Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2 PART 2

Extract from the Clinical Evaluation Report for Ertugliflozin

Proprietary Product Name: Steglatro

Sponsor: Merck Sharpe and Dohme (Australia) Pty Ltd.

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TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of common abbreviations

Abbreviation	Meaning
$HbA1_c$	Glycosylated haemoglobin (haemoglobin (Hb) A1c)
AACE	American Association of Clinical Endocrinologists
ABPM	Ambulatory blood pressure monitoring
ADA	American Diabetes Association
ADME	Absorption, distribution, metabolism and elimination
AE	Adverse event
AHA	Anti-hyperglycaemic agent
ANOVA	Analysis of variance
AUC	Area under the concentration-time curve
AUC_{inf}	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time
$AUC_{inf(dn)}$	Dose normalized (to 1 mg) auc_{inf}
AUC_{last}	Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (Clast)
AV	Atrioventricular
BA	Bioavailability
BE	Bioequivalence
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CKD	Chronic kidney disease
CL (IV)	CL; systemic clearance
CL/F (oral)	Apparent clearance; CL/F
cLDA	Constrained longitudinal data analysis

Abbreviation	Meaning
CLr	Renal clearance
C_{max}	Maximum observed plasma concentration
C_{min}	Lowest concentration observed during the dosing interval
CSR	Clinical study report
CV	Cardiovascular
CVOT	Cardiovascular outcome trial
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
DPP	Dipeptidyl peptidase
E5/S100	Ertugliflozin 5 mg/sitagliptin 100 mg
E15/S100	Ertugliflozin 15 mg/ sitagliptin 100 mg
EASD	European Association for the Study of Diabetes
ECG	Electrocardiograph
ED50	Dose at half maximum effect
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
Ertu/Met	ertugliflozin/metformin
ESRD	End stage renal disease
EU	European Union
F	Bioavailability
FAS	Full analysis set
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FME	Full model estimation

Abbreviation	Meaning
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
GMR	Geometric mean ratio
h	Hour(s)
HCTZ	Hydrochlorothiazide
HDL-C	High-density lipoprotein-cholesterol
hOAT-3	Human organic anion transporter-3
HPLC-MS/MS	High-performance liquid chromatography tandem mass spectrometric
HTCZ	Hydrochlorothiazide
LDA	Longitudinal data analysis
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein-cholesterol
LLOQ	Lower limit of quantitation
L-PGA	L-pyroglutamic acid
LS	Least-squares
MACE	Major adverse cardiovascular event
min	Minute(s)
MR	Modified-release
MRI	Magnetic Resonance Imaging
NONMEM	Non-linear mixed effects modelling
NTX-1	N-terminal telopeptide-1
OAD	Oral anti-diabetic
OC	Osteocalcin

Abbreviation	Meaning
P1NP	Procollagen type 1 amino-terminal propeptide
PD	Pharmacodynamics
PDLC	Pre-defined limit of change
P-gp	P-glycoprotein
PK	Pharmacokinetic
PO	Per os (oral)
popPK	Population pharmacokinetic
PPAS	Per protocol analysis set
PPG	Post-prandial glucose
Q/F	Apparent inter-compartmental clearance
QD	Once daily
QT	Time from the start of the Q wave to the end of the T wave
QTc	QT interval corrected for heart rate
RAAS	Renin-angiotensin-aldosterone system
Rac	Observed accumulation ratio
RNA	Ribonucleic acid
RTG	Renal threshold for glucose
SA	Specific activity
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SGLT1	Sodium-glucose co-transporter 1
SGLT2	Sodium glucose co-transporter 2
SOC	System organ class
SU	Sulfonylurea

Abbreviation	Meaning
$t_{1/2}$	Terminal half-life
T2DM	Type 2 diabetes mellitus
TEAE	Treatment-emergent adverse event
TECOS	Trial Evaluating Cardiovascular Outcomes with Sitagliptin
T_{max}	Time for C_{max}
UGE	Urinary glucose excretion
UGE_{0-24}	Cumulative urinary glucose excretion over 24 hours
UGT	Uridine 5'-diphospho-glucuronosyltransferase
UK	United Kingdom
ULN	Upper limit of normal
US	United States
Vc/F	Apparent Central Volume Of Distribution
Vz/F (oral)	Apparent volume of distribution following oral administration

Please note the first half of this clinical evaluation report is presented in Attachment 2, Part 1.

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Please note the first half of this clinical evaluation report is presented in Attachment 2 PART 1.

Table 70: Analysis strategy for efficacy endpoints

Endpoint (all at Week 26)	Approach	Statistical Method	Analysis Population	Missing Data Approach
Primary				
Change from baseline in A1C	P† S S	cLDA ANCOVA ANCOVA	FAS FAS FAS	Model-based Tipping Point J2R
Key Secondary				
Change from baseline in FPG	P†	cLDA	FAS	Model-based
Change from baseline in body weight	P†	cLDA	FAS	Model-based
Change from baseline in systolic blood pressure	P†	cLDA	FAS	Model-based
Proportion of subjects with A1C at goal <7.0%	P	Log. reg.	FAS	Mult. imp.
Other Endpoints				
Change from baseline in diastolic blood pressure	P†	cLDA	FAS	Model-based
Change from baseline in HOMA-%β	P	cLDA	FAS	Model-based
Time to rescue	P	Kaplan-Meier Log-rank	All Subjects Treated	N/A
Proportion of subjects requiring rescue medication	P	Kaplan-Meier Log-rank	All Subjects Treated	N/A
Change from baseline in EQ-5D-3L score	P†	cLDA	FAS	Model-based

†Analysis performed 2 ways: "excluding rescue" and "including rescue."
A1C=hemoglobin A_{1c}; ANCOVA=analysis of covariance; cLDA=constrained longitudinal data analysis; EQ-5D-3L=EQ-5D 3-level version; FAS=Full Analysis Set; FPG=fasting plasma glucose; HOMA-%β=homeostasis model assessment of β-cell function; J2R=Jump to Reference; Log. reg.=logistic regression; Mult. imp.=multiple imputation; N/A=not applicable; P=Primary; S=Secondary.

1.1.1.

1.1.1.1. Randomisation and blinding

Randomisation occurred centrally using an IVRS/IWRS. Eligible subjects were assigned randomly to 1 of 3 treatment groups in a 1:1:1 ratio to ertugliflozin 5 mg QD, ertugliflozin 15 mg QD, or placebo using a computer-generated randomisation schedule. Randomisation was stratified according to use of a sulfonylurea at Visit 1/Screening (yes/no). Subjects who were < 80% compliant (based on pill count) with the placebo run-in medication were ineligible for randomisation.

A double blind/masking technique was used in this study. Ertugliflozin and matching placebos were packaged identically so that blinding/masking was maintained. The subject, the investigator, sponsor personnel, and personnel from the sponsors' designees, Covance and Parexel, who were involved in the treatment or clinical evaluation of the subjects were unaware of treatment group assignments. Emergency unblinding[1] of a subject's treatment group assignment was done using the central electronic randomisation system (IVRS/IWRS (voice/web)).

1.1.1.2. Analysis populations

The Full Analysis Set (FAS) population was the primary analysis population for all efficacy endpoints. For analyses that used the constrained longitudinal data analysis (cLDA) model, the FAS population, defined separately for each analysis endpoint, consisted of all randomised subjects who: Received at least one dose of study medication; Had a baseline measurement or a post-randomisation measurement for the analysis endpoint subsequent to at least one dose of study medication. For analyses that used the analysis of covariance (ANCOVA) model, the FAS population defined separately for each analysis endpoint, consisted of all randomised subjects who: Received at least one dose of study medication; Had baseline data for the analysis

[1] If a subject's treatment group assignment was unblinded, the circumstances around the unblinding (for example, date and reason) were to be documented and the study Clinical Director notified. Only the principal investigator or designee and the respective subject's code should have been unblinded. Trial site personnel and Merck/Covance personnel directly associated with the conduct of the trial were to remain blinded.

endpoint; Had at least one post-randomisation observation for the analysis endpoint subsequent to at least one dose of study medication. Analyses of the proportions of subjects requiring rescue medication and time to rescue were performed in the All Subjects Treated population.

1.1.1.3. Sample size

Approximately 405 subjects were to be randomised in a 1:1:1 ratio among the 3 treatment groups. The sample size was chosen to provide adequate exposure data to assess safety for 52 weeks. A sample size of 135 subjects per arm was equivalent to an effective sample size of 120 per arm at Week 26 in the power calculation for the primary hypothesis test using the cLDA model. This sample size provided 97% power to detect a true difference of 0.5% in the mean change from baseline in HbA1c between a given ertugliflozin dose and placebo (2-sided test, α=0.05). The half-width of the 95% CI is expected to be 0.25%. The power for succeeding in the primary hypothesis test for both dose levels was approximately 94%.

1.1.1.4. Statistical methods

The analysis strategy for all efficacy endpoints for Phase A is summarised in Table 70. The primary and key secondary hypotheses were tested using an ordered testing procedure which included the tests of HbA1c, FPG, body weight, proportion of subjects with HbA1c < 7.0%, and systolic blood pressure, all using $\alpha = 0.05$ (2-sided). The two tests corresponding to the two doses of ertugliflozin versus placebo in the primary hypotheses were to be conducted in the order of ertugliflozin 15 mg versus placebo followed by ertugliflozin 5 mg versus placebo, for each endpoint. Secondary hypotheses were tested only if success was achieved for both doses in the test of the primary hypothesis. The testing procedure was to be stopped at the first step which failed to meet statistical significance.

To assess whether the treatment effect at Week 26 was consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoint was estimated and plotted within each category of the following classification variables: Baseline HbA1c levels: ≤ or > median; by categories: < 8.0%; 8.0% to < 9.0%; and 9.0% to < 10%; ≥ 10%, and Gender. The consistency of the treatment effect was assessed in the context of a repeated measures ANCOVA (RMANCOVA) method, which is a generalisation of the standard ANCOVA to accommodate repeated measurements. The RMANCOVA model adjusted for treatment, prior AHAs, subgroup, eGFR, and treatment-by-subgroup and treatment-by-time-by subgroup interactions. Time was treated as a categorical variable. An unstructured covariance matrix was used to model the correlation among repeated measurements. Treatment effects and nominal 95% CIs by category for the classification variables listed above were reported as well as presented graphically. Formal statistical testing of treatment by subgroup interactions was not performed.

1.1.1.5. Participant flow

Overall, 987 subjects were screened and 524 subjects were excluded during screening[2]. The remaining 463 subjects were randomised at 85 sites in 12 countries. The number of randomised subjects was balanced across the 3 treatment groups. One subject in the ertugliflozin 15 mg group was randomised but never received study medication. The proportion of subjects who discontinued study medication in Phase A was similar across treatment groups (7.8%, 8.3% and 8.4% in the ertugliflozin 5 mg, 15 mg and placebo groups, respectively) and the most common reason across the 3 treatment groups was withdrawal by subject. A numerically higher incidence of subjects discontinued study medication for an AE in the ertugliflozin 5 mg group than in the ertugliflozin 15 mg and placebo groups, and 3 subjects in the ertugliflozin 15 mg

[2] The most common reason for subjects not being randomised was screen failure. The most common reasons for screen failure were not meeting the inclusion criteria for A1C at Visit 1 relative to a subject's category of background diabetes therapy, and having exclusionary laboratory values.

group compared with none in the other 2 groups discontinued study medication due to meeting the protocol-specified creatinine/eGFR discontinuation criterion.

1.1.1.6. Major protocol violations

Overall, 136 (29.4%) of 462 subjects who received study treatment were reported to have 1 or more major deviations. Although the overall incidence of major deviations was slightly higher in the placebo group than in the ertugliflozin groups, no important differences with regard to specific deviation categories were seen. The most common major deviations were those associated with failure to conduct major/significant evaluations[3], randomisation of subjects who did not meet eligibility criteria and informed consent deviations. Other protocol deviations, including those with a potential to meaningfully impact efficacy analyses (for example, < 75% compliance with study medication, taking glycaemic rescue medication without meeting rescue criteria, taking incorrect study medication, and change of background AHA) occurred at low incidences across the treatment groups.

1.1.1.7. Baseline data

Majority of subjects were male (57%), White (73%) and aged between 45 to 64 years (63%). Baseline demographic and anthropometric characteristics and the distribution of subjects by sulfonylurea use at screening were generally similar between treatment groups; however, the proportion of males was higher in the placebo group than in the ertugliflozin groups. The duration of T2DM was similar across treatment groups. All subjects were on background AHA therapy at screening, and the proportion of subjects receiving metformin + DPP-4 inhibitor (overall 66%) or metformin + SU (overall 34%) at screening was similar across treatment groups. The mean dose of metformin was approximately 2000 mg/day across the 3 treatment groups. Baseline HbA1c, FPG, and eGFR values were similar between groups with majority of subjects having HbA1c < 8% (54%) (Table 71).

[3] The higher incidence of major deviations in the category of failure to conduct major/significant evaluations relative to the other categories was primarily due to 1 site in South Korea (site 1567) that inadvertently omitted the FPG measurement at Visit 3/Week -2 in nearly all of the 39 subjects randomised by the site.

Table 71: Baseline A1C, FPG, eGFR (US units); All subjects treated

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	153		156		153		462	
Baseline A1C (%)								
<8.0	83	(54.2)	82	(52.6)	84	(54.9)	249	(53.9)
8.0 to <9.0	43	(28.1)	47	(30.1)	44	(28.8)	134	(29.0)
9.0 to <10.0	21	(13.7)	20	(12.8)	23	(15.0)	64	(13.9)
≥10.0	5	(3.3)	6	(3.8)	1	(0.7)	12	(2.6)
Unknown	1	(0.7)	1	(0.6)	1	(0.7)	3	(0.6)
Subjects with data	152		155		152		459	
Mean	8.03		8.05		8.00		8.03	
SD	0.93		0.86		0.83		0.88	
Median	7.90		7.90		7.80		7.90	
Range	6.3 to 11.1		5.7 to 10.7		5.8 to 10.6		5.7 to 11.1	
Baseline FPG (mg/dL)								
Subjects with data	152		156		152		460	
Mean	169.6		167.7		171.7		169.7	
SD	37.8		37.7		39.1		38.2	
Median	163.5		162.0		170.5		165.0	
Range	89 to 337		90 to 300		82 to 287		82 to 337	
Baseline eGFR (mL/min/1.73m²)								
30 to <60	1	(0.7)	3	(1.9)	4	(2.6)	8	(1.7)
60 to <90	79	(51.6)	93	(59.6)	85	(55.6)	257	(55.6)
≥90	73	(47.7)	60	(38.5)	64	(41.8)	197	(42.6)
Baseline eGFR (mL/min/1.73m²)								
Subjects with data	153		156		153		462	
Mean	89.9		87.0		86.9		87.9	
SD	17.5		17.5		15.6		16.9	
Median	88.0		84.0		86.0		86.0	
Range	54 to 145		51 to 144		54 to 137		51 to 145	

Baseline value is defined as the Day 1 (Randomization) measurement. If this measurement is not available, the last pre-randomization measurement on or after Week -2 is used as the baseline value.
eGFR based on MDRD formula. Baseline value is defined as the Day 1 (Randomization) measurement. If this measurement is not available, the last pre-randomization measurement on or after Screening is used as the baseline value

Subjects were required to have a history of T2DM for entry into the study. The other most common categories of medical history conditions by SOC were Metabolism and nutrition disorders (76.8%) and Vascular disorders (76.0%). The most common specific medical history conditions were hypertension (71.9%), dyslipidaemia and hyperlipidaemia (27.5% each), obesity (18.0%) and diabetic neuropathy (18.0%) with no clinically important differences among treatment. Subjects screened for this study were to be receiving dual combination therapy with metformin and a DPP-4 inhibitor or an SU; therefore, 100% of subjects were taking drugs used for diabetes. The other most common prior medication categories were agents acting on the renin-angiotensin system (63.0%), lipid-modifying agents (62.3%) and analgesics (33.3%) with no clinically important differences among treatment groups. Following randomisation, subjects were to remain on stable doses of metformin and sitagliptin during the study. The other most common concomitant drug therapeutic categories were lipid-modifying agents (63.4%), agents acting on the renin-angiotensin system (62.6%) and analgesics (37.9%) with no clinically important differences among treatment groups. Mean compliance with study medication was ≥ 98% for each treatment group.

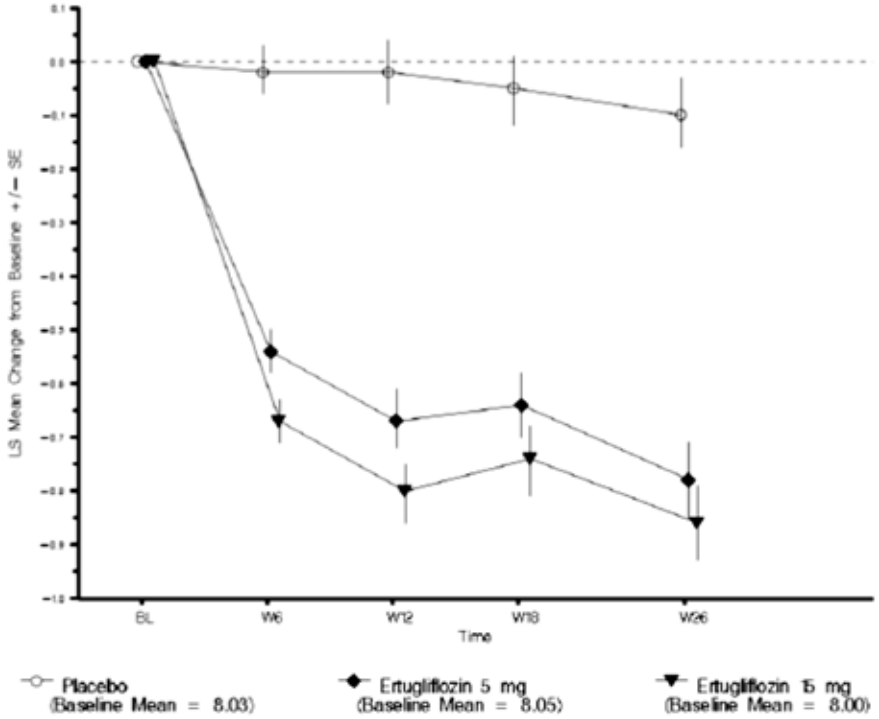
Comment: It is important to note that 41 (8.9%) randomised subjects were incorrectly stratified across the 3 treatment groups, including 33 (7.1%) subjects who were reported as taking an SU at screening but who were not, and 8 (1.7%) subjects who were reported as not taking an SU at screening but who were. Subjects were analysed according to their intended stratum. The sponsors have been requested to clarify if the incidence of incorrect stratification based on SU use prior to screening was similar across all treatment groups and if this could have confounded interpretation of efficacy results.

1.1.1.8. Primary efficacy results

The LS mean reductions from baseline in HbA1c at Week 26 were significantly greater in the ertugliflozin 5 mg and 15 mg groups compared with the placebo group (-0.09%, -0.78% and -0.86% in the placebo, ertugliflozin 5 mg and 15 mg groups, respectively; $p < 0.001$ for both

comparisons). In the ertugliflozin groups, reductions from baseline in HbA1c were observed at Week 6 with subsequent further reductions seen at Week 26. The reduction in HbA1c was numerically greater in the ertugliflozin 15 mg group than in the ertugliflozin 5 mg group at each time point. In the placebo group, there was essentially no change from baseline in HbA1c through Week 18; thereafter, a small reduction in HbA1c was observed at Week 26 (Figure 27).

Figure 27: $HbA1_C$ (%); LS mean change from Baseline over time



The primary efficacy results were robust and supported by the sensitivity analyses (Tables 72 and 73).

Table 72: HbA1c (%); Change from Baseline at Week 26. Repeated measures analysis of covariance subgroup analysis; FAS: excluding rescue approach

Treatment	Baseline N	Baseline Mean (SD)	Week 26 N	Week 26 Mean (SD)	Change From Baseline in A1C at Week 26† N	Change From Baseline in A1C at Week 26† LS Mean (95% CI)	Change From Baseline in A1C at Week 26† Difference in LS Means (95% CI)
Subgroup: Baseline A1C (Median)							
<= Median A1C (7.9 %)							
Placebo	82	7.37 (0.36)	75	7.49 (0.80)	82	0.20 (0.03, 0.38)	
Ertugliflozin 5 mg	79	7.43 (0.36)	74	6.95 (0.58)	79	-0.44 (-0.62, -0.26)	-0.64 (-0.89, -0.40)
Ertugliflozin 15 mg	83	7.38 (0.37)	74	6.99 (0.69)	83	-0.37 (-0.54, -0.19)	-0.57 (-0.82, -0.32)
> Median A1C (7.9 %)							
Placebo	67	8.84 (0.78)	43	8.03 (1.17)	67	-0.42 (-0.63, -0.21)	
Ertugliflozin 5 mg	71	8.77 (0.69)	63	7.57 (0.76)	71	-1.16 (-1.34, -0.97)	-0.74 (-1.02, -0.46)
Ertugliflozin 15 mg	66	8.80 (0.54)	63	7.38 (0.91)	66	-1.40 (-1.59, -1.21)	-0.98 (-1.27, -0.70)
Subgroup: Baseline A1C levels							
<8%							
Placebo	82	7.37 (0.36)	75	7.49 (0.80)	82	0.21 (0.03, 0.38)	
Ertugliflozin 5 mg	79	7.43 (0.36)	74	6.95 (0.58)	79	-0.44 (-0.61, -0.26)	-0.64 (-0.88, -0.40)
Ertugliflozin 15 mg	83	7.38 (0.37)	74	6.99 (0.69)	83	-0.36 (-0.53, -0.19)	-0.57 (-0.81, -0.33)
>=8% to <9%							
Placebo	41	8.30 (0.23)	29	7.72 (0.96)	41	-0.32 (-0.58, -0.06)	
Ertugliflozin 5 mg	46	8.33 (0.26)	41	7.46 (0.80)	46	-0.85 (-1.08, -0.62)	-0.53 (-0.87, -0.18)
Ertugliflozin 15 mg	42	8.46 (0.27)	39	7.02 (0.53)	42	-1.40 (-1.64, -1.16)	-1.08 (-1.43, -0.73)
>=9%							
Placebo	26	9.69 (0.54)	14	8.69 (1.33)	26	-0.54 (-0.89, -0.20)	
Ertugliflozin 5 mg	25	9.58 (0.48)	22	7.77 (0.62)	25	-1.72 (-2.02, -1.41)	-1.17 (-1.63, -0.71)
Ertugliflozin 15 mg	24	9.38 (0.34)	24	7.97 (1.09)	24	-1.41 (-1.72, -1.10)	-0.86 (-1.32, -0.40)
Subgroup: Gender							
Male							
Placebo	97	8.04 (0.91)	77	7.75 (1.08)	97	0.02 (-0.15, 0.19)	
Ertugliflozin 5 mg	77	8.00 (0.93)	69	7.12 (0.80)	77	-0.87 (-1.05, -0.68)	-0.89 (-1.14, -0.64)
Ertugliflozin 15 mg	79	8.07 (0.88)	74	7.13 (0.92)	79	-0.92 (-1.11, -0.74)	-0.94 (-1.19, -0.70)
Female							
Placebo	52	8.02 (1.01)	41	7.59 (0.77)	52	-0.18 (-0.41, 0.05)	
Ertugliflozin 5 mg	73	8.13 (0.79)	68	7.35 (0.64)	73	-0.65 (-0.84, -0.46)	-0.47 (-0.77, -0.17)
Ertugliflozin 15 mg	70	7.93 (0.78)	63	7.21 (0.69)	70	-0.72 (-0.92, -0.53)	-0.54 (-0.85, -0.24)

For baseline and Week 26, N is the number of subjects with non-missing assessments at the specific time point; for Change from Baseline at Week 26, N is the number of subjects in the FAS (i.e., randomized subjects who took at least 1 dose of study medication and had a baseline measurement and at least one assessment after baseline).

† Obtained from a repeated measures ANCOVA model with terms for prior antihyperglycemic medication (metformin + DPP-4 inhibitor /metformin + SU), covariates for eGFR and baseline A1C, treatment, subgroup, treatment-by-subgroup, and treatment-by-time-by-subgroup interactions. Time was fitted as a categorical term.

The analysis was only performed for subgroups with at least 20 subjects in all of the treatment groups in each subgroup category. For subgroup analyses based on factors that are already in the main model, the respective term will appear in the model only once.

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

Table 73: Sensitivity analysis for primary efficacy endpoint

A1C (%): Change from Baseline at Week 26
Jump to Reference Missing Data Approach
Full Analysis Set: Excluding Rescue Approach

Treatment	Baseline N	Baseline Mean (SD)	Week 26 N	Week 26 Mean (SD)	Change from Baseline at Week 26 N	Change from Baseline at Week 26 Mean (SD)	Change from Baseline at Week 26 LS Mean (SE)*
Placebo	152	8 03 (0 93)	119	7 70 (0 98)	149	-0 16 (0 96)	-0 04 (0 08)
Ertugliflozin 5 mg	155	8 05 (0 86)	138	7 24 (0 78)	152	-0 81 (0 81)	-0 68 (0 06)
Ertugliflozin 15 mg	152	8 00 (0 83)	138	7 17 (0 82)	150	-0 86 (0 87)	-0 77 (0 07)

Pairwise Comparison	Difference in LS Means (95% CI)*	p-Value
Ertugliflozin 5 mg vs. Placebo	-0 639 (-0 843, -0 435)	< 0001
Ertugliflozin 15 mg vs. Placebo	-0 725 (-0 930, -0 519)	< 0001

For baseline and Week 26, N is the number of subjects with non-missing assessments at the specific time point; for Change from Baseline at Week 26, N is the number of subjects in the FAS (i e , randomized subjects who took at least 1 dose of study medication and had baseline and at least one assessment after baseline) The Mean and SD for the change from baseline are based on non-missing values

* Based on ANCOVA model using imputed values for missing data based on the Jump to Reference approach, with fixed effects for treatment, prior antihyperglycemic medication (metformin + DPP-4 inhibitor /metformin + SU), baseline eGFR (continuous) and baseline A1C

CI=Confidence Interval, LS=Least Squares, SD=Standard Deviation

A1C (%): Change from Baseline at Week 26
Tipping Point Analysis Missing Data Approach
Full Analysis Set: Excluding Rescue Approach

Improvement Applied to Imputed Data in Placebo (%)	P-values for Comparison of Ertugliflozin 5 mg vs. Placebo: Worsening Applied to Imputed Data in Ertugliflozin 5 mg (%) 3 8	3 9	4	4 1	4 2	4 3	4 4
-1 0	0 4052	0 4507	0 4977	0 5457	0 5945	0 6438	0 6933
-0 9	0 3279	0 3692	0 4123	0 4570	0 5030	0 5499	0 5976
-0 8	0 2610	0 2976	0 3364	0 3771	0 4195	0 4633	0 5083
-0 7	0 2042	0 2360	0 2702	0 3065	0 3449	0 3850	0 4267
-0 6	0 1572	0 1842	0 2136	0 2454	0 2794	0 3155	0 3534
-0 5	0 1190	0 1415	0 1663	0 1936	0 2232	0 2549	0 2888
-0 4	0 0886	0 1069	0 1276	0 1505	0 1757	0 2032	0 2328
-0 3	0 0650	0 0796	0 0963	0 1153	0 1364	0 1597	0 1852
-0 2	0 0469	0 0584	0 0717	0 0870	0 1044	0 1238	0 1454
-0 1	0 0334	0 0422	0 0526	0 0648	0 0788	0 0947	0 1127

Improvement Applied to Imputed Data in Placebo (%)	P-values for Comparison of Ertugliflozin 15 mg vs. Placebo: Worsening Applied to Imputed Data in Ertugliflozin 15 mg (%) 4 8	4 9	5	5 1	5 2	5 3	5 4
-1 0	0 3228	0 3553	0 3889	0 4233	0 4586	0 4944	0 5307
-0 9	0 2651	0 2945	0 3252	0 3570	0 3898	0 4234	0 4578
-0 8	0 2150	0 2412	0 2688	0 2977	0 3277	0 3588	0 3909
-0 7	0 1722	0 1951	0 2196	0 2454	0 2725	0 3009	0 3304
-0 6	0 1362	0 1560	0 1773	0 2000	0 2242	0 2497	0 2764
-0 5	0 1064	0 1232	0 1415	0 1612	0 1824	0 2050	0 2288
-0 4	0 0821	0 0962	0 1116	0 1285	0 1468	0 1665	0 1876
-0 3	0 0626	0 0742	0 0871	0 1013	0 1169	0 1339	0 1522
-0 2	0 0472	0 0566	0 0672	0 0790	0 0921	0 1065	0 1223
-0 1	0 0352	0 0427	0 0513	0 0610	0 0719	0 0839	0 0973
0 0	0 0260	0 0319	0 0387	0 0466	0 0555	0 0655	0 0766

Tipping Point =5 1

Multiple imputation used for missing data values with delta value (worsening or improvement) added as specified

Analysis based on primary analysis model using Rubin's rules to obtain estimate based on imputations

A1C (%): Change from Baseline at Week 26
Analysis of Covariance with LOCF
Full Analysis Set: Excluding Rescue Approach

Treatment	N	Baseline Mean	Baseline (SD)	Week 26 Mean	Week 26 (SD)	Change from Baseline at Week 26 Mean	Change from Baseline at Week 26 (SD)	Change from Baseline at Week 26 LS Mean	Change from Baseline at Week 26 (95% CI)*
Placebo	149	8 03	(0 94)	7 98	(1 17)	-0 05	(0 95)	-0 00	(-0 13, 0 12)
Ertugliflozin 5 mg	150	8 06	(0 86)	7 28	(0 78)	-0 78	(0 83)	-0 74	(-0 86, -0 61)
Ertugliflozin 15 mg	149	8 01	(0 84)	7 17	(0 82)	-0 84	(0 86)	-0 82	(-0 95, -0 69)

Pairwise Comparison	Difference in LS Means* (95% CI)	p-Value
Ertugliflozin 5 mg vs. Placebo	-0 73 (-0 91, -0 55)	< 0 001
Ertugliflozin 15 mg vs. Placebo	-0 81 (-0 99, -0 64)	< 0 001
Root Mean Squared Error of Change	0 79	

*Obtained from an ANCOVA model with terms for treatment, prior antihyperglycemic medication (metformin + DPP-4 inhibitor /metformin + SU) and covariates of baseline A1C and baseline eGFR (continuous)

CI=Confidence Interval, LS =Least Squares, SD=Standard Deviation, LOCF=Last Observation Carried Forward

LS mean reductions in HbA1c at Week 26 were greater (nominal $p < 0.0001$ for both comparisons) in the ertugliflozin groups relative to the placebo group in the J2R analyses, excluding data after initiation of glycaemic rescue therapy. The tipping-point analyses (in which data collected after initiation of glycaemic rescue therapy were also considered) showed that to shift the primary result to a non-significant result, the HbA1c change from baseline among subjects in the ertugliflozin groups with missing data would need to have been substantially worse (over 4.1% and over 5.1% for ertugliflozin 5 mg and 15 mg, respectively) than that

expected under the missing at random assumption. The analysis of HbA1c change from baseline at Week 26 performed using ANCOVA/LOCF, excluding data after initiation of glycaemic rescue therapy also supported the conclusion from the primary analysis. An analysis of change from baseline in HbA1c at Week 26, including data after initiation of glycaemic rescue therapy (which included more subjects with HbA1c measurements at Week 26, particularly in the placebo group, so that the group sizes were almost equal) also showed results which were consistent with the primary analysis.

