.7)
Cardiac disorders	**0**	**(0.0)**	**1**	**(0.0)**	**0**	**(0.0)**
Postural orthostatic tachycardia syndrome	0	(0.0)	1	(0.0)	0	(0.0)
Investigations	**2**	**(0.1)**	**1**	**(0.0)**	**0**	**(0.0)**
Blood pressure orthostatic decreased	1	(0.0)	1	(0.0)	0	(0.0)
Urine output decreased	1	(0.0)	0	(0.0)	0	(0.0)
Metabolism and nutrition disorders	**16**	**(0.6)**	**22**	**(0.8)**	**13**	**(0.5)**
Dehydration	14	(0.5)	19	(0.7)	12	(0.4)
Hypovolaemia	2	(0.1)	5	(0.2)	1	(0.0)
Nervous system disorders	**35**	**(1.3)**	**47**	**(1.7)**	**38**	**(1.4)**
Dizziness postural	4	(0.1)	9	(0.3)	8	(0.3)
Presyncope	9	(0.3)	8	(0.3)	5	(0.2)
Syncope	23	(0.8)	31	(1.1)	26	(0.9)
Vascular disorders	**60**	**(2.2)**	**60**	**(2.2)**	**76**	**(2.8)**
Circulatory collapse	1	(0.0)	3	(0.1)	3	(0.1)
Hypotension	42	(1.5)	38	(1.4)	51	(1.9)
Hypovolaemic shock	3	(0.1)	1	(0.0)	4	(0.1)
Orthostatic hypotension	14	(0.5)	21	(0.8)	19	(0.7)

Genital infections

The incidences of genital mycotic infection (GMI) AEs were higher in the ertugliflozin 5 mg and 15 mg groups than in the placebo group in both males Table 31 and females Table 32.

Table 31 Subjects with Adverse Events of Genital Mycotic Infection – Male, by SOC and PT All Subjects as Treated

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg	
	n	(%)	n	(%)	n	(%)
Subjects in population	1,901		1,948		1,915	
with one or more adverse events	22	(1.2)	86	(4.4)	98	(5.1)
with no adverse events	1,879	(98.8)	1,862	(95.6)	1,817	(94.9)
Infections and infestations	**15**	**(0.8)**	**41**	**(2.1)**	**55**	**(2.9)**
Balanitis candida	5	(0.3)	4	(0.2)	12	(0.6)
Balanoposthitis infective	0	(0.0)	1	(0.1)	0	(0.0)
Fungal balanitis	2	(0.1)	4	(0.2)	1	(0.1)
Genital candidiasis	2	(0.1)	6	(0.3)	12	(0.6)
Genital infection	0	(0.0)	4	(0.2)	3	(0.2)

Genital infection fungal	7	(0.4)	24	(1.2)	26	(1.4)
Penile infection	0	(0.0)	1	(0.1)	4	(0.2)
Reproductive system and breast disorders	**8**	**(0.4)**	**47**	**(2.4)**	**48**	**(2.5)**
Balanoposthitis	8	(0.4)	47	(2.4)	48	(2.5)

Table 32 Subjects with Adverse Events of Genital Mycotic Infection – Female, by SOC and PT All Subjects as Treated

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg	
	n	(%)	n	(%)	n	(%)
Subjects in population	844		798		832	
with one or more adverse events	20	(2.4)	48	(6.0)	65	(7.8)
with no adverse events	824	(97.6)	750	(94.0)	767	(92.2)
Infections and infestations	**20**	**(2.4)**	**47**	**(5.9)**	**65**	**(7.8)**
Genital candidiasis	1	(0.1)	2	(0.3)	3	(0.4)
Genital infection	2	(0.2)	2	(0.3)	1	(0.1)
Genital infection fungal	2	(0.2)	8	(1.0)	16	(1.9)
Vaginal infection	2	(0.2)	8	(1.0)	12	(1.4)
Vulvitis	0	(0.0)	3	(0.4)	2	(0.2)
Vulvovaginal candidiasis	9	(1.1)	13	(1.6)	18	(2.2)
Vulvovaginal mycotic infection	2	(0.2)	12	(1.5)	15	(1.8)
Vulvovaginitis	4	(0.5)	4	(0.5)	2	(0.2)
Reproductive system and breast disorders	**0**	**(0.0)**	**1**	**(0.1)**	**0**	**(0.0)**
Vulvovaginal inflammation	0	(0.0)	1	(0.1)	0	(0.0)

In males, there were 6 (0.3%) subjects in the ertugliflozin 5 mg group, 5 (0.3%) in the 15 mg group, and none in the placebo group who discontinued study medication due to a GMI AE. In females, there were 6 (0.8%) subjects in the 5 mg ertugliflozin group, 4 (0.5%) in the 15 mg ertugliflozin group, and none in the placebo group who discontinued study medication due to a GMI AE. No GMI AEs were serious.

Complicated genital infections

"Complicated" genital infections were defined as SAEs within the GMI CMQ or AEs within the Sponsor-generated CMQ of potentially medically significant genital infections].

In male subjects, the incidence of complicated genital infection AEs was low overall, but higher in the ertugliflozin 5 mg (1.0%) and 15 mg groups (0.9%) than in the placebo group (0.3%). Phimosis was reported in 33 cases (0.9%) for ertugliflozin compared to 2 cases (0.1%) for placebo. In female subjects, incidences of complicated genital infection AEs were low in the ertugliflozin 5 mg (0.4%) and 15 mg (0.4%) groups. There were no complicated genital infection AEs in female subjects in the placebo group.

Fournier's gangrene

No event of Fournier's Gangrene was identified.

There were 4 subjects with AEs of skin necrosis or gas gangrene, 2 in the ertugliflozin 15 mg group and 2 in the placebo group. The AEs for all 4 subjects involved the lower limb.

Urinary tract infection

The incidences of UTI AEs were higher in the ertugliflozin 5 mg (12.2%) and 15 mg (12.0%) groups than in the placebo group (10.2%). The incidences of UTI SAEs were low and not notably different across treatment groups, with 25 (0.9%) subjects in the ertugliflozin 5 mg group, 12 (0.4%) in the ertugliflozin 15 mg group, and 22 (0.8%) in the placebo group.

Complicated urinary tract infection

"Complicated" UTI AEs were defined as SAEs within the UTI CMQ or AEs within the Sponsor-generated CMQ of potentially medically significant events.

The incidences of complicated UTI AEs were low and similar in the ertugliflozin 5 mg (1.5%), 15 mg (0.7%), and placebo groups (1.1%).

Ketoacidosis

Based on internal case review, the percentages of subjects with events meeting the case definition for ketoacidosis (with certain, probable, or possible likelihood) were higher in the ertugliflozin groups than in the placebo group in both the APRFU dataset (Table 33) and the Treatment Period dataset. The percentages of subjects with events meeting the case definition for ketoacidosis with certain, probable, or possible likelihood was higher in all ertugliflozin group (19 subjects [0.3%]) than in the placebo group (2 subjects [0.1%]). There were no fatal cases of ketoacidosis during the Treatment Period. One subject, in the ertugliflozin 15 mg group, had a fatal AE of diabetic ketoacidosis that began 310 days after the subject's last dose of study medication.

Table 33 Summary of Ketoacidosis Case Review Outcomes All Post-randomization Follow-up

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	%	n	%	n	%	n	%
Subjects in population	2745		2746		2747		5493	
Number of subjects with cases sent for case review	29	(1.1)	45	(1.6)	43	(1.6)	88	(1.6)
Number of subjects meeting case definition[†]	2	(0.1)	7	(0.3)	12	(0.4)	19	(0.3)
Classification								
Certain	0	(0.0)	4	(0.1)	5	(0.2)	9	(0.2)
Probable	1	(0.0)	1	(0.0)	6	(0.2)	7	(0.1)
Possible	1	(0.0)	2	(0.1)	3	(0.1)	5	(0.1)
Unlikely	22	0.8)	33	(1.2)	27	(1.0)	60	(1.1)
Unclassifiable	6	(0.2)	5	(0.2)	4	(0.1)	9	(0.2)

In the analysis of time to first ketoacidosis event based on the Treatment Period dataset, the HR for all ertugliflozin group versus the placebo group was 4.74 (95% CI, 1.105 to 20.364)

Table 34 Cox Proportional Hazards Model for Time to First Ketoacidosis All Subjects as Treated All Post-randomization Follow-up

Treatment	N	Number of Subjects with an Event (%)	Person-Years[†]	Rate/100 Person-Years	Hazard Ratio[‡] (95% CI)
All Ertugliflozin	5493	19 (0.35)	19098.39	0.10	4.74 (1.105, 20.364)
Placebo	2745	2 (0.07)	9563.70	0.02	

Amputation

The incidences of non-traumatic limb amputation by location were similar in the ertugliflozin 5 mg (2.0%), 15 mg (2.1%), and placebo (1.6%) groups. The follow-up time-adjusted incidence rates of non-traumatic limb amputation per 100-subject years were similar in the ertugliflozin 5 mg (0.57), 15 mg (0.60), and placebo (0.47) groups.

Table 35 Subjects with Amputations by Location All Post-randomization Follow-up

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg	
	n	(%)	n	(%)	n	(%)
Subjects in population	2,745		2,746		2,747	
with one or more amputations	45	(1.6)	54	(2.0)	57	(2.1)
with no amputations	2,700	(98.4)	2,692	(98.0)	2,690	(97.9)
Surgical and medical procedures	**44**	**(1.6)**	**54**	**(2.0)**	**57**	**(2.1)**
Finger amputation	0	(0.0)	2	(0.1)	0	(0.0)
Foot amputation	11	(0.4)	7	(0.3)	9	(0.3)
Metatarsal excision	1	(0.0)	0	(0.0)	3	(0.1)
Toe amputation	24	(0.9)	33	(1.2)	29	(1.1)
Leg amputation						
Above knee amputation	12	(0.4)	11	(0.4)	18	(0.7)
Below knee amputation	8	(0.3)	8	(0.3)	10	(0.4)
Leg – Unknown Location[†]	0	(0.0)	0	(0.0)	1	(0.0)
Vascular disorders	**1**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Spontaneous amputation	1	(0.0)	0	(0.0)	0	(0.0)

The follow-up-adjusted incidence rates of non-traumatic limb amputation based on the APRFU (all post-randomization follow-up) dataset are presented in Table 36.

Table 36 Analysis of Subjects with Amputation All Post-randomization Follow-up Follow-up-adjusted Incidence Rate

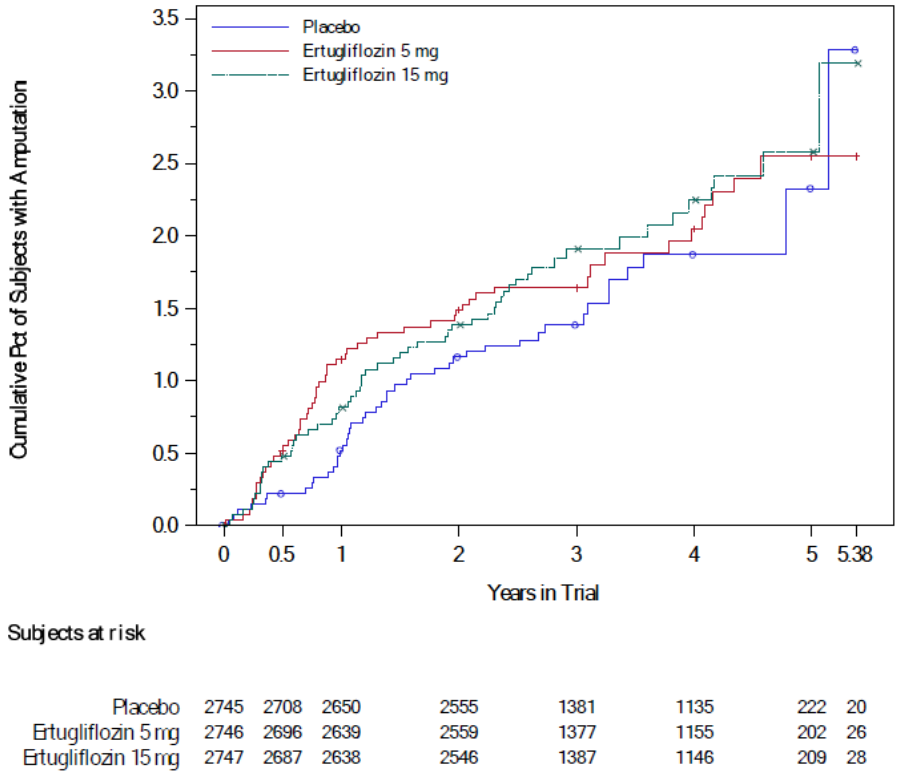
Treatment	Number of Subjects with ≥ 1 Event/Subject-Years Follow-up time (100-Subject-Years Incidence Rate)	Difference vs. Placebo Estimate (95% CI)[†]
Subjects in Population		
Placebo	2745	
Ertugliflozin 5 mg	2746	
Ertugliflozin 15 mg	2747	
All Ertugliflozin	5493	
Subjects with Amputations		
Placebo	45/9483.8 (0.47)	
Ertugliflozin 5 mg	54/9481.2 (0.57)	0.10 (-0.11, 0.31)
Ertugliflozin 15 mg	57/9444.9 (0.60)	0.13 (-0.08, 0.34)
All Ertugliflozin	111/18926.1 (0.59)	0.11 (-0.08, 0.28)

In the Kaplan-Meier curves for time to first amputation for the APRFU dataset is presented in Figure 18.

For the APRFU dataset, relative to the placebo group, the HR for time to the first amputation was 1.23 (95% CI, 0.829 to 1.837) and 1.38 (95% CI, 0.933 to 2.050) for ertugliflozin 5 mg and 15 mg groups, respectively, based on a multivariate model. For the Treatment Period dataset, relative to the placebo

group, the HR for time to the first amputation was 1.23 (95% CI, 0.78 to 1.947) and 1.42 (95% CI, 0.900 to 2.231) for the ertugliflozin 5 mg and 15 mg groups, respectively.

Figure 18 Kaplan-Meier Plot of Time to First Amputation All Subjects as Treated All Post-randomization Follow-up



Based on the multivariate model for the APRFU, the following factors were associated ($p<0.05$) with increased risk for amputation: male gender, history of peripheral arterial disease, history of amputation or peripheral revascularization, higher baseline A1C (%), history of diabetic foot, diuretic use at baseline, and insulin use at baseline.

The distribution of subjects with and without amputations according to baseline risk factors for amputation was generally consistent with the multivariate model findings. Subjects with amputations were more likely to be male, have higher A1C (%) at baseline, have a history of peripheral neuropathy, peripheral arterial disease, amputation, diabetic foot, diabetic retinopathy, and to have been taking diuretics (including loop diuretics) at baseline, and to have been taking insulin at baseline.

Peripheral revascularization

The incidences of peripheral revascularization were similar in the ertugliflozin 5 mg (1.8%), 15 mg (2.0%), and placebo (2.4%) groups. The follow-up time-adjusted incidence rates of peripheral revascularization per 100-subject years were low and similar in the ertugliflozin 5 mg (0.53), 15 mg (0.58), and placebo (0.70) groups.

Fractures

The most common category of confirmed fracture in subjects with at least 1 fracture was low-trauma fracture across treatment groups. The incidences of adjudication-confirmed fractures were similar in the ertugliflozin 5 mg (3.6%), 15 mg (3.7%), and placebo (3.6%) groups (Table 37).

Laboratory Data Related to Bone Metabolism

Subjects treated with ertugliflozin had small increases in mean phosphate and magnesium starting at Week 6 relative to subjects treated with placebo. Mean calcium values remained similar over time across all treatment groups.