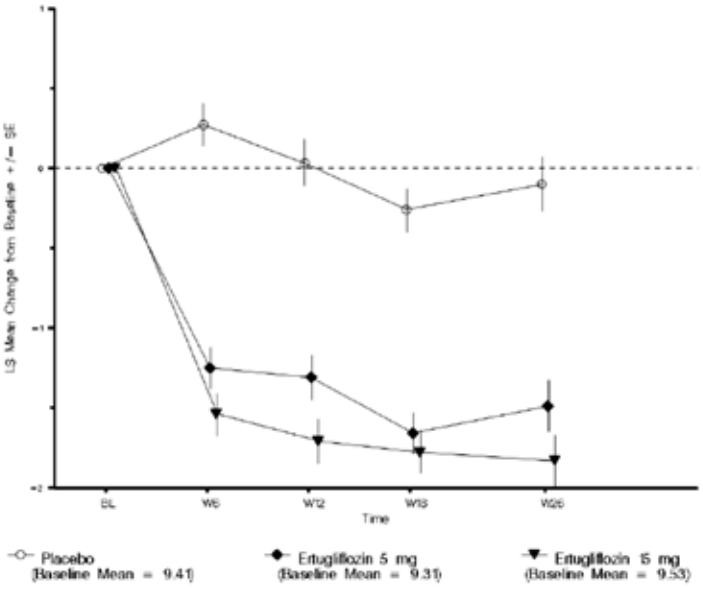
A post-hoc subgroup analysis for gender was included because there was a higher proportion of males in the placebo group (65.4%) compared with the ertugliflozin 5 mg group (51.9%) and the 15 mg group (53.6%). In the ertugliflozin 5 mg and 15 mg groups, mean reductions from baseline in HbA1c at Week 26 were numerically greater in male than in female subjects (Table 72). LS mean reductions from baseline in HbA1c were greater in the ertugliflozin 5 mg and 15 mg groups than in the placebo group across the HbA1c and gender subgroup categories. The improvements in HbA1c in the ertugliflozin groups relative to the placebo group were numerically greater in the subgroup of subjects with a baseline HbA1c level above versus at or below the median HbA1c level (7.9%).

1.1.1.9. Other efficacy results

The raw proportion of subjects with an HbA1c < 7.0% was significantly greater in the ertugliflozin 5 mg and 15 mg groups relative to the placebo group (17%, 32% and 40% in the placebo, ertugliflozin 5 mg and 15 mg groups respectively). The model-based odds of having an HbA1c < 7.0% at Week 26, using multiple imputation for subjects with missing Week 26 data, were significantly greater in the ertugliflozin 5 mg and 15 mg groups than in the placebo group ($p < 0.001$ for both comparisons).

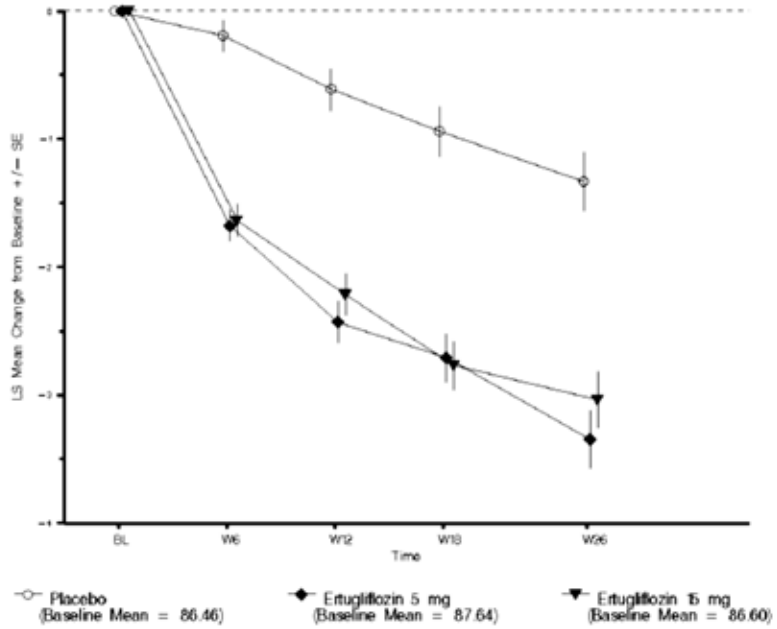
The LS mean reductions from baseline in FPG at Week 26 were significantly greater in the ertugliflozin 5 mg and 15 mg groups than in the placebo group (-0.1, -1.5 and -1.8 mmol/L, respectively) ($p < 0.001$ for both comparisons). In the ertugliflozin 15 mg group, a reduction from baseline in FPG at Week 6 was followed by subsequent small reductions at each time point through Week 26. A similar pattern was observed in the ertugliflozin 5 mg group except that FPG increased slightly between Weeks 18 and 26. The magnitude of the reduction in FPG was numerically greater in the ertugliflozin 15 mg group than in the ertugliflozin 5 mg group at each time point. In the placebo group, small fluctuations from baseline in FPG occurred through Week 26 (Figure 28).

Figure 28: FPG (mmol/L); LS Mean change from Baseline over time. cLDA FAS: excluding rescue approach



The LS mean reductions from baseline in body weight at Week 26 were significantly greater in the ertugliflozin 5 mg and 15 mg groups than in the placebo group (-1.3, -3.46 and -3.0 kg, respectively; $p < 0.001$ for both comparisons). In both ertugliflozin groups and in the placebo group, body weight decreased from baseline at Week 6 (first scheduled post-randomisation assessment) and continued to decrease at each subsequent time point through Week 26. The magnitude of the decrease in body weight was numerically greater in both ertugliflozin groups than in the placebo group at each time point; changes from baseline in body weight through Week 26 were similar between the ertugliflozin 5 mg and 15 mg groups (Figure 29).

Figure 29: Body weight (kg); LS Mean change from Baseline over time. cLDA FAS: excluding rescue approach



In both ertugliflozin groups, sitting SBP decreased from baseline at each time point through Week 18 and then increased slightly at Week 26. In the placebo group, SBP decreased from baseline at Week 12, remained stable at Week 18, and then increased slightly at Week 26.

Changes from baseline in SBP through Week 26 were similar between the ertugliflozin 5 mg and 15 mg groups. The LS mean reductions from baseline in SBP at Week 26 were significantly greater in the ertugliflozin 5 mg and 15 mg groups than in the placebo group (-0.88, -3.8 and -4.8 mmHg, respectively; p = 0.019 and p = 0.002, respectively) (Figure 30). Similarly, DBP decreased from baseline at each time point through Week 18 in both ertugliflozin groups and then increased slightly at Week 26. The LS mean reductions from baseline in DBP at Week 26 were numerically greater in the ertugliflozin 5 mg and 15 mg groups than in the placebo group (Figure 31).

Figure 30: Sitting systolic BP (mmHg); LS Mean change from Baseline over time. cLDA FAS: excluding rescue approach

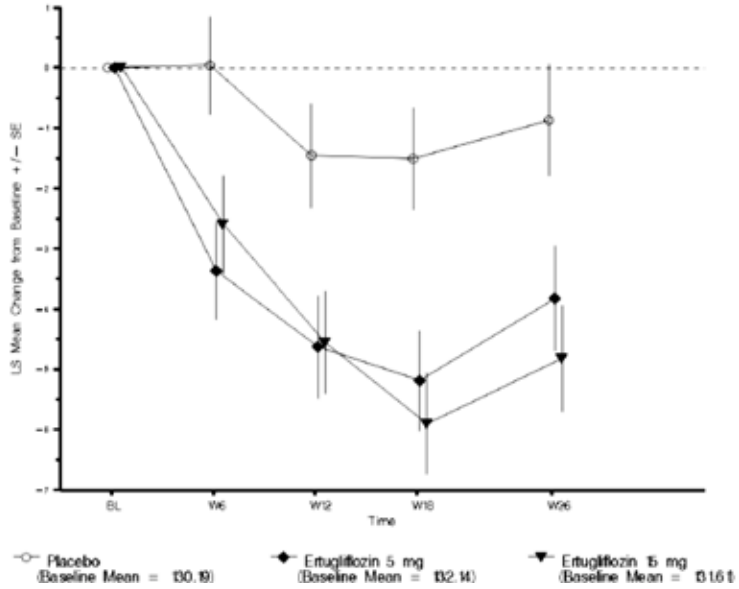
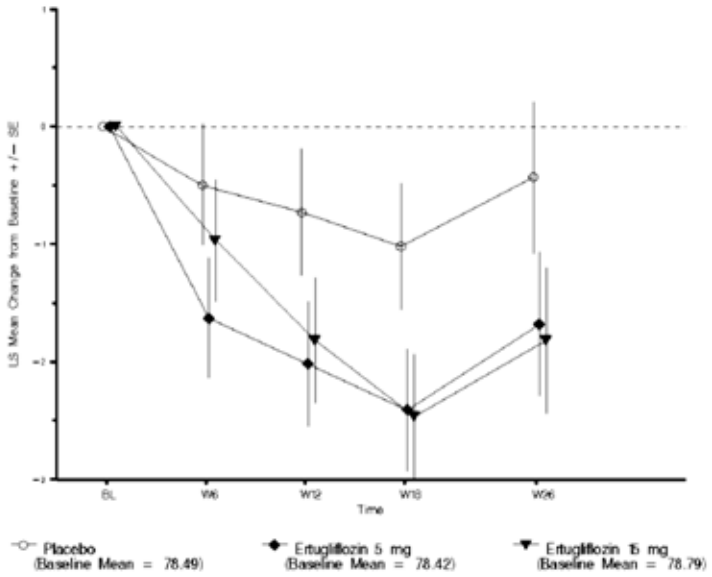
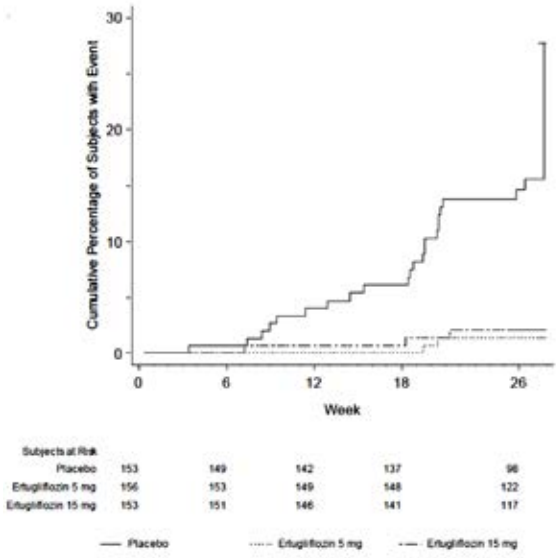


Figure 31: Sitting diastolic BP (mmHg); LS Mean change from baseline over time. cLDA FAS: excluding rescue approach



The cumulative percentage of subjects who received glycaemic rescue medication through Week 26 in the ertugliflozin groups (≤ 2.0% in both groups) was lower than in the placebo group (16.3%)(nominal p < 0.001 for both comparisons)(Figure 32).

Figure 32: Cumulative percentage of subjects with glycaemic rescue therapy. Kaplan-Meier curves; All subjects treated



Ertugliflozin (5 mg and 15 mg) also improved HOMA-%beta, a marker for pancreatic beta-cell function, despite the fact that subjects were already on sitagliptin, an agent known to improve beta-cell function by acting on the GLP-1 receptors on the beta-cells. The LS mean increases from baseline at Week 26 in beta-cell function (excluding data after initiation of glycaemic rescue therapy) was greater in the ertugliflozin 5 mg and 15 mg groups than in the placebo group (nominal $p < 0.001$ for both comparisons).

There was no mean change from baseline in quality of life (assessed by EQ-5D-3L score) in any of the treatment groups.

1.1.1.10. Evaluator commentary

This was a well-conducted pivotal Phase III study which evaluated the efficacy and safety of the addition of ertugliflozin (5 mg and 15 mg QD) compared with the addition of placebo to combination therapy with metformin ≥ 1500 mg/day and sitagliptin 100 mg QD in 463 subjects with T2DM and inadequate glycaemic control. Single-agent or dual therapies are often found to be insufficient to control blood glucose over time due to the progressive nature of diabetes. The addition of a third oral antidiabetic agent, with a different mechanism of action is often needed at a certain point of disease progression. Ertugliflozin, with a distinct mechanism-of-action relative to DPP-4 inhibitors and metformin, is a reasonable choice as a third-line therapy. The study population, with a mean duration of diabetes of 9.5 years and mean HbA1c of 8% despite combination therapy with metformin and sitagliptin, was representative of patients who may need an additional third line therapy.

In this study, the addition of ertugliflozin (5 mg and 15 mg QD) to metformin and sitagliptin provided a significant reduction from baseline in HbA1c at Week 26 compared with the addition of placebo. The time-course of HbA1c reduction showed a large decrease from baseline in HbA1c in both ertugliflozin groups at Week 6 with additional reductions through Week 26. Furthermore, at Week 26, significantly more subjects in the ertugliflozin 5 mg and 15 mg groups met the ADA-recommended HbA1c target of < 7.0% compared with the placebo group. The addition of ertugliflozin (5 mg and 15 mg QD), relative to the addition of placebo, also provided a significant reduction in FPG at Week 26. In addition to demonstrating clinically meaningful improvements in glycaemic control, the addition of ertugliflozin (5 mg and 15 mg QD) provided significantly greater reductions from baseline in body weight and SBP at Week 26 compared with the addition of placebo. These results suggest clinical relevance since more than 70% of study subjects were on antihypertensive medication before randomisation with generally well-

controlled mean SBP values at baseline (approximately 130 mmHg). Furthermore, no meaningful differences in the proportions of subjects taking antihypertensive medication at Week 26 relative to baseline were observed in the ertugliflozin or placebo groups.

Limitations

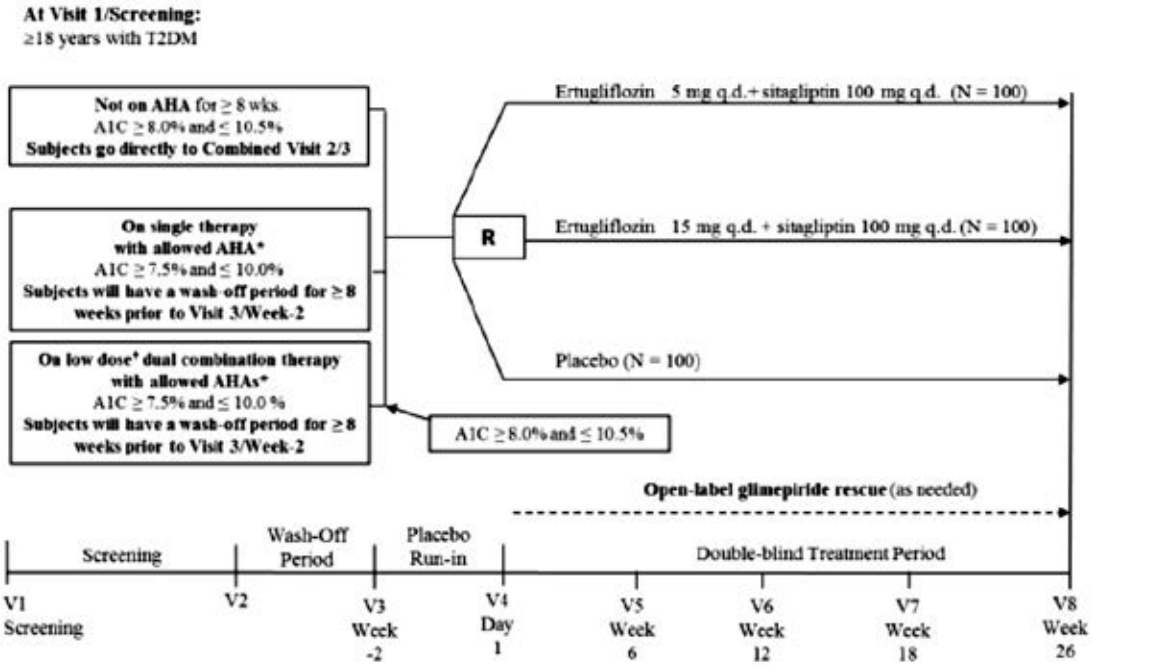
- Evidence of efficacy beyond 6 months not provided in this submission although results of Phase B (Weeks 26 to 52) of the study should provide data on long term efficacy in adults with T2DM and inadequate glycaemic control despite combination therapy with metformin ≥ 1500 mg/day and sitagliptin 100 mg QD.
- Wrong stratification based on prior SU use may have confounded results, although the results did appear to be quite robust.

1.1.2. Study P017/1047 Co-administration with sitagliptin in subjects on diet and exercise alone

1.1.2.1. Study design, objectives

This was a multicentre, randomised, double blind, placebo controlled, parallel-group, clinical trial of ertugliflozin co-administered with sitagliptin in 291 adults with T2DM and inadequate glycaemic control (HbA1c ≥ 8.0% and ≤ 10.5% (≥ 64 mmol/mol and ≤ 91 mmol/mol)) while on diet and exercise. The duration of the study was up to approximately 39 weeks (with 8 scheduled clinic visits) for each subject. This included a 1 week screening period (Visit 1 to 2), an 8 week (or greater) AHA wash-off period (Visit 2 to Visit 3), a 2 week single blind placebo run-in period (Visit 3 to Visit 4), a 26 week double blind period (Visit 4 to Visit 8), and a post-treatment telephone contact 14 days after the last dose of study medication (Figure 33).

Figure 33: Study P017/1047 Overview of study design



* Allowable oral AHAs are metformin, α-glucosidase inhibitor, sulfonylurea and glinide.

† At ≤50% maximum labeled dose of each AHA

A1C=hemoglobin A1c; q.d.=once daily; R=randomization; T2DM=type 2 diabetes mellitus; V=visit; wks.=weeks.

Subjects with an HbA1c of ≥ 8.0% and ≤ 10.5% (≥ 64 mmol/mol and ≤ 91 mmol/mol) at screening while on diet and exercise and not on anti-hyperglycaemic agent (AHA) treatment for ≥ 8 weeks were eligible to directly enter a 2 week, single blind, placebo run-in period. Subjects on monotherapy or low-dose dual combination therapy with an allowable AHA who had an HbA1c of ≥ 7.5% and ≤ 10% (≥ 58 mmol/mol and ≤ 86 mmol/mol) at screening entered a diet/exercise and AHA wash-off period ≥ 8 weeks in duration. Allowable AHAs prior to screening were metformin, α-glucosidase inhibitors, sulfonylureas and glinides. After the diet/exercise and AHA wash-off period, subjects with an HbA1c of ≥ 8.0% and ≤ 10.5% (≥ 64 mmol/mol and ≤ 91 mmol/mol) entered a 2 week, single blind, placebo run-in period. Subjects with adequate compliance during the placebo-run and who met all other entry criteria were eligible to enter the 26 week, double blind treatment period and were randomised in a 1:1:1 ratio to 1 of the following 3 groups: ertugliflozin 5 mg QD plus sitagliptin 100 mg QD (E5/S100), ertugliflozin 15 mg QD plus sitagliptin 100 mg QD (E15/S100) and placebo. Subjects who met progressively more stringent glycaemic rescue criteria during the double blind treatment period were to receive open label glimepiride rescue medication. After initiating glycaemic rescue therapy, subjects were to continue the same dose and regimen of their study medication.

The primary objectives were to assess the following in subjects with T2DM and inadequate glycaemic control on diet and exercise, after 26 weeks: HbA1c- lowering efficacy of E15/S100 and E5/S100 compared with placebo. The secondary objectives were to assess the effects of E15/S100 and E5/S100 compared with placebo on the following parameters: FPG, 2-hour PMG, proportion of subjects at target HbA1c control (HbA1c < 7% (< 53 mmol/mol)) and with HbA1c < 6.5% (48 mmol/mol), SBP, DBP, body weight, proportion of subjects requiring glycaemic rescue therapy (including time to initiation of glycaemic rescue therapy), fasting and post meal indices of beta-cell function (HOMA-%beta, and insulinogenic index with C-peptide). The study was conducted from 25 September 2014 to 23 February 2016 in 10 countries, including 96 trial centres.[4]

1.1.2.2. Inclusion exclusion criteria

The main inclusion criteria were ≥ 18 years of age, BMI ≥ 18 kg/m^2 with diagnosis of T2DM in accordance with ADA guidelines and meeting one of the following criteria:

- Not on AHA for ≥ 8 weeks with a Visit 1/Screening HbA1c ≥ 8.0% and ≤ 10.5% (≥ 64 mmol/mol and ≤ 91 mmol/mol); or
- on single allowable AHA with a Visit 1/Screening HbA1c ≥ 7.5% and ≤ 10.0% (≥ 58 mmol/mol and ≤ 86 mmol/mol); or
- on low-dose dual combination therapy with allowable AHAs with a Visit 1/Screening HbA1c ≥ 7.5% and ≤ 10.0% (≥ 58 mmol/mol and ≤ 86 mmol/mol).

Allowable AHAs prior to screening were: metformin, α-glucosidase inhibitors, sulfonylureas, and glinides; 'low dose' was defined as ≤ 50% of maximum labelled dose of an AHA. Other inclusion and exclusion criteria were similar to those discussed for previous studies.

1.1.2.3. Study treatments

The study treatments are summarised in Table 74. During the placebo run-in and double blind treatment periods, each subject took 3 oral tablets of study medications once daily in the morning, including ertugliflozin 5 mg or matching placebo tablet, ertugliflozin 10 mg or matching placebo tablet, and sitagliptin 100 mg or matching placebo tablet. Subjects who met pre-specified glycaemic criteria (Table 75) and who were rescued were also administered oral open label glimepiride at doses determined to be appropriate by the investigator according to the local approved label. Medications that were prohibited while subjects were receiving

[4] 47 in the United States, 8 in the Czech Republic, 5 in Hungary, 2 in Israel, 11 in the United Kingdom, 2 in the Ukraine, 3 in Bulgaria, 8 in Serbia, 5 in Croatia, and 5 in Estonia

investigational product during the double blind treatment period were identical to those described previously with exception that metformin was also prohibited in this study.

Table 74: Study treatments

Treatment Group	Drug/Dose	Use	Regimen/Treatment Period	Route of Administration
placebo run-in (all groups)	matching placebo for ertugliflozin 5 mg tablet	Placebo (trial drug)	q.d. in the morning for 2 weeks	oral
	matching placebo for ertugliflozin 10 mg tablet			
	matching placebo for sitagliptin 100 mg tablet			
ertugliflozin 5 mg + sitagliptin 100 mg	ertugliflozin 5 mg tablet	experimental (trial drug)	q.d. in the morning for 26 weeks	oral
	matching placebo for ertugliflozin 10 mg tablet	placebo (trial drug)		
	sitagliptin 100 mg tablet	experimental (trial drug)		
ertugliflozin 15 mg + sitagliptin 100 mg	ertugliflozin 5 mg tablet	experimental (trial drug)	q.d. in the morning for 26 weeks	oral
	ertugliflozin 10 mg tablet			
	sitagliptin 100 mg tablet			
Placebo	matching placebo for ertugliflozin 5 mg tablet	Placebo (trial drug)	q.d. in the morning for 26 weeks	oral
	matching placebo for ertugliflozin 10 mg tablet			
	matching placebo for sitagliptin 100 mg tablet			
Rescue medication	open-label glimepiride; dose determined per the investigator's discretion and according to the local approved label.	rescue medication	Initiated after subject meets rescue criteria; q.d. as required	oral
q.d.=once daily				

Table 75: Glycaemic thresholds for rescue

Visit Intervals	Glycemic Thresholds
After Visit 4/Day 1 through Visit 5/Week 6:	FPG consistently >270 mg/dL (15.0 mmol/L)
After Visit 5/Week 6 through Visit 6/Week 12:	FPG consistently >240 mg/dL (13.3 mmol/L)
After Visit 6/Week 12:	FPG consistently >200 mg/dL (11.1 mmol/L)
Note: A consistent value for FPG is defined as a repeat measurement performed within 7 days of notification from the central laboratory. Site should reinforce diet/exercise counseling prior to repeat measurement.	

1.1.2.4. Efficacy variables and outcomes

The efficacy variables assessed in this study were changes from baseline in HbA1c, FPG, 2 h PPG, body weight, blood pressure, proportion of subjects who required glycaemic rescue therapy, time to initiation of rescue and HOMA-%beta. This study also included an MMTT;[5] at Visit 4/Day 1 and Visit 8/Week 26 (or Rescue/ Discontinuation Visit). The primary, key secondary and other efficacy endpoints are summarised in Table 76.

[5] Blood samples (for measurement of glucose and C-peptide) were collected at the following time points relative to the start of the administration of the meal: 0 minutes (glucose and C-peptide), 30 minutes (glucose and C-peptide), and 120 minutes (glucose). Subjects were to take their study medication (double-blind) at the clinic 1 hour before consuming the standard meal for the MMTT at Visit 8/Week 26 (or Rescue/Discontinuation Visit); subjects did not take study medication prior to the MMTT at Visit 4/Day 1. The standard meal for the MMTT consisted of two nutrition bars and one nutrition drink (~680 kcal; 111 g carbohydrate, 14 g fat, 26 g protein). Subjects with hypersensitivity or dietary restrictions to the contents of the standard meal were to be excluded from participation in the MMTT.

Table 76: Analysis strategy for efficacy endpoints

Endpoint/Variable[1]	Approach	Statistical Method	Analysis Population	Missing Data Approach
Primary				
Change from baseline in A1C	P[2] S[2] S[2] S	cLDA ANCOVA ANCOVA ANCOVA	FAS FAS FAS FAS	Model-based Tipping Point J2R LOCF
Key Secondary				
Change from baseline in FPG	P[2]	cLDA	FAS	Model-based
Change from baseline in 2-hr PMG	P	cLDA	FAS	Model-based
Proportion of subjects at target A1C control <7.0%	P[2] S[2]	Logistic regression Logistic regression	FAS FAS	Multiple Imputation Missing= Not at Goal
Change from baseline in body weight	P[2]	cLDA	FAS	Model-based
Change from baseline in systolic blood pressure	P[2]	cLDA	FAS	Model-based
Change from baseline in diastolic blood pressure	P[2]	cLDA	FAS	Model-based
Other				
Time to rescue	P	Kaplan-Meier	All Subjects Treated	N/A
Proportion of patients requiring rescue	P	Log-rank	All Subjects Treated	N/A
Change from baseline in HOMA-%β	P	cLDA	FAS	Model-based
Change from baseline in insulinogenic index	P	cLDA	FAS	Model-based
Change from baseline in fasting C-peptide	P	cLDA	FAS	Model-based
Proportion of subjects at target A1C control <6.5%	P[2]	Logistic regression	FAS	Multiple imputation

A1C=hemoglobin A1c; ANCOVA=analysis of covariance; cLDA=constrained longitudinal data analysis; FAS=Full Analysis Set; FPG=fasting plasma glucose; HOMA %β=homeostasis model assessment of β cell function; J2R=Jump to Reference; N/A=not applicable; P=Primary; S=Secondary.
[1]The time point for all change from baseline endpoints and for A1C targets is Week 26.
[2]Analysis performed 2 ways: "excluding rescue" and "including rescue."

1.1.2.5. Randomisation and blinding

Randomisation occurred centrally using an IVRS/IWRS. Subjects were assigned randomly to one of 3 treatment groups in a 1:1:1 ratio, with once daily administration of the following:

- Ertugliflozin 5 mg and sitagliptin 100 mg (E5/S100); ertugliflozin 15 mg and sitagliptin 100 mg (E15/S100);
- Placebo. Randomisation was stratified by AHA wash-off status (yes/no).

A double blind/masking technique was used in this study. Ertugliflozin and sitagliptin were packaged identically relative to their matching placebos so that blind/masking was maintained. The subject, the investigator, sponsor personnel and personnel from the sponsor's designees who were involved in the treatment or clinical evaluation of the subjects were unaware of the treatment group assignments.

1.1.2.6. Analysis populations

The primary population for efficacy analyses was the Full analysis set (FAS), which included all randomised subjects who took at least one dose of study medication and had at least one measurement of the outcome variable (baseline or post-baseline). For analyses that used the analysis of covariance (ANCOVA) model, the FAS population defined separately for each analysis endpoint, consisted of all randomised subjects who:

- received at least one dose of study treatment;
- had baseline data for the analysis endpoint;
- had at least one post-randomisation observation for the analysis endpoint subsequent to at least one dose of study treatment.

The All subjects treated population was used for the analyses of the proportions of subjects receiving rescue medication and for the time to rescue analyses.

1.1.2.7. Sample size

A sample size of 300 subjects randomised equally among the 3 treatment arms with an effective sample size of 87 per arm at Week 26 provided > 99% power to detect a true difference of 1.0% in the mean change from baseline in HbA1c between a given ertugliflozin plus sitagliptin co-administration dose and placebo (2-sided test, $\alpha = 0.05$). The half-width of the 95% CI was expected to be 0.39%. The power for succeeding in the primary hypothesis test for both dose levels is ~98%.

1.1.2.8. Statistical methods

The primary analysis model for continuous efficacy endpoints was a constrained longitudinal data analysis (cLDA) model proposed by Liang and Zeger. 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. The model included terms for treatment, time, AHA status at screening (yes/no), baseline estimated glomerular filtration rate (eGFR), and the interaction of time by treatment. As a supportive analysis, an ANCOVA model was also used in the FAS population for the primary efficacy endpoint. The ANCOVA model included treatment, AHA status at screening, baseline eGFR, and baseline HbA1c. The last observation carried forward (LOCF) method was used to impute missing data. To explore the impact of missing data on the conclusions of the primary analysis, a detailed accounting of missing data was provided for the primary endpoint. Sensitivity analyses were performed that did not rely on the 'Missing at Random' assumption underlying the primary methodology. These analyses included a tipping-point analysis and a jump-to-reference (J2R) analysis.

All hypotheses were evaluated separately for each ertugliflozin dose level. The primary and key secondary hypotheses were tested using an ordered testing procedure (Table 76). The ordered testing procedure included the tests of HbA1c, FPG, 2-hour PMG, proportion of subjects with HbA1c < 7.0% (53 mmol/mol), body weight, SBP and DBP; each endpoint was tested beginning with E15/S100 versus placebo and continuing to E5/S100 versus placebo, using $\alpha = 0.05$ (2-sided). A secondary hypothesis was only tested if the preceding hypothesis test within the ordered testing sequence was significant. To assess whether the treatment effect at Week 26 was consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoint was estimated and plotted within each category of the following classification variable: Baseline HbA1c levels ≤ or > median; by categories: < 9.0%; ≥ 9.0% (< 74.86 mmol/mol; ≥ 74.86 mmol/mol).

1.1.2.9. Participant flow

In total, 1201 subjects were screened and 910 subjects were excluded during screening.[6] Overall, 97, 98 and 96 subjects were randomised to treatment with placebo, ertugliflozin 5 mg + sitagliptin 100 mg and ertugliflozin 15 mg + sitagliptin 100 mg, respectively. The proportion of subjects who discontinued study medication was numerically lower in the E5/S100 and E15/S100 groups than in the placebo group, primarily due to a numerically larger proportion of subjects in the placebo group who discontinued study medication for 'withdrawal by subject' and for 'lost to follow-up'. Of the 37 subjects who discontinued study medication, 9 subjects discontinued from the study (2 in the E5/S100 group, 1 in the E15/S100 group, and 6 in the placebo group). For subjects who were unwilling to participate in the post-treatment follow-up period, the most common reason for trial discontinuation was lost to follow-up.

1.1.2.10. Major protocol violations

Overall, 28.2% (82/291) of the subjects who received treatment with study medication were reported to have 1 or more major protocol deviations. The overall incidence of major protocol

[6] The most common reason for subjects not being randomised was screen failure. The most common reasons for screen failure were not meeting the inclusion criteria for A1C at Visit 1 relative to a subject's category of background diabetes therapy, and having exclusionary laboratory values.

deviations in the placebo group (41.2%) was about twice that in the co-administration groups (19.4% for E5/S100 and 24.0% for E15/S100), mainly due to higher incidences in the following deviation categories in the placebo group: failure to conduct major/significant evaluations, subjects who did not give appropriate informed consent, and MMTT not being performed. These deviations were not expected to affect efficacy and safety analysis. Other protocol deviations, including those with a potential to meaningfully impact efficacy analyses (for example, < 75% compliance with study medication, taking glycaemic rescue medication without meeting rescue criteria, and taking incorrect study medication) occurred at low incidences across the treatment groups.

1.1.2.11. Baseline data

Baseline demographic and anthropometric characteristics and the distribution of subjects by AHA use at screening were generally similar between treatment groups, with the exception that more subjects in the placebo group were in North America (excluding Central America) compared to the E5/S100 and E15/S100 groups and the median weight was numerically greater for the placebo group compared to the E5/S100 and E15/S100 groups (however, the BMI was similar across the treatment groups). The duration of T2DM was generally similar across treatment groups. Slightly more than half (51.9%) of the subjects were on background AHA therapy, which required wash-off (two-thirds washed-off 1 AHA, and one-third washed-off 2 AHAs). The percentages of subjects on background AHA therapy at screening (Table 77) and with a wash-off status of 'Yes', although not identical, were very similar for each of the treatment groups, and were similar across treatment groups. Another 12% of the patients had received prior AHAs while 36% of the patients were treatment-naïve and had never received treatment with AHAs. The mean baseline FPG was numerically higher in the placebo group (207.5 mg/dL (11.5 mmol/L)) than in the E5/S100 and E15/S100 (198.0 mg/dL (11.0 mmol/L) and 187.7 mg/dL (10.4 mmol/L), respectively). However, the mean baseline HbA1c, across the 3 treatment groups (8.90% to 8.98%) was similar. Mean eGFR values were also similar between groups (Table 78).

Table 77: Duration of type II diabetes mellitus and background AHA therapy; All subjects treated

	Placebo		Ertugliflozin 5 mg + Sitagliptin 100 mg		Ertugliflozin 15 mg + Sitagliptin 100 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	97		98		96		291	
Duration of Type 2 Diabetes Mellitus (years)								
Subjects with data	97		98		96		291	
Mean	6.75		5.68		6.49		6.30	
SD	6.48		5.04		6.53		6.05	
Median	4.90		4.55		5.40		4.90	
Range	0.1 to 34.7		0.0 to 21.4		0.1 to 40.4		0.0 to 40.4	
Background AHA Therapy Status At Screening								
Currently on AHA therapy	50	(51.5)	49	(50.0)	52	(54.2)	151	(51.9)
Not currently on AHA therapy, previously treated	16	(16.5)	15	(15.3)	11	(11.5)	42	(14.4)
Never treated	31	(32.0)	34	(34.7)	33	(34.4)	98	(33.7)
Background AHA Therapy At Screening†								
None	48	(49.5)	49	(50.0)	45	(46.9)	142	(48.8)
Biguanides	47	(48.5)	46	(46.9)	49	(51.0)	142	(48.8)
Other blood glucose lowering agents	0	(0.0)	1	(1.0)	0	(0.0)	1	(0.3)
Sulfonamides, urea derivatives	14	(14.4)	18	(18.4)	17	(17.7)	49	(16.8)
Number of agents								
0	48	(49.5)	49	(50.0)	45	(46.9)	142	(48.8)
1	37	(38.1)	33	(33.7)	36	(37.5)	106	(36.4)
2	12	(12.4)	16	(16.3)	15	(15.6)	43	(14.8)

† Combination blood glucose lowering agents are counted twice, under the each component of the combination.

Table 78: Baseline A1c, FPG, eGFR (US units); All subjects treated

	Placebo		Ertugliflozin 5 mg + Sitagliptin 100 mg		Ertugliflozin 15 mg + Sitagliptin 100 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	97		98		96		291	
Baseline A1C (%)								
<9.0	49	(50.5)	47	(48.0)	49	(51.0)	145	(49.8)
9.0 to <10.0	36	(37.1)	42	(42.9)	31	(32.3)	109	(37.5)
≥10.0	11	(11.3)	9	(9.2)	16	(16.7)	36	(12.4)
Unknown	1	(1.0)	0	(0.0)	0	(0.0)	1	(0.3)
Subjects with data	96		98		96		290	
Mean	8.95		8.90		8.98		8.94	
SD	0.86		0.87		0.87		0.86	
Median	8.90		9.00		8.90		8.95	
Range	7.0 to 10.8		6.2 to 10.7		6.2 to 10.9		6.2 to 10.9	
Baseline FPG (mg/dL)								
Subjects with data	96		98		96		290	
Mean	207.5		198.0		187.7		197.8	
SD	44.9		47.7		46.7		47.0	
Median	213.0		191.5		185.0		193.0	
Range	106 to 316		115 to 312		78 to 310		78 to 316	
Baseline eGFR (mL/min/1.73m²)								
30 to <60	2	(2.1)	1	(1.0)	1	(1.0)	4	(1.4)
60 to <90	52	(53.6)	52	(53.1)	51	(53.1)	155	(53.3)
≥90	42	(43.3)	45	(45.9)	44	(45.8)	131	(45.0)
Unknown	1	(1.0)	0	(0.0)	0	(0.0)	1	(0.3)
Subjects with data	96		98		96		290	
Mean	92.6		90.0		89.5		90.7	
SD	21.6		17.2		18.1		19.0	
Median	87.5		89.0		87.0		88.0	
Range	57 to 171		55 to 137		58 to 142		55 to 171	

Baseline value is defined as the Day 1 (Randomization) measurement. If this measurement is not available, the last pre-randomization measurement on or after Week -2 is used as the baseline value.
eGFR based on MDRD formula. Baseline value is defined as the Day 1 (Randomization) measurement. If this measurement is not available, the last pre-randomization measurement on or after Screening is used as the baseline value.

Subjects were required to have a history of T2DM for entry into the study. The other most common categories of medical history conditions by SOC were Vascular disorders (63.6%), Metabolism and nutrition disorders (51.9%) and Social circumstances (61.2%).[7] The most common specific medical history conditions, unrelated to circumcision, were hypertension (59.1%), obesity (20.6%), hyperlipidaemia (16.8%), and dyslipidaemia (14.4%) with no clinically important differences among treatment groups. Most (82.8%) of the subjects who entered the trial were taking one or more prior medications. The most common prior medication categories were drugs used in diabetes (59.5%), agents acting on the renin-angiotensin system (41.9%) and lipid modifying agents (32.3%) with no clinically important differences among treatment groups. About 66% of the subjects evaluated in this study were either currently on AHA therapy (52%) or had received prior AHA therapy (14%); AHAs used prior to study included metformin (49%) or SUs (17%) and about 15% had received two AHAs prior to this study. The most common concomitant drug therapeutic categories were agents acting on the renin-angiotensin system (43.3%), lipid modifying agents (35.4%), drugs used in diabetes (23.4%, mostly reflecting glycaemic rescue therapy and post-study diabetes treatments) and analgesics (23.4%) with no clinically important differences among treatment groups. Glimepiride, the study specified glycaemic rescue therapy, was used by a numerically higher percentage of subjects in the placebo group (33.0%) than in the E5/S100 group (7.1%) and in the E15/S100 group (0.0%). Mean compliance with study medication was > 98% across each treatment group.

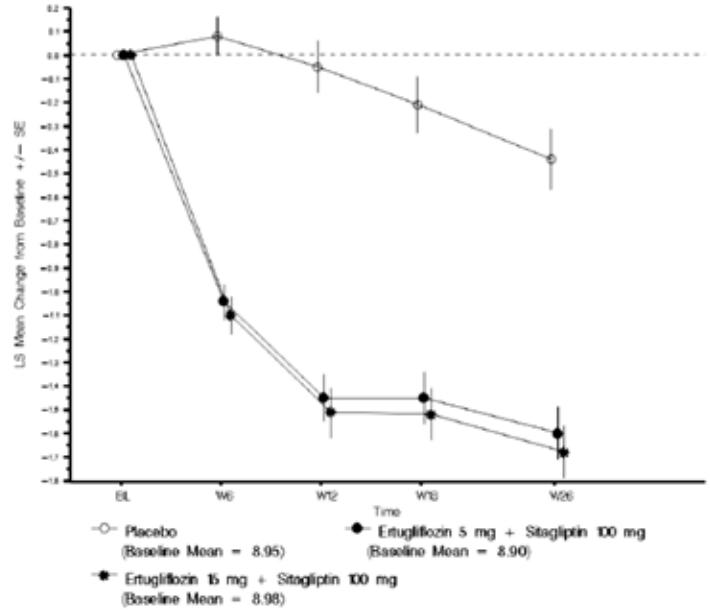
1.1.2.12. Primary efficacy results

The LS mean reduction from baseline in HbA1c at Week 26 was significantly greater in the E15/S100 and E5/S100 groups than in the placebo group (-0.44, -1.60 and -1.68 in placebo E5/S100 and E15/S100 groups, respectively; $p < 0.001$ for both comparisons). Large reductions in HbA1c in the co-administration groups at Week 6 were followed by smaller subsequent reductions through Week 26. The reduction in HbA1c was numerically greater in the E15/S100

[7] Primarily due to the collection of male circumcision status in this study.

group than in the E5/S100 group at each time point. In the placebo group, there was essentially no change from baseline in HbA1c through Week 12; thereafter, a reduction in HbA1c was observed at Week 26 (Figure 34).

Figure 34: HbA1c (%); LS Mean change from baseline over time. cLDA; FAS: excluding rescue approach



The analysis of HbA1c change from baseline at Week 26 performed using ANCOVA/LOCF, excluding data after initiation of glycaemic rescue therapy (Table 79) supported the conclusion from the primary analysis. Unlike the primary analysis methodology, the methodology for the sensitivity analyses does not rely on an assumption of 'missing at random' for missing data. This analysis shows consistent results for both J2R and tipping point analysis (Table 80).

Table 79: HbA1c (%); Change from Baseline at Week 26. Analysis of covariance with LOCF; FAS: excluding rescue approach

Treatment	N	Baseline		Week 26		Change from Baseline at Week 26			
		Mean	(SD)	Mean	(SD)	Mean	(SD)	LS Mean	(95% CI)[1]
Placebo	85	8.96	(0.88)	8.73	(1.43)	-0.23	(1.29)	-0.26	(-0.49, -0.03)
Ertugliflozin 5 mg + Sitagliptin 100 mg	97	8.91	(0.86)	7.37	(1.25)	-1.54	(1.09)	-1.57	(-1.79, -1.36)
Ertugliflozin 15 mg + Sitagliptin 100 mg	92	9.00	(0.88)	7.32	(1.05)	-1.68	(1.07)	-1.68	(-1.90, -1.46)
Pairwise Comparison		Difference in LS Means[1] (95% CI)				p-Value			
Ertugliflozin 5 mg + Sitagliptin 100 mg vs. Placebo		-1.31 (-1.63, -1.00)				<0.001			
Ertugliflozin 15 mg + Sitagliptin 100 mg vs. Placebo		-1.42 (-1.74, -1.10)				<0.001			
Root Mean Squared Error of Change						1.07			

[1]Obtained from an ANCOVA model with terms for treatment, antihyperglycemic medication wash-off status (yes/no) and covariates of baseline A1C and baseline eGFR (continuous).
CI=Confidence Interval; LS =Least Squares; SD=Standard Deviation; LOCF=Last Observation Carried Forward.

Table 80: Sensitivity analysis; J2R and tipping point analysis of primary efficacy endpoint

A1C (%): Change from Baseline at Week 26
Jump to Reference Missing Data Approach
Full Analysis Set: Excluding Rescue Approach

Treatment	Baseline		Week 26		Change from Baseline at Week 26		
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (SE)[1]
Placebo	96	8.95 (0.86)	49	8.01 (1.13)	88	-0.78 (1.06)	-0.51 (0.15)
Ertugliflozin 5 mg + Sitagliptin 100 mg	98	8.90 (0.87)	85	7.16 (1.00)	97	-1.68 (0.90)	-1.49 (0.12)
Ertugliflozin 15 mg + Sitagliptin 100 mg	96	8.98 (0.87)	82	7.28 (1.01)	94	-1.68 (1.07)	-1.56 (0.11)

Pairwise Comparison	Difference in LS Means (95% CI)[1]	p-Value
Ertugliflozin 5 mg + Sitagliptin 100 mg vs. Placebo	-0.981 (-1.343, -0.619)	<.0001
Ertugliflozin 15 mg + Sitagliptin 100 mg vs. Placebo	-1.053 (-1.404, -0.701)	<.0001

For baseline and Week 26, N is the number of subjects with non-missing assessments at the specific time point; for Change from Baseline at Week 26, N is the number of subjects in the FAS (i.e., randomized subjects who took at least 1 dose of study medication and had baseline and at least one assessment after baseline). The Mean and SD for the change from baseline are based on non-missing values.

[1] Based on ANCOVA model using imputed values for missing data based on the Jump to Reference approach, with fixed effects for treatment, antihyperglycemic medication wash-off status (yes, no), baseline eGFR (continuous) and baseline A1C.

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

A1C (%): Change from Baseline at Week 26
Tipping Point Analysis Missing Data Approach
Full Analysis Set: Excluding Rescue Approach

		P-values for Comparison of Ertugliflozin 5 mg + Sitagliptin 100 mg vs. Placebo						
		Worsening Applied to Imputed Data in Ertugliflozin 5 mg + Sitagliptin 100 mg (%)						
		4.7	4.8	4.9	5	5.1	5.2	5.3
Improvement Applied to Imputed Data in Placebo (%)								
	-1.0	0.6157	0.6553	0.6949	0.7343	0.7734	0.8122	0.8504
	-0.9	0.4991	0.5365	0.5743	0.6124	0.6506	0.6887	0.7267
	-0.8	0.3955	0.4298	0.4648	0.5004	0.5365	0.5730	0.6097
	-0.7	0.3062	0.3366	0.3680	0.4004	0.4336	0.4675	0.5019
	-0.6	0.2315	0.2576	0.2850	0.3136	0.3432	0.3739	0.4053
	-0.5	0.1709	0.1927	0.2159	0.2404	0.2661	0.2930	0.3209
	-0.4	0.1232	0.1409	0.1599	0.1803	0.2020	0.2249	0.2491
	-0.3	0.0868	0.1006	0.1158	0.1323	0.1501	0.1692	0.1895
	-0.2	0.0597	0.0702	0.0820	0.0950	0.1092	0.1247	0.1414
	-0.1	0.0401	0.0479	0.0568	0.0667	0.0778	0.0900	0.1034
	0.0	0.0264	0.0320	0.0385	0.0459	0.0543	0.0637	0.0741

		P-values for Comparison of Ertugliflozin 5 mg + Sitagliptin 100 mg vs. Placebo						
		Worsening Applied to Imputed Data in Ertugliflozin 5 mg + Sitagliptin 100 mg (%)						
		4.7	4.8	4.9	5	5.1	5.2	5.3
Improvement Applied to Imputed Data in Placebo (%)								
	-1.0	0.6157	0.6553	0.6949	0.7343	0.7734	0.8122	0.8504
	-0.9	0.4991	0.5365	0.5743	0.6124	0.6506	0.6887	0.7267
	-0.8	0.3955	0.4298	0.4648	0.5004	0.5365	0.5730	0.6097
	-0.7	0.3062	0.3366	0.3680	0.4004	0.4336	0.4675	0.5019
	-0.6	0.2315	0.2576	0.2850	0.3136	0.3432	0.3739	0.4053
	-0.5	0.1709	0.1927	0.2159	0.2404	0.2661	0.2930	0.3209
	-0.4	0.1232	0.1409	0.1599	0.1803	0.2020	0.2249	0.2491
	-0.3	0.0868	0.1006	0.1158	0.1323	0.1501	0.1692	0.1895
	-0.2	0.0597	0.0702	0.0820	0.0950	0.1092	0.1247	0.1414
	-0.1	0.0401	0.0479	0.0568	0.0667	0.0778	0.0900	0.1034
	0.0	0.0264	0.0320	0.0385	0.0459	0.0543	0.0637	0.0741

Tipping Point =5.
Multiple imputation used for missing data values with delta value (worsening or improvement) added as specified.
Analysis based on primary analysis model using Rubin's rules to obtain estimate based on imputations.

LS mean reductions from baseline in HbA1c were numerically greater in the E5/S100 and E15/S100 groups than in the placebo group across the HbA1c subgroup categories (Table 81).

Table 81: HbA1c (%); Change from Baseline at Week 26. Repeated measures analysis of covariance subgroup analysis; FAS: excluding rescue approach

	Baseline		Week 26		Change From Baseline in A1C at Week 26[†]		
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)	Difference in LS Means (95% CI)
Subgroup: Baseline A1C (Median)							
<= Median A1C (9.0 %)							
Placebo	46	8.28 (0.53)	30	7.72 (1.08)	46	-0.03 (-0.35, 0.30)	
Ertugliflozin 5 mg + Sitagliptin 100 mg	53	8.30 (0.62)	50	6.87 (0.93)	53	-1.42 (-1.70, -1.14)	-1.39 (-1.83, -0.96)
Ertugliflozin 15 mg + Sitagliptin 100 mg	49	8.34 (0.53)	46	7.07 (0.95)	49	-1.30 (-1.59, -1.00)	-1.27 (-1.71, -0.83)
> Median A1C (9.0 %)							
Placebo	39	9.76 (0.42)	19	8.47 (1.08)	39	-0.99 (-1.37, -0.62)	
Ertugliflozin 5 mg + Sitagliptin 100 mg	44	9.64 (0.44)	35	7.58 (0.95)	44	-1.80 (-2.12, -1.48)	-0.81 (-1.31, -0.32)
Ertugliflozin 15 mg + Sitagliptin 100 mg	43	9.75 (0.52)	36	7.54 (1.03)	43	-2.22 (-2.54, -1.90)	-1.23 (-1.72, -0.73)
Subgroup: Baseline A1C levels							
<9%							
Placebo	43	8.23 (0.52)	30	7.72 (1.08)	43	-0.05 (-0.39, 0.28)	
Ertugliflozin 5 mg + Sitagliptin 100 mg	46	8.19 (0.59)	44	6.77 (0.90)	46	-1.37 (-1.68, -1.07)	-1.32 (-1.78, -0.86)
Ertugliflozin 15 mg + Sitagliptin 100 mg	46	8.30 (0.52)	43	7.00 (0.95)	46	-1.31 (-1.62, -1.01)	-1.26 (-1.72, -0.81)
>=9%							
Placebo	42	9.70 (0.45)	19	8.47 (1.08)	42	-0.94 (-1.30, -0.57)	
Ertugliflozin 5 mg + Sitagliptin 100 mg	51	9.55 (0.47)	41	7.58 (0.93)	51	-1.79 (-2.09, -1.49)	-0.85 (-1.33, -0.38)
Ertugliflozin 15 mg + Sitagliptin 100 mg	46	9.70 (0.54)	39	7.58 (1.00)	46	-2.14 (-2.45, -1.83)	-1.21 (-1.69, -0.72)

For baseline and Week 26, N is the number of subjects with non-missing assessments at the specific time point; for Change from Baseline at Week 26, 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 after baseline).

[†] Obtained from a repeated measures ANCOVA model with terms for antihyperglycemic medication wash-off status (yes, no), covariates for eGFR, baseline A1C, treatment, subgroup, and treatment-by-subgroup, and treatment-by-time-by-subgroup interactions. Time was fitted as a categorical term.

The analysis was only performed for subgroups with at least 20 subjects in all of the treatment groups in each subgroup category.

For subgroup analyses based on factors that are already in the main model, the respective term will appear in the model only once.

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

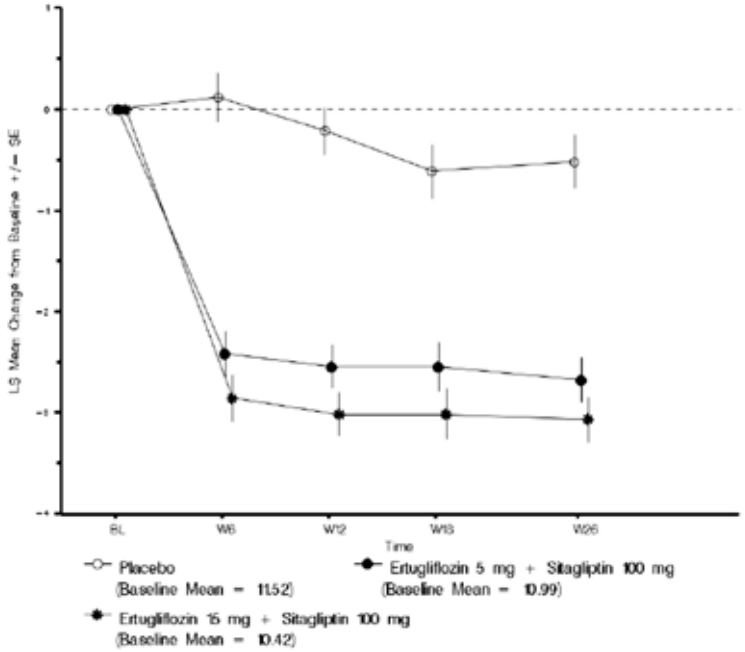
Comment: In subgroup of patients with HbA1c < 9%, the ertugliflozin 5 mg dose showed numerically greater reductions in HbA1c compared to the subgroup with HbA1c ≥ 9%.

1.1.2.13. Other efficacy results

The proportion of patients who had an HbA1c < 7.0% at Week 26 was 8.3%, 35.7% and 31.3% in the placebo, E5/S100 and E15/S100 groups, respectively. The model-based odds of having an HbA1c < 7.0% (< 53 mmol/mol) at Week 26, using multiple imputation for subjects with missing Week 26 data, were significantly greater in the E15/S100 and E5/S100 groups than in the placebo group ($p < 0.001$ for both comparisons). Similar results were observed for proportion of patients with HbA1c < 6.5% at Week 26: 4.2%, 25.5% and 17.7%, respectively.

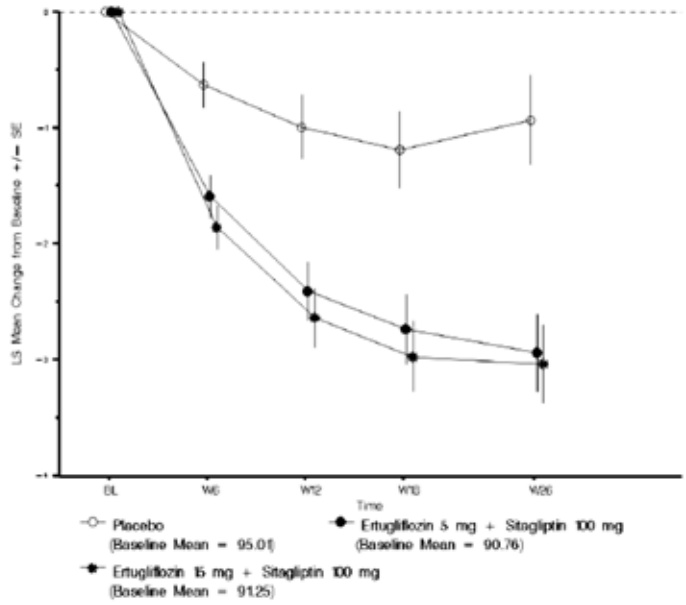
The LS mean reductions from baseline in FPG at Week 26 were significantly greater in the E15/S100 and E5/S100 groups than in the placebo group (-9.3, -48.3 and 55.4mg/dL, respectively; -0.5, -2.7 and -3.1,mmol/L, respectively) ($p < 0.001$ for both comparisons). Large reductions in FPG at Week 6 in the E15/S100 and E5/S100 groups remained stable through Week 26. The magnitude of the reduction in FPG was numerically greater in the E15/S100 group than in the E5/S100 group at each time point. In the placebo group, a slight increase in FPG at Week 6 was followed by a small decrease at Week 26 (Figure 35). The LS mean reductions from baseline in 2 h PMG at Week 26 were significantly greater in the E15/S100 and E5/S100 groups than in the placebo group ($p < 0.001$ for both comparisons), and were numerically greater in the E15/S100 group than in the E5/S100 group (-20.4, -82.9 and -90.0 mg/dL, respectively; -1.1, -4.6 and -5.0mmol/L, respectively).

Figure 35: FPG (mmol/L); Change from Baseline over time. cLDA; FAS: excluding rescue approach



The LS mean reductions from baseline in body weight at Week 26 were significantly greater in the E15/S100 and E5/S100 groups than in the placebo group (-0.9, -2.9 and -3.0kg, respectively; $p < 0.001$ for both comparisons). In the E15/S100 and E5/S100 groups, body weight decreased from baseline at Week 6 and continued to decrease at each subsequent time point through Week 26 with similar reductions observed in both dose groups. In the placebo group, small decreases in body weight at each time point through Week 18 were followed by a slight increase toward baseline at Week 26 (Figure 36).

Figure 36: Body weight (kg); LS Mean change from Baseline over time. cLDA; FAS: excluding rescue approach



The LS mean reductions from baseline in SBP at Week 26 were significantly greater in the E15/S100 and E5/S100 groups than in the placebo group (+2.43, -2.0 and -4.0 mmHg,

respectively; $p < 0.001$ and $p = 0.011$, respectively). In the E15/S100 group, a modest decrease in SBP was seen at Week 6 (first scheduled post-randomisation assessment) and remained generally stable for the rest of the study. In the E5/S100 group, small decreases in SBP at each time point through Week 18 were followed by a slight increase at Week 26. The decrease in SBP in the E15/S100 group was numerically larger than that of the E5/S100 group at Week 26. In the placebo group, a slight decrease in SBP at Week 6 was followed by a small increase through Week 26 (Figure 37). While there were numerical reductions in DBP in the E15/S100 and E5/S100 groups, differences relative to placebo were not significant. In the E15/S100 group, the small decrease in DBP seen at Week 6 was followed by a slight increase toward baseline. Decreases in DBP in the E5/S100 group fluctuated over time. A small numeric increase in DBP was seen in the placebo group over 26 weeks (Figure 38).

Figure 37: Sitting systolic BP (mmHg); LS Mean change from Baseline over time. cLDA; FAS: excluding rescue approach

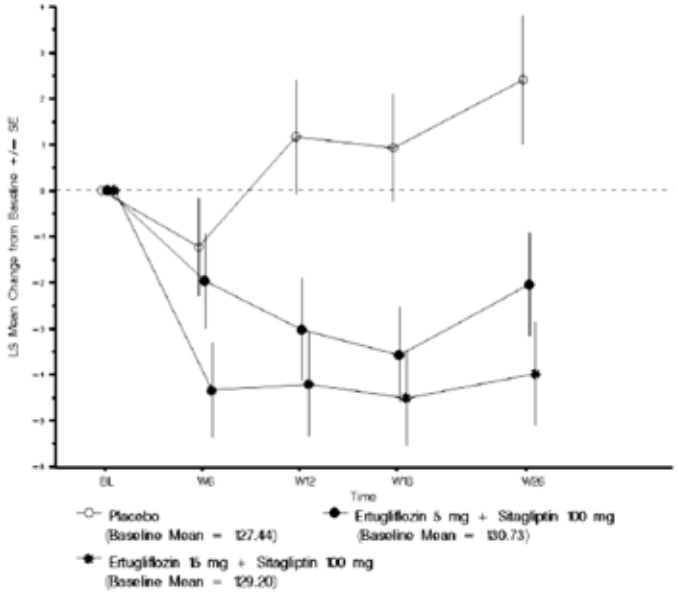
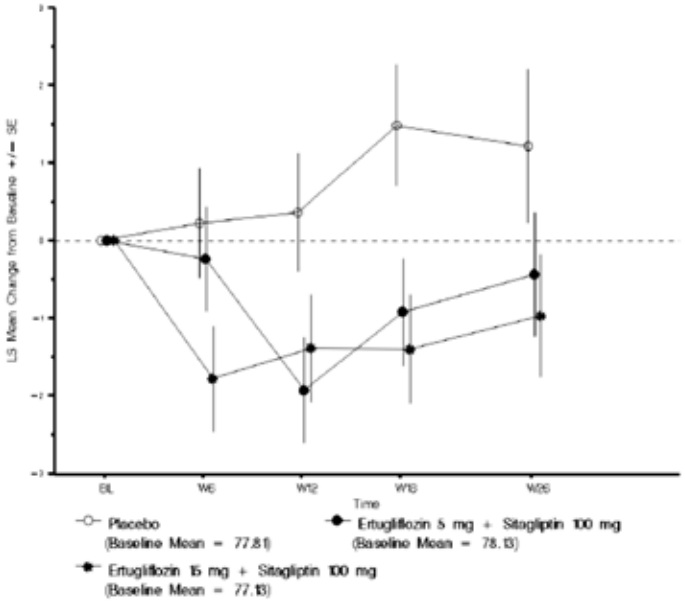


Figure 38: Sitting diastolic BP (mmHg); LS Mean change from Baseline over time. cLDA; FAS: excluding rescue approach



Comment: It is important to note that the proportion of patients on beta-blockers and diuretics was numerically higher in the E5/S100 and E15/S100 groups compared with placebo. This could have confounded interpretation of effects of proposed combination therapy on blood pressure.

The cumulative percentages of subjects who received glycaemic rescue medication through Week 26 in the E15/S100 and E5/S100 groups were lower than in the placebo group (nominal $p < 0.001$ for both comparisons). Glycaemic rescue therapy was received by no subjects in the E15/S100 group, 6.1% of subjects in the E5/S100 group, and 32.0% of subjects in the placebo group (Figure 39). The LS mean increases from baseline in beta-cell function assessed by HOMA-%beta (using C-peptide) at Week 26 (excluding data after initiation of glycaemic rescue therapy) were greater in the E15/S100 and E5/S100 groups than in the placebo group (nominal $p < 0.001$ for both comparisons). Numeric improvements in C-peptide-based insulinogenic index at Week 26 were observed in the E15/S100 and E5/S100 groups relative to the placebo group. Small numerical LS mean reductions from baseline in fasting C-peptide at Week 26 were observed in the E15/S100 and E5/S100 groups relative to the placebo group (Table 82).

Figure 39: Cumulative percentage of subjects with glycaemic rescue therapy. Kaplan-Meier curves: All subjects treated

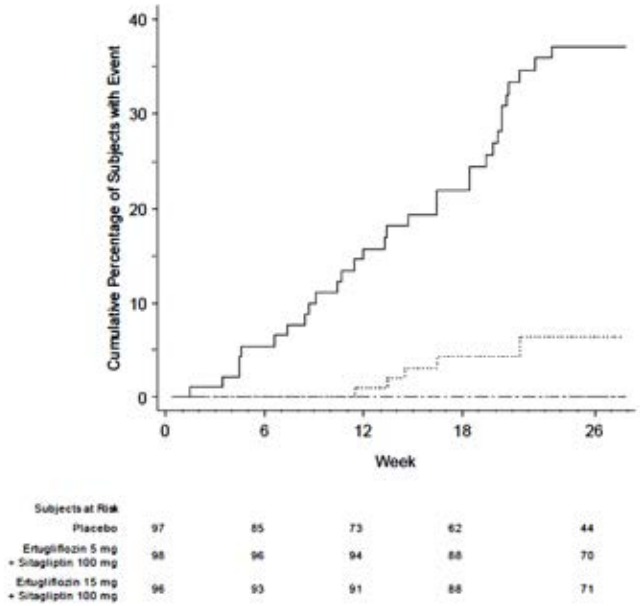


Table 82: Other MMTT results; HOMA beta cell function (%) change from Baseline to Week 26. cLDA; FAS: excluding rescue approach

Treatment	Baseline		Week 26		Change from Baseline at Week 26		
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)*
Placebo	89	35.40 (16.935)	57	43.03 (21.991)	90	3.95 (17.588)	4.13 (-1.71, 9.96)
Ertugliflozin 5 mg + Sitagliptin 100 mg	95	37.34 (20.688)	83	58.80 (27.050)	97	22.01 (23.269)	20.61 (15.73, 25.50)
Ertugliflozin 15 mg + Sitagliptin 100 mg	95	45.36 (27.116)	83	66.61 (25.427)	96	21.76 (28.088)	24.27 (19.40, 29.15)
Pairwise Comparison					Difference in LS Means (95% CI)*		p-Value
Ertugliflozin 5 mg + Sitagliptin 100 mg vs. Placebo					16.49 (9.05, 23.92)		<0.001
Ertugliflozin 15 mg + Sitagliptin 100 mg vs. Placebo					20.15 (12.72, 27.57)		<0.001
Conditional Pooled SD of Change from Baseline					21.76		

For baseline and Week 26, N is the number of subjects with non-missing assessments at the specific timepoint; for Change from Baseline at Week 26, 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, antihyperglycemic medication wash-off status (yes, no), 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.