Table 37 Summary of Confirmed Fractures All Post-randomization Follow-up

	Placebo n (%)	Ertugliflozin 5 mg n (%)	Ertugliflozin 15 mg n (%)
Subjects in population	2745	2746	2747
With ≥1 fracture	98 (3.6)	99 (3.6)	102 (3.7)
High trauma fracture	14 (0.5)	16 (0.6)	10 (0.4)
Low trauma fracture	82 (3.0)	81 (2.9)	92 (3.3)
Pathological fracture	1 (<0.1)	2 (0.1)	0 (0.0)
Stress fracture	1 (<0.1)	1 (<0.1)	0 (0.0)
Any other fracture (not listed above)	0 (0.0)	0 (0.0)	0 (0.0)

Changes in renal function

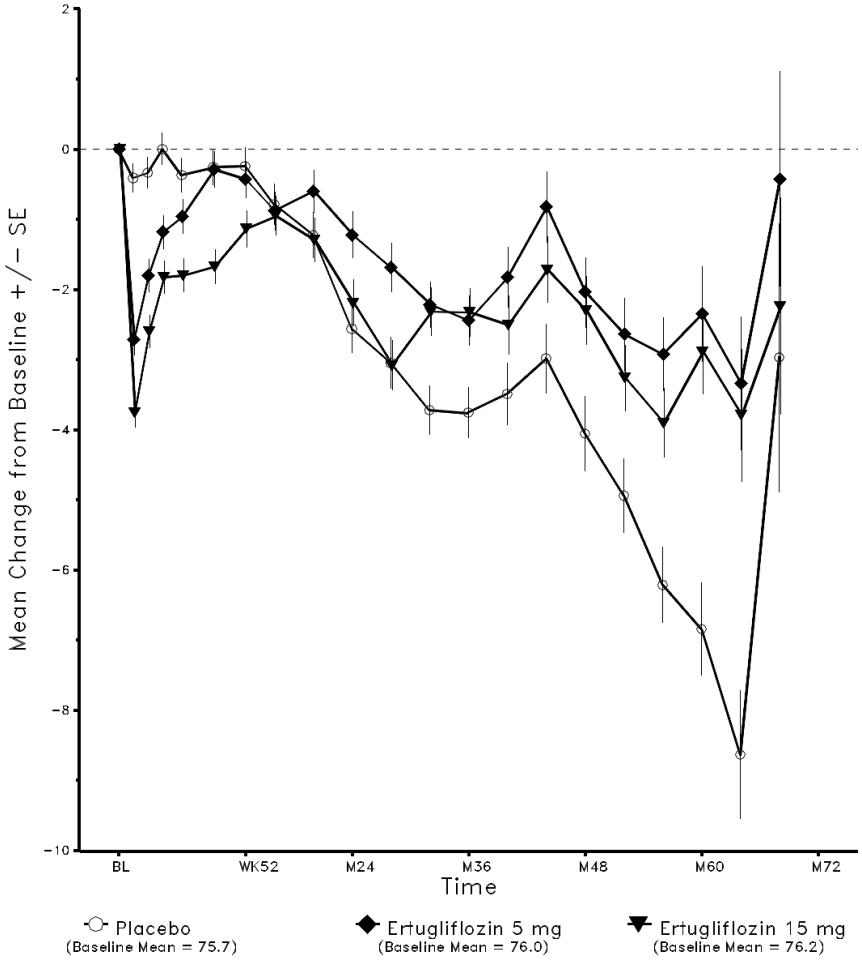
eGFR changes over time

Initial reductions in eGFR (MDRD formula) were observed in all treatment groups with subsequent increases in the ertugliflozin groups until Week 52, at which time the mean change (mL/min/1.73 m^2) from baseline was -0.4 and -1.1 in the ertugliflozin 5 mg and 15 mg groups, respectively, and -0.2 in the placebo group (Figure 19). At Month 60, the mean changes from baseline in the ertugliflozin 5 mg and 15 mg groups (-2.4 and -2.9, respectively) were smaller compared with the placebo group (-6.8). The increase towards baseline in the eGFR observed after Month 60 in the ertugliflozin and placebo groups may be an artifact of the low numbers of subjects at the later timepoints.

The proportions of subjects with at least 1 occurrence of a decrease >30% from baseline in eGFR were similar in the ertugliflozin 5 mg (17.2%), 15 mg (18.2%) and placebo (17.6%) groups. The proportions of subjects with at least 1 decrease >50% from baseline in eGFR were lower in the ertugliflozin 5 mg group (2.2%) and similar in the ertugliflozin 15 mg group (2.8%), relative to the placebo group (3.3%).

The proportions of subjects with a decrease >30% from baseline in eGFR at their last on-treatment assessment was similar in the ertugliflozin 5 mg (6.6%), 15 mg (6.6%), and placebo (7.8%) groups. The proportions of subjects with a decrease from baseline >50% at their last on-treatment assessment were low and similar in the ertugliflozin 5 mg (1.0%), 15 mg (1.0%), and placebo (1.4%) groups.

Figure 19 eGFR (mL/min/1.73 m^2): Mean Change From Baseline Over Time (Mean±SE) (All Subjects as Treated)



Renal-related AEs

The incidences of renal-related AEs were not notably different in the ertugliflozin 5 mg (4.2%), 15 mg (4.3%), and placebo (4.7%) groups. Incidences of AEs related to decreased eGFR or increased creatinine were similar in the ertugliflozin 5 mg (2.1%), 15 mg (3.4%), and placebo (2.4%) groups.

No renal-related events meeting adjudication criteria were adjudicated as very likely or probably related to study medication, and the numbers of events adjudicated as possibly related to study medication were lower in the ertugliflozin 5 mg (6 events) and 15 mg (9 events) groups than in the placebo (19 events) group.

Table 38 Subjects With Renal-related Adverse Events by SOC and PT All Subjects as Treated

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	2,745		2,746		2,747		5,493	
with one or more adverse events	129	(4.7)	114	(4.2)	117	(4.3)	231	(4.2)
with no adverse events	2,616	(95.3)	2,632	(95.8)	2,630	(95.7)	5,262	(95.8)
Renal and urinary disorders	**129**	**(4.7)**	**114**	**(4.2)**	**117**	**(4.3)**	**231**	**(4.2)**
Acute kidney injury	60	(2.2)	48	(1.7)	53	(1.9)	101	(1.8)
Azotaemia	1	(0.0)	1	(0.0)	1	(0.0)	2	(0.0)

Nephropathy toxic	0	(0.0)	1	(0.0)	0	(0.0)	1	(0.0)
Oliguria	1	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Renal failure	31	(1.1)	21	(0.8)	30	(1.1)	51	(0.9)
Renal impairment	47	(1.7)	49	(1.8)	36	(1.3)	85	(1.5)

Urinary albumin: creatinine ratio

Median percent increases in UACR (urinary albumin: creatinine ratio) over time were smaller in the ertugliflozin groups than in the placebo group (Table 39). Additionally, the proportions of subjects with albuminuria regression (i.e, improvement from micro- to normo-albuminuria or from macro- to micro- or normo-albuminuria) were higher and the proportions of subjects with albuminuria progression (i.e, deterioration from normo- to micro- or macro- albuminuria, or from micro- to macro-albuminuria) were lower in the ertugliflozin groups compared with the placebo group (Table 40).

Table 39 Urinary Albumin/Creatinine Ratio (mg/g): Summary Statistics of Percent Change From Baseline Over Time (All Subjects as Treated)

		Time Point Median	Percent Change From Baseline at Time Point Median		
Treatment	N	(Q1, Q3)	(Q1, Q3)	Min	Max
Baseline					
Placebo	2684	19.00 (6.00, 66.50)			
Ertugliflozin 5 mg	2686	18.00 (6.00, 68.00)			
Ertugliflozin 15 mg	2660	19.00 (6.00, 69.00)			
Week 18					
Placebo	2478	18.00 (6.00, 67.00)	0.00 (-44.44, 66.67)	-99.9	73340.0
Ertugliflozin 5 mg	2472	15.00 (6.00, 53.00)	-13.40 (-53.52, 50.00)	-99.8	70316.7
Ertugliflozin 15 mg	2450	13.00 (5.00, 54.00)	-14.71 (-55.53, 50.00)	-99.8	44666.7
Week 52					
Placebo	2257	20.00 (6.00, 70.00)	5.41 (-40.00, 96.34)	-99.9	151300
Ertugliflozin 5 mg	2306	17.00 (6.00, 59.00)	-2.53 (-50.00, 66.67)	-99.9	69750.0
Ertugliflozin 15 mg	2277	15.00 (6.00, 56.00)	-6.82 (-50.00, 66.67)	-99.9	49866.7
Month 24					
Placebo	2025	21.00 (7.00, 79.00)	17.14 (-38.00, 140.00)	-99.9	77520.0
Ertugliflozin 5 mg	2125	17.00 (7.00, 63.00)	0.73 (-48.96, 100.00)	-99.8	131700
Ertugliflozin 15 mg	2084	16.00 (6.00, 59.50)	1.06 (-47.78, 95.26)	-99.9	69466.7
Month 36					
Placebo	1841	21.00 (8.00, 86.00)	27.03 (-38.46, 177.78)	-99.9	53500.0
Ertugliflozin 5 mg	1933	19.00 (7.00, 68.00)	13.33 (-49.34, 120.37)	-99.7	172050
Ertugliflozin 15 mg	1915	17.00 (7.00, 59.00)	3.33 (-49.44, 100.00)	-99.9	22450.0
Month 48					
Placebo	745	24.00 (8.00, 90.00)	50.00 (-33.33, 227.27)	-99.2	16881.8
Ertugliflozin 5 mg	825	24.00 (9.00, 78.00)	33.33 (-36.84, 200.00)	-99.3	20533.3
Ertugliflozin 15 mg	835	17.00 (7.00, 59.00)	21.25 (-42.86, 150.00)	-99.1	36942.9
Month 60					
Placebo	692	23.00 (8.00, 91.00)	48.53 (-28.57, 222.41)	-99.0	44840.0
Ertugliflozin 5 mg	780	22.00 (8.00, 87.00)	30.99 (-40.00, 200.00)	-97.9	58940.0
Ertugliflozin 15 mg	771	18.00 (7.00, 65.00)	20.00 (-45.83, 150.00)	-99.9	60809.1

Table 40 Albuminuria Progression or Regression: Summary of Subjects Over Time All Subjects as Treated

	Placebo n/m (%)	Ertugliflozin 5 mg n/m (%)	Ertugliflozin 15 mg n/m (%)
Week 18			
Subjects with albuminuria progression	267/2478 (10.8)	188/2472 (7.6)	188/2450 (7.7)
Subjects with albuminuria regression	264/2478 (10.7)	368/2472 (14.9)	360/2450 (14.7)
Week 52			
Subjects with albuminuria progression	292/2257 (12.9)	220/2306 (9.5)	232/2277 (10.2)

Subjects with albuminuria regression	230/2257 (10.2)	337/2306 (14.6)	336/2277 (14.8)
Month 24			
Subjects with albuminuria progression	342/2025 (16.9)	257/2125 (12.1)	230/2084 (11.0)
Subjects with albuminuria regression	201/2025 (9.9)	303/2125 (14.3)	288/2084 (13.8)
Month 36			
Subjects with albuminuria progression	334/1841 (18.1)	283/1933 (14.6)	239/1915 (12.5)
Subjects with albuminuria regression	202/1841 (11.0)	267/1933 (13.8)	274/1915 (14.3)
Month 48			
Subjects with albuminuria progression	160/745 (21.5)	161/825 (19.5)	124/835 (14.9)
Subjects with albuminuria regression	74/745 (9.9)	96/825 (11.6)	102/835 (12.2)
Month 60			
Subjects with albuminuria progression	153/692 (22.1)	145/780 (18.6)	113/771 (14.7)
Subjects with albuminuria regression	73/692 (10.5)	88/780 (11.3)	114/771 (14.8)

Hypoglycaemia

Sub-studies

Background antihyperglycemic agents (AHAs) were to be kept constant during the first 18 weeks of the study unless glycemic rescue was needed, or subjects experienced clinically significant hypoglycemia. After Week 18, subjects were to receive standard of care for glycemic control.

Through Week 18 in the insulin with or without metformin sub-study, the incidences of symptomatic hypoglycemia were similar in the ertugliflozin 5 mg (26.4%), 15 mg (26.5%), and placebo (28.5%) groups. The incidences of documented hypoglycemia (symptomatic and asymptomatic combined) were similar in the ertugliflozin 5 mg (39.4%), 15 mg (38.9%), and placebo (37.5%) groups.

Through Week 18 in the SU monotherapy sub-study, all episodes of symptomatic hypoglycemia occurred in the ertugliflozin 5 mg (5.5%) and 15 mg (3.7%) groups. The incidences of documented hypoglycemia (symptomatic and asymptomatic combined) were 7.3% in the ertugliflozin 5 mg group, 9.3% in the ertugliflozin 15 mg group, and 4.2% in the placebo group. There were no incidences of severe hypoglycemia.

Through Week 18 in the metformin with SU sub-study, the incidences of symptomatic hypoglycemia were similar in the ertugliflozin 5 mg (11.0%), 15 mg (12.4%), and placebo (7.7%) groups. The incidences of documented hypoglycemia (symptomatic and asymptomatic combined) were higher in the ertugliflozin 15 mg group (26.5%) than in the placebo group (14.5%); the incidences of documented hypoglycemia (symptomatic and asymptomatic combined) were similar in the ertugliflozin 5 mg (20.0%) and placebo groups. The incidences of severe hypoglycemia were low in the ertugliflozin 5 mg (2.0%), 15 mg (1.8%), and placebo (0.9%) groups.

Main study

In the Treatment Period of the VERTIS CV main study, the incidences of symptomatic hypoglycemia were not notably different in the ertugliflozin 5 mg (28.0%), 15 mg (26.5%), and placebo (28.8%) groups. The incidences of documented hypoglycemia (symptomatic and asymptomatic combined) were similar in the ertugliflozin 5 mg (45.0%), 15 mg (44.4%), and placebo (44.3%) groups. The incidences of severe hypoglycemia were low and similar in the ertugliflozin 5 mg (5.0%), 15 mg (5.4%), and placebo (5.9%) groups.

The incidences of documented and severe hypoglycaemia in the sub-studies and in the main study in Table 41.

Table 41 Documented and Severe Hypoglycemia All Subjects as Treated

	Placebo	Ertugliflozin 5 mg	Ertugliflozin 15 mg
Insulin with or without Metformin Sub-study (18 weeks; Excluding Rescue)	**N=347**	**N=348**	**N=370**
Documented Hypoglycemia (symptomatic and asymptomatic), n (%)	130 (37.5)	137 (39.4)	144 (38.9)
Documented Symptomatic Hypoglycemia, n (%)	93 (26.8)	85 (24.4)	92 (24.9)
Severe Hypoglycemia, n (%)	12 (3.5)	13 (3.7)	19 (5.1)
Asymptomatic Hypoglycemia	86 (24.8)	105 (30.2)	100 (27.0)
SU Monotherapy Sub-study (18 weeks; Excluding Rescue)	**N=48**	**N=55**	**N=54**
Documented Hypoglycemia (symptomatic and asymptomatic), n (%)	2 (4.2)	4 (7.3)	5 (9.3)
Documented Symptomatic Hypoglycemia, n (%)	0	3 (5.5)	2 (3.7)
Severe Hypoglycemia, n (%)	0	0	0
Asymptomatic Hypoglycemia, n (%)	2 (4.2)	3 (5.5)	5 (9.3)
Metformin with SU Sub-study (18 weeks; Excluding Rescue)	**N=117**	**N=100**	**N=113**
Documented Hypoglycemia (symptomatic and asymptomatic), n (%)	17 (14.5)	20 (20.0)	30 (26.5)
Documented Symptomatic Hypoglycemia, n (%)	9 (7.7)	9 (9.0)	14 (12.4)
Severe Hypoglycemia, n (%)	1 (0.9)	2 (2.0)	3 (1.8)
Asymptomatic Hypoglycemia, n (%)	14 (12.0)	16 (16.0)	26 (23.0)
Main Study[a] (Treatment Period; Including Rescue)	**N=2745**	**N=2746**	**N=2747**
Documented Hypoglycemia (symptomatic and asymptomatic), n (%)	1215 (44.3)	1237 (45.0)	1220 (44.4)
Documented Symptomatic Hypoglycemia, n (%)	759 (27.7)	740 (26.9)	695 (25.3)
Severe Hypoglycemia, n (%)	162 (5.9)	136 (5.0)	148 (5.4)
Asymptomatic Hypoglycemia, n (%)	1017 (37.0)	1076 (39.2)	1042 (37.9)

Pancreatitis

The numbers of subjects with adjudication-confirmed pancreatitis events were low and similar in the ertugliflozin 5 mg (0.4%), 15 mg (0.2%), and placebo (0.4%) groups.

Hepatic events

No hepatic events submitted for adjudication were adjudicated as very likely or probably related to study medication in the ertugliflozin groups compared with 1 event in each of these causality categories in the placebo group. There were 6 subjects with hepatic events (each subject had 1 event) adjudicated as possibly related to study medication in each treatment group.

Small mean decreases from baseline in ALT and AST were observed over time in the ertugliflozin and placebo groups.

In the standard PDLC analysis, there were 3 subjects (0.1%) in the ertugliflozin 5 mg group, 2 (0.1%) in the 15 mg group, and none in the placebo group with ALT or AST values >20 X ULN at any visit. In a post hoc analysis based on local and core laboratory results combined, the proportions of subjects meeting this

PDLC criterion were similar in the ertugliflozin 5 mg (5 subjects [0.2%]), 15 mg (6 subjects [0.2%]), and placebo (3 subjects [0.1%]) groups.

In the standard PDLC analysis, 1 subject (0.0%) in the ertugliflozin 5 mg group, 2 (0.1%) in the ertugliflozin 15 mg group, and 3 (0.1%) in the placebo group had an ALT or AST value ≥3 X ULN with a concurrent bilirubin value >2 X ULN at any visit. In a post hoc analysis based on local and core laboratory results combined, the proportions of subjects meeting this PDLC criterion were not notably different between the ertugliflozin 5 mg (4 subjects [0.1%]), 15 mg (4 subjects [0.1%]), and placebo (9 subjects [0.3%]) groups.