C-peptide-based insulinogenic index (IGI) (ng/mL per mg/dL): Change from Baseline at Week 26
cLDA
Full Analysis Set: Excluding Rescue Approach

Treatment	Baseline		Week 26		Change from Baseline at Week 26		
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)*
Placebo	88	0.03 (0.023)	60	0.03 (0.027)	90	0.00 (0.030)	0.00 (-0.02, 0.03)
Ertugliflozin 5 mg + Sitagliptin 100 mg	94	0.03 (0.033)	85	0.05 (0.096)	97	0.02 (0.089)	0.02 (0.00, 0.04)
Ertugliflozin 15 mg + Sitagliptin 100 mg	94	0.02 (0.016)	80	0.05 (0.118)	95	0.03 (0.116)	0.03 (0.01, 0.05)
Pairwise Comparison					Difference in LS Means (95% CI)*		p-Value
Ertugliflozin 5 mg + Sitagliptin 100 mg vs. Placebo					0.02 (-0.01, 0.05)		0.222
Ertugliflozin 15 mg + Sitagliptin 100 mg vs. Placebo					0.03 (-0.00, 0.06)		0.087
Conditional Pooled SD of Change from Baseline					0.09		

For baseline and Week 26, N is the number of subjects with non-missing assessments at the specific timepoint; for Change from Baseline at Week 26, 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, antihyperglycemic medication wash-off status (yes, no), 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.

Fasting C-peptide (ng/mL): Change from Baseline at Week 26
cLDA
Full Analysis Set: Excluding Rescue Approach

Treatment	Baseline		Week 26		Change from Baseline at Week 26		
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)*
Placebo	90	2.40 (0.984)	57	2.51 (1.005)	91	-0.02 (0.796)	0.04 (-0.20, 0.29)
Ertugliflozin 5 mg + Sitagliptin 100 mg	96	2.18 (0.950)	84	2.23 (1.037)	98	0.03 (0.811)	-0.04 (-0.24, 0.16)
Ertugliflozin 15 mg + Sitagliptin 100 mg	95	2.57 (1.321)	83	2.38 (1.253)	96	-0.21 (1.286)	-0.13 (-0.33, 0.07)
Pairwise Comparison					Difference in LS Means (95% CI)*		p-Value
Ertugliflozin 5 mg + Sitagliptin 100 mg vs. Placebo					-0.08 (-0.39, 0.23)		0.601
Ertugliflozin 15 mg + Sitagliptin 100 mg vs. Placebo					-0.17 (-0.48, 0.14)		0.271
Conditional Pooled SD of Change from Baseline					0.90		

For baseline and Week 26, N is the number of subjects with non-missing assessments at the specific timepoint; for Change from Baseline at Week 26, 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, antihyperglycemic medication wash-off status (yes, no), 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.

1.1.2.14. Evaluator commentary

This was well-conducted pivotal Phase III study which evaluated the efficacy and safety of initial combination treatment with ertugliflozin (5 mg or 15 mg QD) and sitagliptin (100 mg QD) relative to placebo in 291 subjects with T2DM and inadequate glycaemic control on diet and exercise. Dual therapy with ertugliflozin and sitagliptin provides two AHAs with different mechanisms of action; neither is associated with hypoglycaemia or weight gain. Ertugliflozin inhibits renal glucose reabsorption, resulting in urinary glucose excretion, and thereby reducing plasma glucose and HbA1c. Sitagliptin enhances the incretin axis, thereby increasing insulin secretion and reducing glucagon concentrations, and, in turn, lowering hepatic glucose production. Combining these agents provides complementary mechanisms leading to robust glucose-lowering efficacy, with low risk for hypoglycaemia.

In subjects with T2DM and inadequate glycaemic control on diet and exercise, treatment with the initial combination of ertugliflozin (5 mg QD or 15 mg QD) and sitagliptin 100 mg QD for 26 weeks provides clinically meaningful reductions from baseline in HbA1c, FPG, and 2-hour PMG relative to placebo. The initial combination therapy also results in a greater proportion of subjects with HbA1c < 7% (< 53 mmol/mol) relative to placebo and reduces body weight and

sitting SBP relative to placebo. Although the mean sitting SBP for subjects in this study was approximately 130 mmHg and about 50% of subjects were on antihypertensive medication, sitting SBP was reduced from baseline at Week 26 by approximately 2 and 4 mmHg in the E5/S100 and E15/S100 groups, respectively.

Although this study was not designed to formally compare the 5 mg and 15 mg ertugliflozin doses, there were numerically greater reductions in HbA1c, FPG, 2-hour PMG, body weight and sitting SBP with the E15/S100 combination, relative to the E5/S100 combination, although the differences between the 2 co-administration groups were small for these endpoints.

Limitations

Maintenance of efficacy of initial combination therapy with ertugliflozin (5 mg and 15 mg QD) and sitagliptin (100 mg QD) was not evaluated beyond 6 months in T2DM patients with inadequate glycaemic control on diet and exercise.

1.2. Other efficacy studies

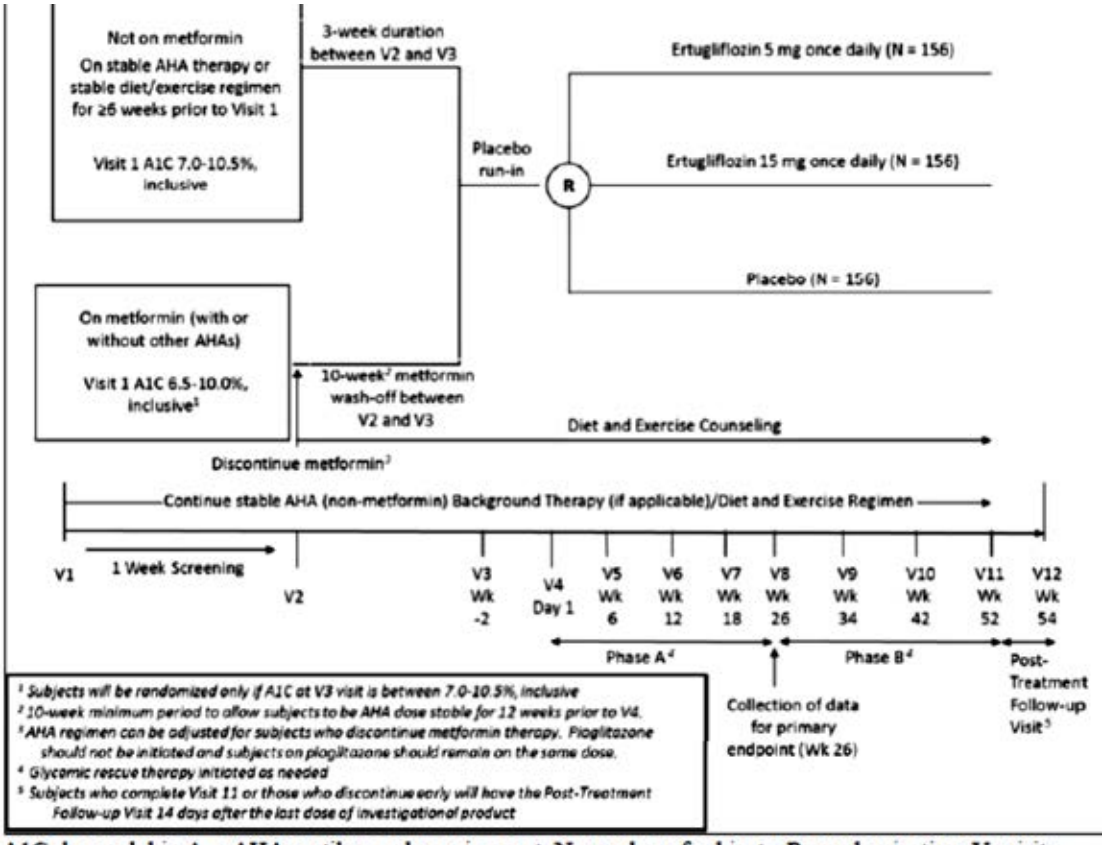
There was one Phase III study (Study P001/1016) in subjects with T2DM who have Stage 3 CKD (eGFR ≥ 30 to < 60 mL/min/1.73 m^2) and two Phase II dose finding studies (discussed in section 7.3.2 below).

1.2.1. Study P001/1016

1.2.1.1. Study design, objectives

This was a Phase III, multicentre, randomised, double blind, placebo controlled, parallel-group clinical trial of ertugliflozin in subjects with T2DM and Stage 3 CKD (moderate renal impairment; eGFR ≥ 30 to < 60 mL/min/1.73m^2). The double blind treatment period was 52 weeks in duration and divided into two 26 week phases (Phase A; Weeks 0 to 26; Phase B; Weeks 26 to 52). Results from Phase A are presented in this submission and results from Phase B will be prepared later at the end of the study. An overview of the study design is provided in Figure 40.

Figure 40: Study P001/1016 Overview of study design



A1C=hemoglobin A_{1c}; AHA=antihyperglycemic agent; N=number of subjects; R=randomization; V=visit; Wk=week.

The primary objectives of the study were to assess the following in subjects with T2DM and inadequate glycaemic control on standard diabetes therapy with a Visit 3/Week 2; eGFR of ≥ 30 to < 60 mL/min/1.73m^2, after 26 weeks: the HbA1c-lowering efficacy of the addition of ertugliflozin 15 mg QD and 5 mg QD compared to the addition of placebo; and safety and tolerability of ertugliflozin. The secondary objectives were to assess effects of both ertugliflozin doses (15 mg and 5 mg QD) compared to placebo on body weight, FPG, SBP, DBP and proportion of subjects with HbA1c < 7% (53mmol/mol) at Week 26. The study was conducted from 3 December 2013 to 11 Mar 2016 (last subject visit for Phase A) in 13 countries, including 171 trial centres.[8]

1.2.1.2. Inclusion/exclusion criteria

Approximately 468 subjects ≥ 25 years of age, BMI > 18kg/m^2 with T2DM diagnosed in accordance with ADA guidelines, Stage 3 CKD, and inadequate glycaemic control (HbA1c ≥ 7.0% and ≤ 10.5% (≥ 53 mmol/mol and ≤ 91 mmol/mol)) on treatment with standard diabetes therapy(-ies) and who met all enrolment criteria were planned to be randomised. Allowable standard diabetes therapy included diet/exercise therapy and AHA monotherapy or combination therapy. Allowable AHAs included injectable and oral agents except metformin, rosiglitazone and other SGLT2 inhibitors. Details of inclusion and exclusion criteria are summarised in Table 83). Eligible subjects were randomised to one of the 3 treatment groups (ertugliflozin 15 mg QD, ertugliflozin 5 mg QD or matching placebo) (Table 84). Subjects who were < 80% compliant (based on pill count) with the placebo run-in medication were ineligible for randomisation. During the remainder of the trial, compliance to double blind treatment was

[8] 9 in Argentina, 13 in Bulgaria, 11 in Columbia, 10 in Hungary, 10 in Israel, 11 in Mexico, 8 in the Philippines, 9 in Poland, 19 in Romania, 10 in Russia, 9 in South Africa, 10 in the United Kingdom, and 42 in the United States.

assessed by subject report.[9] Subjects who met progressively more stringent glycaemic rescue criteria (Table 85) were to have their AHA regimen adjusted or initiate treatment with a new AHA(s), with intensification of the subject's regimen managed as considered appropriate by the investigator. Subjects on insulin were to maintain a stable dose unless they met glycaemic rescue criteria. In this study, variations in insulin dose ≤ 15% relative to baseline (Visit 4/Randomisation) were considered stable.

Table 83: Study P001/1017 Main inclusion and exclusion criteria

Study P001/1017 Main inclusion and exclusion criteria
Main inclusion criteria
1. T2DM according to ADA guidelines and ≥ 25 years of age, BMI > 18kg/m^2.
2. Meet one of the following criteria: a. Subject is not on metformin: Subject is on stable diabetes therapy (diet/exercise therapy alone or AHA monotherapy or combination therapy) for ≥ 6 weeks prior to Visit 1/Screening with a Visit 1/Screening A1C of 7.0% to 10.5% (53 to 91 mmol/mol), inclusive. Note: Allowable AHAs include injectable and oral agents except metformin, rosiglitazone, and other SGLT2 inhibitors or b. Subject is on metformin: Subject is on metformin (with or without diet/exercise therapy or other AHA therapy) with a Visit 1/Screening A1C of 6.5% to 10.0% (48 to 86 mmol/mol), inclusive, and is willing to undergo a 10 week metformin wash-off period. Note: Subjects who wash-off metformin can have their AHAs adjusted (that is, dose change of current AHA(s) or initiation of new AHA) with the exception of pioglitazone. Subjects on pioglitazone should remain on the same dose and pioglitazone must not be initiated in subjects who are not already on pioglitazone.
3. Have an eGFR of ≥ 30 to < 60 mL/min/1.73m^2 (calculated using the MDRD formula). Note: Subjects who do not meet the eGFR entry criterion may have one repeat determination performed if the investigator considers the Visit 1/Screening result to be inconsistent with prior determinations.
4. At Visit 3/Week -2: a. Have an A1C of 7.0% to 10.5% (53-91 mmol/mol), inclusive, in subjects who have undergone metformin wash-off. 9. Have an eGFR of ≥ 30 to < 60 mL/min/1.73m^2 (calculated using the MDRD formula) with < 10 mL/min/1.73m^2 change in eGFR from Visit 1 to Visit 3.
5. At Visit 4/ Randomisation (Day 1): a. Be ≥ 80% compliant with the single blind placebo run-in medication (as determined by site-performed pill count).

[9] Subjects were directed to bring any used and unused study medication bottles to each visit. The investigator was to maintain a complete and current accountability record of the blinded study medication. Compliance with the placebo run-in medication was monitored by study personnel at the site, at the end of the placebo run-in on Visit 4/ Randomisation (Day 1), by comparing the returned single-blind study medication with the amount dispensed and the information reported by the subject.

Main exclusion criteria Besides the usual exclusion criteria for other Phase III studies, the following were specific for this study in patients with Stage 3 CKD.
1. Has a history of other secondary causes of diabetes (for example, genetic syndromes, secondary pancreatic diabetes, and diabetes due to endocrinopathies, drug or chemical induced, and post-organ transplant).
2. Has a history of nephrotic range proteinuria (> 3000 mg/day) with hypoalbuminaemia and oedema.
3. Has a history of rapidly progressive glomerulonephritis, lupus nephritis, renal or systemic vasculitis, renal artery stenosis with renovascular hypertension, or ischemic nephropathy.
4. Has a history of familial renal glucosuria.
5. Has a history of renal dialysis or renal transplant or renal disease requiring treatment with any immunosuppressive agent.
6. Has a known hypersensitivity or intolerance to any SGLT2 inhibitor.
7. Meets any of the following criteria: Subject is on a weight loss program and is not weight stable; Subject is on a weight loss medication (for example, orlistat, phentermine/topiramate, lorcaserin) and is not weight stable; Subject is on other medications associated with weight changes (for example, antipsychotic agents) and is not weight stable; Subject has undergone bariatric surgery > 12 months prior to Visit 1/Screening and is not weight stable; Subject has undergone bariatric surgery within 12 months of Visit 1/Screening. Note: Weight-stable is defined as < 5% change in body weight in the last 6 months.
8. Has been treated with any of the following agents (not permitted within 12 weeks of Visit 1/Screening or during the pre-randomisation period): Rosiglitazone; other SGLT2 inhibitors.
9. Has active, obstructive uropathy or indwelling urinary catheter.

Table 84: Study treatments

Treatment Group	Drug	Dose/Potency	Route of Administration	Regimen	Use
Placebo Run-in (all treatment groups)	Ertugliflozin 10 mg Matching Placebo	0 mg tablet	Oral	q.d. for 2 weeks	Experimental (trial drug)
	Ertugliflozin 5 mg Matching Placebo	0 mg tablet	Oral	q.d. for 2 weeks	Experimental (trial drug)
Ertugliflozin 15 mg Group	Ertugliflozin 10 mg	10 mg tablet	Oral	q.d. for 52 weeks[1]	Experimental (trial drug)
	Ertugliflozin 5 mg	5 mg tablet	Oral	q.d. for 52 weeks[1]	Experimental (trial drug)
Ertugliflozin 5 mg Group	Ertugliflozin 5 mg	5 mg tablet	Oral	q.d. for 52 weeks[1]	Experimental (trial drug)
	Ertugliflozin 10 mg Matching Placebo	0 mg tablet	Oral	q.d. for 52 weeks[1]	Experimental (trial drug)
Placebo Group	Ertugliflozin 10 mg Matching Placebo	0 mg tablet	Oral	q.d. for 52 weeks[1]	Experimental (trial drug)
	Ertugliflozin 5 mg Matching Placebo	0 mg tablet	Oral	q.d. for 52 weeks[1]	Experimental (trial drug)

CSR=clinical study report; q.d.=once daily.
[1]The 52-week treatment period of this study included a 26-week Phase A and 26-week Phase B. This CSR presents results from Phase A. A separate CSR including results from Phase B will be prepared at the end of the overall study.

Table 85: Glycaemic thresholds for rescue

Visit Interval	Glycemic Threshold
After Visit 4/Randomization through Visit 5/Week 6:	FPG consistently >270 mg/dL (15.0 mmol/L)
After Visit 5/Week 6 through Visit 6/Week 12:	FPG consistently >240 mg/dL (13.3 mmol/L)
After Visit 6/Week 12 through Visit 8/Week 26:	FPG consistently >200 mg/dL (11.1 mmol/L)
After Visit 8/Week 26:	FPG consistently >200 mg/dL (11.1 mmol/L) or A1C >8.0% (64 mmol/mol)

A1C=hemoglobin A_{1c}; FPG=fasting plasma glucose.
Note: A consistent value for FPG was defined as a repeat measurement performed within 3-7 days of notification from the central laboratory. Sites should have reinforced diet/exercise counseling prior to repeat measurement.

1.2.1.3. Blinding and randomisation

A double blind/masking technique;[10] was used in this study. Randomisation was done centrally using IVRS/IWRS. Subjects were assigned randomly to 1 of 3 treatment groups in a 1:1:1 ratio to ertugliflozin 5 mg QD, ertugliflozin 15 mg QD, or placebo using a computer generated randomisation schedule. Randomisation was stratified according to the following factors: 1) subject's Visit 3/Week -2 eGFR value: eGFR ≥ 30 to < 45 mL/min/1.73m^2 and eGFR ≥ 45 to < 60 mL/min/1.73m^2 , 2) medical history of CV disease or heart failure;[11] (yes/no); 3) treatment with insulin at randomisation (yes/no).

1.2.1.4. Efficacy endpoints and statistical methods

The primary analysis model for continuous efficacy endpoints was a constrained longitudinal data analysis (cLDA) model proposed by Liang and Zeger. 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. The model included terms for treatment, eGFR stratum, baseline treatment with insulin stratum, time, and the interaction of time by treatment. All hypotheses were

[10] Ertugliflozin and matching placebos were packaged identically so that blind/masking was maintained. The subject, the investigator, Sponsor personnel, and personnel from the Sponsors' designees, Covance and Parexel, who were involved in the treatment of clinical evaluation of the subjects were unaware of the group assignments.
[11] Subjects with CV history: defined as those subjects with a medical history of CV, peripheral vascular, cerebrovascular, or non-cardiac atherosclerotic disease, including (but not limited to) one or more of the following terms: ischemic cardiac disease, coronary artery disease, cerebrovascular accident, transient ischemic attack, peripheral vascular disease, and renal artery stenosis. Hypertension was not considered a CV disease for the purpose of this trial. Subjects with heart failure history: defined as those subjects with a medical history of heart failure, including (but not limited to) one or more of the following terms: left ventricular dysfunction, right ventricular failure, heart failure, and congestive heart failure.

evaluated separately for each ertugliflozin dose level. The primary and key secondary hypotheses were tested using an ordered testing procedure. The ordered testing procedure included the tests of HbA1c (initially tested for stratum of eGFR ≥ 30 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2; and then for secondary endpoints in the ≥ 45 mL/min/1.73 m^2 stratum), body weight, systolic blood pressure, FPG, percentage of subjects with HbA1c < 7.0% (53 mmol/mol), all beginning with ertugliflozin 15 mg versus placebo and continuing to ertugliflozin 5 mg versus placebo for each endpoint, using α = 0.05 (2-sided). Secondary hypotheses, all of which applied only to the eGFR ≥ 45 to < 60 mL/min/1.73 m^2 stratum, were tested only if success was achieved for both doses in the test of the primary hypothesis (Table 86). As supportive analyses, the HbA1c change from baseline at Week 26 was also analysed using an ANCOVA model in the FAS population for the Overall Cohort and each eGFR stratum separately. The ANCOVA model included treatment, baseline treatment with insulin stratum, and baseline value for the analysis by eGFR stratum, and used the same model with an additional term for eGFR stratum for the analysis in the Overall Cohort. The LOCF method was used to impute missing values.

Table 86: Analysis strategy for efficacy endpoints in Phase A

Endpoint/Variable (Description, Week 26)	Approach	Statistical Method	Analysis Population	Missing Data Approach
Primary (Overall Cohort)				
Change from baseline in A1C	P†	cLDA	FAS	Model-based
	S	ANCOVA	FAS	LOCF
Key Secondary (eGFR ≥45 stratum)				
Change from baseline in A1C	P†	cLDA	FAS	Model-based
	S	ANCOVA	FAS	LOCF
Change from baseline in body weight	P†	cLDA	FAS	Model-based
Change from baseline in systolic blood pressure	P†	cLDA	FAS	Model-based
Change from baseline in FPG	P†	cLDA	FAS	Model-based
Proportion of subjects with A1C at goal (<7.0%)	P†	Logistic regression	FAS	Multiple Imputation
Other Endpoints				
eGFR ≥45 stratum				
Change from baseline in diastolic blood pressure	P†	cLDA	FAS	Model-based
Time to rescue	P	Kaplan-Meier Log-rank	All Subjects Treated	N/A
Proportion of subjects requiring rescue	P	Kaplan-Meier Log-rank	All Subjects Treated	N/A
eGFR <45 stratum				
Change from baseline in • A1C • FPG • Body weight • Systolic and diastolic blood pressure	P†	cLDA	FAS	Model-based
	S	ANCOVA	FAS	LOCF
Proportion of subjects with A1C at goal (<7.0%)	P†	Logistic regression	FAS	Multiple Imputation

†Analysis performed 2 ways: "excluding rescue" and "including rescue."
A1C=hemoglobin A_{1c}; ANCOVA=analysis of covariance; cLDA=constrained longitudinal data analysis; eGFR=estimated glomerular filtration rate; FAS=Full Analysis Set; FPG=fasting plasma glucose; LOCF=last observation carried forward; N/A=not applicable; P=Primary; S=Secondary.

An unusual placebo-response in analyses of change from baseline in HbA1c led to an investigation of potential metformin use (an excluded medication) by study subjects. Available samples collected during the treatment period were assayed and revealed that metformin had been taken by several subjects during the study. Post-hoc analyses in subjects with and without positive metformin assay results were added after the pre-specified HbA1c analysis results identified an unusual placebo response in the Overall Cohort and Stage 3A CKD stratum, characterised by notable decreases in HbA1c between Week 18 and Week 26. Metformin was not allowed as a concomitant background medication in this study. Because concomitant metformin use could confound the comparison of ertugliflozin versus placebo, several post-hoc analyses were added to evaluate the treatment response in subjects with (1) at least one positive metformin assay result at any time point; and (2) no positive metformin assay results (Table 87).

Table 87: Post-hoc analysis

Description	eGFR Stratum (mL/min/1.73 m²)	Metformin Assay Status
Efficacy Endpoints: Tables		
A1C (%): Change from Baseline at Week 26	Overall	at least one positive
		without positive
	<45	without positive
	≥ 45	without positive
FPG (mg/dL): Change from Baseline at Week 26	Overall	without positive
	≥ 45	without positive
Body Weight (kg): Change from Baseline at Week 26	Overall	without positive
	≥ 45	without positive
Efficacy Endpoints: Figures		
A1C (%): LS Means With Change Over Time	Overall	at least one positive
		without positive
	<45	without positive
	≥ 45	without positive
FPG (mg/dL): LS Means With Change Over Time	Overall	without positive
	≥ 45	without positive
Body Weight (kg): LS Means With Change Over Time	Overall	without positive
	≥ 45	without positive
PK Endpoints: Tables		
Cumulative Proportion of Subjects with Positive Metformin Assay Results Over Time	Overall, <45, and ≥ 45	NA
Proportion of Subjects with Metformin Assay Results Over Time	Overall, <45, and ≥ 45	NA
Listing of Metformin Plasma Concentrations (ng/mL)	NA	NA
Demographics and Baseline Characteristics: Tables		
Subject Characteristics. Gender, Age, Race, Ethnicity, Region, Height, Weight, BMI and Stratification Factors	Overall	without positive
	≥ 45	without positive
Subject Characteristics. Baseline CV Risk Factors, Diabetes Characteristics and Other Factors	Overall	without positive
	≥ 45	without positive
Duration of Type 2 Diabetes Mellitus and Background AHA Therapy	Overall	without positive
	≥ 45	without positive
Baseline A1C, FPG, eGFR (US units)	Overall	without positive
	≥ 45	without positive
Safety Endpoints: Tables		
Analysis of Documented and Severe Hypoglycemia Adverse Events	Overall	without positive
	<45	without positive
	≥ 45	without positive

Abbreviations: A1C=hemoglobin A_{1C}; AHA=antihyperglycemic agent; BMI=body mass index; CKD=chronic kidney disease; CV=cardiovascular; eGFR=estimated glomerular filtration rate; FPG=fasting plasma glucose; LS=least squares; NA=not applicable; PK=pharmacokinetic; US=United States.

Efficacy and safety tables and figures used the excluding rescue approach.

1.2.1.5. Analysis sets and sample size

The primary population for efficacy analyses was the Full analysis set (FAS), which included all randomised subjects who took at least one dose of study medication and had at least one measurement of the outcome variable (baseline or post-baseline). For analyses that used the analysis of covariance (ANCOVA) model, the FAS population, defined separately for each analysis endpoint, consisted of all randomised subjects who: Received at least one dose of study medication: Had baseline data for the analysis endpoint: Had at least one post-randomisation observation for the analysis endpoint subsequent to at least one dose of study medication. Analyses of the proportions of subjects requiring rescue medication and time to rescue were performed in the All subjects treated population. Approximately 468 subjects were planned to be enrolled in this trial and randomised equally among the 3 treatment groups. A sample size of 156 subjects per group (equivalent to an effective sample size of 144 subjects per group at Week 26) was estimated to provide 90% power to detect a true difference of 0.38% in the mean change from baseline in HbA1c between a given ertugliflozin dose and placebo. The power for succeeding in the primary hypothesis test for both dose levels was approximately 81%.

1.2.1.6. Patient disposition and protocol violations

Overall, 1709 subjects were screened and 1241 subjects were excluded during screening and the only reason for subjects not being randomised was screen failure mainly due to not meeting

the inclusion criteria for eGFR and/or the HbA1c and diabetes therapy requirements at Visit 1/Screening. Overall, 158, 156 and 154 were randomised to ertugliflozin 5 mg, 15 mg and placebo, respectively with similar proportions of subjects discontinuing study medication in Phase A (10.8%, 10.3% and 11%, respectively). Across the 3 treatment groups, the most common reasons for study medication discontinuation were for AEs and for withdrawal by subject. A numerically higher incidence of subjects discontinued study medication for an AE in the ertugliflozin 5 mg group (10) than in the ertugliflozin 15 mg and placebo groups (5 each) Withdrawal by subject was numerically higher in the ertugliflozin 15 mg and placebo groups than in the ertugliflozin 5 mg group. Other reasons for study medication discontinuation were similar between groups. Overall, 48.4% (226/ 467) of subjects who received treatment with study medication were reported to have 1 or more major protocol deviations. Although the overall incidence of major protocol deviations was slightly higher in the placebo group than in the ertugliflozin groups, no important differences with regard to specific deviation categories were seen. The most common major deviations were those associated with informed consent deviations, failure to conduct major/significant evaluations, eligibility criteria deviations, and receiving glycaemic rescue medication without meeting glycaemic rescue criteria and these were not expected to affect safety or efficacy conclusions. Other protocol deviations, including those with a potential to meaningfully impact efficacy analyses (for example, < 75% compliance with study medication and taking incorrect study medication) occurred at low incidences across the treatment groups. The cumulative proportions of subjects with at least one positive metformin assay result (concentration ≥ LLOQ) increased over time, with a total of 78 (16.7%) subjects in the overall cohort having at least one sample that was positive for metformin during the study. The percentages of subjects with positive assay results were similar across the 3 treatment groups. A greater percentage of subjects in the Stage 3A CKD stratum had a positive sample (58 (19.3%) subjects in total) than in the Stage 3B CKD stratum (20 (12.0%) subjects in total). It is possible that the percentage of subjects using metformin at or before Week 26 was underestimated because fewer samples were available for metformin testing at Week 26 than at earlier time-points.

1.2.1.7. Baseline data

Overall, 49.5% of subjects were males, the mean age was 67.3 years, 81.4% were White, 56.4% were using insulin and approximately 50% had a history of CV disease or heart failure. Furthermore, 159 subjects (34%) were stratified to the Stage 3B CKD stratum (eGFR > 30 and ≤ 45 mL/min/1.73m^2) and 308 (66%) to the Stage 3A CKD stratum (eGFR > 45 and ≤ 60 mL/min/1.73m^2). There were no notable differences between treatment groups for these baseline characteristics. Some of these subjects were mis-stratified, and their data were analysed according to the intended stratum rather than the actual stratum. There were no notable differences in baseline characteristics between treatment groups in the 166 subjects analysed in the Stage 3B CKD stratum and 301 subjects analysed in the Stage 3A CKD stratum, respectively. A total of 106 (22.6%) randomised subjects were incorrectly stratified across the 3 treatment groups, a majority of which were mis-stratified to medical history of CV disease or heart failure (86 subjects; 18.4%).[12] The net result is that the ertugliflozin 5 mg and 15 mg groups have 6 and 9 fewer subjects, respectively, with a history of CV disease in the study population. The sponsors state that this is unlikely to impact the efficacy analyses and safety analyses because this stratification factor was not included in any analyses.

[12] Two types of errors were made in the CV disease stratification. In 34 of the 86 cases (16, 7, and 11 subjects in the placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg groups, respectively), subjects were assigned to the CV stratum without actually having a medical history term qualifying as having CV disease. A large number of these cases occurred where medical history terms of hypertension or dyslipidaemia were erroneously used to categorise subjects as having CV disease. The remaining 52 errors in CV mis-stratification (19, 13, and 20 subjects in the placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg groups, respectively) occurred because subjects with a medical history of CV disease were not randomised to the CV stratum.

The mean duration of T2DM (approximately 14 years) was not meaningfully different across treatment groups. More than 95% of subjects in each treatment group were on background AHA therapy at screening. The majority of these subjects were receiving insulin and analogs for injection (55.9%) and/or sulphonamides, urea derivatives (40.3%) (Table 88). Subject demographic and anthropometric characteristics of T2DM duration and background AHAs, and of CV risk factors and diabetes characteristics for the Stage 3A CKD and Stage 3B CKD strata, the Insulin and Sulfonylurea subgroups, and for the subgroup of subjects without a positive metformin assay result did not show any notable differences relative to the Overall Cohort. Baseline HbA1c, FPG, and eGFR values were similar between groups. The mean HbA1c was 8.15%, and the mean eGFR was 46.6 mL/min/1.73 m^2 (Table 89). Baseline characteristics for the overall cohort and overall cohort excluding subjects having positive metformin assay results were similar: 49.5% and 50.1% of subjects were male; mean baseline HbA1c was 8.15% and 8.14%, mean eGFR was 46.6 mL/min/1.73 m^2 and 46.1mL/min/1.73 m^2; and 24.6% and 22.4% of subjects were on metformin at screening, respectively. Similar results were observed for baseline characteristics for the Stage 3A CKD stratum and Stage 3A CKD stratum (excluding subjects having positive metformin assay results). Subjects were required to have a history of T2DM with stage 3 CKD for entry into the study. The other most common categories of medical history conditions by SOC were Vascular disorders (94.2% of all subjects treated), Metabolism and nutrition disorders (86.1%) and Surgical and medical procedures (58.5%). The most common specific medical history conditions were hypertension (89.3%), dyslipidaemia (32.1%), and hyperlipidaemia (31.0%) with no clinically important differences among treatment groups. Drugs used for diabetes were taken by 97.6% of subjects. Subjects using metformin were to have washed-off prior to randomisation. Metformin and metformin hydrochloride were listed as prior medications for 123 (26.3%) and 43 (9.2%) subjects, respectively. The other most common prior medication categories were agents acting on the renin-angiotensin system (85.7%), lipid modifying agents (78.4%) and analgesics (56.1%) with no clinically important differences among treatment groups. The most common concomitant drug categories were drugs used in diabetes (94.9% of all subjects treated), agents acting on the renin-angiotensin system (86.9%) and lipid modifying agents (79.4%) with no clinically important differences among treatment groups. Mean compliance with study medication was ≥ 97.7% across treatment groups.

Table 88: Duration of type II diabetes mellitus and background AHA therapy; All subjects treated

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	154		158		155		467	
Duration of Type 2 Diabetes Mellitus (years)								
Subjects with data	154		158		155		467	
Mean	13.13		14.87		14.49		14.17	
SD	8.09		8.97		8.48		8.54	
Median	12.50		13.60		14.60		13.30	
Range	0.2 to 41.4		0.1 to 44.2		0.4 to 46.4		0.1 to 46.4	
Background AHA Therapy Status At Screening								
Currently on AHA therapy	151	(98.1)	153	(96.8)	148	(95.5)	452	(96.8)
Not currently on AHA therapy, previously treated	1	(0.6)	5	(3.2)	5	(3.2)	11	(2.4)
Never treated	2	(1.3)	0	(0.0)	2	(1.3)	4	(0.9)
Background AHA Therapy At Screening†								
None	3	(1.9)	5	(3.2)	7	(4.5)	15	(3.2)
Alpha Glucosidase Inhibitors	0	(0.0)	2	(1.3)	3	(1.9)	5	(1.1)
Biguanides	36	(23.4)	41	(25.9)	38	(24.5)	115	(24.6)
Dipeptidyl peptidase 4 (DPP-4) inhibitors	21	(13.6)	22	(13.9)	20	(12.9)	63	(13.5)
GLP-1 receptor agonists	7	(4.5)	3	(1.9)	3	(1.9)	13	(2.8)
Insulins and Analogs for Injection	85	(55.2)	89	(56.3)	87	(56.1)	261	(55.9)
Other blood glucose lowering agents	4	(2.6)	3	(1.9)	4	(2.6)	11	(2.4)
Sulfonamides, urea derivatives	63	(40.9)	65	(41.1)	60	(38.7)	188	(40.3)
Thiazolidinediones	4	(2.6)	3	(1.9)	2	(1.3)	9	(1.9)
Background AHA Therapy At Screening†								
Number of agents								
0	3	(1.9)	5	(3.2)	7	(4.5)	15	(3.2)
1	90	(58.4)	88	(55.7)	94	(60.6)	272	(58.2)
2	53	(34.4)	56	(35.4)	39	(25.2)	148	(31.7)
3+	8	(5.2)	9	(5.7)	15	(9.7)	32	(6.9)

† Combination blood glucose lowering agents are counted twice, under the each component of the combination.

Table 89: Baseline $HbA1_C$, FPG, eGFR (US units); All subject treated

	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	154		158		155		467	
Baseline A1C (%)								
<8.0	72	(46.8)	75	(47.5)	70	(45.2)	217	(46.5)
8.0 to <9.0	51	(33.1)	43	(27.2)	53	(34.2)	147	(31.5)
≥9.0	29	(18.8)	36	(22.8)	28	(18.1)	93	(19.9)
Unknown	2	(1.3)	4	(2.5)	4	(2.6)	10	(2.1)
Subjects with data	152		154		151		457	
Mean	8.08		8.20		8.17		8.15	
SD	0.89		1.02		0.87		0.93	
Median	8.00		8.00		8.00		8.00	
Range	6.0 to 10.4		6.4 to 11.9		6.4 to 10.6		6.0 to 11.9	
Baseline FPG (mg/dL)								
Subjects with data	154		157		155		466	
Mean	156.9		160.9		157.5		158.5	
SD	56.4		56.4		47.8		53.6	
Median	151.0		152.0		151.0		151.0	
Range	50 to 367		45 to 486		72 to 301		45 to 486	
Baseline eGFR (mL/min/1.73m²)								
<30	6	(3.9)	1	(0.6)	5	(3.2)	12	(2.6)
30 to <60	139	(90.3)	151	(95.6)	138	(89.0)	428	(91.6)
60 to <90	9	(5.8)	6	(3.8)	12	(7.7)	27	(5.8)
<50	102	(66.2)	93	(58.9)	96	(61.9)	291	(62.3)
50 to <60	43	(27.9)	59	(37.3)	47	(30.3)	149	(31.9)
≥60	9	(5.8)	6	(3.8)	12	(7.7)	27	(5.8)
Subjects with data	154		158		155		467	
Mean	46.0		46.8		46.9		46.6	
SD	9.4		7.8		9.1		8.8	
Median	46.0		48.0		47.0		47.0	
Range	22 to 81		28 to 64		26 to 85		22 to 85	

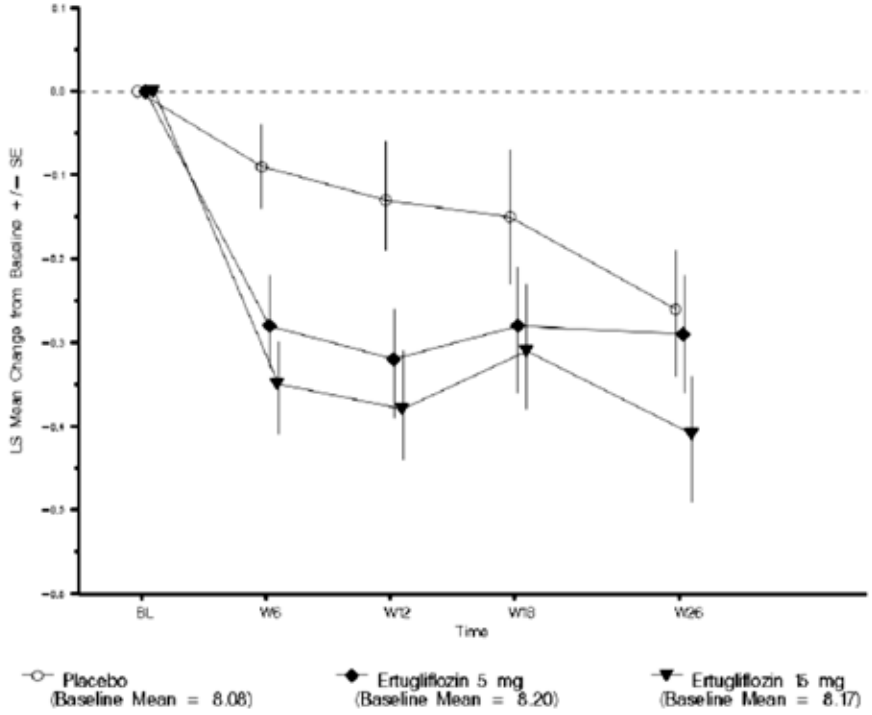
Baseline value is defined as the Day 1 (Randomization) measurement. If this measurement is not available, the last pre-randomization measurement on or after Week -2 is used as the baseline value.
eGFR based on MDRD formula. Baseline value is defined as the Day 1 (Randomization) measurement. If this measurement is not available, the last pre-randomization measurement on or after Screening is used as the baseline value.

1.2.1.8. Primary efficacy results

Although the LS mean reduction from baseline in HbA1c at Week 26 in the ertugliflozin 15 mg group was numerically greater than in the placebo group, the between-group difference was not statistically significant; the LS mean reduction in the ertugliflozin 5 mg group was similar to that

of the placebo group (-0.26%, -0.29 and -0.41% in placebo, ertugliflozin 5 mg and 15 mg groups, respectively). Hypothesis testing within the ordered testing procedure was therefore stopped at this step, and secondary hypotheses were not formally tested. In the ertugliflozin groups, reductions from baseline in HbA1c were observed at Week 6 (first scheduled post-randomisation assessment) and were followed by subsequent reductions through Week 26. The magnitude of the reduction in HbA1c was numerically greater in the ertugliflozin 15 mg group than in the ertugliflozin 5 mg group at each time point. Despite a notable reduction in HbA1c in the placebo group, separation from the placebo group was observed for the ertugliflozin 5 mg group through Week 12 and for the ertugliflozin 15 mg group through Week 18. After Week 18, a sharp reduction in HbA1c in the placebo group was observed (Figure 41).

Figure 41: $HbA1_C$ (%); LS Mean change from over time. cLDA. FAS: Excluding rescue approach.



Suspected use of metformin may have confounded the analysis of glycaemic efficacy, and therefore metformin concentrations were assayed in retained plasma samples. Results of the post-hoc analysis of change from baseline in HbA1c at Week 26 excluding subjects having a positive metformin assay result. The LS mean reduction from baseline in HbA1c at Week 26 was greater in the ertugliflozin 15 mg group and numerically greater in the ertugliflozin 5 mg group compared with the placebo group (-0.13%, -0.31% and -0.52% in placebo, ertugliflozin 5 mg and 15 mg groups, respectively). For the ertugliflozin 15 mg versus placebo comparison, the 95% CI for the between-group difference excluded 0. Exclusion of subjects having a positive metformin assay result markedly dampened the HbA1c response in the placebo group[13], with little impact to the ertugliflozin groups.

1.2.1.9. Sensitivity analysis

The rate of missing data was similar across the 3 treatment groups. In the primary analysis, Week 26 data were missing from 39 (25.3%), 33 (20.9%) and 30 (19.4%) subjects in the placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg groups, respectively. Glycaemic rescue

[13] In the placebo group, the estimated decrease in HbA1c from baseline at Week 26 was reduced by nearly half after removal of subjects having a positive metformin assay result.

therapy was reported for 11 (7.1%), 12 (7.6%), and 5 (3.2%) subjects in the placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg groups, respectively. However, as the primary hypothesis test was not significant, sensitivity analyses were not provided in this study report.

In the Stage 3A CKD stratum (excluding data after initiation of glycaemic rescue therapy), the LS mean reduction from baseline in HbA1c at Week 26 was greater in the ertugliflozin 15 mg group, and numerically greater in the ertugliflozin 5 mg groups, relative to the placebo group (-0.28, -0.31 and -0.37 in placebo, ertugliflozin 5 mg and 15 mg groups, respectively, respectively) with greater separation between ertugliflozin and placebo evident in the post-hoc analysis in subjects without positive metformin assay (-0.09, -0.28 and -0.44, respectively). In the analysis of the overall Stage 3B CKD stratum, the LS mean changes in HbA1c from baseline at Week 26 were -0.24%, -0.25% and -0.45% in placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg groups, respectively. Unlike in the Overall Cohort and Stage 3A CKD stratum, there was no early or sustained separation of the ertugliflozin and placebo groups and excluding data from subjects with a positive metformin assay in the Stage 3B CKD stratum had little impact on HbA1c reductions with no notable differences in any treatment group.

1.2.1.10. Other efficacy results

In the Stage 3A CKD stratum, there were no significant differences between treatment groups for change from baseline in body weight, sitting SBP, FPG and proportion of subjects with HbA1c < 7% at Week 26. No post-hoc analyses of change from baseline in body weight, FPG, sitting SBP and proportion of subjects with HbA1c < 7% at Week 26 were performed in subjects without a positive metformin assay result.

1.3. Phase II dose finding studies

1.3.1. Study P016/1006

This was a Phase II, randomised, double blinded, double dummy, placebo-and active controlled, 6 arm (placebo, 4 active doses of PF-04971729 (ertugliflozin) and 1 dose of sitagliptin), parallel-group, 2-period study. This study was the first to assess the efficacy of the ertugliflozin on both glycaemic control and body weight in subjects with T2DM.

1.3.1.1. Patient disposition, protocol violations

A total of 375 subjects were assigned to study treatment and were included in the metformin run-in. Of these 375 subjects, 328 (87.5%) were randomised to 1 of 6 treatment groups: 54 subjects were each assigned to placebo and PF-04971729 1 mg QD and 55 subjects were each assigned to sitagliptin 100 mg QD, PF-04971729 5 mg QD, 10 mg QD, and 25 mg QD. Most subjects completed the study ranging from 80.0% (PF-04971729 10 mg QD) to 94.5% (sitagliptin 100 mg QD). A total of 42 (12.8%) subjects discontinued from randomised treatment (placebo = 18.5%; sitagliptin 100 mg = 5.5%; PF-04971729 1 mg QD = 7.4%; PF-04971729 5 mg QD = 10.9%; , PF-04971729 10 mg QD = 20% and PF-04971729 25 mg QD = 14.5%). Reasons for discontinuation from randomised treatment related to study drug included AE for 3 subjects and insufficient response for 3 subjects.

Comment: The incidence of protocol deviations in each of the treatment groups was not provided. The link to the source Table 16.2.2 listed in the CSR did not work.

1.3.1.2. Baseline demographics and patient characteristics

All subjects received prior diabetes treatment as per protocol; treatment-naïve subjects were ineligible. Overall, 44.4% to 63.6% of subjects received prior hypertension treatments and 34.5% to 50.9% of the subjects received prior lipid-modifying treatments. The proportion of subjects who received concomitant diabetes medications was small and reflected instances of subjects withdrawn due to loss of glycaemic control (that is, hyperglycaemia). A total of 8 subjects were withdrawn prematurely, post randomisation, due to hyperglycaemia (5 subjects)

or insufficient clinical response (3 subjects). Diabetes medications initiated after withdrawal in these subjects (that is, before Day 84) included glimepiride, glibenclamide, insulin glargine and increase in dose of background metformin. A total of 4 subjects required a dose reduction or discontinuation in sponsor-provided metformin concomitant treatment. A total of 7 subjects required a dose reduction or discontinuation in hypertension concomitant treatment. No subjects required a dose reduction or discontinuation of lipid-modifying concomitant treatment. A total of 8 subjects required an increase in dose or initiation of lipid-modifying concomitant treatment post randomisation.

Demographic characteristics (gender, age, weight, and race) were similar across treatment Groups. Majority of subjects were male and the percentage of female subjects in each treatment group ranged from 25.5% (PF-04971729 5 mg QD) to 44.4% (placebo).

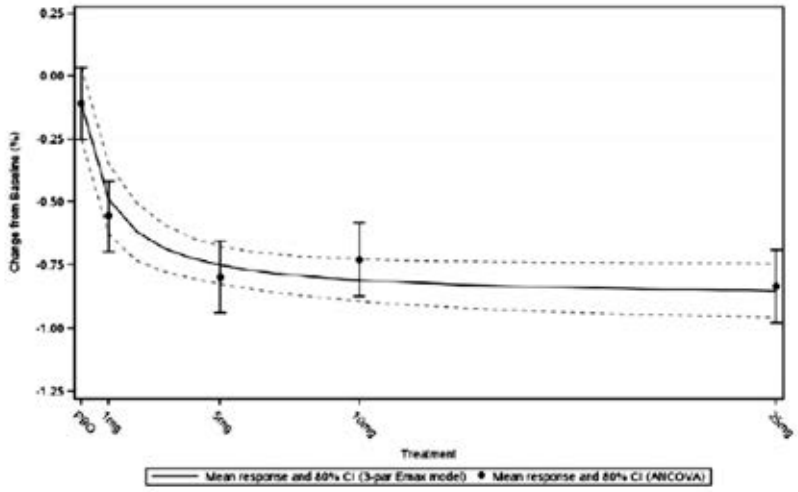
The mean age of subjects ranged from 53.1 to 57.3 years of age and individual values ranged from 25 to 70 years and most subjects were between the ages of 45 and 64 years in all treatment groups. Most subjects were White (41.8% to 54.5%); other races included Asian (range, 36.4% to 43.6%), black (range, 0% to 10.9%), and other races (5.5% to 13.0%). There were more subjects who were not Hispanic/Latino (65.5% to 70.4%) than Hispanic/Latino (29.6% to 34.5%) in each treatment group.

Treatment groups were well balanced in baseline disease characteristics. All subjects had a primary diagnosis of T2DM. The mean duration since first diagnosis to the screening visit ranged from 6.0 to 6.7 years (range, 0.1 to 30.0 years) among treatment groups. The mean baseline HbA1c ranged from 7.88% to 8.30% among treatment groups. The mean baseline weight and BMI ranged from 81.81 to 85.74 kg and 29.8 to 31.1 kg/m^2, respectively, among treatment groups. The mean baseline SBP and DBP ranged from 124.9 to 127.9 mm Hg and 78.19 to 79.15 mm Hg, respectively, among treatment groups. Medical history findings were also similar across treatment groups.

1.3.1.3. Primary efficacy results

At Week 12, there was a statistically significant improvement (decrease) in HbA1c for each ertugliflozin treatment group and for the sitagliptin group compared with placebo; the placebo adjusted LSM change from baseline was -0.45, -0.69, -0.62, -0.72 and -0.76 in the ertugliflozin 1 mg, 5 mg, 10 mg, 25 mg and sitagliptin 100 mg groups, respectively. There was a statistically significant ($p < 0.0001$) linear trend (that is, increased effect with increased dose) for change from baseline in HbA1c at Week 12 (Figure 42).

Figure 42: Dose response analysis (3-parameter E_{max}) of percent change from Baseline in HbA1c at Week 12; FAS: LOCF



Source: Figure 14.2.1.2.4.5
Abbreviations: CI=confidence interval; ANCOVA=analysis of covariance; HbA_{1c}=glycosylated hemoglobin A_{1c}; LOCF=last observation carried forward; FAS=Full Analysis Set; E_{max}=maximum effect
FAS was based on primary endpoint HbA_{1c}. ANCOVA and E_{max} were both used for LOCF data.

1.3.1.4. Other efficacy results

Beginning at Week 2 and continuing to Weeks 4 and 8, there was a statistically significant improvement (decrease) in HbA1c for each ertugliflozin and the sitagliptin treatment groups compared with placebo. These statistically significant improvements (decreases) in HbA1c for each treatment group versus placebo were also observed for the PPAS, except for the ertugliflozin 1 mg and 25 mg treatment groups versus placebo at Week 2. A sensitivity analysis using MMRM on all observed cases showed results consistent with results of the primary analysis. There was a treatment-by-baseline HbA1c interaction; the higher the baseline HbA1c, the greater the placebo adjusted decrease from baseline in HbA1c at Week 12. The duration of T2DM did not impact the change from baseline in HbA1c.

The proportion of subjects achieving HbA1c < 7% was higher in the ertugliflozin and sitagliptin treatment groups compared with placebo (44%, 42.9%, 38.6%, 36.2%, 43.9% and 15.6% in the ertugliflozin 1 mg, 5 mg, 10 mg, 25 mg, sitagliptin 100 mg and placebo groups, respectively) with similar results observed for HbA1c < 6.5% (12.0%, 20.4%, 13.6%, 14.9%, 25.5% and 6.7%, respectively).

At Week 12, there was a statistically significant improvement (decrease) in FPG for each ertugliflozin dose and the sitagliptin treatment group compared with placebo; the placebo adjusted change from baseline was -21, -26, -34, -32 and -21 mg/dL in the ertugliflozin 1 mg, 5 mg, 10 mg, 25 mg and sitagliptin 100 mg groups, respectively (-1.2, -1.4, -1.9, -1.8 and -1.1 mmol/L, respectively). These improvements in FPG were observed from Week 2 onwards.

At Week 12, there was a statistically significant improvement (decrease) in body weight for each ertugliflozin dose group compared with placebo while the sitagliptin group failed to show any significant difference in body weight; the placebo adjusted change from baseline was -1.15%, -1.75%, 2.15%, -1.91% and +0.45% in the ertugliflozin 1 mg, 5 mg, 10 mg, 25 mg and sitagliptin 100 mg groups, respectively. There was a linear trend (that is, increased effect with increased dose) for change from baseline in body weight at Week 12 as the test of linear trend was statistically significant ($p < 0.0001$). The PPAS and the sensitivity analysis on observed cases using MMRM showed consistent results. There was no interaction between change from baseline in body weight and baseline HbA1c or duration of T2DM.

At Week 12, there were statistically significant improvements (decreases) in SBP for PF-04971729 5 mg, 10 mg, and 25 mg treatment groups versus placebo at alpha level 0.10 (one-sided). The p-values ranged from 0.056 to 0.096. The placebo group had a decrease in SBP from baseline of 0.55 mm Hg. For the PF-04971729 treatment groups, the magnitude of the change from baseline ranged from a decrease of 2.69 to 4.03 mm Hg. At Week 12, there was no statistically significant difference from placebo in SBP for sitagliptin. The sitagliptin group had a decrease in SBP from baseline of 1.09 mm Hg. Similar improvements were observed in the DBP with PF-04971729.

The proportion of subjects with HbA1c < 7%, no hypoglycaemic episodes, and no weight gain at Week 12 was highest in ertugliflozin treatment groups (42%, 38.8%, 34.1%, 34.0%, 27.5% and 8.9% in the ertugliflozin 1 mg, 5 mg, 10 mg, 25 mg, sitagliptin 100 mg and placebo groups, respectively). The proportion of subjects with HbA1c < 7%, blood pressure < 130/80 mm Hg, and no weight gain at Week 12 was highest in ertugliflozin treatment groups (18%, 20.5%, 18.2%, 14.9%, 14.4% and 3.9%, respectively).

Comment: Could the sponsors clarify lack of any dose response for ertugliflozin for both the composite endpoints: proportion of subjects with HbA1c < 7%, no hypoglycaemic episodes, no weight gain at Week 12 and proportion of subjects with HbA1c < 7%, blood pressure < 130/80 mm Hg, and no weight gain at Week 12 (ertugliflozin 5 mg showed higher response rates compared to both ertugliflozin 10 mg and 25 mg).

At Week 2, the median percent change from baseline in fasting serum insulin levels showed an increase for placebo and sitagliptin and a decrease for all ertugliflozin groups with results maintained at Week 12 (Table 90). The median percent change from baseline to Week 12 in fasting serum C-peptide levels was an increase for placebo, sitagliptin, and PF-04971729 1 mg QD and a decrease for PF-04971729 5 mg, 10 mg, and 25 mg QD (Table 91).

Table 90: Number and proportion of subjects achieving composite benefit in glycaemic control, body weight and blood pressure at Week 12

Number (%) of Subjects	Placebo	Sitagliptin 100 mg QD	PF-04971729 1 mg QD	PF-04971729 5 mg QD	PF-04971729 10 mg QD	PF-04971729 25 mg QD
Number of subjects with no missing Week 12 observation.	45	51	50	49	44	47
Subjects with HbA_{1c} <7%, no HAE, and no weight gain at Week 12	4 (8.9)	14 (27.5)	21 (42.0)	19 (38.8)	15 (34.1)	16 (34.0)
Subjects with HbA_{1c} <7%, BP <130/80 mm Hg, and no weight gain at Week 12	2 (4.4)	2 (3.9)	9 (18.0)	13 (26.5)	8 (18.2)	7 (14.9)

Table 91: Summary of the baseline and percent change from Baseline in fasting serum insulin (UIU/mL) at Weeks 2 and 12 (observed cases)

	Placebo	Sitagliptin 100 mg QD	PF-04971729 1 mg QD	PF-04971729 5 mg QD	PF-04971729 10 mg QD	PF-04971729 25 mg QD
Baseline						
N	51	51	52	52	52	51
Mean	10.18	11.21	8.72	10.42	9.45	9.04
SD	6.19	9.00	5.61	7.82	7.23	6.62
Median	8.48	7.96	6.47	7.55	8.11	7.03
Week 2 Percent Change From Baseline						
N	49	48	50	45	46	45
Mean	19.71	15.05	1.72	-0.50	-9.37	-6.80
SD	62.837	56.371	46.461	63.038	31.328	33.643
Median	10.30	0.92	-15.93	-16.97	-11.51	-14.72
Week 12 Percent Change From Baseline						
N	41	48	48	45	41	44
Mean	12.63	14.05	3.45	3.98	-14.91	-15.98
SD	44.390	57.733	43.853	60.049	34.371	35.782
Median	2.84	4.07	-1.43	-8.24	-18.35	-20.20

Source: Table 14.2.11.5
Measurements which fell out of the protocol-specified visit windows were excluded.
Abbreviations: N=number of subjects; QD=once daily; SD=standard deviation; UIU=units International units

1.3.2. Study P042/1004

This was a randomised, double blind, double dummy, placebo and active controlled, 5 arm (placebo, 3 doses of PF-04971729 (1 mg, 5 mg and 25 mg) and 1 dose of HCTZ), parallel group study. Subjects completed the screening procedures to determine eligibility, followed by a 3 week run-in period when subjects received blinded placebo and certain classes of background medications for management of hypertension were withdrawn under close, outpatient monitoring. Subjects who required rescue medication for BP control could have undergone a longer run-in period to a maximum of 6 weeks to stabilise BP. The study was conducted from 26 May 2010 to 25 February 2011 at 37 centres in a 5 countries: India (9), Malaysia (6), Taiwan (3), Serbia (5) and USA (14). The primary objective was to evaluate the dose-response of PF-04971729 administered once daily (QD) for 4 weeks on SBP in adults with T2DM. The secondary objectives were to evaluate the dose-response of PF-04971729 administered QD for 4 weeks in adults with T2DM on BP, pulse rate, trough vital signs and on glycaemic control. Tertiary objectives were to evaluate the effect of a range of oral doses of PF-04971729 as well as 12.5 mg QD dose of HCTZ administered for 4 weeks in adults with T2DM on exploratory biomarkers of renin-angiotensin-aldosterone system (RAAS) activation.

The primary efficacy endpoint was the placebo adjusted change from baseline in average, 24 hour SBP using 24 hour ABPM at Week 4. Secondary efficacy endpoints included placebo adjusted change from baseline at Week 4 in the following variables measured by 24 hour ABPM: daytime and night-time average SBP (mm Hg); 24 hour average, daytime and night-time average DBP (mm Hg); 24 hour average, daytime and night time average pulse rate (bpm) and 24 hour urinary glucose excretion (UGE; g/24 hours). Secondary efficacy endpoints also included placebo adjusted change from baseline at Weeks 1, 2, 3, and 4 in the following variables: average of the triplicates measured by automated BP device: trough SBP (mmHg); trough DBP (mmHg); trough pulse rate (bpm); and change from baseline of FPG (mg/dL) at Weeks 2 and 4.

Statistical inference was made on the primary endpoint: change from baseline on average, 24 hour SBP at Week 4.

A total of 194 subjects were randomised and 193 subjects received at least 1 dose of blinded treatment regimen. None of the subjects were withdrawn due to AEs. Most subjects were

between the ages of 45 and 64 years. Most subjects were White (102 subjects), followed by Asian (66 subjects), Black (22 subjects), and other (3 subjects).

There was a statistically significant decrease from baseline in the primary efficacy endpoint, average, 24 hour SBP at Week 4 for all doses of PF-04971729 (1 mg, 5 mg and 25 mg) versus placebo. The average decreases were approximately 3 to 4 mmHg in magnitude. There was also a statistically significant decrease of approximately 3 mm Hg from baseline in the average, 24 hour SBP at Week 4 for HCTZ versus placebo. There was a linear trend for dose response; with the effect at 5 mg being higher than 1 mg, although there was no further reduction in SBP with the 25 mg dose of PF-04971729.

There was a statistically significant decrease from baseline in daytime, average SBP (of about 3 to 4mmHg) at Week 4 for all doses of PF-04971729 (1 mg, 5 mg, and 25 mg) versus placebo. There was also a statistically significant decrease from baseline (about 3 mmHg) in the daytime, average SBP at Week 4 for HCTZ versus placebo. Although there were numerically greater decreases from baseline in night time, average SBP at Week 4 for HCTZ and PF-04971729 treatment groups compared to placebo, differences did not reach statistical significance**.** There was a statistically significant decrease from baseline in 24 hour and daytime average DBP at Week 4 for all doses of PF-04971729 (1 mg, 5 mg and 25 mg) versus placebo with mean decreases of about 2 mmHg. There was also a statistically significant decrease from baseline in the 24 hour and daytime average DBP at Week 4 for HCTZ versus placebo. There were numerically greater decreases from baseline in night time, average DBP at Week 4 for HCTZ and PF-04971729 treatment groups compared to placebo, reaching statistically significant differences for PF-04971729 1 mg and 5 mg versus placebo. There was a statistically significant decrease from baseline in 24 hour and daytime average heart rate at Week 4 for PF-04971729 1 mg and 25 mg versus placebo. The mean decreases were approximately 1 to 2 bpm in magnitude. The magnitude of change was deemed clinically insignificant. There was not a statistically significant decrease from baseline in the 24 hour and daytime average heart rate at Week 4 for HCTZ or PF-04971729 5 mg versus placebo. There were no statistically significant changes from baseline in night time heart rate for any treatment group versus placebo at Week 4.

Consistent with the mechanism of ertugliflozin, there was a statistically significant increase in 24 hour UGE and decrease in FPG at Week 4 for all 3 dose groups of ertugliflozin (1 mg, 5 mg and 25 mg QD) versus placebo although the 25 mg dose did not lead to much greater increase in UGE or decrease in FPG compared to the 5 mg dose. In contrast, there was no change from baseline in the 24 hour UGE or FPG at Week 4 for HCTZ or placebo.

Overall, ertugliflozin results in clinically meaningful lowering in BP (primary endpoint) with magnitude of effect being at least comparable to HCTZ with no clear evidence of a dose response beyond the 5 mg dose. Although the 5 mg dose also showed significant increase in UGE and decrease in FPG (secondary endpoints), there was only minimal further improvement with the ertugliflozin 25 mg dose. The proposed 15 mg dose of ertugliflozin was not evaluated in this study.