Hypersensitivity

The incidences of potential hypersensitivity events were similar in the ertugliflozin 5 mg (4.4%), 15 mg (5.2%), and placebo groups (4.4%). The incidences of serious potential hypersensitivity AEs were low and similar in the ertugliflozin 5 mg (0.3%), 15 mg (0.3%), and placebo (0.4%) groups.

Malignancy

Malignancies were assessed via analyses of neoplasm AEs of malignant or unspecified potential (MedDRA SMQ Malignant or unspecified tumours). The overall incidences of these AEs in the APRFU dataset were similar in the ertugliflozin 5 mg (5.9%), 15 mg (5.5%), and placebo (5.5%) groups. Follow-up time-adjusted incidence rates of per 100-subject years were also similar in the ertugliflozin 5 mg (1.7), 15 mg (1.6), and placebo (1.6) groups. Similar results were observed in analyses of these AEs with onset >180 days after first dose of study medication in subjects treated for >6 months (180 days).

An evaluation of AEs within the high-level group term of renal and urinary tract neoplasms malignant and unspecified showed that bladder and kidney neoplasms were more common in the ertugliflozin groups than in the placebo group (Table 42).

Table 42 Subjects with Renal and urinary tract neoplasms malignant and unspecified Events with Onset Greater Than 180 Days After First Dose - All Subjects as Treated for Greater Than 180 Days All Post-randomization Follow-up

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg	
	n	(%)	n	(%)	n	(%)
Renal and urinary tract neoplasms malignant and unspecified	**7**	**(0.3)**	**15**	**(0.6)**	**15**	**(0.6)**
Bladder cancer	2	(0.1)	4	(0.2)	3	(0.1)
Bladder cancer recurrent	0	(0.0)	2	(0.1)	0	(0.0)
Bladder transitional cell carcinoma	2	(0.1)	2	(0.1)	2	(0.1)
Clear cell renal cell carcinoma	0	(0.0)	1	(0.0)	0	(0.0)
Metastatic carcinoma of the bladder	0	(0.0)	0	(0.0)	1	(0.0)
Papillary renal cell carcinoma	0	(0.0)	0	(0.0)	1	(0.0)
Renal cancer	1	(0.0)	3	(0.1)	2	(0.1)
Renal cell carcinoma	0	(0.0)	2	(0.1)	2	(0.1)
Renal neoplasm	2	(0.1)	0	(0.0)	2	(0.1)
Transitional cell carcinoma	0	(0.0)	1	(0.0)	2	(0.1)

Within the HLGT renal and urinary tract neoplasms malignant and unspecified, all events were either renal or bladder neoplasms. One subject in the ertugliflozin 15 mg group reported both a renal and a bladder malignancy. Smoking is a major risk factor for bladder cancer, and it was notable that 83% of subjects with a bladder malignancy (83% in the ertugliflozin groups and 80% in the placebo group)

reported current or past tobacco use compared with 54% of subjects in the overall study. There were 29 subjects with incident bladder neoplasms, 13 in the ertugliflozin 5 mg group, 11 in the ertugliflozin 15 mg group, and 5 in the placebo group. However, 2 subjects in the ertugliflozin 5 mg group and 1 in the placebo group had recurrences of pre-existing bladder cancers. Twelve (50%) of the subjects who developed bladder neoplasms in the ertugliflozin groups had hematuria at baseline compared to only 1 (20%) subject in the placebo group. A case series review was performed to identify subjects with hematuria at baseline, pre-existing bladder cancer, exposure to study medication of less than 6 months, or time-to-onset of less than one year. Following exclusion of these subjects, there remained 3 subjects in the ertugliflozin 5 mg group, 4 in the ertugliflozin 15 mg group and 3 in the placebo group.

There were 18 subjects with incident renal neoplasms, 7 subjects in the ertugliflozin 5 mg group, 8 in the ertugliflozin 15 mg group (including one subject who also had bladder malignancy) and 3 in the placebo group. Of the subjects with a renal malignancy, 73% in the ertugliflozin groups and 33% in the placebo group reported current or past tobacco use, which is a risk factor for renal cancer. In the ertugliflozin groups, 1 subject had pre-existing renal cancer compared to none in the placebo group, 3 subjects in the ertugliflozin groups were diagnosed with renal cancer within less than a year from start of treatment compared to 1 in the placebo group, and 1 subject in the ertugliflozin 5 mg group was exposed to study medication for less than 6 months (onset Day 44) compared with none in the placebo group. Four subjects in the ertugliflozin groups and 1 in the placebo group had hematuria at baseline. Using the same exclusion criteria as for bladder neoplasms, there were 4 subjects in the ertugliflozin 5 mg group, 4 subjects in the ertugliflozin 15 mg group, and 1 subject in the placebo group.

Venous thromboembolism

The incidences of adjudication-confirmed venous thromboembolism events were low (<1%) and similar across the ertugliflozin and placebo groups.

Laboratory findings

Small mean increases from baseline in hemoglobin in the ertugliflozin 5 mg and 15 mg groups (0.40 to 0.70 g/dL) were observed at Week 6 and persisted through Month 60. A slight mean decrease from baseline in the placebo group (-0.10 to -0.20 g/d) was observed at Week 6 and persisted through Month 60.

Small mean decreases from baseline in uric acid in the ertugliflozin 5 mg and 15 mg groups (-0.26 mg/dL and -0.30 mg/dL, respectively) were observed at Week 6 and persisted through Month 60. Mean values over time in the placebo group were similar to baseline through Month 60.

Small increases in mean percent change from baseline over time in LDL-C were observed in the ertugliflozin groups relative to the placebo group.

Vital signs

No meaningful differences in mean pulse rate after 1 or 3 minutes of standing were observed between the ertugliflozin and placebo groups through Week 26. No meaningful changes from baseline in ECG parameters were observed across the ertugliflozin and placebo groups.

Safety in special populations

Elderly

Subjects <65 and ≥65 years of age

The safety in subjects <65 and ≥65 years of age is presented in Table 43.

Table 43 Adverse Event Summary by Age Category (<65 Years or ≥65 Years) All Subjects as Treated

	Placebo				Ertugliflozin 5 mg				Ertugliflozin 15 mg				All Ertugliflozin			
	<65 yrs		>=65 yrs		<65 yrs		>=65 yrs		<65 yrs		>=65 yrs		<65 yrs		>=65 yrs	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	1,375		1,370		1,347		1,399		1,371		1,376		2,718		2,775	
with one or more adverse events	1,159	(84.3)	1,190	(86.9)	1,120	(83.1)	1,237	(88.4)	1,131	(82.5)	1,194	(86.8)	2,251	(82.8)	2,431	(87.6)
with no adverse event	216	(15.7)	180	(13.1)	227	(16.9)	162	(11.6)	240	(17.5)	182	(13.2)	467	(17.2)	344	(12.4)
with drug-related[†] adverse events	253	(18.4)	348	(25.4)	299	(22.2)	411	(29.4)	307	(22.4)	423	(30.7)	606	(22.3)	834	(30.1)
with serious adverse events	461	(33.5)	529	(38.6)	392	(29.1)	566	(40.5)	423	(30.9)	514	(37.4)	815	(30.0)	1,080	(38.9)
with serious drug-related adverse events	14	(1.0)	27	(2.0)	15	(1.1)	25	(1.8)	11	(0.8)	22	(1.6)	26	(1.0)	47	(1.7)
who died	45	(3.3)	72	(5.3)	52	(3.9)	79	(5.6)	55	(4.0)	79	(5.7)	107	(3.9)	158	(5.7)
discontinued drug due to an adverse event	76	(5.5)	112	(8.2)	70	(5.2)	137	(9.8)	76	(5.5)	125	(9.1)	146	(5.4)	262	(9.4)
discontinued drug due to a drug-related adverse event	22	(1.6)	29	(2.1)	30	(2.2)	61	(4.4)	29	(2.1)	60	(4.4)	59	(2.2)	121	(4.4)
discontinued drug due to a serious adverse event	40	(2.9)	62	(4.5)	30	(2.2)	61	(4.4)	36	(2.6)	54	(3.9)	66	(2.4)	115	(4.1)
discontinued drug due to a serious drug-related adverse event	2	(0.1)	5	(0.4)	4	(0.3)	8	(0.6)	3	(0.2)	9	(0.7)	7	(0.3)	17	(0.6)
Subjects in population	1375		1370		1347		1399		1371		1376		2718		2775	
with urinary tract infection adverse event	122	(8.9)	157	(11.5)	135	(10.0)	201	(14.4)	132	(9.6)	198	(14.4)	267	(9.8)	399	(14.4)
with genital mycotic infection adverse event (female)[†]	8	(2.0)	12	(2.7)	23	(6.4)	25	(5.7)	29	(7.1)	36	(8.5)	52	(6.8)	61	(7.1)
with genital mycotic infection adverse event (male)[‡]	10	(1.0)	12	(1.3)	43	(4.3)	43	(4.5)	52	(5.4)	46	(4.8)	95	(4.9)	89	(4.7)
with hypovolemia adverse event	45	(3.3)	61	(4.5)	40	(3.0)	78	(5.6)	49	(3.6)	69	(5.0)	89	(3.3)	147	(5.3)
with renal related adverse event	44	(3.2)	85	(6.2)	36	(2.7)	78	(5.6)	40	(2.9)	77	(5.6)	76	(2.8)	155	(5.6)

Subjects <75 and ≥75 years age

The safety in subjects <75 and ≥75 years of age is presented in Table 44.

Table 44 Subjects with Selected Special Interest Adverse Events by Age Category (<75 Years or ≥75 Years) All Subjects as Treated

	Placebo				Ertugliflozin 5 mg				Ertugliflozin 15 mg			
	<75 yrs		>=75 yrs		<75 yrs		>=75 yrs		<75 yrs		>=75 yrs	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	2,435		310		2,457		289		2,443		304	
with one or more adverse events	2,077	(85.3)	272	(87.7)	2,099	(85.4)	258	(89.3)	2,060	(84.3)	265	(87.2)
with no adverse event	358	(14.7)	38	(12.3)	358	(14.6)	31	(10.7)	383	(15.7)	39	(12.8)
with drug-related† adverse events	515	(21.1)	86	(27.7)	630	(25.6)	80	(27.7)	645	(26.4)	85	(28.0)
with serious adverse events	866	(35.6)	124	(40.0)	840	(34.2)	118	(40.8)	811	(33.2)	126	(41.4)
with serious drug-related adverse events	31	(1.3)	10	(3.2)	37	(1.5)	3	(1.0)	28	(1.1)	5	(1.6)
who died	95	(3.9)	22	(7.1)	116	(4.7)	15	(5.2)	117	(4.8)	17	(5.6)
discontinued drug due to an adverse event	160	(6.6)	28	(9.0)	174	(7.1)	33	(11.4)	168	(6.9)	33	(10.9)
discontinued drug due to a drug-related adverse event	45	(1.8)	6	(1.9)	71	(2.9)	20	(6.9)	75	(3.1)	14	(4.6)
discontinued drug due to a serious adverse event	86	(3.5)	16	(5.2)	83	(3.4)	8	(2.8)	75	(3.1)	15	(4.9)
discontinued drug due to a serious drug-related adverse event	5	(0.2)	2	(0.6)	11	(0.4)	1	(0.3)	9	(0.4)	3	(1.0)
Subjects in population	2435		310		2457		289		2443		304	
with urinary tract infection adverse event	235	(9.7)	44	(14.2)	288	(11.7)	48	(16.6)	274	(11.2)	56	(18.4)
with genital mycotic infection adverse event (female)†	17	(2.3)	3	(2.8)	44	(6.3)	4	(4.0)	56	(7.8)	9	(8.1)
with genital mycotic infection adverse event (male)‡	21	(1.2)	1	(0.5)	73	(4.1)	13	(6.9)	91	(5.3)	7	(3.6)
with hypovolemia adverse event	88	(3.6)	18	(5.8)	98	(4.0)	20	(6.9)	97	(4.0)	21	(6.9)
with renal related adverse event	109	(4.5)	20	(6.5)	90	(3.7)	24	(8.3)	96	(3.9)	21	(6.9)

NYHA class

Subjects with NYHA Class II (N=1,289) and NYHA Class III (N=139): In the NYHA Class II subgroup, there was a lower number of subjects in the ertugliflozin 5 mg group (398) than in the ertugliflozin 15 mg group (441) and placebo group (450). In the NYHA Class III subgroup, there was a greater number of subjects in the ertugliflozin 5 mg group (56) and ertugliflozin 15 mg group (46) than in the placebo group (37).

In the NYHA Class II and NYHA Class III subgroups, results for AE summary measures are presented below.

Table 45 Adverse Event Summary All Subjects as Treated Who had Baseline NYHA Class II

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	450		398		441		839	
with one or more adverse events	368	(81.8)	311	(78.1)	349	(79.1)	660	(78.7)
with no adverse event	82	(18.2)	87	(21.9)	92	(20.9)	179	(21.3)
with drug-related† adverse events	62	(13.8)	63	(15.8)	82	(18.6)	145	(17.3)
with serious adverse events	167	(37.1)	160	(40.2)	167	(37.9)	327	(39.0)
with serious drug-related adverse events	6	(1.3)	5	(1.3)	2	(0.5)	7	(0.8)
who died	30	(6.7)	36	(9.0)	26	(5.9)	62	(7.4)
discontinued drug due to an adverse event	25	(5.6)	21	(5.3)	28	(6.3)	49	(5.8)
discontinued drug due to a drug-related adverse event	3	(0.7)	8	(2.0)	10	(2.3)	18	(2.1)
discontinued drug due to a serious adverse event	18	(4.0)	13	(3.3)	17	(3.9)	30	(3.6)
discontinued drug due to a serious drug-related adverse event	1	(0.2)	2	(0.5)	2	(0.5)	4	(0.5)

Table 46 Adverse Event Summary All Subjects as Treated Who had Baseline NYHA Class III

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	37		56		46		102	
with one or more adverse events	29	(78.4)	44	(78.6)	42	(91.3)	86	(84.3)
with no adverse event	8	(21.6)	12	(21.4)	4	(8.7)	16	(15.7)
with drug-related[T] adverse events	5	(13.5)	9	(16.1)	9	(19.6)	18	(17.6)
with serious adverse events	17	(45.9)	24	(42.9)	24	(52.2)	48	(47.1)
with serious drug-related adverse events	1	(2.7)	1	(1.8)	1	(2.2)	2	(2.0)
who died	3	(8.1)	5	(8.9)	4	(8.7)	9	(8.8)
discontinued drug due to an adverse event	1	(2.7)	2	(3.6)	3	(6.5)	5	(4.9)
discontinued drug due to a drug-related adverse event	0	(0.0)	1	(1.8)	1	(2.2)	2	(2.0)
discontinued drug due to a serious adverse event	0	(0.0)	1	(1.8)	0	(0.0)	1	(1.0)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Table 47 Adverse Events - All Subjects as Treated Who had Baseline NYHA Class II

			Difference in % vs Placebo	
Treatment	n	(%)	Estimate (95% CI)[†]	p-value[†]
Subjects in population				
Placebo	450			
Ertugliflozin 5 mg	398			
Ertugliflozin 15 mg	441			
All Ertugliflozin	839			
Subjects in population (male)				
Placebo	302			
Ertugliflozin 5 mg	280			
Ertugliflozin 15 mg	282			
All Ertugliflozin	562			
Subjects in population (female)				
Placebo	148			
Ertugliflozin 5 mg	118			
Ertugliflozin 15 mg	159			
All Ertugliflozin	277			
with one or more adverse events associated with urinary tract infection				
Placebo	39	(8.7)		
Ertugliflozin 5 mg	39	(9.8)	1.1 (-2.8, 5.2)	0.569
Ertugliflozin 15 mg	51	(11.6)	2.9 (-1.1, 6.9)	0.151
All Ertugliflozin	90	(10.7)	2.1 (-1.5, 5.3)	0.240
with one or more adverse events associated with genital mycotic infection (male)				
Placebo	0	(0.0)		
Ertugliflozin 5 mg	5	(1.8)	1.8 (0.5, 4.1)	0.020
Ertugliflozin 15 mg	11	(3.9)	3.9 (2.2, 6.9)	0.001
All Ertugliflozin	16	(2.8)	2.8 (1.6, 4.6)	0.003
with one or more adverse events associated with genital mycotic infection (female)				
Placebo	1	(0.7)		
Ertugliflozin 5 mg	5	(4.2)	3.6 (-0.0, 8.9)	0.052
Ertugliflozin 15 mg	7	(4.4)	3.7 (0.2, 8.2)	0.041
All Ertugliflozin	12	(4.3)	3.7 (0.3, 6.9)	0.037