1.3.3. Evaluator commentary on other efficacy studies

Dose selection for the pivotal Phase III studies was based on dose-response modelling of efficacy endpoints (HbA1c, FPG, body weight) from Study P016/1006 (12 week Phase II dose ranging study) as well as 24 hour UGE (mechanism biomarker) in T2DM subjects from Study P042/1004 (4 week Phase II dose ranging study). In study P006/1016, the ertugliflozin 10 mg dose showed numerically lesser improvement compared to the 5 mg dose for the primary efficacy endpoint of change from baseline to Week 12 in HbA1c, while both 10 and 25 mg doses had numerically fewer proportion of subjects with HbA1c < 7% (and < 6.5%) at Week 12 compared with the 5 mg dose. It is noted that FPG, body weight and reduction in SBP/DBP appeared to be numerically greater with the 10 mg and 25 mg doses compared with

the 5 mg dose. In the other Phase II dose ranging Study P042/1004, ertugliflozin results in clinically meaningful lowering in BP (primary endpoint) with magnitude of effect being at least comparable to HCTZ with no clear evidence of a dose response beyond the 5 mg dose. Although the 5 mg dose also showed significant increase in UGE and decrease in FPG (secondary endpoints), there was only minimal further improvement with the ertugliflozin 25 mg dose. Considering the fact that the proposed 15 mg dose of ertugliflozin was not evaluated in this pivotal dose ranging Phase II study, the selection of the ertugliflozin 15 mg dose for the Phase III studies appears to be arbitrary.

SGLT2 inhibitors lower the renal threshold for glucose and increase urinary glucose excretion (UGE), resulting in decreased plasma glucose (PG) in patients with hyperglycaemia, as well as a mild osmotic diuresis and a net caloric loss (by loss of glucose) promoting weight loss. The effect of SGLT2 inhibitors to augment UGE is diminished in subjects with CKD, since the rate of UGE is proportional to the GFR (as well as to the PG concentration). The efficacy of ertugliflozin in improving glycaemic control and reducing body weight may thus be affected in this population, and the Phase III Study P001/1016 evaluated the efficacy of ertugliflozin in 468 subjects with T2DM who have Stage 3 CKD (eGFR ≥ 30 to < 60 mL/min/1.73 m^2). Since glucose lowering efficacy is related to eGFR, it was expected that efficacy will be greater in subjects with Stage 3A CKD (eGFR ≥ 45 to < 60 mL/min/1.73m^2) relative to subjects with Stage 3B CKD (eGFR ≥ 30 to < 45 mL/min/1.73m^2). It is important to note that the primary efficacy hypothesis test was not significant, and this precluded formal testing of subsequent hypotheses in the ordered testing procedure. Post hoc efficacy analysis excluding data from patients with positive metformin assay showed evidence of reduction of HbA1c with ertugliflozin 15 mg (based on the nominal 95% CI) compared with placebo in the overall cohort and the Stage 3A CKD stratum (eGFR > 45 to ≤ 60ml/min/1.73m^2). However, there were no significant differences between treatment groups for change from baseline in body weight, FPG, sitting SBP and proportion of subjects with HbA1c < 7% and no post hoc analysis was done for these parameters. Unlike in the Overall Cohort and Stage 3A CKD stratum, there was no early or sustained separation of the ertugliflozin and placebo groups excluding data from subjects with a positive metformin assay in the Stage 3B CKD stratum had little impact on HbA1c reductions with no notable differences in any treatment group.

Overall, this study failed to provide unequivocal evidence for efficacy of proposed ertugliflozin in patients with moderate renal impairment. It is important to note that although ertugliflozin was studied in combination with other AHAs including insulin and SUs in this study, it cannot be used as evidence of efficacy of ertugliflozin in combination with insulin and SUs. Furthermore, excluding patients on metformin makes extrapolating data difficult.

1.4. Analyses performed across trials: pooled and meta analyses

1.4.1. Assessment of efficacy in subgroups: Pooled population

The subgroup assessments in the individual studies are limited since the studies were sized to assess endpoints in the overall study population and not within smaller subgroups. Hence, two pooled populations (placebo controlled pool and ertugliflozin/metformin pool) were created to allow for more robust subgroup assessments and to evaluate the consistency of response across patients with differing characteristics.

A pooled population of 3 placebo controlled studies (Studies P003/1022, P007/1017, and P006/1015) was supported by certain common features: randomised (1:1:1), placebo controlled, double blind design; same duration (Phase A of 26 weeks); enrolled subjects with T2DM with similar HbA1c entry criteria (7.0% to 10.5%); same treatment period visit structure; and included the same treatment groups (ertugliflozin 15 mg and 5 mg, and placebo). The 3 placebo controlled studies differed only in the background diabetes treatment: one examined ertugliflozin 15 mg and 5 mg as monotherapy (Study P003/1022) and the other studies

examined the efficacy of ertugliflozin 15 mg and 5 mg as add-on therapy to metformin (Study P007/1017) or as an add-on to dual therapy with metformin and sitagliptin (Study P006/1015).

The ertugliflozin/metformin pool includes 2 placebo controlled studies of similar design and duration (Studies P007/1017 and P006/1015) in which subjects were on background metformin therapy. Three studies which included ertugliflozin in combination with sitagliptin; Studies P005/1019, P006/1015, P017/1047 could not be pooled to support proposed ertugliflozin/ sitagliptin FDC because there was no common comparator group among the 3 studies.

1.4.2. Efficacy results in Placebo controlled pooled population

Baseline demographic characteristics of the population included in the placebo controlled pool were found to be well balanced across the placebo, ertugliflozin 5 mg and 15 mg treatment groups. The mean age of the subjects was 57.3 years, 52.6% were male, the mean baseline BMI was 31.5 kg/m^2, 73.4% of subjects were White (15.1% were Asian, and 6.6% were Black). The mean duration of T2DM was 7.5 years and mean baseline HbA1c was 8.1%. The mean baseline eGFR was 88.9 mL/min/1.73 m^2. The majority of subjects had mild renal impairment (eGFR > 60 to < 90 mL/min/1.73 m^2) and only about 3% of subjects in each study had a baseline eGFR > 45 to < 60 mL/min/1.73 m^2. Due to the study exclusion criteria, only 1 subject had a baseline eGFR < 45 mL/min/1.73 m^2. The majority of subjects were from North America (excluding Central America) or Europe.

Change from baseline in HbA1c and body weight at Week 26 and proportion of subjects with HbA1c< 7% at Week 26 were analysed in the pooled analyses.

The pooled analysis of the change from baseline in HbA1c at 26 weeks (ER) showed clinically meaningful decreases with ertugliflozin 15 mg and 5 mg compared with placebo ((difference in LS means: -0.91% and -0.76%, respectively) (Table 92) and generally numerically greater HbA1c lowering with ertugliflozin 15 mg than 5 mg across subgroups.

Table 92: HbA1c (%); Change from Baseline at Week 26. FAS: excluding rescue approach; Placebo controlled pool

	Baseline		Week 26		Change from baseline at Week 26		
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)[†]
Placebo	512	8.11 (0.91)	359	7.77 (1.03)	515	-0.15 (0.93)	0.00 (-0.08, 0.08)
Ertugliflozin 5 mg	515	8.09 (0.88)	462	7.28 (0.80)	519	-0.77 (0.87)	-0.76 (-0.84, -0.68)
Ertugliflozin 15 mg	504	8.16 (0.97)	448	7.21 (0.85)	509	-0.95 (0.92)	-0.91 (-0.99, -0.83)

Pairwise comparison	Difference in LS Means (95% CI)[†]
Ertugliflozin 5 mg versus Placebo	-0.76 (-0.87, -0.65)
Ertugliflozin 15 mg versus Placebo	-0.91 (-1.02, -0.80)
Conditional Pooled SD of Change from Baseline= 0.85	

For baseline and Week 26, N is the number of subjects with non-missing assessments at the specific time point; for Change from Baseline at Week 26, N is the number of subjects in the full analysis set (i.e., randomized subjects who took at least 1 dose of study medication and had at least one measurement 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, trial, baseline eGFR and the interaction of time by treatment. Time is treated as a categorical variable.

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

Although clinically meaningful efficacy was observed in both genders, it was numerically higher in male subjects than female subjects. This gender difference was not evident in the subgroup analyses of 2 large studies that were not included in the pool of placebo controlled studies (Studies P002/1013 and P005/1019). Clinically meaningful efficacy was also observed across all age groups and younger subjects had numerically larger HbA1c lowering compared to older subjects. As expected, subjects with higher baseline HbA1c values showed larger reductions from baseline in HbA1c compared with subjects with lower baseline HbA1c. Clinically

meaningful improvements in HbA1c change from baseline were observed for subjects with mild renal impairment (eGFR > 60 to < 90 mL/min/1.73 m^2) (difference from placebo was -0.70 and -0.80 with ertugliflozin 5 mg and 15 mg, respectively) with greater improvement shown for subjects with normal eGFR (> 90 mL/min/1.73 m^2) (-0.88 and -1.12, respectively). In the subgroup with baseline eGFR < 60 mL/min/1.73 m^2 , only ertugliflozin 15 mg showed reduction in HbA1c (-0.08 and -0.41, respectively) and these results were consistent with the post-hoc analysis of HbA1c lowering from Study P001/1016. Otherwise, no notable differences in placebo adjusted responses were observed among the subgroups of race, ethnicity, region, baseline BMI and duration of T2DM. The pooled analysis for subjects reaching the goal of HbA1c < 7.0% showed that more than twice the number of subjects reached the goal after treatment with ertugliflozin 15 mg or5 mg compared to placebo (15.3%, 32.2% and 38.7% with placebo, ertugliflozin 5 mg and 15 mg, respectively). The odds ratio for achieving HbA1c < 7.0% was numerically higher with ertugliflozin 15 mg compared to 5 mg.

The pooled analysis of the change from baseline in body weight showed a similar reduction for ertugliflozin 15 mg and 5 mg compared with placebo (difference in LS means:-1.79 kg and -1.81 kg, respectively). The placebo adjusted LS mean reduction from baseline in body weight was numerically higher in subjects with a higher baseline BMI (≥ 35 kg/m^2) than a lower baseline BMI (< 35 kg/m^2) although the difference is generally modest for overweight subjects relative to obese subjects (25 to < 30 kg/m^2 versus 30 to < 35 kg/m^2). No notable differences were observed among the subgroups of age, gender, race, region, baseline HbA1c, and duration of T2DM. In the subgroup with baseline eGFR < 60 mL/min/1.73 m^2, smaller reductions from baseline in body weight were observed, as expected based on the mechanism of action.

1.4.3. Pooled efficacy results in ertugliflozin/ metformin studies

Subject demographic and baseline characteristics were well balanced across the ertugliflozin 5 mg, 15 mg and placebo treatment groups in the pooled ertugliflozin/metformin combination studies (Table 93). The mean age of the subjects was 57.7 years, 50.9% were male, the mean baseline BMI was 31.0 kg/m^2, 69.1% of subjects were White, 17.9% were Asian, and 6.7% were Black. The mean duration of T2DM was 8.6 years. Mean baseline HbA1c was 8.1%. The mean baseline eGFR was 89.4 mL/min/1.73 m^2 and majority of subjects had mild renal impairment (eGFR ≥ 60 to < 90 mL/min/1.73 m^2).[14] The median metformin dose at randomisation was 2000mg/day in both groups. The most common metformin dose at randomisation in both groups was 2000 mg/day (46.7% and 51.7% of subjects in the ertugliflozin and placebo groups, respectively). In the ertugliflozin groups, 14.7% and 19.7% of subjects received 1500 mg/day or > 1500 to < 2000 mg/day at randomisation, respectively.

[14] A small proportion of subjects in each study had a baseline eGFR ≥ 45 to < 60 mL/min/1.73 m^2 (ranging from 2.5% to 3.1%). Due to the study exclusion criteria, only 1 subject had a baseline eGFR <45 mL/min/1.73 m^2

Table 93: Ertugliflozin/metformin FDC pool; baseline demographics and disease characteristics. All subjects treated

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	362		363		358		721		1,083	
Gender										
Male	198	(54.7)	178	(49.0)	175	(48.9)	353	(49.0)	551	(50.9)
Female	164	(45.3)	185	(51.0)	183	(51.1)	368	(51.0)	532	(49.1)
Age (Years)										
<65	280	(77.3)	288	(79.3)	280	(78.2)	568	(78.8)	848	(78.3)
>=65	82	(22.7)	75	(20.7)	78	(21.8)	153	(21.2)	235	(21.7)
Mean	57.2		57.7		58.1		57.9		57.7	
SD	9.0		8.7		9.2		8.9		9.0	
Median	58.0		59.0		59.0		59.0		59.0	
Range	24 to 80		26 to 81		29 to 84		26 to 84		24 to 84	
Race										
American Indian Or Alaska Native	5	(1.4)	1	(0.3)	5	(1.4)	6	(0.8)	11	(1.0)
Asian	64	(17.7)	67	(18.5)	63	(17.6)	130	(18.0)	194	(17.9)
Black Or African American	22	(6.1)	24	(6.6)	27	(7.5)	51	(7.1)	73	(6.7)
Multiple	19	(5.2)	23	(6.3)	15	(4.2)	38	(5.3)	57	(5.3)
White	252	(69.6)	248	(68.3)	248	(69.3)	496	(68.8)	748	(69.1)
Ethnicity										
Hispanic Or Latino	67	(18.5)	59	(16.3)	59	(16.5)	118	(16.4)	185	(17.1)
Not Hispanic Or Latino	293	(80.9)	304	(83.7)	299	(83.5)	603	(83.6)	896	(82.7)
Not Reported	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)
Unknown	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)
Region										
North America (excluding Central America)	85	(23.5)	93	(25.6)	84	(23.5)	177	(24.5)	262	(24.2)
South America (including Central America)	23	(6.4)	14	(3.9)	17	(4.7)	31	(4.3)	54	(5.0)
Region										
Europe (including Russia)	141	(39.0)	144	(39.7)	148	(41.3)	292	(40.5)	433	(40.0)
Asia	70	(19.3)	71	(19.6)	71	(19.8)	142	(19.7)	212	(19.6)
South Africa	39	(10.8)	35	(9.6)	37	(10.3)	72	(10.0)	111	(10.2)
Australia/New Zealand	4	(1.1)	6	(1.7)	1	(0.3)	7	(1.0)	11	(1.0)
Baseline BMI (kg/m2)										
<25	55	(15.2)	44	(12.1)	38	(10.6)	82	(11.4)	137	(12.7)
25 to <30	123	(34.0)	115	(31.7)	121	(33.8)	236	(32.7)	359	(33.1)
30 to <35	109	(30.1)	128	(35.3)	121	(33.8)	249	(34.5)	358	(33.1)
>=35	75	(20.7)	76	(20.9)	78	(21.8)	154	(21.4)	229	(21.1)
Subjects with data	362		363		358		721		1083	
Mean	30.5		31.0		31.0		31.0		30.8	
SD	5.5		5.1		5.2		5.2		5.3	
Median	30.0		30.9		30.8		30.8		30.5	
Range	18 to 67		19 to 48		19 to 54		19 to 54		18 to 67	

Table 93 (continued): Ertugliflozin/metformin FDC pool; baseline demographics and disease characteristics. All subjects treated

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	362		363		358		721		1,083	
Baseline A1C (%)										
<8.0	179	(49.4)	189	(52.1)	185	(51.7)	374	(51.9)	553	(51.1)
8.0 to <9.0	113	(31.2)	109	(30.0)	106	(29.6)	215	(29.8)	328	(30.3)
>=9.0	67	(18.5)	62	(17.1)	62	(17.3)	124	(17.2)	191	(17.6)
Unknown†	3	(0.8)	3	(0.8)	5	(1.4)	8	(1.1)	11	(1.0)
Subjects with data	359		360		353		713		1072	
Mean	8.1		8.1		8.1		8.1		8.1	
SD	0.9		0.9		0.9		0.9		0.9	
Median	8.0		7.9		7.9		7.9		7.9	
Range	6 to 11		6 to 11		6 to 11		6 to 11		6 to 11	
Baseline A1C (mmol/mol)										
<63.94	179	(49.4)	189	(52.1)	185	(51.7)	374	(51.9)	553	(51.1)
63.94 to <74.86	113	(31.2)	109	(30.0)	106	(29.6)	215	(29.8)	328	(30.3)
>=74.86	67	(18.5)	62	(17.1)	62	(17.3)	124	(17.2)	191	(17.6)
Unknown†	3	(0.8)	3	(0.8)	5	(1.4)	8	(1.1)	11	(1.0)
Subjects with data	359		360		353		713		1072	
Mean	65.1		64.6		64.7		64.7		64.8	
SD	10.0		9.6		9.7		9.7		9.8	
Median	63.9		62.8		62.8		62.8		62.8	
Range	40 to 98		39 to 100		39 to 92		39 to 100		39 to 100	
Baseline eGFR (mL/min/1.73m2)										
<45	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.1)	1	(0.1)
45 to <60	9	(2.5)	9	(2.5)	13	(3.6)	22	(3.1)	31	(2.9)
60 to <90	172	(47.5)	201	(55.4)	174	(48.6)	375	(52.0)	547	(50.5)
>=90	181	(50.0)	153	(42.1)	170	(47.5)	323	(44.8)	504	(46.5)
Subjects with data	362		363		358		721		1083	
Mean	90.9		88.1		89.3		88.7		89.4	
SD	18.8		17.5		18.7		18.1		18.4	
Median	89.5		86.0		88.0		87.0		88.0	
Range	47 to 173		51 to 144		42 to 178		42 to 178		42 to 178	
Duration of Type 2 Diabetes Mellitus (Years)										
< 5	114	(31.5)	125	(34.4)	101	(28.2)	226	(31.3)	340	(31.4)
5 to <10	126	(34.8)	106	(29.2)	130	(36.3)	236	(32.7)	362	(33.4)
>=10	122	(33.7)	132	(36.4)	127	(35.5)	259	(35.9)	381	(35.2)
Duration of Type 2 Diabetes Mellitus (Years)										
Subjects with data	362		363		358		721		1083	
Mean	8.6		8.7		8.6		8.6		8.6	
SD	6.1		6.2		5.5		5.8		5.9	
Median	7.2		7.4		7.9		7.7		7.6	
Range	0 to 39		0 to 29		0 to 34		0 to 34		0 to 39	

† Not included in summary statistics.

For A1C, baseline value is defined as the Day 1 (Randomization) measurement. If this measurement is not available, the last pre-randomization measurement on or after Week -2 is used as the baseline value.

eGFR is based on MDRD formula. Baseline value is defined as the Day 1 (Randomization) measurement. If this measurement is not available, the last pre-randomization measurement on or after screening is used as the baseline value.

The LS mean reductions from baseline in HbA1c at Week 26 were greater in the ertugliflozin 15 mg and 5 mg groups than in the placebo group (difference in LS means: -0.83% and -0.69% with ertugliflozin 5 mg and 15 mg, respectively)(Table 94).

Table 94: HbA1c (%); Change from Baseline at Week 26. FAS: excluding rescue approach; ertugliflozin/metformin FDC pool

	Baseline		Week 26		Change from baseline at Week 26		
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)[†]
Placebo	359	8.11 (0.91)	270	7.78 (1.03)	362	-0.17 (0.94)	-0.06 (-0.15, 0.04)
Ertugliflozin 5 mg	360	8.06 (0.88)	329	7.27 (0.78)	363	-0.76 (0.88)	-0.75 (-0.84, -0.66)
Ertugliflozin 15 mg	353	8.07 (0.89)	324	7.19 (0.78)	358	-0.92 (0.86)	-0.89 (-0.98, -0.80)
Pairwise comparison					Difference in LS Means (95% CI)[†]		
Ertugliflozin 5 mg versus Placebo					-0.69 (-0.82, -0.57)		
Ertugliflozin 15 mg versus Placebo					-0.83 (-0.95, -0.70)		
Conditional Pooled SD of Change from Baseline= 0.81							

For baseline and Week 26, N is the number of subjects with non-missing assessments at the specific time point; for Change from Baseline at Week 26, N is the number of subjects in the full analysis set (i.e., randomized subjects who took at least 1 dose of study medication and had at least one measurement 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, trial, baseline eGFR and the interaction of time by treatment. Time is treated as a categorical variable.

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

In general, clinically meaningful reductions from baseline in HbA1c were observed with ertugliflozin 15 mg and ertugliflozin 5 mg compared to placebo across all subgroup categories. In general, ertugliflozin 15 mg had a numerically greater placebo adjusted HbA1c reduction from baseline compared with ertugliflozin 5 mg within each subgroup category. The placebo adjusted LS mean reduction from baseline in HbA1c was greater in subjects with a higher baseline HbA1c (median (7.9) or ≥ 9.0%) versus a lower baseline HbA1c (< median (7.9) or < 9.0%). The placebo adjusted LS mean reduction from baseline in HbA1c was greater in subjects with normal renal function compared with subjects with renal impairment. At baseline, 46.5% of subjects had normal renal function (eGFR > 90 mL/min/1.73 m^2), 50.5% of subjects had mild renal impairment (eGFR > 60 to < 90 mL/min/1.73 m^2), and 2.9% of subjects had Stage 3 CKD (eGFR > 45 to < 60 mL/min/1.73 m^2). Subjects with mild renal impairment had clinically meaningful reductions in HbA1c relative to placebo with both doses of ertugliflozin.

The proportions of subjects reaching the HbA1c goal of < 7.0% in the ertugliflozin 15 mg (39.9%) and 5 mg (33.9%) groups were greater than in the placebo group (16.3%). The odds of reaching the HbA1c goal of < 7.0% at Week 26 were greater in the ertugliflozin 15 mg and 5 mg groups than in the placebo group. The LS mean reductions from baseline in body weight at Week 26 were greater in the ertugliflozin 15 mg and 5 mg groups than in the placebo group (difference in LS means: -1.66 kg and -1.83 kg, respectively). In general, the placebo adjusted LS mean reductions from baseline in body weight at Week 26 were consistent across the subgroups evaluated. The placebo adjusted LS mean reduction from baseline in body weight was numerically higher in subjects with a higher baseline BMI (≥ 35 kg/m^2) than a lower baseline BMI (< 35 kg/m^2) although the difference is generally modest for overweight subjects relative to Class I obese subjects (25 to < 30 kg/m^2 versus 30 to < 35 kg/m^2). No notable differences were observed among the subgroups of age, gender, race, region, baseline HbA1c, and duration of T2DM. In the subgroup with baseline eGFR < 60 mL/min/1.73 m^2, smaller reductions from baseline in body weight were observed, as expected based on the mechanism of action (Table 95).

Table 95: Body weight (kg); Change from Baseline at Week 26. Subgroup analysis; FAS: excluding rescue approach ertugliflozin/metformin FDC pool

					Change from Baseline in Weight at Week 26†		
	Baseline		Week 26			LS Mean	Difference in LS Means Relative to Placebo
Treatment	N	Mean (SD)	N	Mean (SD)	N	(95% CI)	(95% CI)
Subgroup: Age (Years)							
<65							
Placebo	276	86.70 (19.06)	215	85.80 (18.65)	276	-1.34 (-1.69, -0.98)	
Ertugliflozin 5 mg	286	88.20 (17.90)	269	84.87 (17.63)	286	-3.15 (-3.49, -2.82)	-1.82 (-2.30, -1.33)
Ertugliflozin 15 mg	275	87.35 (18.36)	255	84.60 (17.81)	275	-2.94 (-3.29, -2.60)	-1.61 (-2.10, -1.11)
≥65							
Placebo	76	80.42 (17.20)	65	78.54 (17.74)	76	-1.23 (-1.80, -0.65)	
Ertugliflozin 5 mg	70	77.91 (15.24)	67	75.31 (14.95)	70	-3.17 (-3.76, -2.58)	-1.94 (-2.77, -1.12)
Ertugliflozin 15 mg	76	80.73 (14.93)	69	78.08 (15.01)	76	-3.11 (-3.68, -2.54)	-1.88 (-2.69, -1.07)
<Median (59)							
Placebo	179	86.89 (20.29)	134	85.91 (19.66)	179	-1.33 (-1.78, -0.88)	
Ertugliflozin 5 mg	180	89.02 (17.69)	170	85.36 (16.97)	180	-3.37 (-3.80, -2.94)	-2.04 (-2.66, -1.42)
Ertugliflozin 15 mg	164	87.94 (18.21)	151	85.25 (17.97)	164	-2.92 (-3.37, -2.47)	-1.59 (-2.23, -0.95)
≥Median (59)							
Placebo	173	83.74 (17.10)	146	82.47 (17.61)	173	-1.33 (-1.74, -0.92)	
Ertugliflozin 5 mg	176	83.27 (17.62)	166	80.51 (17.80)	176	-2.94 (-3.33, -2.54)	-1.61 (-2.18, -1.04)
Ertugliflozin 15 mg	187	84.14 (17.42)	173	81.43 (16.80)	187	-3.03 (-3.42, -2.65)	-1.71 (-2.27, -1.14)
Subgroup: Gender							
Male							
Placebo	192	91.71 (19.02)	147	91.19 (18.51)	192	-1.19 (-1.61, -0.77)	
Ertugliflozin 5 mg	174	92.21 (17.26)	161	89.05 (17.11)	174	-3.27 (-3.69, -2.84)	-2.08 (-2.68, -1.48)
Ertugliflozin 15 mg	172	91.11 (17.12)	162	88.29 (17.05)	172	-2.86 (-3.29, -2.43)	-1.67 (-2.27, -1.07)
Female							
Placebo	160	77.70 (15.51)	133	76.30 (15.51)	160	-1.48 (-1.92, -1.04)	
Ertugliflozin 5 mg	182	80.40 (16.51)	175	77.36 (16.01)	182	-3.04 (-3.44, -2.64)	-1.57 (-2.16, -0.97)
Ertugliflozin 15 mg	179	80.93 (17.17)	162	78.14 (16.35)	179	-3.10 (-3.51, -2.69)	-1.62 (-2.22, -1.02)

1.5. Evaluator's conclusions on clinical efficacy

The proposed indication is :'Steglatro (ertugliflozin) is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus as monotherapy when metformin is considered inappropriate due to intolerance or in combination with other anti-hyperglycaemic agents.'

The clinical development program supporting the above proposed indication was planned, conducted and analysed in accordance with the US and European Union (EU) regulatory guidance documents that were in effect at the time that the Phase III program was initiated. The study design, efficacy endpoints complied with the TGA adopted EMA guidelines for the development of medications for treatment of T2DM.

A total of 4863 subjects were randomly assigned to study medication: 3413 subjects were randomly assigned to receive ertugliflozin (co-administered with sitagliptin in Studies P005/1019 and P017/1047), 766 subjects were randomly assigned to receive placebo, and 684 subjects were randomly assigned to receive active comparators (sitagliptin, glimepiride) (Table 96).

Table 96: Number of subjects randomised in the Phase III studies

Study	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Placebo	Active Comparator (Sitagliptin, Glimepiride)	Total
P003/1022 Monotherapy	156	152	153	--	461
P007/1017 Add-on to metformin	207	205	209	--	621
P002/1013 Ertugliflozin vs glimepiride	448	441	--	437	1326
P005/1019 Ertugliflozin plus sitagliptin factorial	493†	493‡	--	247	1233
P006/1015 Add-on to metformin plus sitagliptin	156	154	153	--	463
P017/1047 Ertugliflozin plus sitagliptin	98§	96§	97	--	291
P001/1016 Renal impairment	158	156	154	--	468
Total	1716	1697	766	684	4863

† Includes ertugliflozin 5 mg (n=250) and ertugliflozin 5 mg/sitagliptin 100 mg (n=243)
‡ Includes ertugliflozin 15 mg (n=248) and ertugliflozin 15 mg/sitagliptin 100 mg (n=245)
§ Ertugliflozin co-administered with sitagliptin. Study did not include treatment with ertugliflozin alone

With the exception of the moderate renal impairment study (Study P001/1016), the mean age of the subjects was similar across the Phase III studies, ranging from 55.1 to 59.1 years the mean BMI was similar across all studies, ranging from 30.8 to 33.0 kg/m^2. The mean baseline HbA1c ranged from 7.8% to 8.9% and mean FPG ranged from 8.8 to 11.0mmol/L in these studies. The subjects in the co-administration of ertugliflozin and sitagliptin study (Study P017/1047) had the highest baseline HbA1c and FPG. With the exception of Study P001/1016, the mean baseline eGFR was similar across the Phase III studies, ranging from 87.2 to 92.4 mL/min/1.73 m^2. The mean duration of T2DM ranged from 5.0 years in Study P003/1022 to 14.2 years in Study P001/1016. The proportion of subjects with microvascular complications was lowest in Study P003/1022 compared to the other studies; while the proportion of subjects with microvascular complications was highest in Study P001/1016. With the exception of Study P001/1016, the AHA usage at randomisation varied from none to 2 agents (metformin and sitagliptin) depending on the study design. Across the Phase III studies, a high proportion of subjects were receiving concomitant hypertension medication (ranging from 47.8% to 94.0%) and anti-dyslipidaemia medication (ranging from 32.0% to 77.5%). The proportion of subjects with a history of CV disease was lowest in Study P003/1022 compared to the other studies; while the proportion of subjects with a history of CV disease was highest in Study P001/1016. Overall, patients evaluated in the 7 Phase III studies were representative of the target population for ertugliflozin monotherapy and combination therapy (Table 97).