Treatment	n	(%)	Difference in % vs Placebo	
			Estimate (95% CI)[†]	p-value[†]
with one or more symptomatic hypoglycemia[‡] adverse events				
Placebo	102	(22.7)		
Ertugliflozin 5 mg	92	(23.1)	0.4 (-5.2, 6.2)	0.877
Ertugliflozin 15 mg	79	(17.9)	-4.8 (-10.0, 0.5)	0.078
All Ertugliflozin	171	(20.4)	-2.3 (-7.1, 2.3)	0.339
with one or more adverse events associated with hypovolemia				
Placebo	18	(4.0)		
Ertugliflozin 5 mg	18	(4.5)	0.5 (-2.3, 3.4)	0.707
Ertugliflozin 15 mg	8	(1.8)	-2.2 (-4.6, 0.0)	0.053
All Ertugliflozin	26	(3.1)	-0.9 (-3.3, 1.1)	0.396

Table 48 Adverse Events - All Subjects as Treated Who had Baseline NYHA Class III

Treatment	n	(%)	Difference in % vs Placebo	
			Estimate (95% CI)[†]	p-value[†]
Subjects in population				
Placebo	37			
Ertugliflozin 5 mg	56			
Ertugliflozin 15 mg	46			
All Ertugliflozin	102			
Subjects in population (male)				
Placebo	26			
Ertugliflozin 5 mg	40			
Ertugliflozin 15 mg	35			
All Ertugliflozin	75			
Subjects in population (female)				
Placebo	11			
Ertugliflozin 5 mg	16			
Ertugliflozin 15 mg	11			
All Ertugliflozin	27			
with one or more adverse events associated with urinary tract infection				
Placebo	2	(5.4)		
Ertugliflozin 5 mg	4	(7.1)	1.7 (-11.5, 12.6)	0.740
Ertugliflozin 15 mg	5	(10.9)	5.5 (-8.3, 18.7)	0.376
All Ertugliflozin	9	(8.8)	3.4 (-9.6, 11.9)	0.511
with one or more adverse events associated with genital mycotic infection (male)				
Placebo	0	(0.0)		
Ertugliflozin 5 mg	0	(0.0)	0.0 (-13.0, 8.9)	1.000
Ertugliflozin 15 mg	1	(2.9)	2.9 (-10.4, 14.7)	0.389
All Ertugliflozin	1	(1.3)	1.3 (-11.7, 7.2)	0.556
with one or more adverse events associated with genital mycotic infection (female)				
Placebo	0	(0.0)		
Ertugliflozin 5 mg	0	(0.0)	0.0 (-26.6, 20.0)	1.000
Ertugliflozin 15 mg	1	(9.1)	9.1 (-19.0, 38.5)	0.317
All Ertugliflozin	1	(3.7)	3.7 (-23.0, 18.6)	0.523

Treatment	n	(%)	Difference in % vs Placebo	
			Estimate (95% CI)[†]	p-value[†]

with one or more symptomatic hypoglycemia‡ adverse events				
Placebo	7	(18.9)		
Ertugliflozin 5 mg	15	(26.8)	7.9 (-10.5, 24.4)	0.385
Ertugliflozin 15 mg	11	(23.9)	5.0 (-13.6, 22.5)	0.585
All Ertugliflozin	26	(25.5)	6.6 (-10.5, 20.2)	0.423
with one or more adverse events associated with hypovolemia				
Placebo	1	(2.7)		
Ertugliflozin 5 mg	3	(5.4)	2.7 (-9.1, 12.4)	0.539
Ertugliflozin 15 mg	2	(4.3)	1.6 (-10.0, 12.3)	0.692
All Ertugliflozin	5	(4.9)	2.2 (-9.3, 8.9)	0.574

Table 49 Subjects with Renal Impairment Adverse Events (Incidence >0% in One or More Treatment Groups) All Subjects as Treated Who had Baseline NYHA Class II

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	450		398		441		839	
with one or more adverse events of renal impairment	22	(4.9)	19	(4.8)	27	(6.1)	46	(5.5)
with no adverse events of renal impairment	428	(95.1)	379	(95.2)	414	(93.9)	793	(94.5)
Renal and urinary disorders	**22**	**(4.9)**	**19**	**(4.8)**	**27**	**(6.1)**	**46**	**(5.5)**
Acute kidney injury	10	(2.2)	10	(2.5)	10	(2.3)	20	(2.4)
Azotaemia	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Nephropathy toxic	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.1)
Oliguria	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Renal failure	6	(1.3)	0	(0.0)	6	(1.4)	6	(0.7)
Renal impairment	5	(1.1)	9	(2.3)	11	(2.5)	20	(2.4)

Table 50 Subjects with Renal Impairment Adverse Events (Incidence >0% in One or More Treatment Groups) All Subjects as Treated Who had Baseline NYHA Class III

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	37		56		46		102	
with one or more adverse events of renal impairment	1	(2.7)	2	(3.6)	5	(10.9)	7	(6.9)
with no adverse events of renal impairment	36	(97.3)	54	(96.4)	41	(89.1)	95	(93.1)
Renal and urinary disorders	**1**	**(2.7)**	**2**	**(3.6)**	**5**	**(10.9)**	**7**	**(6.9)**
Acute kidney injury	1	(2.7)	1	(1.8)	4	(8.7)	5	(4.9)
Renal failure	0	(0.0)	0	(0.0)	1	(2.2)	1	(1.0)
Renal impairment	0	(0.0)	1	(1.8)	0	(0.0)	1	(1.0)

In the NYHA Class III subgroup, specific AEs that occurred with a notably higher incidence in all ertugliflozin group than in the placebo group, that were not similarly observed in the overall VERTIS CV population, were atrial fibrillation (10 [9.8%] versus 0 [0%], respectively) and hypoglycemia (31 [30.4%] versus 7 [18.9%], respectively (Table 51).

While a difference in the incidence of atrial fibrillation AEs was observed between all ertugliflozin and placebo groups in the NYHA Class III subgroup, none of these AEs were assessed as related to the study medication by the investigator. Two of the subjects had a prior medical history of atrial fibrillation, 1 had an implantable defibrillator, and all had multiple risk factors for atrial fibrillation. Only 3 of the 10 subjects experienced serious atrial fibrillation.

Hypoglycaemia is a specific PT which includes events reported after initiation of glycemic rescue therapy (through Week 18) and events reported after Week 18, when subjects were permitted to initiate additional AHA therapy to manage glycemic control. Symptomatic and documented (symptomatic and asymptomatic) hypoglycemia through Week 18, that exclude post-rescue data, were analysed.

In the NYHA Class III subgroup, the incidences of hypoglycemia in all ertugliflozin group were not notably different from the placebo group across hypoglycemia categories, including severe hypoglycemia, which occurred in 2 (2.0%) subjects in all ertugliflozin group and 2 (5.4%) subjects in the placebo group (Table 51).

Table 51 Cardiac disorder, Metabolic disorders- Subjects With Adverse Events (Incidence >0% in One or More Treatment Groups) All Subjects as Treated Who had Baseline NYHA Class II

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)
Cardiac disorders	**12**	**(32.4)**	**19**	**(33.9)**	**24**	**(52.2)**	**43**	**(42.2)**
Acute coronary syndrome	0	(0.0)	0	(0.0)	1	(2.2)	1	(1.0)
Acute myocardial infarction	1	(2.7)	1	(1.8)	5	(10.9)	6	(5.9)
Angina pectoris	2	(5.4)	0	(0.0)	3	(6.5)	3	(2.9)
Angina unstable	1	(2.7)	3	(5.4)	4	(8.7)	7	(6.9)
Arrhythmia	1	(2.7)	0	(0.0)	1	(2.2)	1	(1.0)
Atrial fibrillation	0	(0.0)	5	(8.9)	5	(10.9)	10	(9.8)
Atrial flutter	1	(2.7)	1	(1.8)	1	(2.2)	2	(2.0)
Atrioventricular block	0	(0.0)	1	(1.8)	0	(0.0)	1	(1.0)
Atrioventricular block complete	0	(0.0)	1	(1.8)	0	(0.0)	1	(1.0)
Atrioventricular block first degree	0	(0.0)	1	(1.8)	1	(2.2)	2	(2.0)
Atrioventricular block second degree	1	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)
Bradycardia	0	(0.0)	1	(1.8)	0	(0.0)	1	(1.0)
Bundle branch block left	1	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)
Bundle branch block right	1	(2.7)	0	(0.0)	1	(2.2)	1	(1.0)
Cardiac arrest	1	(2.7)	0	(0.0)	1	(2.2)	1	(1.0)
Cardiac failure	2	(5.4)	6	(10.7)	3	(6.5)	9	(8.8)
Cardiac failure acute	1	(2.7)	1	(1.8)	0	(0.0)	1	(1.0)
Cardiac failure chronic	1	(2.7)	2	(3.6)	3	(6.5)	5	(4.9)
Cardiac failure congestive	2	(5.4)	1	(1.8)	3	(6.5)	4	(3.9)
Cardiac ventricular thrombosis	0	(0.0)	0	(0.0)	1	(2.2)	1	(1.0)
Congestive cardiomyopathy	0	(0.0)	1	(1.8)	0	(0.0)	1	(1.0)
Coronary artery disease	0	(0.0)	0	(0.0)	1	(2.2)	1	(1.0)
Coronary artery stenosis	0	(0.0)	2	(3.6)	1	(2.2)	3	(2.9)
Extrasystoles	1	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)
Hypertensive cardiomyopathy	0	(0.0)	1	(1.8)	1	(2.2)	2	(2.0)
Intracardiac thrombus	0	(0.0)	1	(1.8)	0	(0.0)	1	(1.0)
Ischaemic cardiomyopathy	0	(0.0)	1	(1.8)	0	(0.0)	1	(1.0)
Left ventricular dysfunction	0	(0.0)	0	(0.0)	1	(2.2)	1	(1.0)
Long QT syndrome	0	(0.0)	0	(0.0)	1	(2.2)	1	(1.0)
Mitral valve incompetence	1	(2.7)	0	(0.0)	2	(4.3)	2	(2.0)
Myocardial infarction	1	(2.7)	0	(0.0)	1	(2.2)	1	(1.0)
Myocardial ischaemia	0	(0.0)	0	(0.0)	1	(2.2)	1	(1.0)
Palpitations	0	(0.0)	0	(0.0)	1	(2.2)	1	(1.0)
Pericarditis	0	(0.0)	0	(0.0)	1	(2.2)	1	(1.0)
Right ventricular enlargement	1	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)
Supraventricular extrasystoles	0	(0.0)	0	(0.0)	1	(2.2)	1	(1.0)
Tricuspid valve incompetence	0	(0.0)	0	(0.0)	1	(2.2)	1	(1.0)
Ventricular arrhythmia	0	(0.0)	1	(1.8)	0	(0.0)	1	(1.0)
Ventricular extrasystoles	0	(0.0)	1	(1.8)	2	(4.3)	3	(2.9)
Ventricular tachycardia	0	(0.0)	0	(0.0)	1	(2.2)	1	(1.0)

Metabolism and nutrition disorders	**13**	**(35.1)**	**27**	**(48.2)**	**25**	**(54.3)**	**52**	**(51.0)**
Hyperlipidaemia	0	(0.0)	1	(1.8)	1	(2.2)	2	(2.0)
Hypertriglyceridaemia	0	(0.0)	0	(0.0)	1	(2.2)	1	(1.0)
Hyperuricaemia	0	(0.0)	1	(1.8)	3	(6.5)	4	(3.9)
Hypocalcaemia	1	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)
Hypoglycaemia	7	(18.9)	17	(30.4)	14	(30.4)	31	(30.4)
Hypokalaemia	1	(2.7)	0	(0.0)	0	(0.0)	0	(0.0)
Metabolic acidosis	0	(0.0)	1	(1.8)	0	(0.0)	1	(1.0)
Steroid diabetes	0	(0.0)	0	(0.0)	1	(2.2)	1	(1.0)
Type 2 diabetes mellitus	1	(2.7)	0	(0.0)	5	(10.9)	5	(4.9)
Vitamin D deficiency	0	(0.0)	0	(0.0)	1	(2.2)	1	(1.0)

Table 52 Analysis of Documented and Severe Hypoglycemia Episodes up to Week 18 Excluding Rescue All Subjects as Treated Who Have Baseline NYHA Class III

Treatment	n	(%)	Difference in % vs Placebo Estimate (95% CI)[†]
Subjects in population			
Placebo	37		
Ertugliflozin 5 mg	56		
Ertugliflozin 15 mg	46		
All Ertugliflozin	102		
With one or more episodes of:			
Documented symptomatic			
Placebo	3	(8.1)	
Ertugliflozin 5 mg	9	(16.1)	8.0 (-7.2, 21.4)
Ertugliflozin 15 mg	5	(10.9)	2.8 (-12.0, 16.5)
All Ertugliflozin	14	(13.7)	5.6 (-8.6, 15.7)
Asymptomatic			
Placebo	5	(13.5)	
Ertugliflozin 5 mg	15	(26.8)	13.3 (-4.3, 28.8)
Ertugliflozin 15 mg	8	(17.4)	3.9 (-13.1, 19.8)
All Ertugliflozin	23	(22.5)	9.0 (-7.1, 21.3)
Documented (symptomatic and asymptomatic)			
Placebo	6	(16.2)	
Ertugliflozin 5 mg	20	(35.7)	19.5 (0.8, 35.9)
Ertugliflozin 15 mg	11	(23.9)	7.7 (-10.5, 24.8)
All Ertugliflozin	31	(30.4)	14.2 (-2.8, 27.5)
Severe			
Placebo	2	(5.4)	
Ertugliflozin 5 mg	1	(1.8)	-3.6
Ertugliflozin 15 mg	1	(2.2)	-3.2
All Ertugliflozin	2	(2.0)	-3.4
Requiring non-medical assistance			
Placebo	1	(2.7)	
Ertugliflozin 5 mg	1	(1.8)	-0.9
Ertugliflozin 15 mg	1	(2.2)	-0.5
All Ertugliflozin	2	(2.0)	-0.7

Safety in moderate renal impairment (stage 3, 3A and 3B CKD)

At baseline (ITT population), a total of 1,776 (21.5%) subjects had Stage 3 CKD, of which 1,319 (16.0%) subjects had Stage 3A CKD (baseline eGFR 45 to <60 mL/min/1.73 m^2), and 457 (5.5%) subjects had Stage 3B CKD (baseline eGFR 30 to <45 mL/min/1.73 m^2).

Summary measures of AEs in the Stage 3A CKD and 3B CKD subgroups in Table 53 and

Table 54.

Table 53 Adverse Event Summary All Subjects as Treated in Subjects with Baseline eGFR 45 to <60 mL/min/1.73m²

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	439		465		413		878	
with one or more adverse events	394	(89.7)	422	(90.8)	372	(90.1)	794	(90.4)
with no adverse event	45	(10.3)	43	(9.2)	41	(9.9)	84	(9.6)
with drug-related[†] adverse events	114	(26.0)	141	(30.3)	132	(32.0)	273	(31.1)
with serious adverse events	180	(41.0)	191	(41.1)	151	(36.6)	342	(39.0)
with serious drug-related adverse events	8	(1.8)	8	(1.7)	5	(1.2)	13	(1.5)
who died	17	(3.9)	26	(5.6)	18	(4.4)	44	(5.0)
discontinued due to an adverse event	29	(6.6)	51	(11.0)	34	(8.2)	85	(9.7)
discontinued due to a drug-related adverse event	5	(1.1)	24	(5.2)	12	(2.9)	36	(4.1)
discontinued due to a serious adverse event	16	(3.6)	24	(5.2)	19	(4.6)	43	(4.9)
discontinued due to a serious drug-related adverse event	0	(0.0)	3	(0.6)	2	(0.5)	5	(0.6)

Table 54 Adverse Event Summary All Subjects as Treated in Subjects with Baseline eGFR 30 to <45 mL/min/1.73m²

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	158		152		147		299	
with one or more adverse events	141	(89.2)	139	(91.4)	129	(87.8)	268	(89.6)
with no adverse event	17	(10.8)	13	(8.6)	18	(12.2)	31	(10.4)
with drug-related[†] adverse events	52	(32.9)	45	(29.6)	51	(34.7)	96	(32.1)
with serious adverse events	70	(44.3)	61	(40.1)	71	(48.3)	132	(44.1)
with serious drug-related adverse events	8	(5.1)	2	(1.3)	7	(4.8)	9	(3.0)
who died	11	(7.0)	8	(5.3)	12	(8.2)	20	(6.7)
discontinued due to an adverse event	22	(13.9)	15	(9.9)	20	(13.6)	35	(11.7)
discontinued due to a drug-related adverse event	9	(5.7)	5	(3.3)	10	(6.8)	15	(5.0)
discontinued due to a serious adverse event	11	(7.0)	6	(3.9)	8	(5.4)	14	(4.7)
discontinued due to a serious drug-related adverse event	3	(1.9)	1	(0.7)	3	(2.0)	4	(1.3)

Results for AEs by SOC, SAEs, and Tier 1 AEs (symptomatic hypoglycaemia, UTI, GMI, and hypovolemia AEs) in the Stage 3A, and Stage 3B CKD subgroups in Table 55 and Table 56.

Table 55 Analysis of Subjects With Tier 1 Adverse Events All Subjects as Treated in Subjects with Baseline eGFR 45 to <60 mL/min/1.73m²

Treatment	n	(%)	Difference in % vs Placebo Estimate (95% CI)[†]	Difference in % vs Placebo p-value[†]
Subjects in population				
Placebo	439			
Ertugliflozin 5 mg	465			
Ertugliflozin 15 mg	413			
Subjects in population (male)				
Placebo	294			
Ertugliflozin 5 mg	302			
Ertugliflozin 15 mg	261			
Subjects in population (female)				
Placebo	145			
Ertugliflozin 5 mg	163			
Ertugliflozin 15 mg	152			
with one or more adverse events associated with urinary tract infection				
Placebo	58	(13.2)		
Ertugliflozin 5 mg	70	(15.1)	1.8 (-2.7, 6.4)	0.427
Ertugliflozin 15 mg	56	(13.6)	0.3 (-4.2, 5.0)	0.882
with one or more adverse events associated with genital mycotic infection (male)				
Placebo	1	(0.3)		
Ertugliflozin 5 mg	10	(3.3)	3.0 (1.0, 5.7)	0.007
Ertugliflozin 15 mg	12	(4.6)	4.3 (2.0, 7.6)	<0.001
with one or more adverse events associated with genital mycotic infection (female)				
Placebo	5	(3.4)		
Ertugliflozin 5 mg	8	(4.9)	1.5 (-3.5, 6.4)	0.525
Ertugliflozin 15 mg	11	(7.2)	3.8 (-1.5, 9.5)	0.149
with one or more symptomatic hypoglycemia[‡] adverse events				
Placebo	161	(36.7)		
Ertugliflozin 5 mg	172	(37.0)	0.3 (-6.0, 6.6)	0.922
Ertugliflozin 15 mg	144	(34.9)	-1.8 (-8.2, 4.6)	0.583
with one or more adverse events associated with hypovolemia				
Placebo	27	(6.2)		
Ertugliflozin 5 mg	35	(7.5)	1.4 (-2.0, 4.7)	0.413
Ertugliflozin 15 mg	18	(4.4)	-1.8 (-4.9, 1.3)	0.243

Table 56 Analysis of Subjects With Tier 1 Adverse Events All Subjects as Treated in Subjects with Baseline eGFR 30 to <45 mL/min/1.73m²

Treatment	n	(%)	Difference in % vs Placebo Estimate (95% CI)†	Difference in % vs Placebo p-value†
Subjects in population				
Placebo	158			
Ertugliflozin 5 mg	152			
Ertugliflozin 15 mg	147			
Subjects in population (male)				
Placebo	100			
Ertugliflozin 5 mg	93			
Ertugliflozin 15 mg	90			
Subjects in population (female)				
Placebo	58			
Ertugliflozin 5 mg	59			
Ertugliflozin 15 mg	57			
with one or more adverse events associated with urinary tract infection				
Placebo	19	(12.0)		
Ertugliflozin 5 mg	15	(9.9)	-2.2 (-9.3, 5.0)	0.544
Ertugliflozin 15 mg	23	(15.6)	3.6 (-4.2, 11.6)	0.360
with one or more adverse events associated with genital mycotic infection (male)				
Placebo	0	(0.0)		
Ertugliflozin 5 mg	2	(2.2)	2.2 (-1.6, 7.5)	0.141
Ertugliflozin 15 mg	1	(1.1)	1.1 (-2.6, 6.0)	0.292
with one or more adverse events associated with genital mycotic infection (female)				
Placebo	3	(5.2)		
Ertugliflozin 5 mg	1	(1.7)	-3.5 (-12.7, 4.5)	0.303
Ertugliflozin 15 mg	6	(10.5)	5.4 (-5.2, 16.8)	0.287
with one or more symptomatic hypoglycemia‡ adverse events				
Placebo	63	(39.9)		
Ertugliflozin 5 mg	60	(39.5)	-0.4 (-11.2, 10.5)	0.943
Ertugliflozin 15 mg	49	(33.3)	-6.5 (-17.2, 4.3)	0.237
with one or more adverse events associated with hypovolemia				
Placebo	12	(7.6)		
Ertugliflozin 5 mg	9	(5.9)	-1.7 (-7.7, 4.2)	0.558
Ertugliflozin 15 mg	15	(10.2)	2.6 (-3.9, 9.4)	0.424

Adjudicated fractures

The incidences of adjudication-confirmed fractures overall, and by low- and high-trauma categories, in the Stage 3 and 3A CKD subgroups in Table 57 and Table 58.

Table 57 Summary of Confirmed Fractures All Subjects as Treated Who Have Baseline eGFR 45 to <60 mL/min/1.73 m²

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	439		465		413		878	
With ≥1 fracture	19	(4.3)	20	(4.3)	16	(3.9)	36	(4.1)
High trauma fracture	3	(0.7)	5	(1.1)	1	(0.2)	6	(0.7)
Low trauma fracture	16	(3.6)	14	(3.0)	15	(3.6)	29	(3.3)
Pathological fracture	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)

Table 58 Summary of Confirmed Fractures All Subjects as Treated Who Have Baseline eGFR 30 to <45 mL/min/1.73 m²

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	158		152		147		299	
With ≥1 fracture	3	(1.9)	6	(3.9)	10	(6.8)	16	(5.4)
High trauma fracture	1	(0.6)	1	(0.7)	1	(0.7)	2	(0.7)
Low trauma fracture	2	(1.3)	5	(3.3)	9	(6.1)	14	(4.7)

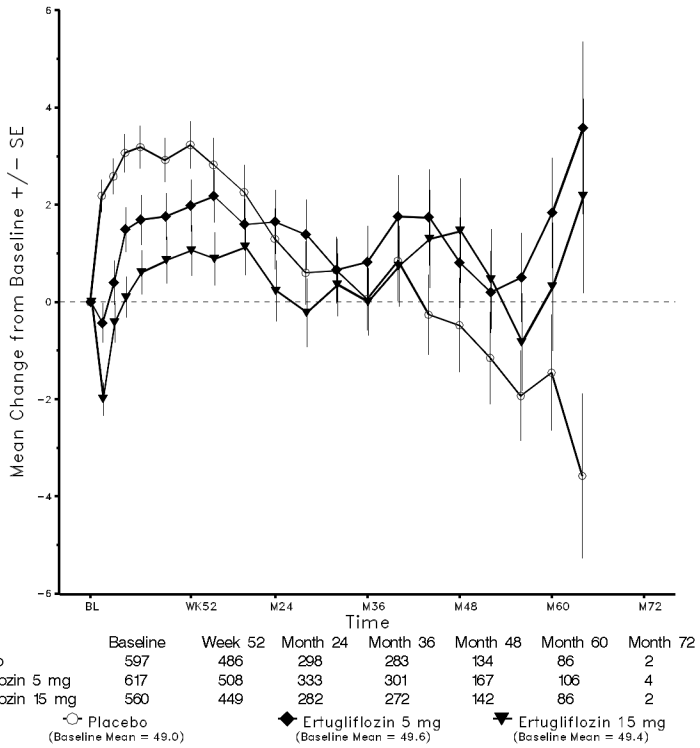
Renal function (eGFR) and renal events

In the Stage 3 CKD subgroup, an initial small decline in mean eGFR at Week 6 in the ertugliflozin groups was followed by eGFR values that were near or above baseline for the remainder of the study Figure 20.

Results in the Stage 3A CKD and Stage 3B CKD were consistent (Figure 21

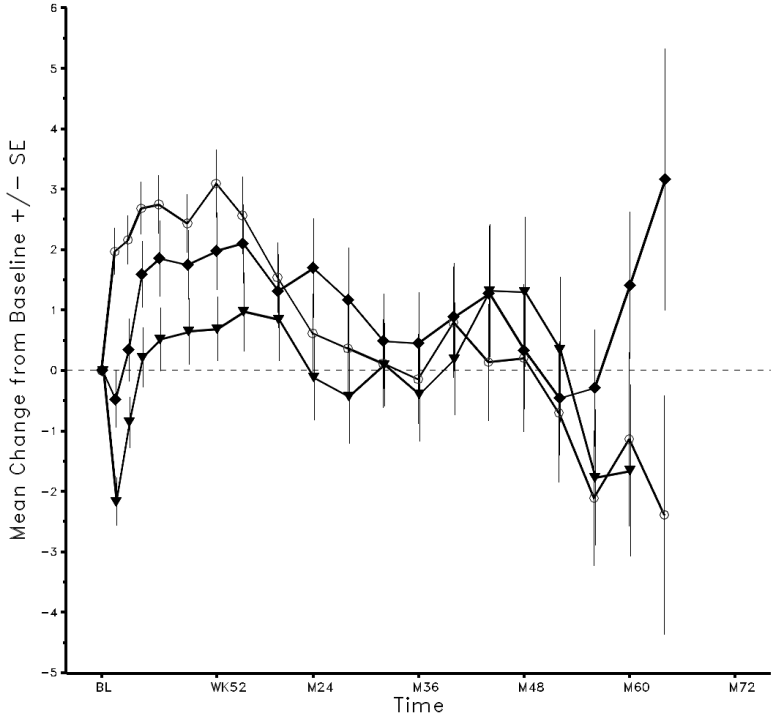
Figure 22)

Figure 20 eGFR (mL/min/1.73m²): Mean Change from Baseline Over Time (Mean ± SE): in Subjects With Baseline eGFR 30 to <60 mL/min/1.73 m²



	Baseline	Week 52	Month 24	Month 36	Month 48	Month 60	Month 72
Placebo	597	486	298	283	134	86	2
Ertugliflozin 5 mg	617	508	333	301	167	106	4
Ertugliflozin 15 mg	560	449	282	272	142	86	2

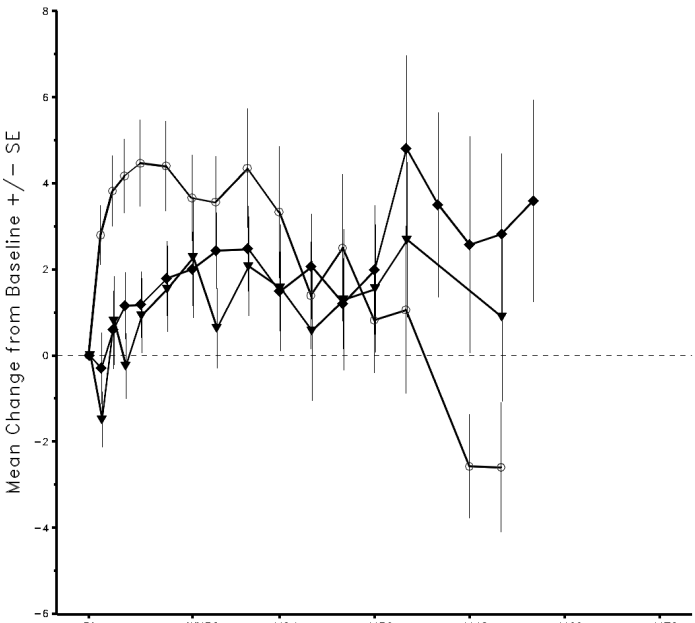
Figure 21 eGFR (mL/min/1.73m^2): Mean Change from Baseline Over Time (Mean ± SE): in Subjects With Baseline eGFR 45 to <60 mL/min/1.73 m^2



	Baseline	Week 52	Month 24	Month 36	Month 48	Month 60	Month 72
Placebo	439	368	223	223	101	65	2
Ertugliflozin 5 mg	465	391	255	228	132	85	4
Ertugliflozin 15 mg	413	344	224	216	113	67	2

Placebo (Baseline Mean = 52.7) Ertugliflozin 5 mg (Baseline Mean = 53.0) Ertugliflozin 15 mg (Baseline Mean = 53.3)

Figure 22 eGFR (mL/min/1.73m^2): Mean Change From Baseline Over Time (Mean ± SE): in Subjects With Baseline eGFR 30 to <45 mL/min/1.73 m^2



	Baseline	Week 52	Month 24	Month 36	Month 48	Month 60
Placebo	158	118	75	60	33	21
Ertugliflozin 5 mg	152	117	78	73	35	21
Ertugliflozin 15 mg	147	105	58	56	29	19

Placebo (Baseline Mean = 38.9) Ertugliflozin 5 mg (Baseline Mean = 39.0) Ertugliflozin 15 mg (Baseline Mean = 38.4)

The incidences of renal-related AEs in the Stage 3, Stage 3A, and Stage 3B CKD subgroups in

Table 59,

Table 60,

Table 61). No subjects with Stage 3 CKD had a renal event adjudicated as very likely or probably related to study medication, and the numbers of renal events adjudicated as possibly related to study medication were low and similar across treatment groups.

Table 59 Subjects With Renal-related Adverse Events by SOC and PT
All Subjects as Treated in Subjects With Baseline eGFR 30 to <60 mL/min/1.73 m²

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	597		617		560		1,177	
with one or more adverse events	61	(10.2)	60	(9.7)	56	(10.0)	116	(9.9)
with no adverse events	536	(89.8)	557	(90.3)	504	(90.0)	1,061	(90.1)
Renal and urinary disorders	**61**	**(10.2)**	**60**	**(9.7)**	**56**	**(10.0)**	**116**	**(9.9)**
Acute kidney injury	32	(5.4)	23	(3.7)	30	(5.4)	53	(4.5)
Azotaemia	1	(0.2)	0	(0.0)	1	(0.2)	1	(0.1)
Nephropathy toxic	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Oliguria	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Renal failure	17	(2.8)	14	(2.3)	11	(2.0)	25	(2.1)
Renal impairment	18	(3.0)	28	(4.5)	17	(3.0)	45	(3.8)

Table 60 Subjects With Renal-related Adverse Events by SOC and PT
All Subjects as Treated in Subjects With Baseline eGFR 45 to <60 mL/min/1.73 m²

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	439		465		413		878	
with one or more adverse events	36	(8.2)	41	(8.8)	33	(8.0)	74	(8.4)
with no adverse events	403	(91.8)	424	(91.2)	380	(92.0)	804	(91.6)
Renal and urinary disorders	**36**	**(8.2)**	**41**	**(8.8)**	**33**	**(8.0)**	**74**	**(8.4)**
Acute kidney injury	20	(4.6)	16	(3.4)	16	(3.9)	32	(3.6)
Nephropathy toxic	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Oliguria	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Renal failure	11	(2.5)	4	(0.9)	8	(1.9)	12	(1.4)
Renal impairment	11	(2.5)	22	(4.7)	11	(2.7)	33	(3.8)

Table 61 Subjects With Renal-related Adverse Events by SOC and PT
All Subjects as Treated in Subjects With Baseline eGFR 30 to <45 mL/min/1.73 m²

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	158		152		147		299	
with one or more adverse events	25	(15.8)	19	(12.5)	23	(15.6)	42	(14.0)
with no adverse events	133	(84.2)	133	(87.5)	124	(84.4)	257	(86.0)
Renal and urinary disorders	**25**	**(15.8)**	**19**	**(12.5)**	**23**	**(15.6)**	**42**	**(14.0)**
Acute kidney injury	12	(7.6)	7	(4.6)	14	(9.5)	21	(7.0)
Azotaemia	1	(0.6)	0	(0.0)	1	(0.7)	1	(0.3)
Renal failure	6	(3.8)	10	(6.6)	3	(2.0)	13	(4.3)
Renal impairment	7	(4.4)	6	(3.9)	6	(4.1)	12	(4.0)

Safety related to drug-drug interactions and other interactions

Drug interactions were not investigated in this study.

Discontinuation due to adverse events

The incidences of AEs leading to discontinuation of study medication are presented in Table 62.