Table 97: Demographic and baseline characteristics, study by study comparison; All subjects treated

	P003/1022 Monotherapy n (%)	P007/1017 Add-on to Metformin n (%)	P002/1013 Ertugliflozin vs. Glimepiride n (%)	P005/1019 Ertugliflozin+Sitagliptin factorial n (%)	P006/1015 Add-on to Metformin+Sitagliptin n (%)	P017/1047 Ertugliflozin+Sitagliptin n (%)	P001/1016 Renal Impairment n (%)
Subjects in population	461	621	1325	1232	462	291	467
Gender							
Male	261 (56.6)	288 (46.4)	642 (48.5)	664 (53.9)	263 (56.9)	167 (57.4)	231 (49.5)
Female	200 (43.4)	333 (53.6)	683 (51.5)	568 (46.1)	199 (43.1)	124 (42.6)	236 (50.5)
Age (years)							
Subjects with data	461	621	1325	1232	462	291	467
Mean	56.4	56.6	58.2	55.1	59.1	55.6	67.3
SD	11.0	8.8	9.6	10.1	9.0	10.0	8.6
Median	57.0	58.0	59.0	56.0	60.0	56.0	67.0
Range	23.0 to 87.0	24.0 to 79.0	22.0 to 86.0	21.0 to 85.0	34.0 to 84.0	32.0 to 78.0	35.0 to 87.0
Age Category1 (years)							
<65	341 (74.0)	524 (84.4)	989 (74.6)	1033 (83.8)	324 (70.1)	233 (80.1)	162 (34.7)
>=65	120 (26.0)	97 (15.6)	336 (25.4)	199 (16.2)	138 (29.9)	58 (19.9)	305 (65.3)
Age Category2 (years)							
<75	446 (96.7)	617 (99.4)	1275 (96.2)	1204 (97.7)	449 (97.2)	283 (97.3)	366 (78.4)
>=75	15 (3.3)	4 (0.6)	50 (3.8)	28 (2.3)	13 (2.8)	8 (2.7)	101 (21.6)
Race							
Asian	39 (8.5)	100 (16.1)	239 (18.0)	131 (10.6)	94 (20.3)	0 (0.0)	45 (9.6)
Black	29 (6.3)	64 (10.3)	61 (4.6)	46 (3.7)	9 (1.9)	13 (4.5)	19 (4.1)
White	386 (83.7)	411 (66.2)	966 (72.9)	989 (80.3)	337 (72.9)	263 (90.4)	380 (81.4)
Other	7 (1.5)	46 (7.4)	59 (4.5)	66 (5.4)	22 (4.8)	15 (5.2)	23 (4.9)
Ethnicity							
Hispanic or Latino	103 (22.3)	113 (18.2)	273 (20.6)	425 (34.5)	72 (15.6)	105 (36.1)	87 (18.6)
Not Hispanic or Latino	358 (77.7)	507 (81.6)	1051 (79.3)	807 (65.5)	389 (84.2)	186 (63.9)	379 (81.2)
Not Reported	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Unknown [1]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Region							
North America (excluding Central America)	308 (66.8)	169 (27.2)	383 (28.9)	375 (30.4)	93 (20.1)	143 (49.1)	134 (28.7)
South America (including Central America)	9 (2.0)	21 (3.4)	133 (10.0)	210 (17.0)	33 (7.1)	0 (0.0)	54 (11.6)
Europe (including Russia)	118 (25.6)	224 (36.1)	597 (45.1)	510 (41.4)	209 (45.2)	148 (50.9)	186 (39.8)
Asia	6 (1.3)	85 (13.7)	174 (13.1)	116 (9.4)	127 (27.5)	0 (0.0)	80 (17.1)
South Africa	20 (4.3)	111 (17.9)	38 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	13 (2.8)
Australia/New Zealand	0 (0.0)	11 (1.8)	0 (0.0)	21 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Weight (kg)							
Subjects with data	461	621	1325	1232	462	291	467
Mean	92.9	84.9	86.8	88.7	86.9	92.3	88.5
SD	23.2	16.9	19.6	21.5	19.6	21.3	19.8
Median	89.9	84.2	85.4	86.5	85.7	90.0	87.0
Range	47.1 to 208.0	42.6 to 139.9	41.2 to 194.0	39.6 to 245.3	37.8 to 167.8	45.5 to 186.0	46.7 to 144.8

Table 97 (continued): Demographic and baseline characteristics, study by study comparison; All subjects treated

	P003/1022 Monotherapy n (%)	P007/1017 Add-on to Metformin n (%)	P002/1013 Ertugliflozin vs. Glimepiride n (%)	P005/1019 Ertugliflozin+ Sitagliptin factorial n (%)	P006/1015 Add-on to Metformin+ Sitagliptin n (%)	P017/1047 Ertugliflozin+ Sitagliptin n (%)	P001/1016 Renal Impairment n (%)
Height (cm)							
Subjects with data	461	621	1325	1232	462	291	467
Mean	167.4	165.5	166.0	166.4	167.7	168.8	164.7
SD	10.5	10.3	10.0	10.6	10.1	11.1	9.7
Median	167.6	165.0	166.0	166.2	167.6	169.0	164.0
Range	142.8 to 205.0	138.0 to 195.1	137.1 to 198.0	91.0 to 203.2	140.0 to 195.0	138.0 to 203.2	141.0 to 191.1
Baseline BMI (kg/m²)							
<25	30 (6.5)	67 (10.8)	156 (11.8)	136 (11.0)	70 (15.2)	24 (8.2)	39 (8.4)
25 to <30	150 (32.5)	206 (33.2)	451 (34.0)	410 (33.3)	153 (33.1)	81 (27.8)	131 (28.1)
30 to <35	134 (29.1)	217 (34.9)	404 (30.5)	360 (29.2)	141 (30.5)	113 (38.8)	146 (31.3)
>=35	147 (31.9)	131 (21.1)	314 (23.7)	326 (26.5)	98 (21.2)	73 (25.1)	151 (32.3)
Subjects with data	461	621	1325	1232	462	291	467
Mean	33.0	30.9	31.4	31.9	30.8	32.2	32.5
SD	6.7	4.7	6.1	6.3	6.0	6.1	6.1
Median	31.9	30.7	30.6	30.7	30.3	31.6	31.5
Range	20.4 to 67.9	18.9 to 40.9	17.4 to 77.9	18.4 to 64.6	17.5 to 67.1	20.9 to 57.4	20.3 to 54.6
Baseline A1C (%)							
<8.0	224 (48.6)	304 (49.0)	847 (63.9)	363 (29.5)	249 (53.9)	32 (11.0)	217 (46.5)
8.0 to <9.0	145 (31.5)	194 (31.2)	431 (32.5)	458 (37.2)	134 (29.0)	113 (38.8)	147 (31.5)
>=9.0	90 (19.5)	115 (18.5)	46 (3.5)	390 (31.7)	76 (16.5)	145 (49.8)	93 (19.9)
Unknown [a]	2 (0.4)	8 (1.3)	1 (0.1)	21 (1.7)	3 (0.6)	1 (0.3)	10 (2.1)
Subjects with data	459	613	1324	1211	459	290	457
Mean	8.2	8.1	7.8	8.6	8.0	8.9	8.1
SD	1.0	0.9	0.6	1.0	0.9	0.9	0.9
Median	8.0	8.0	7.7	8.4	7.9	9.0	8.0
Range	6.5 to 11.2	5.7 to 11.3	5.8 to 10.9	5.1 to 12.3	5.7 to 11.1	6.2 to 10.9	6.0 to 11.9
Baseline A1C (mmol/mol)							
<63.94	224 (48.6)	304 (49.0)	847 (63.9)	363 (29.5)	249 (53.9)	32 (11.0)	217 (46.5)
63.94 to <74.86	145 (31.5)	194 (31.2)	431 (32.5)	458 (37.2)	134 (29.0)	113 (38.8)	147 (31.5)
>=74.86	90 (19.5)	115 (18.5)	46 (3.5)	390 (31.7)	76 (16.5)	145 (49.8)	93 (19.9)
Unknown [a]	2 (0.4)	8 (1.3)	1 (0.1)	21 (1.7)	3 (0.6)	1 (0.3)	10 (2.1)
Subjects with data	459	613	1324	1211	459	290	457
Mean	66.2	65.2	61.7	70.0	64.3	74.2	65.6
SD	10.7	9.9	6.6	11.0	9.6	9.4	10.1
Median	63.9	63.9	60.7	68.3	62.8	74.3	63.9
Range	47.5 to 98.9	38.8 to 100.0	39.9 to 95.6	32.2 to 110.9	38.8 to 97.8	44.3 to 95.6	42.1 to 106.6
Baseline FPG (mg/dL)							
Subjects with data	450	602	1322	1224	460	290	466
Mean	180.1	168.4	161.0	180.4	169.7	197.8	158.5
SD	47.4	43.8	34.8	47.8	38.2	47.0	53.6
Median	170.0	159.0	156.0	173.5	165.0	193.0	151.0
Range	53.0 to 325.0	88.0 to 337.0	62.0 to 330.0	38.0 to 401.0	82.0 to 337.0	78.0 to 316.0	45.0 to 486.0
Baseline FPG (mmol/L)							
Subjects with data	450	602	1322	1224	460	290	466
Mean	10.0	9.3	8.9	10.0	9.4	11.0	8.8
SD	2.6	2.4	1.9	2.7	2.1	2.6	3.0
Median	9.4	8.8	8.7	9.6	9.2	10.7	8.4
Range	2.9 to 18.0	4.9 to 18.7	3.4 to 18.3	2.1 to 22.3	4.6 to 18.7	4.3 to 17.5	2.5 to 27.0
Baseline eGFR (mL/min/1.73m²)							
<30	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	12 (2.6)
30 to <45	0 (0.0)	1 (0.2)	4 (0.3)	2 (0.2)	0 (0.0)	0 (0.0)	153 (32.8)
45 to <60	17 (3.7)	23 (3.7)	50 (3.8)	25 (2.0)	8 (1.7)	4 (1.4)	275 (58.9)
60 to <90	251 (54.4)	290 (46.7)	713 (53.8)	588 (47.7)	257 (55.6)	155 (53.3)	27 (5.8)
>=90	193 (41.9)	307 (49.4)	557 (42.0)	616 (50.0)	197 (42.6)	131 (45.0)	0 (0.0)
Unknown [a]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.3)	0 (0.0)
Subjects with data	461	621	1325	1231	462	290	467
Mean	87.7	90.5	87.2	92.4	87.9	90.7	46.6
SD	18.6	19.3	18.5	20.0	16.9	19.0	8.8
Median	86.0	89.0	86.0	90.0	86.0	88.0	47.0
Range	47.0 to 181.0	42.0 to 178.0	28.0 to 162.0	35.0 to 196.0	51.0 to 145.0	55.0 to 171.0	22.0 to 85.0

Table 97 (continued): Demographic and baseline characteristics, study by study comparison; All subjects treated

	P003/1022 Monotherapy n (%)	P007/1017 Add-on to Metformin n (%)	P002/1013 Ertugliflozin vs. Glimepiride n (%)	P005/1019 Ertugliflozin+Sita gliptin factorial n (%)	P006/1015 Add-on to Metformin+Sitagliptin n (%)	P017/1047 Ertugliflozin+Sita gliptin n (%)	P001/1016 Renal Impairment n (%)
Duration of Type 2 Diabetes Mellitus (years)							
<5	282 (61.2)	234 (37.7)	512 (38.6)	540 (43.8)	106 (22.9)	148 (50.9)	63 (13.5)
5 to <10	106 (23.0)	203 (32.7)	470 (35.5)	404 (32.8)	159 (34.4)	76 (26.1)	99 (21.2)
>=10	73 (15.8)	184 (29.6)	343 (25.9)	288 (23.4)	197 (42.6)	67 (23.0)	305 (65.3)
Subjects with data	461	621	1325	1232	462	291	467
Mean	5.0	8.0	7.5	6.9	9.5	6.3	14.2
SD	5.1	6.0	5.7	5.4	5.7	6.0	8.5
Median	3.5	6.8	6.3	5.7	8.8	4.9	13.3
Range	0.0 to 39.9	0.2 to 38.9	0.2 to 49.6	0.2 to 35.5	0.2 to 34.3	0.0 to 40.4	0.1 to 46.4
Diabetic Microvascular Complications[2]							
Yes	59 (12.8)	124 (20.0)	264 (19.9)	213 (17.3)	116 (25.1)	45 (15.5)	467 (100.0)
No	402 (87.2)	497 (80.0)	1061 (80.1)	1019 (82.7)	346 (74.9)	246 (84.5)	0 (0.0)
AHA (alone or in combination) at Randomization[3]							
Currently on AHA therapy	1 (0.2)	621 (100.0)	1325 (100.0)	1232 (100.0)	462 (100.0)	0 (0.0)	435 (93.1)
Insulin	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	265 (56.7)
Metformin	1 (0.2)	621 (100.0)	1325 (100.0)	1232 (100.0)	461 (99.8)	0 (0.0)	0 (0.0)
Sulfonylurea	0 (0.0)	2 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	204 (43.7)
Thiazolidinediones	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (1.9)
DPP4	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)	460 (99.6)	0 (0.0)	69 (14.8)
Other AHA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	29 (6.2)
Number of AHA therapies at Randomization							
1	1 (0.2)	618 (99.5)	1324 (99.9)	1230 (99.8)	3 (0.6)	0 (0.0)	303 (64.9)
2	0 (0.0)	3 (0.5)	1 (0.1)	2 (0.2)	459 (99.4)	0 (0.0)	122 (26.1)
3 or more	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (2.1)
None	460 (99.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	291 (100.0)	32 (6.9)
History of Cardiovascular Disease							
CAD	30 (6.5)	74 (11.9)	177 (13.4)	145 (11.8)	59 (12.8)	34 (11.7)	176 (37.7)
PAD	1 (0.2)	14 (2.3)	30 (2.3)	38 (3.1)	17 (3.7)	15 (5.2)	45 (9.6)
Heart Failure	2 (0.4)	13 (2.1)	52 (3.9)	48 (3.9)	6 (1.3)	16 (5.5)	58 (12.4)
Cerebrovascular	7 (1.5)	19 (3.1)	70 (5.3)	52 (4.2)	17 (3.7)	11 (3.8)	54 (11.6)
History of Hypertension							
Yes	271 (58.8)	441 (71.0)	965 (72.8)	760 (61.7)	339 (73.4)	173 (59.5)	437 (93.6)
No	190 (41.2)	180 (29.0)	360 (27.2)	472 (38.3)	123 (26.6)	118 (40.5)	30 (6.4)
Related Concomitant Medication							
Hypertensives	249 (54.0)	423 (68.1)	906 (68.4)	729 (59.2)	322 (69.7)	139 (47.8)	439 (94.0)
ACE/ARB	223 (48.4)	375 (60.4)	799 (60.3)	658 (53.4)	288 (62.3)	120 (41.2)	398 (85.2)
Dyslipidemia Medication	245 (53.1)	349 (56.2)	693 (52.3)	535 (43.4)	286 (61.9)	93 (32.0)	362 (77.5)
Statin	225 (48.8)	314 (50.6)	610 (46.0)	468 (38.0)	257 (55.6)	79 (27.1)	318 (68.1)
Diuretic	96 (20.8)	205 (33.0)	360 (27.2)	253 (20.5)	113 (24.5)	57 (19.6)	260 (55.7)
Loop Diuretic	12 (2.6)	12 (1.9)	28 (2.1)	14 (1.1)	13 (2.8)	5 (1.7)	112 (24.0)

BMI = Body Mass Index, SD = Standard Deviation.

[1] Not included in summary statistics.

[2] Includes preferred terms reported as medical history related to diabetic neuropathy, diabetic retinopathy, and diabetic nephropathy.

[3] Combination blood glucose lowering agents are counted twice, under the each component of the combination.

Baseline value is defined as the Day 1 (Randomization) measurement. If this measurement is not available, the last pre-randomization measurement on or after Week -2 is used as the baseline value.

eGFR based on MDRD formula. Baseline value is defined as the Day 1 (Randomization) measurement. If this measurement is not available, the last pre-randomization measurement on or after Screening is used as the baseline value.

1.5.1. Ertugliflozin (5 mg and 15 mg QD) as 'monotherapy when metformin is considered inappropriate due to intolerance'

Evidence to support use of ertugliflozin as monotherapy was provided by the well-conducted pivotal Phase III placebo controlled Study P003/1022 in 461 adult T2DM patients who had inadequate glycaemic control on diet and exercise (refer to Section 7.2.1).

- Ertugliflozin 5 mg and 15 mg once daily provided statistically significant and clinically relevant improvements in glycaemic control (HbA1c, FPG and proportion of subjects with HbA1c < 7%) and body weight at Week 26 compared with placebo.
- These results represent the initial data of ertugliflozin treatment in T2DM subjects who were not receiving any other background anti-hyperglycaemic medication and demonstrate robust HbA1c lowering in this treatment setting.

- While the study was not powered to formally compare efficacy of the 2 doses, the 15 mg dose of ertugliflozin provided a numerically greater reduction of HbA1c, FPG and body weight relative to the 5 mg dose.

1.5.2. Ertugliflozin (5 mg and 15 mg QD) in combination with other AHAs

1.5.2.1. Second line therapy as add-on to metformin

The pivotal Phase III Study 007/1017 provided evidence of efficacy of the addition of ertugliflozin (5 mg and 15 mg) over placebo in treatment of 621 subjects with T2DM and inadequate glycaemic control on metformin monotherapy at a dose ≥ 1500 mg/day.

- Both ertugliflozin 15 mg and 5 mg produced robust, statistically and clinically significant greater reductions from baseline to Week 26 in HbA1c compared with placebo. Other measures of glycaemia also showed significant improvements with ertugliflozin, including reducing FPG and increasing the proportion of subjects reaching an HbA1c < 7%.
- Ertugliflozin 5 mg and 15 mg treatment also produced significantly greater reductions in body weight and systolic and diastolic blood pressure.
- Although study was not designed to compare the two doses of ertugliflozin, the 15 mg dose showed greater improvements in HbA1c, FPG and proportion of subjects with A1c < 7% compared with the 5 mg dose.
- The multicentre, randomised, double blind, active-controlled, parallel-group clinical Study P002/1013 compared the efficacy and safety of ertugliflozin to glimepiride (median dose of 3 mg) in 1326 subjects with T2DM and inadequate glycaemic control on a stable dose of metformin monotherapy (≥ 1500 mg/day).
- Ertugliflozin 15 mg met the pre-specified criteria for non-inferiority to glimepiride (where the mean glimepiride dose was 3.0 mg daily) for HbA1c reduction at 52 weeks of treatment. A clinically meaningful reduction from baseline in HbA1c at Week 52 was observed with the 5 mg dose of ertugliflozin; however, this did not meet the non-inferiority requirements relative to glimepiride.
- The HbA1c reductions observed in both ertugliflozin groups were evident by Week 6 and glycaemic efficacy was durable through Week 52. Although the Week 52 HbA1c reductions in the ertugliflozin groups were numerically smaller relative to glimepiride, FPG was numerically lower with both ertugliflozin doses compared with glimepiride at Week 52.
- Ertugliflozin (5 mg and 15 mg) also led to greater reductions in body weight and SBP compared to glimepiride; bodyweight for 15 mg was formally tested and test was successful.
- The COD (of the HbA1c response between Week 26 and Week 52) was used to assess durability of treatment with ertugliflozin after reaching peak efficacy; the COD was numerically higher in the glimepiride group compared with the ertugliflozin 5 mg and 15 mg groups indicating there was a more rapid loss of HbA1c response in the glimepiride group than in the ertugliflozin groups after Week 26.

Study P017/1047 was a randomised, double blind, placebo controlled pivotal Phase III study to evaluate initial combination therapy with ertugliflozin and sitagliptin in 293 subjects with T2DM and inadequate glycaemic control on diet and exercise (refer to Section 7.2.6):

- Treatment with the initial combination of ertugliflozin (5 mg QD or 15 mg QD) and sitagliptin 100 mg QD for 26 weeks provided clinically meaningful reductions from baseline in HbA1c, FPG, and 2-hour PMG and resulted in greater proportion of subjects with HbA1c < 7% relative to placebo.
- The initial ertugliflozin+sitagliptin combination therapy also led to significant reduction in body weight and sitting SBP relative to placebo.

- although this study was not designed to formally compare the 5 mg and 15 mg ertugliflozin doses, there were numerically greater reductions in HbA1c, FPG, 2-hour PMG, body weight and sitting SBP with the E15/S100 combination, relative to the E5/S100 combination.

1.5.2.2. Third line of therapy

The randomised, double blind, placebo controlled pivotal Phase III Study P006/1015 evaluated the efficacy and safety of the addition of ertugliflozin (5 mg and 15 mg QD) compared with the addition of placebo to combination therapy with metformin ≥ 1500 mg/day and sitagliptin 100 mg QD in 463 subjects with T2DM and inadequate glycaemic control.

- The addition of ertugliflozin (5 mg and 15 mg QD) to metformin and sitagliptin provided a significant improvements in glycaemic endpoints at Week 26 (HbA1c, FPG and proportion of subjects with HbA1c < 7.0%) compared with the placebo group.
- The addition of ertugliflozin (5 mg and 15 mg QD) provided significantly greater reductions from baseline in body weight and SBP at Week 26 compared with the addition of placebo.

The randomised, double blind, parallel-group, factorial pivotal Phase III Study P005/1019 evaluated the efficacy and safety of the co-administration of ertugliflozin (5 mg QD and 15 mg QD) with sitagliptin 100 mg QD compared with the individual treatments alone at corresponding dose strengths, in 1233 subjects with T2DM and inadequate glycaemic control on metformin monotherapy (median dose of 2000 mg/day).

- The LS mean reductions at Week 26 were robust, clinically meaningful and significantly greater in both combination groups (E15/S100 and E5/S100) relative to the individual component treatment groups at corresponding dose strengths.
- About 50% of the subjects achieved glycaemic goal (HbA1c < 7%) with combination treatment, relative to treatment with the individual components (about 26 to 33%).
- Marked reductions in FPG were also observed in all treatment groups, with significantly greater reductions in the combination groups relative to the individual component treatment groups at corresponding dose strengths. The LS mean reductions from baseline in 2 h PPG (assessed in a subset of subjects who participated in a MMTT) at Week 26 were similar across the treatment groups, except for the E15/S100 group, where larger reductions were observed relative to the individual component treatments at corresponding dose strengths.
- The number of subjects who required glycaemic rescue therapy was lower in the combination therapy groups with no subjects in the E15/S100 requiring rescue therapy.
- Reductions in body weight and sitting SBP were observed in the 4 ertugliflozin treated groups.
- No meaningful difference was observed between the 2 co-administration groups (E15/S100 and E5/S100) for HbA1c-related endpoints, although there was a trend toward better efficacy for E15/S100 relative to E5/S100 for FPG and 2 h PPG. However, interpretation was limited as this study was not powered to detect differences between the 2 combination groups.

1.5.3. Efficacy in special populations

In the moderate renal impairment study (Study P001/1016) involving 468 T2DM patients, the within-group change from baseline in HbA1c in the ertugliflozin groups was smaller than in other studies, as expected. However, interpretation was confounded by the placebo effect (due to use of metformin) and a post-hoc analysis excluding subjects who had a positive metformin assay result showed that ertugliflozin 15 mg provides greater reductions in HbA1c than placebo (based on the nominal 95% CI) in subjects with Stage 3 CKD (overall cohort). Very similar results were observed in subjects with Stage 3A CKD. However, there were no significant

differences between treatment groups for change from baseline in body weight, FPG, sitting SBP and proportion of subjects with HbA1c < 7% and no post hoc analysis was done for these parameters. Unlike in the Overall Cohort and Stage 3A CKD stratum, there was no early or sustained separation of the ertugliflozin and placebo groups excluding data from subjects with a positive metformin assay in the Stage 3B CKD stratum had little impact on HbA1c reductions with no notable differences in any treatment group.

Subgroup analyses showed that following treatment with ertugliflozin, the improvements in HbA1c was generally similar across subgroups defined by age, sex, race, geographic region, baseline BMI and duration of T2DM. However, ertugliflozin was associated with greater reductions in HbA1c in subgroups with higher baseline HbA1c values (≥ 8% compared to those < 8%) and also higher eGFR values (patients with normal or mild renal impairment compared to those with moderate renal impairment).

1.5.4. Limitations of efficacy data

- Although proposed indication states that ertugliflozin (as an adjunct to diet and exercise) can be used in combination with other anti-hyperglycaemic agents, it has only been evaluated in combination with metformin and DPP-4 inhibitor (sitagliptin). Efficacy and safety of ertugliflozin in combination with sulphonylureas or insulin therapy has not been evaluated in randomised, double blind, controlled studies as was done for other SGLT2 inhibitors which have been approved in Australia. it is important to note that although ertugliflozin was studied in combination with other AHAs including insulin and SUs in T2DM patients with moderate renal impairment, the results from this study cannot be used to support use of ertugliflozin in combination with insulin and SUs. Furthermore, efficacy/ safety of ertugliflozin in combination with other anti-hyperglycaemic treatments such as acarbose, thiazolidinediones and glucagon-likepeptide-1 (GLP-1) analogues have not been evaluated.
- This submission only included results from Phase A (up to 26 weeks in all Phase III studies except Study P002/1013 (Phase A was at 52 weeks for this study which compared ertugliflozin with glimepiride in T2DM patients with inadequate glycaemic control on metformin therapy). Hence long term maintenance of efficacy of ertugliflozin in the proposed indications will require confirmation and data from the ongoing Phase B of all 7 Phase III studies should help to address this. The sponsors are required to submit these data for evaluation as soon as it is available.
- Ertugliflozin produced significant reduction in body weight across all studies. However, effect on ertugliflozin on body composition (waist circumference, body fat) was not evaluated in any of the studies.

2. Clinical safety

2.1. Studies providing evaluable safety data

Safety was evaluated in 29 Phase I, 2 Phase II and 7 Phase III clinical studies, including exposure to ertugliflozin in 4418 subjects. In addition, two Phase III studies, a cardiovascular (CV) outcomes trial (Study P004/1021) and, a 26 week Phase III Asia Pacific regional study (Study P012/1045) are still recruiting at the time of this submission with no further information presented in the submitted dossier.

2.1.1. Pivotal studies that assessed safety as the sole primary outcome

None.

2.1.2. Pivotal and/or main efficacy studies

Seven Phase III studies provided safety data and all of these studies evaluated two doses of ertugliflozin (5 mg and 15 mg once daily):

- Monotherapy Study P003/1022
- Placebo controlled add-on to metformin Study P007/1017
- Ertugliflozin versus glimepiride add on metformin Study P002/1013
- Ertugliflozin + Sitagliptin factorial Study P005/1019
- Add-on to metformin and sitagliptin Study P006/1015
- Ertugliflozin+sitagliptin initial combination Study P017/1047
- Moderate renal impairment Study P001/1016.

The Placebo controlled (PBO) Pool contains the safety data to Week 26 from 3 similarly designed Phase III studies with a placebo comparator. The Broad Pool contains the data from 7 Phase III studies, including those in the PBO Pool, studies with active comparators, and a study in subjects with moderate renal impairment. The PBO Pool includes safety results from 3 trials (Studies P003/1022, P006/1015, P007/1017) which have a similar design, a common 26 week duration of treatment with a placebo control, and similar enrolment criteria (for example, subjects ≥ 18 years of age with T2DM and inadequate glycaemic control with HbA1c >7.0% and ≤ 10.5%), differing mainly by background diabetes treatment. Two placebo controlled studies, Studies P001/1016 and P017/1047, were not included because they enrolled a special population (Study P001/1016 which enrolled subjects with moderate renal impairment), or did not include an ertugliflozin only treatment arm (Study P017/1047 which compared co-administration of ertugliflozin and sitagliptin to placebo). Both of these studies are included in the Broad Pool. In the PBO Pool, the groups presented are ertugliflozin 5 mg, ertugliflozin 15 mg, all ertugliflozin (ertugliflozin 5 mg combined with ertugliflozin 15 mg), and placebo. A larger pooled population, the Broad Pool, includes safety results from 7 Phase III studies. This pool supports and extends assessments performed in the PBO Pool, and due to the larger sample size, also allows for detection of adverse events with lower incidence. In the Broad Pool, the groups presented are ertugliflozin 5 mg, ertugliflozin 15 mg, all ertugliflozin (ertugliflozin 5 mg combined with ertugliflozin 15 mg), and non-ertugliflozin. The non-ertugliflozin group in this pool contains subjects taking placebo (including some who switched to metformin or glimepiride after Week 26) and subjects in active comparator groups (glimepiride or sitagliptin) (Table 98).

Table 98: Summary of pooling strategy for Phase III studies

Protocol Number	Short Title	Placebo-controlled Pool	Broad Pool
003/1022	Monotherapy Study	X†	X‡
006/1015	Add-on to Metformin and Sitagliptin Study	X†	X‡
007/1017	Placebo-controlled Add-on to Metformin Study	X†	X‡
001/1016	Moderate Renal impairment Study		X‡
002/1013	Ertugliflozin vs Glimepiride as Add-on to Metformin Study		X‡
005/1019	Ertugliflozin+Sitagliptin Factorial Study		X‡
017/1047	Ertugliflozin+Sitagliptin Initial Combination Study		X§

† Includes Phase A only
‡ Includes Phase A and Phase B to last data available date
§ Includes the complete study data

The safety analyses were performed in the All Subjects as Treated (ASaT) population, consisting of all randomised subjects who received at least 1 dose of study medication. In the PBO pool, which includes Phase A results from 3 studies with Phase A/Phase B designs, the Phase A Treatment Period for subjects who entered Phase B included safety data from the first dose of randomised study medication to the first dose of Phase B study medication. For subjects who did not enter Phase B, the Treatment Period included AEs occurring up to 14 days after the final dose of study medication, and included results from laboratory and ECG evaluations performed up to 2 days after the final dose of study medication. In the Broad pool, the Treatment Period included safety data from the first dose of randomised study medication through the data cut-off for the 6 studies contributing to this pool with Phase A/B designs. For subjects in these 6 studies who discontinued study medication before the data cut-off dates, and for all subjects in the completed 26 week Ertugliflozin+Sitagliptin Initial Combination Study P017/1047, the Treatment Period included AEs up to 14 days after the final dose of study medication, and included results from laboratory and ECG evaluations performed up to 2 days after the final dose of study medication.

For all of the Phase III studies, safety evaluations included the collection of AEs, laboratory tests (haematology, chemistry, and urinalysis), sitting blood pressure, orthostatic blood pressure (supine to standing), pulse rate (sitting, supine, and standing), weight, centrally-read 12-lead ECGs, and self-monitored blood glucose. In the Placebo controlled Add-on to Metformin Study (Study P007/1017), bone mineral density by dual-energy x-ray absorptiometry (DXA) of the lumbar spine, total hip, femoral neck, and distal forearm was measured at baseline, Weeks 26, 52 and 104 and evaluated by a central evaluation facility. Study P007/1017 and the Moderate Renal Impairment Study (Study P001/1016) also included measurement of parathyroid hormone (PTH) and markers of bone turnover including serum carboxy-terminal cross-linking telopeptides of type I collagen (CTX), procollagen type I N terminal propeptide (P1NP) and serum procollagen type I N-terminal propeptide (PINP).

The types of AE analyses included overall summary measures of AEs, AEs by SOC, specific AEs , fatal and non-fatal SAEs, investigator defined drug related AEs and AEs that resulted in discontinuation from study medication.

For lipid panel, laboratory, ECG, and vital sign data, at least one measurement obtained subsequent to at least one dose of trial treatment was required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement was also required. Safety analysis was based on observed data only. No imputation was performed for missing data except where noted otherwise.

Unblinded safety data from the Phase III studies in the ertugliflozin development program were monitored by an external data monitoring committee (DMC);[15] to supplement routine blinded safety monitoring by the study teams. Additionally, 5 pre-specified event types (cardiovascular;[16] fracture, pancreatitis, renal, and hepatic events) were subject to adjudication by separate, blinded, external clinical adjudication committees and potential events of ketoacidosis were subject to blinded, internal case review.

Comment: The following sections of the report will focus on evaluation of safety data from the two pooled datasets from the Phase III development program. Review of safety

[15] The voting members of the committee were external to the sponsors. The members of the DMC were not involved with the program in any other way (for example, they could not be study investigators) and had no competing interests that could have affected their roles with respect to the study. The DMC included 4 clinicians experienced in diabetes and/or CV disease and 1 external statistician; this was in addition to the unblinded study statistician who was a non-voting member of the committee.

[16] A Cardiovascular Adjudication Committee adjudicated, in a blinded fashion, potential cases of CV events, venous thromboembolic events, hospitalisation for heart failure, and all deaths in all Phase III studies as well as the single Phase II study with a duration of at least 12 weeks. The pre-specified program-wide meta-analysis of the CV endpoint major adverse cardiac events plus (MACE+) was based on these adjudication results.

results from individual Phase III studies showed results which were consistent with the pooled analyses. As a result of periodic MedDRA updates, the AE encoding used in the Pooled safety analyses was different from the AE encoding used in Phase III CSRs. For the individual studies, Version 18.1 of MedDRA was used for AE encoding, which was current at the time of database lock for data included in this submission.

2.1.3. Other studies

2.1.3.1. Studies with evaluable safety data: dose finding and pharmacology

Ertugliflozin was administered in two Phase II studies (Studies P042/1004 and P016/1006) to 335 subjects with T2DM. The Phase I program included 29 studies and a total of 688 subjects who received at least 1 dose of ertugliflozin (≤ 4 mg up to 300 mg), either alone or in combination with another drug; 600 healthy subjects, 82 subjects with T2DM (including 22 subjects with varying degrees of renal impairment), and 6 subjects with moderate hepatic impairment.

2.1.3.2. Studies evaluable for safety only

None.

2.1.4. Studies that assessed safety as the sole primary outcome

None.