Table 62 Subjects with Adverse Events Resulting in Discontinuation From Study Medication Incidence >0.1% of Subjects in One or More Treatment Groups All Subjects as Treated

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg	
	n	(%)	n	(%)	n	(%)
Subjects in population	2,745		2,746		2,747	
with one or more adverse events resulting in discontinuation from study medication	188	(6.8)	207	(7.5)	201	(7.3)
with no adverse events resulting in discontinuation from study medication	2,557	(93.2)	2,539	(92.5)	2,546	(92.7)
Cardiac disorders	**26**	**(0.9)**	**13**	**(0.5)**	**15**	**(0.5)**
Acute myocardial infarction	3	(0.1)	2	(0.1)	5	(0.2)
Gastrointestinal disorders	**19**	**(0.7)**	**11**	**(0.4)**	**21**	**(0.8)**
Diarrhoea	6	(0.2)	1	(0.0)	2	(0.1)
Nausea	2	(0.1)	1	(0.0)	6	(0.2)
General disorders and administration site conditions	**10**	**(0.4)**	**12**	**(0.4)**	**10**	**(0.4)**
Fatigue	3	(0.1)	5	(0.2)	2	(0.1)
Infections and infestations	**14**	**(0.5)**	**29**	**(1.1)**	**26**	**(0.9)**
Urinary tract infection	4	(0.1)	2	(0.1)	6	(0.2)
Injury, poisoning and procedural complications	**4**	**(0.1)**	**8**	**(0.3)**	**2**	**(0.1)**
Investigations	**9**	**(0.3)**	**9**	**(0.3)**	**9**	**(0.3)**
Metabolism and nutrition disorders	**4**	**(0.1)**	**9**	**(0.3)**	**13**	**(0.5)**
Musculoskeletal and connective tissue disorders	**8**	**(0.3)**	**6**	**(0.2)**	**8**	**(0.3)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**26**	**(0.9)**	**29**	**(1.1)**	**32**	**(1.2)**
Nervous system disorders	**25**	**(0.9)**	**28**	**(1.0)**	**21**	**(0.8)**
Dizziness	1	(0.0)	11	(0.4)	4	(0.1)
Ischaemic stroke	6	(0.2)	2	(0.1)	2	(0.1)
Renal and urinary disorders	**25**	**(0.9)**	**26**	**(0.9)**	**22**	**(0.8)**
Polyuria	2	(0.1)	6	(0.2)	0	(0.0)

Reproductive system and breast disorders	**2**	**(0.1)**	**13**	**(0.5)**	**8**	**(0.3)**
Vulvovaginal pruritus	1	(0.0)	4	(0.1)	5	(0.2)
Skin and subcutaneous tissue disorders	**10**	**(0.4)**	**5**	**(0.2)**	**8**	**(0.3)**

Use in pregnancy and lactation

Pregnant or nursing women were excluded from this study. Women of childbearing potential were to undergo pregnancy testing and to use an acceptable method of contraception during the study. Nonetheless, if a woman became pregnant, study medication was to be stopped and pregnancy was to be followed up until birth or termination of the pregnancy. There was 1 pregnancy reported during the study (ertugliflozin 5 mg group) that resulted in the birth of a healthy infant.

Overdose

In a few instances, subjects reported taking doses other than the protocol-specified doses of study medication. No overdoses were associated with an AE.

Drug Abuse

Drug abuse and dependence potential of ertugliflozin has not been characterized. Based on the mechanism of action and current post-marketing experience, ertugliflozin is unlikely demonstrate abuse potential.

Post marketing experience

Ertugliflozin

Over the cumulative interval from market introduction to 31-MAY-2020, the Sponsor has received 620 post-marketing AE reports containing 1,009 AEs (901 nonserious, 108 serious) involving patients treated with ertugliflozin. The SOCs in which AEs were most commonly reported were General disorders and administration site conditions, Infections and Infestations, and Gastrointestinal disorders.

Of the 108 SAEs reported in patients treated with ertugliflozin, the most commonly reported PTs were diabetic ketoacidosis (11 SAEs), acute kidney injury (4 SAEs), and urinary tract infection (4 SAEs). Of the 11 diabetic ketoacidosis events, ertugliflozin was withdrawn in 9 cases and action taken was unknown with 2 patients. The outcome for 8 of the 11 patients was recovered or recovering from the event, 1 patient did not recover at the time of the report and the outcome was unknown in 2 patients. Diabetic ketoacidosis is a listed AE in the ertugliflozin label. Review of these post-marketing safety reports did not reveal any new safety findings.

Ertugliflozin/metformin FDC

Over the cumulative interval from market introduction to 31-MAY-2020, the Sponsor has received 59 post-marketing AE reports containing 101 AEs (77 nonserious, 24 serious) involving patients treated with ertugliflozin/metformin FDC. The SOCs in which AEs were most commonly reported were Gastrointestinal disorders, Injury, poisonings and procedural complications, and General disorders and administration site conditions.

Of the 24 SAEs reported in patients treated with ertugliflozin/metformin, the most commonly reported PTs were diabetic ketoacidosis (3 SAEs), adverse event (2 SAEs), and dry mouth (2 SAEs). Review of these post-marketing safety reports did not reveal any new safety findings.

3.5.1. Discussion on clinical safety

The established safety profile of ertugliflozin is based on the original ertugliflozin application submitted for treatment of T2DM. The current safety evaluation is based on data from the completed VERTIS CV study. The target population were patients with T2DM and established CV disease.

In the VERTIS CV study, 5,493 subjects were treated with ertugliflozin, with 5,323 subjects (97%) for at least 52 weeks, 5173 subjects (94%) for at least 2 years, 2,839 subjects (52%) for at least 3 years and 2,339 subjects (43%) for at least 4 years. The mean duration of exposure on treatment was about 153 weeks for ertugliflozin 147 weeks for placebo. The mean duration on study was 182 weeks for ertugliflozin and placebo, respectively.

The incidences of SAEs were similar across the treatment groups; 35%, 34% and 36% for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, respectively. The most frequently reported SAEs for were in the SOC Cardiac disorders (13.2% and 14.0% vs 15.8% for ertugliflozin 5 mg and 15 mg vs placebo), e.g. acute myocardial infarction/ myocardial infarction, cardiac arrest and angina unstable. There were slightly more fatal cases in the ertugliflozin groups (4.8% and 4.9%) compared with the placebo group (4.3%).

The most frequently reported AEs with an outcome of death were within the SOC Cardiac disorders (e.g. cardiac arrest, myocardial infarction) and the SOC General disorders (PT death).

Discontinuation rates due to AE were slightly higher for ertugliflozin 5 mg and 15 mg (7.5% and 7.3%) compared to placebo (6.8%). The most frequently reported AEs leading to study drug discontinuation was dizziness; 0.4% and 0.1% vs <0.1% for ertugliflozin 5 mg and 15 mg vs placebo.

Urinary tract infections

The incidence of UTIs was slightly higher for ertugliflozin 5 mg (12.2%) and 15 mg (12.0%) compared to placebo (10.2%). The incidence of SAEs of UTIs was low across the treatment groups (1.5%, 0.7% and 1.1% for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo).

Genital infections

The incidence of genital infections was dose-dependently increased in females (4.4% and 5.1% vs 1.2%) and males (6.0% and 7.8% vs 2.4%) for ertugliflozin 5 mg and 15 mg as compared to placebo. Phimosis was reported in 33 cases (0.9%) for ertugliflozin compared with 2 cases (0.1%) for placebo.

Volume depletion

The incidence of AEs of volume depletion was similar for ertugliflozin 5 mg and 15 mg (4.3%) compared with placebo (3.8%).

Renal function

In the VERTIS CV study, treatment with ertugliflozin was associated with an initial decrease in eGFR which returned towards baseline. However, at 60 months of treatment, the mean changes in eGFR from baseline was smaller for ertugliflozin 5 mg and 15 mg groups (-2.4 and -2.9 mL/min/1.73 m^2, respectively) compared with the placebo (-6.8 mL/min/1.73 m^2).

The incidence of renal-related adverse events was similar for ertugliflozin 5 mg and 15 mg (4.2% and 4.3%) compared to placebo (4.7%).

Fractures

The incidences of adjudication-confirmed fractures were similar for ertugliflozin 5 mg (3.6%), 15 mg (3.7%) and placebo (3.6%). In the subgroup of patients with eGFR 30 to <45 mL/min/1.73 m^2, the

incidence of fractures was increased for ertugliflozin 5 mg (3.9%) and 15 mg (6.8%) compared with placebo (1.6%).

Amputations

In the VERTIS CV study, subjects with events of non-traumatic lower limb amputation were reported with an incidence of 2.0% (0.57 subjects with event/100 PY), 2.1% (0.60 subjects with event/100 PY) and 1.6% (0.47 subjects with event/100 PY) for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo groups. The event rate of lower limb amputations was 0.75 and 0.96 vs 0.74 events per 100 PY for ertugliflozin 5 mg and ertugliflozin 15 mg vs placebo. The proposed wording on lower limb amputations in the SmPC (section 4.4) has been adequately updated with the event rates**.**

Diabetic ketoacidosis

The incidence of DKA/ketoacidosis was higher for all ertugliflozin group (0.3%; n=19) compared to placebo (0.1%; n=2), corresponding to an incidence rate of 0.10 and 0.02 subjects per 100 PY for all ertugliflozin and placebo. Six of the 21 confirmed cases of ketoacidosis were classified as non-serious (1 in the placebo group and 5 in the ertugliflozin group). Three of these six non-serious cases were adjudicated as 'possible', 2 as 'probable,' and one as 'certain' cases of ketoacidosis.

Hypoglycaemic events

The incidence of documented hypoglycaemia was high and similar across the treatment groups (45% and 44% vs 44%). In the sub-study when ertugliflozin was added to insulin with or without metformin, the incidences of documented hypoglycaemia were similar across treatment groups (39% and 39% vs 38%). When ertugliflozin was added to SU, the incidences were, 7.3%, 9.3% and 4.2% for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, respectively. When ertugliflozin was added to metformin with SU, the incidences of hypoglycaemia were 20%, 26% and 14% for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, respectively.

Pancreatitis

The numbers of subjects with adjudication-confirmed pancreatitis events were low and similar in the ertugliflozin 5 mg (0.4%), 15 mg (0.2%), and placebo (0.4%) groups.

Hepatic events

The proportion of subjects with increases in ALT or AST that met a PDLC >3X ULN or PDLC >20X ULN were low (0.1-0.2% across all groups). No ertugliflozin-treated subject experienced hepatic events that were adjudicated as very likely or probably related to study medication.

Hypersensitivity

The incidences of potential hypersensitivity events were similar in the ertugliflozin 5 mg (4.4%), 15 mg (5.2%), and placebo groups (4.4%). The incidences of serious potential hypersensitivity AEs were low and similar in the ertugliflozin 5 mg (0.3%), 15 mg (0.3%), and placebo groups (0.4%).

Malignancy

The overall incidences of malignancies were similar in the ertugliflozin 5 mg (5.9%), 15 mg (5.5%), and placebo (5.5%) groups. However, the incidences of AEs in the HLGT of Renal and urinary tract neoplasms malignant and unspecified (predominantly bladder and renal cancers) were higher in the ertugliflozin groups compared with the placebo group (0.7% and 0.7% vs 0.3% for ertugliflozin 5 mg and 15 mg vs placebo). The results were similar in subjects treated for >6 months and with onset >6 months after first dose of study medication (0.6% and 0.6% vs 0.3% for ertugliflozin 5 mg and 15 mg vs placebo).

Venous thromboembolism

The incidences of adjudication-confirmed venous thromboembolism events were low (<1%) and similar across the ertugliflozin and placebo groups.

Fournier's gangrene

No event of Fournier's gangrene was identified. There were 4 subjects with AEs of skin necrosis or gas gangrene, 2 in the ertugliflozin 15 mg group and 2 in the placebo group. The AEs for all 4 subjects involved the lower limb.

Laboratory findings

Results of laboratory findings were in general consistent with the results reported in the original application for ertugliflozin.

Subgroups

Effect by age

In the VERTIS CV study, 903 subjects (about 11%) were above 75 years of age. Overall, the incidence of AEs and SAEs were higher for subjects with ≥75 than <75 years of age. In both subjects ≥75 and <75 years of age, the incidence of genital infections and UTIs was higher for ertugliflozin than for placebo. The incidence of volume depletion was higher for ertugliflozin than for placebo in subjects ≥75 years of age and was balanced for subjects <75 years. The incidence of renal events was slightly higher for ertugliflozin tan for placebo in subjects ≥75 years; however, was higher for placebo than for ertugliflozin in subjects <75 years.

Effect NYHA class

In total 1,289 subjects (16%) with NYHA class II and 139 subjects (1.7%) with NYHA class III were included in the VERTIS CV study. SAEs and deaths were more frequent in patients with HF, with the highest frequencies observed in patients in NYHA class III. In the NYHA class II subgroup, the incidences of SAEs, volume depletion and renal events were in line with the overall population. In the NYHA class III group, the incidence of renal events (3.6% and 10.9% vs 2.7%) was dos-dependently higher for ertugliflozin than for placebo. Four of the 5 cases with renal AEs in the 15 mg ertugliflozin group, were secondary to non-renal events (infectious and cardiac causes). The remaining case reported acute renal failure and was assessed as non-serious and mild in intensity. Moreover, in one of the two cases in the 5 mg ertugliflozin group and in the only case in the placebo group, the renal events were secondary caused by infections.

Of note in the NYHA class III, a higher incidence of atrial fibrillation ertugliflozin (9.8% vs 0%) and hypoglycaemia (30% vs 19%) was observed for ertugliflozin compared to placebo. However, none of the cases of atrial fibrillation for ertugliflozin were assessed as related by the Investigator, only 3 cases were serious, and all cases had risk factors in the medical history. In analyses of symptomatic and documented hypoglycaemia through week 18, excluding post-rescue data, the incidences of hypoglycaemia were similar for ertugliflozin and placebo in the subgroup with NYHA class III.

Effect by renal function

A total of 1,776 (22%) subjects had Stage 3 CKD, of which 1,319 subjects had Stage 3A CKD (baseline eGFR 45 to <60 mL/min/1.73 m^2), and 457 subjects had Stage 3B CKD (baseline eGFR 30 to <45 mL/min/1.73 m^2).

The incidence of SAEs was slightly higher in subjects with eGFR 30 to <45 mL/min/1.73m^2 (44.1% vs 44.3%) than in subjects with eGFR 45 to <60 mL/min/1.73m^2 (39.0% vs 41.0%); however, the SAE incidence rate was similar for all ertugliflozin and placebo in both subgroups.

The incidence rate of AEs leading to discontinuation was higher for all ertugliflozin (9.7%) than for placebo (6.6%) in subjects with eGFR 45 to <60 mL/min/1.73m^2; however, were higher for placebo (13.9%) than for all ertugliflozin (11.7%) in subjects with eGFR 30 to <45 mL/min/1.73m^2.

The safety profile in stage 3 CKD subgroup was in general consistent with the overall population. Overall, there was no major differences in the incidences of UTIs, genital infections and hypoglycaemia in the subgroup of moderate renal impairment compared to the overall population. The incidence of volume depletion was overall increased, compared with the overall population; although, similar across the treatment arms.

However, in the subgroup of patients with eGFR 30 to <45 mL/min/1.73 m^2, the incidence of fractures was increased for ertugliflozin 5 mg (3.9%) and 15 mg (6.8%) compared with placebo (1.6%). Moreover, the frequency of renal events was higher in the stage 3B CKD stratum (12.5% and 15.6% vs 15.8%) across all treatment groups, compared with the stage 3A CKD population (8.8% and 8.0% vs 8.2%) and the overall population. This is expected and considered related to the underlying renal disease in the 3B CKD subgroup. In the CKD stage 3 subgroup, the eGFR for ertugliflozin returned to baseline and remained near or above baseline to the end of the study. In the CKD 1 and 2 subgroups, the eGFR returned towards baseline but remined below baseline throughout the study. Initially (0-6 weeks), the rate of decrease in eGFR was faster in the CKD stage 1 subgroup and slower in the CKD stage 3 subgroup (both for ertugliflozin and placebo). The difference may be due to higher eGFR in patients with CKD stage 1 and 2 and a low degree of proteinuria in the CKD stage 3 population. In VERTIS CV, most patients (60%) were within the normal range of albuminuria at baseline. Micro-albuminuria (≥ 30 to ≤ 300 mg/g) was present in 30.2% of the subjects and macro-albuminuria (>300 mg/g) in 9.2%. The median baseline UACR in CKD stage 3 patients were 31 (8-117) and 30 (8-136) mg/g for placebo and ertugliflozin, respectively. Similar patterns of eGFR changes over time in subjects with eGFR <60 mL/min have been observed in the CVOT for other SGLT2 inhibitors, which also has been performed in subjects with relatively low levels of proteinuria and at lower risk of kidney events.

3.5.2. Conclusions on clinical safety

The safety profile in patients with T2DM and established CV disease seems to be rather similar to the one previously documented for ertugliflozin.

The safety profile in subjects with moderate renal impairment was in general consistent with the overall population. Overall, there was no major differences in the incidences of UTIs, genital infections and hypoglycaemia in the subgroup of moderate renal impairment compared to the overall population. The incidence of volume depletion was overall increased, compared with the overall population, although similar across the treatment arms.

However, in the subgroup of patients with eGFR 30 to <45 mL/min/1.73 m^2, the incidence of fractures was increased for ertugliflozin compared with placebo. Moreover, the frequency of renal events was higher in the stage 3B CKD stratum (eGFR 30-45) across all treatment groups, compared with the stage 3A CKD population (eGFR 45-60). This is expected and considered related to the underlying renal disease in the 3B CKD subgroup.

The study included a substantial number of elderly subjects (≥75 years of age) with no indication of a different safety profile, supporting the proposed changes to the SmPC for this population.

In the NYHA class II, a relevant number of patients was included. The incidences of SAEs, volume depletion and renal events in the NYHA class II were in line with the overall population. In the NYHA class III subgroup, the incidence of renal events was dos-dependently increased for ertugliflozin compared with placebo but most of the cases with renal AEs were secondary to non-renal events (infectious and cardiac

causes). Data provided does not raise any safety concern with the use of ertugliflozin in patients with HF NYHA class III. However, data in NYHA class III should be interpreted with caution due to a limited number of patients (n=139).

3.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

4. Risk management plan

The WSA submitted an updated RMP version with this application, version 2. The (main) proposed RMP changes were the following:

- completion of VERTIS-CV trial for ertugliflozin
- to align with the new GVP Module V (Rev.2) guidance

Summary of significant changes in this RMP:

RMP section	Update information
Part II: Module SIII – clinical trial exposure	Updated patient exposure data
Part II: Module SIV – Population not studied in clinical trials	Updated with results of VERTIS-CV
Part II: Module SV – Post-authorisation experience	Updated patient exposure data
Part II: Module SVII.2 – New safety concerns and reclassification with a submission of an updated RMP	Proposed removal of safety concerns with rationale for exclusion to incorporate the VERTIS-CV results and per GVP Module V (rev. 2) guidance
Part II: Module SVII.3.1 Presentation of Important identified risks and important potential risks	Updated to incorporate the VERTIS-CV results and to align with GVP Module V (rev. 2) guidance
Part II: Module SVIII – summary of the safety concerns	Removed/reclassified safety concerns to incorporate the results of VERTIS-CV and align with GVP Module V (Rev 2) guidance
Part III: Module III.1 Routine Pharmacovigilance activities	Removed/reclassified safety concerns to incorporate the results of VERTIS-CV and align with GVP Module V (Rev 2) guidance
Part III: Module III.2 Additional Pharmacovigilance activities	Removed/reclassified safety concerns to incorporate the results of VERTIS-CV and align with GVP Module V (Rev 2) guidance.
Part III: Module III.3 Summary table of additional pharmacovigilance activities	Removed/reclassified safety concerns to incorporate the results of VERTIS-CV and align with GVP Module V (Rev 2) guidance.

Part V: Module V.1 Routine Risk minimisation measures	Removed/reclassified safety concerns to incorporate the results of VERTIS-CV and align with GVP Module V (Rev 2) guidance.
Part V: Module V.2 Additional Risk minimisation measures	Removed/reclassified safety concerns to incorporate the results of VERTIS-CV and align with GVP Module V (Rev 2) guidance.
Part V: Module V.3 Summary of Risk minimisation measures	Removed/reclassified safety concerns to incorporate the results of VERTIS-CV and align with GVP Module V (Rev 2) guidance.
Part VI: Module II.A list of important risks and missing information	Removed/reclassified safety concerns to incorporate the results of VERTIS-CV and align with GVP Module V (Rev 2) guidance.
Part VI: Module II.B summary of important risks	Removed/reclassified safety concerns to incorporate the results of VERTIS-CV and align with GVP Module V (Rev 2) guidance.

The RMP version 2.0 is approvable.

4.1. Overall conclusion on the RMP

☒The changes to the RMP are acceptable.

5. Changes to the Product Information

As a result of this variation, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are being updated to reflect the data from the CV outcome study. The Package Leaflet (PL) is updated accordingly.

In addition, corrections have been made in the list of local representatives in the PL.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

5.1.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the WSA and has been considered acceptable for the following reasons:

The changes to the package leaflet are minimal and do not require user consultation with target patient groups.

6. Benefit-Risk Balance

6.1. Therapeutic Context

6.1.1. Disease or condition

Based on the submitted data on CV safety, the MAH wish to extend the indication for Steglatro and Segluromet as follows:

"Steglatro is indicated for the treatment of ~~in~~ adults ~~aged 18 years and older~~ with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise ~~to improve glycaemic control~~:

- as monotherapy ~~in patients for whom the use of~~ when metformin is considered inappropriate due to intolerance or contraindications.
- in addition to other medicinal products for the treatment of diabetes.

~~(~~For study results with respect to combinations of therapies, ~~and~~ effects on glycaemic control, cardiovascular events, and the populations studied, see sections 4.4, 4.5, and 5.1.~~)~~"

"Segluromet is indicated in adults for the treatment of ~~aged 18 years and older with~~ type 2 diabetes mellitus as an adjunct to diet and exercise ~~to improve glycaemic control~~:

- in patients ~~not adequately~~ insufficiently controlled on their maximally tolerated dose of metformin alone
- in combination with ~~in patients on their maximally tolerated doses of metformin in addition to~~ other medicinal products for the treatment of diabetes in patients insufficiently controlled with metformin and these products
- in patients already being treated with the combination of ertugliflozin and metformin as separate tablets.

~~(~~For study results with respect to combinations of therapies, ~~and~~ effects on glycaemic control, cardiovascular events and the population studied, see sections 4.4, 4.5 and 5.1.~~)~~

6.1.2. Available therapies and unmet medical need

Patients with diabetes are at high risk for adverse outcomes from ASCVD, HF, and CKD. Patients with T2DM have a 2- to 4- fold increased risk of CV disease relative to those without T2DM, and CV disease is the leading cause of death and complications in patients with T2DM.

In large outcome studies, members of the SGLT2 inhibitor class have been shown to reduce the risk of CV and renal outcomes in subjects with and without T2DM. A consistent finding in all of these studies is a robust effect of SGLT2 inhibitor treatment on reducing the risk of HHF. Preservation of renal function has also been a consistent finding in these studies.

Current diabetes and cardiovascular society guidelines have been significantly impacted by the results of these outcome studies. The 2020 American Diabetes Association Standards of Care recommends that if ASCVD predominates, a GLP-1 receptor agonist or an SGLT2 inhibitor with proven CV disease benefit, if eGFR is adequate, should be used for the treatment of patients with T2DM. However, if HF and/or CKD predominates, the use of a SGLT2 inhibitor with proven benefit in reducing HF and/or CKD progression, if

eGFR is adequate, should be used (if tolerated).

6.1.3. Main clinical study

The VERTIS CV study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, event-driven study. This study was intended to address two overarching objectives: the first focused on CV safety (non-inferiority) and the second focused on CV and renal efficacy (superiority).

The study evaluated two doses of ertugliflozin, 5 mg and 15 mg qd, compared to placebo. The primary endpoint, MACE, was evaluated using the pooled data from the two active treatment arms.

In addition, three glycaemic sub-studies of 18 weeks duration in subjects receiving specific background anti-hyperglycaemic treatments were included to evaluate the efficacy of ertugliflozin in combinations not previously studied: 1) insulin with or without metformin, 2) SU monotherapy and 3) metformin and SU.

In total 8,246 patients were randomised in the study with 2,752 subjects in the ertugliflozin 5 mg group, 2,747 in the ertugliflozin 15 mg group, and 2,747 subjects in the placebo group. The mean duration on study was 3.5 years. The study population is considered representative of the target population of T2DM patients at high CV risk, and 76% of the patients were on concomitant treatment with metformin.

In a pre-specified analysis, the efficacy of ertugliflozin was evaluated in patients with Stage 3 CKD. In the VERTIS CV study, 21.5% of the subjects (1 776 patients) had an eGFR 30 – 60 mL/min/1.73 m^2 at baseline (Stage 3 CKD).

6.2. Favourable effects

The study met its primary endpoint as non-inferiority for MACE was shown for the "All ertugliflozin" group (HR 0.97; 95% CI: 0.848, 1.114). Non-inferiority was also shown for each of the two doses (5 mg and 15 mg) but it is noted that the HR for the higher dose was 1.04 compared to 0.91 for the lower dose. No meaningful differences were observed for the components of MACE compared to placebo. The Kaplan-Meier curves separated slightly after about 6 months but converged again after about three years.

A post-hoc analysis was conducted, where the CV death component of MACE was replaced by "All-cause death", which showed a comparable HR (0.97; 95% CI: 0.867 to 1.093) as for the primary analysis.

The subgroup analysis generally showed consistent findings across the subgroups. Although point estimates for the HR varied somewhat, the 95% CI was within the non-inferiority margin also for all large subgroups.

Superiority could not be demonstrated for the key secondary endpoint "CV death or HHF" (HR 0.88; 95% CI: 0.750, 1.034). The outcome was comparable when "CV death" was exchanged by "All-cause death or HHF" (HR: 0.90; 95.8% CI; 0.776 to 1.032). The findings were generally consistent across subgroups. The secondary endpoint "total CV death/HHF events" (i.e. not censored at the time of the first event), showed a reduction in the total number of events (HR 0.82 95% CI 0.716, 0.945).

"CV death" was analysed separately as a secondary endpoint. There was no noticeable difference between treatment groups (HR 0.92; 95% CI: 0.767, 1.113).

A comparable outcome was observed for the secondary endpoint "All-cause death" (HR: 0.93; 95% CI, 0.797 to 1.081).

The secondary endpoint "time to first HHF" was not subject to hypothesis testing but the analysis showed a 30% reduction of the risk with a CI excluding 1 (HR 0.70; 95% CI:0.539, 0.902). Comparable outcomes were observed for both doses (HR 0.71 and 0.68 for the 5 mg and 15 mg dose, respectively).

The Kaplan-Meier curves separated early and the separation continued for the duration of the study. The data was further supported by the analysis of recurrent HF hospital admissions and mortality in subjects with a first HHF event, which was lower in the ertugliflozin treated groups compared to placebo.

Other CV efficacy endpoints analyzed in VERTIS CV were time to first MACE+, fatal or non-fatal MI, fatal or non-fatal stroke and HHF. Apart from a reduction of the risk of HHF, no differences were observed between the ertugliflozin treated groups and placebo.

Composite of renal events

No formal hypothesis testing of the composite of renal events (renal death, renal dialysis/transplant, or doubling of serum creatinine from baseline) was performed, but it is noted that the 19% reduction of events in the ertugliflozin treated groups was not statistically significant since the CI includes 1 (HR 0.81; 95% CI: 0.630, 1.036). The Kaplan-Meier curve show a separation of the curves over time. The outcome is mainly driven by the effect on serum creatinine, whereas other components of the composite endpoint were rare and balanced between groups.

Glycaemic control and cardiometabolic endpoints

In the study, beneficial effects on HbA1c, body weight and blood pressure were observed with ertugliflozin treatment. The changes observed at week 18, after which the anti-hyperglycaemic treatment could be adjusted, were of comparable magnitude as observed in previous clinical studies with ertugliflozin.

Use in patients with renal impairment

In the overall Stage 3 CKD population, ertugliflozin treatment resulted in a modest decrease in HbA1c of 0.27% (5 mg dose) and 0.28% (15 mg dose), in line with the data from the dedicated study in patients with Stage 3 CKD assessed in the MAA. In contrast to the previous study, no increase is observed with increasing dose. The calculated odds of achieving HbA1c <7.0% was higher with ertugliflozin (20.7% and 17.0% for the 5 mg and 15 mg dose, respectively) compared to placebo (12.9%), but still modest. Statistically significant reductions of FPG were observed for both doses.

Comparable results were observed for the Stage 3A CKD subgroup (GFR 45-60), where a reduction of 0.27% (5 mg dose) and 0.31% (15 mg dose) was observed, whereas the effect on HbA1c was further attenuated in the subgroup with Stage 3B CKD subgroup (GFR 30-45) with no statistically significant difference observed with the 15 mg dose compared to placebo.

Descriptive data show that eGFR was maintained in patients with CKD stage 3a and 3b during ertugliflozin treatment. The relative risk reduction in the time to first HHF appears to be preserved in patients with baseline eGFR <60 mL/min/1.73 m^2 (HR 0.50 (95% CI; 0.33, 0.76)). The effects of ertugliflozin on SBP and body weight were largely comparable for patients with CKD3 compared to the overall population. The effect on glycaemic control in patients with eGFR 30-45 was attenuated (about -0.2% to -0.3%, placebo adjusted).

Glycaemic sub-studies

Add-on to insulin with or without metformin

When added to a background therapy of insulin with or without metformin, ertugliflozin resulted in a statistically significant decrease in HbA1c of -0.58% with the 5 mg dose and -0.65% with the 15 mg dose (placebo-adjusted). Statistically significant decreases in FPG were also observed and the proportion of patients achieving the target of HbA1c <7.0% were twice as high (20.7% and 21.1% for ertugliflozin 5 mg and 15 mg respectively, vs 10.7% for placebo). A placebo-adjusted decrease in body weight of -1.62 kg (5 mg dose) and -1.88 kg (15 mg dose) was also observed. A statistically significant reduction of SBP vs placebo was observed whereas the decrease in DBP did not reach statistical significance.

Add-on to SU monotherapy

No statistically significant effect could be demonstrated when ertugliflozin was given as add-on to monotherapy with SU. The placebo-adjusted change in HbA1c was -0.35% with the 5 mg dose and -0.22% with the 15 mg dose. The effect on body weight was also modest (placebo-adjusted: -1.07 kg and -0.52 kg for the 5 mg and 15 mg dose, respectively), and SBP and DBP increased compared to placebo.

Add-on to metformin and SU

When added to metformin and SU, ertugliflozin resulted in a statistically significant decrease in HbA1c of -0.66% with the 5 mg dose and -0.75% with the 15 mg dose (placebo-adjusted). Statistically significant decreases in FPG were also observed and the proportion of patients achieving the target of HbA1c <7.0% were almost three times as high (37.0% and 32.7% for ertugliflozin 5 mg and 15 mg respectively, vs 12.8% for placebo). A placebo-adjusted decrease in body weight of -1.57 kg (5 mg dose) and -1.94 kg (15 mg dose) was also observed. Only modest reductions of SBP and DBP vs placebo were observed, none of which reached statistical significance.

6.3. Uncertainties and limitations about favourable effects

The MAH proposes to lower the limit for initiation of ertugliflozin treatment to eGFR 45 mL/min/1.73 m^2 and to allow treatment down to an eGFR of 30 mL/min/1.73 m^2. The new data provided indicate that there may be beneficial effects on renal function, HHF, SBP and body weight in patients with eGFR 30-60 mL/min/1.73 m^2. The outcomes with regards to beneficial effects on renal function and HHF in the overall population could not be formally tested for statistical significance, but the observed outcomes are in line with those reported for other SGLT2i and possibly reflects a class effect.

Results from the post-hoc subgroup analyses from other SGLT2i suggest a reduced CV and renal benefit in those patients without albuminuria (and thus the largest benefits in patients with macro-albuminuria) at baseline, as shown in CANVAS (CV trial) and DECLARE-TIMI (only renal (currently) available), although such results are hampered by the limited data available.

6.4. Unfavourable effects

The current safety evaluation is based on data from the completed VERTIS CV study. The target population were patients with T2DM and established CV disease.

In the VERTIS CV study, 5,493 subjects were treated with ertugliflozin, with 5,323 subjects (97%) for at least 52 weeks, 5173 subjects (94%) for at least 2 years, 2,839 subjects (52%) for at least 3 years and 2,339 subjects (43%) for at least 4 years. The mean duration of exposure on treatment was about 153 weeks for ertugliflozin 147 weeks for placebo. The mean duration on study was 182 weeks for ertugliflozin and placebo, respectively.

The incidences of SAEs were similar across the treatment groups; 35%, 34% and 36% for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, respectively. The most frequently reported SAEs for were in the SOC Cardiac disorders (13.2% and 14.0% vs 15.8% for ertugliflozin 5 mg and 15 mg vs placebo).

Discontinuation rates due to AE were slightly higher for ertugliflozin 5 mg and 15 mg (7.5% and 7.3%) compared to placebo (6.8%). The most frequently reported AEs leading to study drug discontinuation was dizziness; 0.4% and 0.1% vs <0.1% for ertugliflozin 5 mg and 15 mg vs placebo.

Urinary tract infections

UTIs was reported slightly more often for ertugliflozin 5 mg (12.2%) and 15 mg (12.0%) than for placebo (10.2%).

Genital infections

The incidence of genital infections was dose-dependently increased in females (4.4% and 5.1% vs 1.2%) and males (6.0% and 7.8% vs 2.4%) for ertugliflozin 5 mg and 15 mg as compared to placebo.

Volume depletion

The incidence of AEs of volume depletion was similar for ertugliflozin 5 mg and 15 mg (4.3%) compared with placebo (3.8%).

Renal function

Treatment with ertugliflozin was associated with an initial decrease in eGFR which returned towards baseline. However, at 60 months of treatment, the mean changes in eGFR from baseline was smaller for ertugliflozin 5 mg and 15 mg groups (-2.4 and -2.9 mL/min/1.73 m^2, respectively) compared with the placebo (-6.8 mL/min/1.73 m^2).

The incidence of renal-related adverse events was similar for ertugliflozin 5 mg and 15 mg (4.2% and 4.3%) compared to placebo (4.7%).

Fractures

The incidences of adjudication-confirmed fractures were similar for ertugliflozin 5 mg (3.6%), 15 mg (3.7%) and placebo (3.6%).

Amputations

Subjects with events of non-traumatic lower limb amputation were reported with an incidence of 2.0% (0.57 subjects with event/100 PY), 2.1% (0.60 subjects with event/100 PY) and 1.6% (0.47 subjects with event/100 PY) for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo groups. The event rate of lower limb amputations was 0.75 and 0.96 vs 0.74 events per 100 PY for ertugliflozin 5 mg and ertugliflozin 15 mg vs placebo. The proposed wording on lower limb amputations in the SmPC has been adequately updated with the event rates.

Diabetic ketoacidosis

The incidence of DKA/ketoacidosis was higher for all ertugliflozin group (0.3%; n=19) compared to placebo (0.1%; n=2), corresponding to an incidence rate of 0.10 and 0.02 subjects per 100 PY for all ertugliflozin and placebo.

Hypoglycaemic events

The incidence of documented hypoglycaemia was high and similar across the treatment groups (45% and 44% vs 44%). In the sub-study when ertugliflozin was added to insulin with or without metformin, the incidences of documented hypoglycaemia were similar across treatment groups (39% and 39% vs 38%). When ertugliflozin was added to SU, the incidences were, 7.3%, 9.3% and 4.2% for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, respectively. When ertugliflozin was added to metformin with SU, the incidences of hypoglycaemia were 20%, 26% and 14% for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, respectively.

Pancreatitis

The numbers of subjects with adjudication-confirmed pancreatitis events were low and similar in the ertugliflozin 5 mg (0.4%), 15 mg (0.2%), and placebo (0.4%) groups.

Hepatic events

The proportion of subjects with increases in ALT or AST that met a PDLC >3X ULN or PDLC >20X ULN were low (0.1-0.2% across all groups). No ertugliflozin-treated subject experienced hepatic events that were adjudicated as very likely or probably related to study medication.

Hypersensitivity

The incidences of potential hypersensitivity events were similar in the ertugliflozin 5 mg (4.4%), 15 mg (5.2%), and placebo groups (4.4%). The incidences of serious potential hypersensitivity AEs were low and similar in the ertugliflozin 5 mg (0.3%), 15 mg (0.3%), and placebo groups (0.4%).

Malignancy

The overall incidences of malignancies were similar in the ertugliflozin 5 mg (5.9%), 15 mg (5.5%), and placebo (5.5%) groups.

Venous thromboembolism

The incidences of adjudication-confirmed venous thromboembolism events were low (<1%) and similar across the ertugliflozin and placebo groups.

Fournier's gangrene

No event of Fournier's gangrene was identified. There were 4 subjects with AEs of skin necrosis or gas gangrene, 2 in the ertugliflozin 15 mg group and 2 in the placebo group. The AEs for all 4 subjects involved the lower limb.

Laboratory findings

Results of laboratory findings were in general consistent with the results reported in the original application for ertugliflozin.

Subgroups

Effect by age

In the VERTIS CV study, 903 subjects (about 11%) were above 75 years of age. Overall, the incidence of AEs and SAEs were higher for subjects with ≥75 than <75 years of age. In both subjects ≥75 and <75 years of age, the incidence of genital infections and UTIs was higher for ertugliflozin than for placebo. The incidence of volume depletion was higher for ertugliflozin than for placebo in subjects ≥75 years of age and was balanced for subjects <75 years. The incidence of renal events was slightly higher for ertugliflozin tan for placebo in subjects ≥75 years; however, was higher for placebo than for ertugliflozin in subjects <75 years

Effect NYHA class

In total 1,289 subjects (16%) with NYHA class II and 139 subjects (1.7%) with NYHA class III were included in the VERTIS CV study. SAEs and deaths were more frequent in patients with HF, with the highest frequencies observed in patients in NYHA class III. In the NYHA class II subgroup, the incidences of SAEs, volume depletion and renal events were in line with the overall population. In the NYHA class III group, the incidence of renal events (3.6% and 10.9% vs 2.7%) was dos-dependently higher for

ertugliflozin than for placebo but most of the cases with renal AEs were secondary to non-renal events (infectious and cardiac causes).

Effect by renal function

A total of 1,776 (22%) subjects had Stage 3 CKD, of which 1,319 subjects had Stage 3A CKD (baseline eGFR 45 to <60 mL/min/1.73 m^2), and 457 subjects had Stage 3B CKD (baseline eGFR 30 to <45 mL/min/1.73 m^2).

The incidence of SAEs was slightly higher in subjects with eGFR 30 to <45 mL/min/1.73m^2 (44.1% vs 44.3%) than in subjects with eGFR 45 to <60 mL/min/1.73m^2 (39.0% vs 41.0%); however, the SAE incidence rate was similar for all ertugliflozin and placebo in both subgroups.

The incidence rate of AEs leading to discontinuation was higher for all ertugliflozin (9.7%) than for placebo (6.6%) in subjects with eGFR 45 to <60 mL/min/1.73m^2; however, were higher for placebo (13.9%) than for all ertugliflozin (11.7%) in subjects with eGFR 30 to <45 mL/min/1.73m^2.

The safety profile in stage 3 CKD subgroup was in general consistent with the overall population. Overall, there was no major differences in the incidences of UTIs, genital infections and hypoglycaemia in the subgroup of moderate renal impairment compared to the overall population. The incidence of volume depletion was overall increased, compared with the overall population; although similar across the treatment arms.

However, in the subgroup of patients with eGFR 30 to <45 mL/min/1.73 m^2, the incidence of fractures was increased for ertugliflozin 5 mg (3.9%) and 15 mg (6.8%) compared with placebo (1.6%). Moreover, the frequency of renal events was higher in the stage 3B CKD stratum (12.5% and 15.6% vs 15.8%) across all treatment groups, compared with the stage 3A CKD population (8.8% and 8.0% vs 8.2%) and the overall population. This is expected and considered related to the underlying renal disease in the 3B CKD subgroup.

6.5. Uncertainties and limitations about unfavourable effects

Data provided does not raise any safety concern with the use of ertugliflozin in patients with HF NYHA class II or III. However, data in NYHA class III should be interpreted with caution due to a limited number of patients (n=139).

6.6. Effects Table

Table 1. Effects Table for ertugliflozin CV data (data cut-off: 16 March 2019)

Effect	Short description	Unit	Treatment (ERTU)	Control (Plc)	Uncertainties / Strength of evidence	References
Favourable Effects						
MACE	CV death, non-fatal MI, non-fatal stroke Non-inferiority	rate/ 100 PY	1.76	1.90	HR 0.97 (0.848, 1.114) p < 0.001	VERTIS CV study
CV death or HHF	Superiority	rate/ 100 PY	2.34	2.66	HR 0.88 (0.750, 1.034) n.s.	VERTIS CV study
Renal composite	Renal death, renal dialysis/	rate/ 100	0.93	1.15	HR 0.81 (0.630, 1.036)	VERTIS CV study

Effect	Short description	Unit	Treatment (ERTU)	Control (Plc)	Uncertainties / Strength of evidence	References
	transplant, or doubling of serum creatinine from baseline	PY			n.s.	
Time to First HHF		rate/ 100 PY	0.73	1.05	HR 0.70 (0.539, 0.902) P = 0.006	VERTIS CV study
HbA1c Stage 3 CKD	Change from baseline to week 18 LS Mean (95%CI)	%	5 mg -0.52 (-0.60, -0.45)	-0.26 (-0.33, -0.18)	-0.27 (-0.37, -0.17) p<0.001	VERTIS CV study
			15 mg -0.53 (-0.61, -0.46)		-0.28 (-0.38, -0.17) p<0.001	
HbA1c Add-on to insulin+met	Change from baseline to week 18 LS Mean (95%CI)	%	5 mg -0.77 (-0.86, -0.67)	-0.19 (-0.29, -0.09)	-0.58 (-0.71, -0.44) p<0.001	Glycaemic sub-study VERTIS
			15 mg -0.84 (-0.93, -0.74)		-0.65 (-0.78, -0.51) p<0.001	
HbA1c Add-on to met+SU	Change from baseline to week 18 LS Mean (95%CI)	%	5 mg -0.89 (-1.06, -0.71)	-0.23 (-0.39, -0.06)	-0.66 (-0.89, -0.43) p<0.001	Glycaemic sub-study VERTIS
			15 mg -0.98 (-1.14, -0.82)		-0.75 (-0.98, -0.53) p<0.001	
Unfavourable Effects						
Any SAE		n (%)	5 mg: 958 (34.9) 15 mg: 937 (34.1)	990 (36.1)		VERTIS CV study
Volume depletion		n (%)	5 mg: 118 (4.3) 15 mg: 118 (4.3)	106 (3.9)		
UTIs			5 mg: 336 (12.2) 15 mg: 330 (12.0)	279 (10.2)		
Genital infections (females)			5 mg: 48 (6.0) 15 mg: 65 (7.8)	20 (2.4)		
Genital infections (males)			5 mg: 86 (4.4) 15 mg: 98 (5.1)	22 (1.2)		
Renal AEs		n (%)	5 mg: 114 (4.2) 15 mg: 117 (4.3)	129 (4.7)		
Fractures		n (%)	5 mg: 99 (3.6) 15 mg: 102 (3.7)	98 (3.6)		
Amputations		n (%)	5 mg: 54 (2.0) 15 mg: 57 (2.1)	45 (1.6)		
Documented hypoglycaemia		n (%)	5 mg: 1,237 (45.0) 15 mg: 1,220 (44.4)	1,215 (44.3)		
DKA events		n (%)	All ERTU: 19 (0.3)	2 (0.07)		
Effect of renal function						
Any SAEs						

Effect	Short description	Unit	Treatment (ERTU)	Control (Plc)	Uncertainties / Strength of evidence	References
eGFR 45 to <60		n (%)	5 mg: 191 (41.1) 15 mg: 151(36.6)	180 (41.0)		
eGFR 30 to <45		n (%)	5 mg: 61 (40.1) 15 mg: 71(48.3)	70 (44.3)		
Volume depletion						
eGFR 45 to <60		n (%)	5 mg: 35 (7.5) 15 mg: 18 (4.4)	27 (6.2)		
eGFR 30 to <45		n (%)	5 mg: 9 (5.9) 15 mg: 15 (10.2)	12 (7.6)		
Renal events						
eGFR 45 to <60		n (%)	5 mg: 41 (8.8) 15 mg: 33 (8.0)	36 (8.2)		
eGFR 30 to <45		n (%)	5 mg: 19 (12.5) 15 mg: 23 (15.6)	25 (15.8)		
Fractures						
eGFR 45 to <60		n (%)	5 mg: 20 (4.3) 15 mg: 16 (3.9)	19 (4.3)		
eGFR 30 to <45		n (%)	5 mg: 6 (3.9) 15 mg: 10 (6.8)	3 (1.9)		
Effect of NYHA class						
Any SAE						
NYHA class II		n (%)	5 mg: 160 (40.2) 15 mg: 167 (37.9)	167 (37.1)		
NYHA class III		n (%)	5 mg: 24 (42.9) 15 mg: 34 (52.2)	17 (45.9)		
Volume depletion						
NYHA class II		n (%)	5 mg: 18 (4.5) 15 mg: 8 (1.8)	18 (4.0)		
NYHA class III		n (%)	5 mg: 3 (5.4) 15 mg: 2 (4.3)	1 (2.7)		
Renal events						
NYHA class II		n (%)	5 mg: 19 (4.8) 15 mg: 27 (6.1)	18 (4.9)		
NYHA class III		n (%)	5 mg: 2 (3.6) 15 mg: 5 (10.9)	1 (2.7)		
Effect of age						
Any SAEs						
<75 years		n (%)	5 mg: 840 (34.2) 15 mg: 811 (33.2)	866 (35.6)		
≥75 years		n (%)	5 mg: 118 (46.8) 15 mg: 126(41.4)	124 (40.0)		
Volume depletion						
<75 years		n (%)	5 mg: 98 (4.0) 15 mg: 97 (4.0)	88 (3.6)		
≥75 years		n (%)	5 mg: 20 (6.9) 15 mg: 21 (6.9)	18 (5.8)		
Renal events						
<75 years		n (%)	5 mg: 90 (3.7) 15 mg: 96 (3.9)	109 (4.5)		
≥75 years		n (%)	5 mg: 24 (8.3) 15 mg: 21 (6.9)	20 (6.5)		

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

VERTIS CV was primarily conducted to investigate the impact of ertugliflozin treatment on CV risk in patients with T2DM. Since the majority (76.3%) of patients were on concomitant treatment with metformin, the data is of relevance for both Steglatro (ertugliflozin) and the FDC Segluromet (ertugliflozin + metformin).

The trial showed non-inferiority of ertugliflozin to placebo on the primary outcome MACE whereas superiority was not shown. The point estimate is below 1 but somewhat higher than for other products in the class, in spite of the fact that a high proportion of patients with established CV disease was included in the VERTIS CV study.

A statistically significant lower risk of hospitalisations due to HF compared to placebo was observed, whereas no difference compared to placebo could be shown on CV death or all-cause mortality. A lower risk (of the same magnitude) of hospitalisation for HF has also been documented for other products in the class and is not unexpected considering the diuretic effect. The relative risk reduction for hospitalisation due to HF was 30% while the absolute reduction was only 1.1%.

The impact on renal events was investigated and the data indicate that progression of nephropathy was slower in the ertugliflozin group compared to the placebo group, as indicated by a slower increase in serum creatinine. Thus, the data provided give no indication of a negative effect on renal function. Similar results with respect to renal events have been described for other SGLT2-inhibitors.

The data from VERTIS CV on HF and other CV outcomes are of interest for the prescribers and is reflected in section 5.1 of the SmPC. The indication is proposed to be amended by removal of the wording "to improve glycaemic control" and the addition of a cross-reference to study results on cardiovascular events in section 5.1 of the SmPC. Previously, this broadening of the indication has been reserved for products with a documented superior effect on MACE compared to placebo (albeit that the upper CI has been very close to 1 for all products). Based on the mechanism of action and support from other products in the class, the finding is considered as highly plausible and thus, ertugliflozin is considered to have additional effects in addition to the glucose lowering effect.

The data from the glycaemic sub-studies investigating the effect of ertugliflozin as on add-on to 1) insulin with or without metformin, and 2) metformin with SU, showed clinically relevant effects with ertugliflozin treatment and these data should be reflected in the SmPC. The third glycaemic sub-study on the combination of ertugliflozin to SU monotherapy however failed to show any clinically relevant effect.

No major safety concerns arise from the data provided. The safety profile in patients with T2DM and established CV disease seems to be rather similar to the one previously documented for ertugliflozin.

The safety profile in subjects with moderate renal impairment was in general consistent with the overall population. Overall, there was no major differences in the incidences of UTIs, genital infections and hypoglycaemia in the subgroup of moderate renal impairment compared to the overall population. The incidence of volume depletion was overall increased, compared with the overall population; although, similar across the treatment arms. However, in the subgroup of patients with eGFR 30 to <45 mL/min/1.73 m^2, the incidence of fractures was increased for ertugliflozin compared with placebo. Moreover, the frequency of renal events was higher in the stage 3B CKD stratum (eGFR 30-45) across all treatment groups, compared with the stage 3A CKD population (eGFR 45-60). This is expected and considered related to the underlying renal disease in the 3B CKD subgroup.

The study included a substantial number of elderly subjects (≥75 years of age) with no indication of a different safety profile, supporting the proposed changes to the SmPC for this population. Data provided do not raise any safety concern with the use of ertugliflozin in patients with HF NYHA class II or III. However, data in NYHA class III should be interpreted with caution due to a limited number of patients (n=139).

With this application the eGFR limit for initiation of treatment is lowered to 45 mL/min/1.73 m^2 and the limit for discontinuation is lowered to 30 mL/min/1.73 m^2. The MAH has provided data supporting that patients with eGFR 30-60 have additional benefits in terms of preservation of renal function and a reduced risk of HHF with ertugliflozin treatment, which outweigh the loss of glycaemic effects in this population. No safety concerns arise from the data presented for patients with eGFR 30-60.

6.7.2. Balance of benefits and risks

The VERTIS CV study provides important information concerning the long-term safety of ertugliflozin as well as the effect on cardiovascular outcomes. The indication in section 4.1 of the SmPC has been modified to reflect the glycaemic and CV benefits of ertugliflozin by removing the reference to the surrogate goal "to improve glycaemic control" and by inserting a cross reference to the results of the VERTIS CV study presented in section 5.1.

Sufficient data supporting the lowering of the eGFR limit for initiation of treatment to 45 mL/min/1.73 m^2 and to lower the limit for discontinuation to 30 mL/min/1.73 m^2 has been provided. The data show that this population have additional benefits in terms of preservation of renal function and a reduced risk of HHF with ertugliflozin treatment which outweigh the loss of glycaemic effects in this population.

In addition, relevant information on the efficacy and safety of ertugliflozin when used in combination with insulin with or without metformin, and in combination with metformin and SU, has been provided. Clinically relevant effects on glycaemic control have been shown and no new safety concerns arise from the data provided. Relevant information on efficacy and safety related to the combinations has been included in the SmPC.

6.8. Conclusions

The overall B/R of Steglatro and Segluromet in the updated indication is considered positive.