2.2. Patient exposure

Overall 6068 subjects were treated across the Phase I to Phase III studies of which 4418 were exposed to ertugliflozin (Table 99). The number of subjects in each individual trial included in the PBO or Broad Pools by treatment group is summarised in Table 100.

Table 99: Exposure in the ertugliflozin development program

Protocol Number	Phase	Short Title	Ertu Exposed/ Non-exposed
29 Studies	1	NA	674/14
P042/1004	2	4-Week Dose-ranging Study	116/77
P016/1006	2	12-Week Dose-ranging Study	219/109
P001/1016	3	Moderate Renal Impairment Study	313/154
P002/1013	3	Ertugliflozin vs Glimepiride as Add-on to Metformin Study	888/437
P003/1022	3	Monotherapy Study	308/153
P005/1019	3	Ertugliflozin +Sitagliptin Factorial Study	985/247
P006/1015	3	Add-on to Metformin and Sitagliptin Study	309/153
P007/1017	3	Placebo-controlled Add-on to Metformin Study	412/209
P017/1047	3	Ertugliflozin + Sitagliptin Initial Combination Study	194/97
Total			4418/1650
Abbreviations: CV = cardiovascular, NA = not applicable			

Table 100: Subjects by trial and treatment group: all subjects treated in PBO controlled and Broad pools

	Placebo n (%)	Ertugliflozin 5 mg n (%)	Ertugliflozin 15 mg n (%)	All Ertugliflozin n (%)	Total n (%)
Subjects in population	515	519	510	1,029	1,544
P003/1022	153 (29.7)	156 (30.1)	152 (29.8)	308 (29.9)	461 (29.9)
P006/1015	153 (29.7)	156 (30.1)	153 (30.0)	309 (30.0)	462 (29.9)
P007/1017	209 (40.6)	207 (39.9)	205 (40.2)	412 (40.0)	621 (40.2)

	Non-Ertugliflozin n (%)	Ertugliflozin 5 mg n (%)	Ertugliflozin 15 mg n (%)	All Ertugliflozin n (%)	Total n (%)
Subjects in population	1,450	1,716	1,693	3,409	4,859
P001/1061	154 (10.6)	158 (9.2)	155 (9.2)	313 (9.2)	467 (9.6)
P002/1013	437 (30.1)	448 (26.1)	440 (26.0)	888 (26.0)	1,325 (27.3)
P003/1022	153 (10.6)	156 (9.1)	152 (9.0)	308 (9.0)	461 (9.5)
P005/1019	247 (17.0)	493 (28.7)	492 (29.1)	985 (28.9)	1,232 (25.4)
P006/1015	153 (10.6)	156 (9.1)	153 (9.0)	309 (9.1)	462 (9.5)
P007/1017	209 (14.4)	207 (12.1)	205 (12.1)	412 (12.1)	621 (12.8)
P017/1047	97 (6.7)	98 (5.7)	96 (5.7)	194 (5.7)	291 (6.0)

In the PBO Pool, 1544 subjects were randomised and received at least 1 dose of study medication in the 3 studies The mean observation period on study medication through 26 weeks was not notably different in the ertugliflozin 5 mg and 15 mg groups (174.8 and 172.6 days, respectively) relative to the placebo group (170.2 days). Treatment compliance was similar and high across groups in the PBO Pool and majority of subjects in all groups (99.0%) reported taking ≥ 75% of study medication. The proportions of subjects who discontinued study medication were not notably different in the ertugliflozin 5 mg and 15 mg groups and the all ertugliflozin group relative to the placebo group. The most common reasons for discontinuation from study medication in the total group were discontinuation due to an AE and withdrawal by subject. Of the 1545 randomised subjects, 94.2% completed Phase A while on study medication or after premature discontinuation of study medication. The proportion of subjects who completed Phase A was similar across the treatment groups with withdrawal by subject and lost to follow-up being most common reasons for study discontinuation.

Baseline demographic and anthropometric characteristics were similar between groups. The mean age, BMI and eGFR was 57.3 years, 31.5 kg/m^2 and 88.9 mL/min/1.73m^2, respectively. The majority of subjects in the PBO Pool were White (73.4%); 15.1% were Asian, and 6.6% were Black or African American. There were slightly more males (52.6%) than females (47.4%). The mean duration of T2DM for subjects in the PBO Pool was 7.5 years Baseline HbA1c and fasting plasma glucose (FPG) were similar between groups, with a mean baseline HbA1c of 8.1% and mean FPG of (9.6 mmol/L) across all groups. Diabetic microvascular complications were included in the medical history of 19.4% of all subjects. Most subjects (70.2%) were on an AHA at the time of randomisation, reflecting the use of background AHA therapy in the designs of 2 of the 3 studies in the PBO Pool, with the most common AHA therapy being metformin (70.1%), followed by DPP-4 inhibitors (29.9%). More subjects were on only 1 AHA therapy at the time of randomisation (40.3%), while 30.1% were on 2 AHA therapies.

The proportion of subjects with a history of CV disease was similar between groups in the overall pooled population, 10.6% had a history of coronary artery disease, 2.1% had a history of peripheral vascular disease, 1.4% had a history of heart failure, and 2.8% had a history of cerebrovascular disease. The proportion of subjects with a history of hypertension was high

(68.1% of all subjects) and was similar between groups; the proportion of subjects with a history of hyperlipidaemia was also high (65.3%) and similar between groups.

The Broad Pool includes data through completion of Study P017/1047 and includes Phase A data and Phase B data up to the LDA date for the other 6 studies. In the Broad Pool, 4859 subjects were randomised and received at least 1 dose of study medication in the 7 studies. Of the 3409 subjects who received at least 1 dose of ertugliflozin (5 or 15 mg), 3128, 2575 and 371 subjects received treatment with any dose of ertugliflozin for at least 25 weeks, 50 weeks, and 76 weeks, respectively. The mean duration of treatment with ertugliflozin was 355.7 days. A total of 1450 subjects were randomised to the non-ertugliflozin group, and 867 of these subjects received treatment for at least 50 weeks, with a mean duration of 354.9 days.

Treatment compliance was similar and high across groups in the Broad Pool. The majority of subjects in all groups (98.8%) reported taking >75% of study medication. More subjects were randomised and treated in the ertugliflozin 5 mg and 15 mg groups relative to the non-ertugliflozin group. Of the 4864 randomised subjects, 48.1% of subjects completed the study; most studies were ongoing in Phase B at the time of the data cut-off. The proportion of subjects who completed the study was numerically higher in the ertugliflozin 5 mg and 15 mg groups relative to the non-ertugliflozin group. The proportion of subjects who discontinued study medication was not notably different in the ertugliflozin 5 mg and 15 mg groups and the all ertugliflozin group relative to the non-ertugliflozin group.

The most common reasons for discontinuation from study medication in all groups were withdrawal by subject, lost to follow-up, hyperglycaemia, and discontinuation due to an AE with no notable differences between the groups. In the Broad pool, the mean age was 57.8 years, 25.8% of subjects were ≥ 65 years, and 4.5% were ≥ 75 years of age. The mean BMI and eGFR was 31.7 kg/m^2 and 85.3 mL/min/1.73m^2 respectively; 47.0% had an eGFR in the range of 60 to < 90 mL/min/1.73m^2, and 41.2% of subjects had an eGFR ≥ 90 mL/min/1.73m^2). Majority of subjects were White (76.8%), 13.3% were Asian, and 5.0% were Black or African American; there were slightly more males (51.8%) than females (48.2%). The mean duration of T2DM for subjects Broad Pool was 7.9 years and numerically higher proportion of subjects (38.8%) had a duration of T2DM < 5 years, relative to those with a duration of T2DM from 5 to < 10 years (31.2%), or ≥ 10 years (30.0%).

Baseline HbA1c and FPG were similar between groups, the mean baseline HbA1c was 8.2% and the mean FPG was 171.4 mg/dL (9.5 mmol/L) across all groups**.** Diabetic microvascular complications were included in the medical history of 26.6% of all subjects. Most subjects (83.9%) were on an AHA at the time of randomisation, with the most common AHA therapy being metformin (74.9%), followed by DPP-4 inhibitors (10.9%), insulin (5.5%) and sulfonylurea (4.3%). Most subjects were on 1 AHA therapy at the time of randomisation (71.7%), while 12.0% were on 2 AHA therapies. The proportion of subjects with a history of CV disease was similar between groups; in the overall pooled population, 14.3% had a history of coronary artery disease, 3.3% had a history of peripheral vascular disease, 4.0% had a history of heart failure, and 4.8% had a history of cerebrovascular disease. The proportion of subjects with a history of hypertension was high (69.7%) and similar between groups. Similarly, the proportion of subjects with a history of hyperlipidaemia was high (62.1%) and similar between groups.

Comment: The exposure to proposed doses of ertugliflozin (5 mg and 15 mg QD) was adequate to evaluate safety for proposed indication. Evaluation of long-term safety beyond 6 months was limited as data from Phase B durations ranging from 52 to 104 weeks) of the Phase III studies was not provided in this submission.

2.3. Adverse events

2.3.1. All adverse events (irrespective of relationship to study treatment)

2.3.1.1. Integrated safety analyses

PBO controlled pool

The incidence of subjects with 1 or more AEs was similar across the placebo (51.1%; 263/515), ertugliflozin 5 mg (45.5%; 236/519) and ertugliflozin 15 mg (50.4%; 257/510) groups. AEs in the Infection and infestations SOC were the most frequently reported in all groups (> 15%), with a slightly higher incidence in the placebo group relative to the ertugliflozin groups. AEs in the Metabolism and nutrition disorders SOC were reported at a higher incidence in the placebo group relative to the ertugliflozin 5 mg and 15 mg groups; this was predominantly related to a higher incidence of AEs of hyperglycaemia. There were 2 SOCs in which the incidence of AEs was higher with ertugliflozin: relative to placebo: the Renal and urinary disorders SOC (pollakiuria and polyuria most common) and the Reproductive system/ breast disorders SOC (balanoposthitis and vulvovaginal pruritus most common). Common AEs reported at incidence > 2% in the 'all ertugliflozin' group were URTI (3.5%), UTI (2.5%), vulvovaginal mycotic infection (2.7%), hypoglycaemia (3.3%) and headache (3.2%), Among AEs that occurred in greater than or equal to 2% of subjects in any group, the only event that occurred at a higher incidence (that is, 95% CI excluded 0) in either of the ertugliflozin dose groups or the all ertugliflozin group relative to the placebo group was vulvovaginal mycotic infection (0.6%, 2.7% and 2.7% in placebo, ertugliflozin 5 mg and 15 mg groups, respectively).

Broad pool

The overall incidence of subjects with 1 or more AEs was similar across the non-ertugliflozin (64.8%; 940/1450), ertugliflozin 5 mg (62.6%; 1074/1716) and ertugliflozin 15 mg (62%; 1049/1693) groups. AEs in the Infection and infestations SOC were the most frequently reported in all groups (> 30%), but were not notably different across groups. . The incidence of AEs by SOC was higher in ertugliflozin-treated subjects relative to subjects in the non-ertugliflozin group in 3 SOC categories: the Reproductive system and breast disorders SOC (balanoposthitis and vulvovaginal pruritus most common), the Neoplasms benign, malignant, and unspecified SOC and Ear and labyrinth SOC (Table 101). AEs in the Metabolism and nutrition disorders SOC were reported at a higher incidence in the non-ertugliflozin group relative to the ertugliflozin 5 mg and 15 mg groups related to a higher incidence of AEs of hypoglycaemia, predominately related to events associated with glimepiride (active comparator in P002/1013). Common AEs in the 'all ertugliflozin' group in the Broad pool included URTI (4.2%), UTI (5.4%), hypoglycaemia (6.8%) and headache (3.3%). Among AEs that occurred in ≥ 2% of subjects in any group, those that occurred at a higher incidence (that is, 95% CI excluded 0) in either of the ertugliflozin dose groups or the all ertugliflozin group relative to the non-ertugliflozin group were vulvovaginal mycotic infections and weight decreased (Table 102). Of the AEs that occurred in < 2% of subjects in all groups, those that occurred at a higher incidence in either of the ertugliflozin dose groups or the all ertugliflozin group relative to the non-ertugliflozin group included preferred terms that were related to Special Safety Topics and not related to Special Safety Topics. Those related to Special Safety Topics were: balanitis candida, genital candidiasis, genital infection fungal, vulvovaginitis, balanoposthitis, pruritus genital, vaginal infection, vulvovaginal candidiasis, dry mouth, thirst, pollakiuria, polyuria, hypotension, blood creatinine increased and glomerular filtration rate decreased. Those not related to Special Safety Topics were: gastritis, insomnia, fungal infection, neuralgia, sciatica, alopecia, dermatitis allergic, vulvovaginal pruritus and varicose veins.

Table 101: Broad pool, including rescue approach subjects with AEs by SOC (incidence > 0% in 1 or more treatment groups); All subjects as treated

	Non-Ertugliflozin		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	1,450		1,716		1,693		3,409	
with one or more adverse events	940	(64.8)	1,074	(62.6)	1,049	(62.0)	2,123	(62.3)
with no adverse events	510	(35.2)	642	(37.4)	644	(38.0)	1,286	(37.7)
Blood and lymphatic system disorders	25	(1.7)	23	(1.3)	25	(1.5)	48	(1.4)
Cardiac disorders	43	(3.0)	63	(3.7)	51	(3.0)	114	(3.3)
Congenital, familial and genetic disorders	3	(0.2)	3	(0.2)	6	(0.4)	9	(0.3)
Ear and labyrinth disorders	14	(1.0)	32	(1.9)	27	(1.6)	59	(1.7)
Endocrine disorders	2	(0.1)	4	(0.2)	6	(0.4)	10	(0.3)
Eye disorders	39	(2.7)	50	(2.9)	33	(1.9)	83	(2.4)
Gastrointestinal disorders	187	(12.9)	239	(13.9)	195	(11.5)	434	(12.7)
General disorders and administration site conditions	63	(4.3)	64	(3.7)	72	(4.3)	136	(4.0)
Hepatobiliary disorders	12	(0.8)	21	(1.2)	21	(1.2)	42	(1.2)
Immune system disorders	7	(0.5)	11	(0.6)	5	(0.3)	16	(0.5)
Infections and infestations	458	(31.6)	542	(31.6)	512	(30.2)	1,054	(30.9)
Injury, poisoning and procedural complications	77	(5.3)	85	(5.0)	89	(5.3)	174	(5.1)
Investigations	121	(8.3)	110	(6.4)	145	(8.6)	255	(7.5)
Metabolism and nutrition disorders	326	(22.5)	243	(14.2)	247	(14.6)	490	(14.4)

Table 101: Broad pool including rescue approach subjects with AEs by SOC (incidence > 0% in 1 or more treatment groups); All subjects as treated

	Non-Ertugliflozin		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)
Musculoskeletal and connective tissue disorders	177	(12.2)	198	(11.5)	181	(10.7)	379	(11.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	14	(1.0)	22	(1.3)	32	(1.9)	54	(1.6)
Nervous system disorders	145	(10.0)	161	(9.4)	151	(8.9)	312	(9.2)
Psychiatric disorders	38	(2.6)	41	(2.4)	47	(2.8)	88	(2.6)
Renal and urinary disorders	70	(4.8)	98	(5.7)	103	(6.1)	201	(5.9)
Reproductive system and breast disorders	29	(2.0)	76	(4.4)	80	(4.7)	156	(4.6)
Respiratory, thoracic and mediastinal disorders	84	(5.8)	91	(5.3)	82	(4.8)	173	(5.1)
Skin and subcutaneous tissue disorders	63	(4.3)	79	(4.6)	79	(4.7)	158	(4.6)
Social circumstances	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.0)
Vascular disorders	44	(3.0)	70	(4.1)	62	(3.7)	132	(3.9)
NULL	0	(0.0)	1	(0.1)	1	(0.1)	2	(0.1)

Every subject is counted a single time for each applicable row and column.
A system organ class appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
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Table 102: Broad pool including rescue approach subjects with AEs (incidence ≥ 2% in 1 or more treatment groups); All subjects as treated

	Non-Ertugliflozin		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	1,450		1,716		1,693		3,409	
with one or more adverse events	940	(64.8)	1,074	(62.6)	1,049	(62.0)	2,123	(62.3)
with no adverse events	510	(35.2)	642	(37.4)	644	(38.0)	1,286	(37.7)
Cardiac disorders	**43**	**(3.0)**	**63**	**(3.7)**	**51**	**(3.0)**	**114**	**(3.3)**
Eye disorders	**39**	**(2.7)**	**50**	**(2.9)**	**33**	**(1.9)**	**83**	**(2.4)**
Gastrointestinal disorders	**187**	**(12.9)**	**239**	**(13.9)**	**195**	**(11.5)**	**434**	**(12.7)**
Constipation	25	(1.7)	40	(2.3)	31	(1.8)	71	(2.1)
Diarrhoea	73	(5.0)	55	(3.2)	37	(2.2)	92	(2.7)
Nausea	31	(2.1)	25	(1.5)	26	(1.5)	51	(1.5)
General disorders and administration site conditions	**63**	**(4.3)**	**64**	**(3.7)**	**72**	**(4.3)**	**136**	**(4.0)**
Infections and infestations	**458**	**(31.6)**	**542**	**(31.6)**	**512**	**(30.2)**	**1,054**	**(30.9)**
Bronchitis	43	(3.0)	43	(2.5)	35	(2.1)	78	(2.3)
Influenza	50	(3.4)	47	(2.7)	36	(2.1)	83	(2.4)
Nasopharyngitis	68	(4.7)	77	(4.5)	72	(4.3)	149	(4.4)
Upper respiratory tract infection	73	(5.0)	81	(4.7)	62	(3.7)	143	(4.2)
Urinary tract infection	92	(6.3)	94	(5.5)	90	(5.3)	184	(5.4)
Vulvovaginal mycotic infection	4	(0.3)	34	(2.0)	32	(1.9)	66	(1.9)
Injury, poisoning and procedural complications	77	**(5.3)**	**85**	**(5.0)**	**89**	**(5.3)**	**174**	**(5.1)**
Investigations	**121**	**(8.3)**	**110**	**(6.4)**	**145**	**(8.6)**	**255**	**(7.5)**
Weight decreased	11	(0.8)	21	(1.2)	40	(2.4)	61	(1.8)
Metabolism and nutrition disorders	**326**	**(22.5)**	**243**	**(14.2)**	**247**	**(14.6)**	**490**	**(14.4)**
Hyperglycaemia	49	(3.4)	40	(2.3)	33	(1.9)	73	(2.1)
Hypoglycaemia	214	(14.8)	115	(6.7)	118	(7.0)	233	(6.8)

Table 102: Broad pool including rescue approach subjects with AEs (incidence ≥ 2% in 1 or more treatment groups); All subjects as treated

Musculoskeletal and connective tissue disorders	**177**	**(12.2)**	**198**	**(11.5)**	**181**	**(10.7)**	**379**	**(11.1)**
Arthralgia	35	(2.4)	28	(1.6)	30	(1.8)	58	(1.7)
Back pain	46	(3.2)	49	(2.9)	47	(2.8)	96	(2.8)
Nervous system disorders	**145**	**(10.0)**	**161**	**(9.4)**	**151**	**(8.9)**	**312**	**(9.2)**
Dizziness	25	(1.7)	34	(2.0)	29	(1.7)	63	(1.8)
Headache	51	(3.5)	55	(3.2)	59	(3.5)	114	(3.3)
Psychiatric disorders	**38**	**(2.6)**	**41**	**(2.4)**	**47**	**(2.8)**	**88**	**(2.6)**
Renal and urinary disorders	**70**	**(4.8)**	**98**	**(5.7)**	**103**	**(6.1)**	**201**	**(5.9)**
Reproductive system and breast disorders	**29**	**(2.0)**	**76**	**(4.4)**	**80**	**(4.7)**	**156**	**(4.6)**
Respiratory, thoracic and mediastinal disorders	**84**	**(5.8)**	**91**	**(5.3)**	**82**	**(4.8)**	**173**	**(5.1)**
Cough	26	(1.8)	39	(2.3)	33	(1.9)	72	(2.1)
Skin and subcutaneous tissue disorders	**63**	**(4.3)**	**79**	**(4.6)**	**79**	**(4.7)**	**158**	**(4.6)**
Vascular disorders	**44**	**(3.0)**	**70**	**(4.1)**	**62**	**(3.7)**	**132**	**(3.9)**

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

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2.3.2. Other studies

2.3.2.1. Phase I studies

Six hundred (600) healthy subjects were enrolled in the Phase I studies and of these, 586 subjects received at least one dose of ertugliflozin and 14 subjects only received placebo. Over the course of the studies, no deaths, SAEs or severe AEs were reported in healthy subjects. However, 296 (49.3%) subjects reported 573 AEs, of these: 263 AEs were reported by 134 (38.3%) subjects during a treatment sequence in which they were given ertugliflozin alone; 238 AEs were reported by 130 (41.7%) subjects during a sequence in which they were administered ertugliflozin in combination with other drugs or comparators group; 62 AEs were reported by 47 (39.2%) subjects during a sequence in which they received other drugs or were in the comparator alone group; and 25 (31.6%) subjects reported 28 AEs during a sequence in which they received placebo. Two subjects discontinued treatment due to an adverse event (influenza like illness and ALT increased); neither event was considered treatment related by the investigator. The most frequently reported AEs categorised by treatment received were: headache (9.7%), nausea (5.7%), vomiting (2.9%), fatigue (2.9%), abdominal discomfort (2.6%) and diarrhoea (2.6%) in subjects receiving ertugliflozin alone; diarrhoea (11.9%), headache (9.6%), abdominal pain (5.1%), and nausea (5.1%) in subjects who received ertugliflozin in combination with other drugs or comparators; headache (9.2%), diarrhoea (5.8%) and nausea (3.3%) in subjects who received other drugs or comparators alone; and headache (5.1%), dizziness (3.8%), diarrhoea (5.1%) and constipation (2.5%) in subjects administered placebo.

In the group of healthy subjects who received ertugliflozin doses of ≥ 100 mg (maximum proposed daily dose is 15 mg), which included 7 subjects who received a single dose of 300 mg, 52 subjects who received a single dose of 100 mg and 8 subjects who received 100 mg for 14 days, no new AEs were reported (that is, that were not seen at lower doses) and AEs reported in more than one subject were generally similar to those reported at lower doses. Overall, the most concerning PD effect that was identified in the studies discussed in the PK/PD sections of the current report was the evidence of dose-independent bone resorption following treatment with ertugliflozin but not sitagliptin in the Phase II Study, P016/1006.

Phase II studies

Across the 2 Phase II studies, a total of 7 on-treatment SAEs were reported, 4 of which occurred in subjects taking ertugliflozin. No deaths were reported in the Phase II program. Overall, there were no unanticipated safety signals/tolerability issues.

2.3.3. Treatment related adverse events (adverse drug reactions)

2.3.3.1. Integrated safety analyses

Placebo controlled pool

The incidence of drug-related AEs was higher in both the ertugliflozin 5 mg (14.3%;74/519) and 15 mg (14.7%; 75/510) groups relative to the placebo group (9.3%;48/515), mainly due to numerically increased incidence of AEs related to genital mycotic infections and osmotic diuresis in ertugliflozin-treated subjects relative to placebo.

Broad Pool

The incidence of drug-related AEs was slightly higher in the ertugliflozin 5 mg (18.4%; 316/1716) and ertugliflozin 15 mg (19.2%; 325/1693) groups compared to the non-ertugliflozin (16.5%; 239/1450) group, mainly due to numerically increased incidence of AEs related to genital mycotic infections and osmotic diuresis in ertugliflozin-treated subjects relative to the non-ertugliflozin group.

2.3.4. Deaths and other serious adverse events

2.3.4.1. Integrated safety analyses

Placebo controlled pool

There were no deaths in the PBO Pool. The incidence of SAEs was low and similar across the placebo (2.9%; 15/515), ertugliflozin 5 mg (3.3%; 17/519) and ertugliflozin 15 mg (2.4%; 12/510) groups. Non-fatal SAEs occurred across multiple SOCs with no obvious pattern. Few specific AE preferred terms occurred in more than 1 ertugliflozin or placebo treated subject and only one SAE, a transient ischemic attack in the ertugliflozin 15 mg group, was considered to be drug-related.

Broad pool

The incidence of death was low in all groups but slightly numerically higher in the ertugliflozin groups relative to the non-ertugliflozin group (0.6%, 0.5% and 0.2% in ertugliflozin 5 mg, 15 mg and non-ertugliflozin groups, respectively). The numerical difference was related to slight differences in several different AEs leading to death, with no discernible pattern. The incidence of death was similarly low across groups when examined in the All Post-randomisation Follow-up analysis, with smaller numerical between treatment differences relative to the on-treatment analysis (there were 2 additional deaths in the ertugliflozin groups, 1 in each dose group, and 3 additional deaths in the non-ertugliflozin group): 0.6%, 0.5% and 0.4% in the ertugliflozin 5 mg, 15 mg and non-ertugliflozin groups, respectively**.** As anticipated in this subject population, the most commonly reported fatal events in all groups were related to cardiovascular death (those in the Cardiac disorders SOC and specific events in other SOCs such as sudden death), based on investigator reported preferred terms and not the results of the cardiovascular adjudication committee**.**

The incidence of SAEs was low and similar across the ertugliflozin 5 mg (6.4%; 110/1716), ertugliflozin 15 mg (5.8%; 98/1693) and non-ertugliflozin (5.5%; 80/1450) groups. Few specific AE preferred terms were reported in more than 5 subjects (angina pectoris and pneumonia) in any ertugliflozin dose group and more commonly than in the non-ertugliflozin group and there were no patterns suggesting meaningful imbalances in the incidence of specific AE preferred terms.

2.3.5. Discontinuations due to adverse events

2.3.5.1. Integrated safety analyses

Placebo controlled pool

The incidence of AEs resulting in discontinuation from study medication was low and similar across the placebo (1.7%; 9/515), ertugliflozin 5 mg (2.3%; 12/519) and ertugliflozin 15 mg (1.4% (7/510) groups. The only discernible pattern was a numerically higher occurrence of discontinuations in ertugliflozin treated subjects due to AEs related to genital mycotic infections.

Broad pool

The incidence of AEs resulting in discontinuation of study medication was low and similar across the ertugliflozin 5 mg (4.1%; 70/1716), ertugliflozin 15 mg (4.4%; 74/1693) and non-ertugliflozin (4.1%; 60/1450) groups. AEs resulting in discontinuation from study medication that occurred in at least 4 subjects in any ertugliflozin group and at a numerically higher frequency than in the non ertugliflozin group were the following: vulvovaginal candidiasis, vulvovaginal mycotic infection, glomerular filtration rate decreased, acute kidney injury, balanoposthitis and pollakiuria.

2.3.6. Evaluation of issues with possible regulatory impact

2.3.6.1. Liver function and liver toxicity

Broad pool

The Broad Pool was the focus of the liver safety evaluations because it is the largest pool and most suitable for identifying infrequent events. The proportion of subjects having any measurement meeting the PDLC criterion of AST or ALT ≥ 3 x ULN at any time point was similar in the ertugliflozin 5 mg group (13 subjects: 0.8%) and ertugliflozin 15 mg group (17 subjects: 1.0%) relative to the non-ertugliflozin group (19 subjects: 1.3%). The proportion of subjects having any measurement meeting the PDLC criterion of AST or ALT > 5X the ULN was low and similar in the ertugliflozin 5 mg group (4 subjects; 0.2%), ertugliflozin 15 mg group (4 subjects; 0.2%), and non-ertugliflozin group (2 subjects; 0.1%). Only 1 subject (0.1%) in the ertugliflozin 15 mg group and 1 subject (0.1%) in the non-ertugliflozin group had any measurement meeting the PDLC criterion of AST or ALT > 10 x ULN. In the Broad Pool, there was no notable difference in the proportion of subjects experiencing an AE of ALT increased in the ertugliflozin 5 mg and 15 mg groups (0.7% and 0.8%, respectively) and the non-ertugliflozin group (0.8%). In addition, 2 subjects (0.1%) in the non-ertugliflozin group had an event of hepatic enzyme increased.

In the Broad Pool, 2 subjects (0.1%), both in the non-ertugliflozin group, had concurrent measurements of ALT or AST ≥ 3 x ULN and a total bilirubin ≥ 2 x ULN.

No ertugliflozin-treated subject met the definition for a Hy's law case. Each of the events meeting a PDLC criterion > 5 x ULN or > 10 x ULN was adjudicated as to causality. A total of 11 subjects in the Broad Pool met the criteria for hepatic adjudication: 4 in the ertugliflozin 5 mg group, 4 in the ertugliflozin 15 mg group, and 3 in the non-ertugliflozin group. Among these cases, none were adjudicated as 'very likely' or 'probable'. Four cases in the ertugliflozin 5 mg group, 2 in the ertugliflozin 15 mg group, and 2 in the non-ertugliflozin group were adjudicated 'possible 'All other cases were adjudicated as 'doubtful' or 'not related'. Of the 6 ertugliflozin-treated subjects with an event adjudicated as possibly related to study medication, 2 subjects were using acetaminophen, 1 subject was hepatitis C antibody positive, 2 others events resolved on treatment, and the last case resolved following interruption of study medication; this subject restarted study medication and subsequent testing of liver enzymes was normal. Only one event led to discontinuation in an ertugliflozin treated subject.

PBO pool

In the PBO Pool, there were decreases in ALT and AST in the ertugliflozin 5 mg and 15 mg groups which were greater in magnitude than in the placebo group which persisted from Week 6 until Week 26. There were 3 AEs that described increases in ALT values: 2 AEs of ALT increased (1 in the ertugliflozin 15 mg group and 1 in the placebo group) and 1 AE of hepatic enzyme increased (placebo group; met PDLC criteria for an ALT ≥ 3 x ULN). None of these events were serious or severe; only the AE of hepatic enzyme increased in the subject in the placebo group was deemed related to study treatment by the investigator. In addition, there were 2 placebo-treated subjects with non-serious AEs of AST increased. Neither subject met the PDLC criterion of ≥ 3 x ULN during Phase A of the study.

2.3.7. Renal function and renal toxicity

2.3.7.1. Integrated safety analyses

In the PBO pool, treatment with ertugliflozin is associated with small transient decreases in eGFR at Week 6 that returned to or towards baseline at Week 26**.** In a longer term study (Study P002/1013), there were transient modest reductions from baseline in mean eGFR at Week 6 in both ertugliflozin groups, but mean eGFR values in both ertugliflozin groups were above baseline between Week 26 and Week 52 eGFR. In subjects with moderate renal impairment (Study P001/1016), the decrease in eGFR at Week 6 was slightly larger than in the PBO Pool (around 1 mL/min/1.73 m^2 more). In these subjects, although there was some attenuation of the decrease in eGFR after Week 6, eGFR did not return to baseline at Week 26.

In the PBO Pool, the proportion of subjects who had any occurrence of a decrease in eGFR of > 30% from baseline was similar in the ertugliflozin 5 mg, 15 mg and placebo groups (2.6%, 2.8% and 2.8%, respectively). At the last value on treatment, the proportion of subjects with a decrease in eGFR of > 30% was also not notably different in the ertugliflozin 5 mg and 15 mg groups (5 subjects: 1.0% in both groups) relative to the placebo group (3 subjects: 0.6%) Only 1 (0.2%) subject in the ertugliflozin 15 mg group and 1 (0.2%) in the placebo group had any occurrence of a decrease in eGFR of > 50%. No subject had a last value with a decrease of > 50%. In the Broad Pool, the incidence of subjects with any decrease in eGFR of > 30% was not notably different in the ertugliflozin 5 mg and 15 mg groups relative to the non-ertugliflozin group (5.7%, 6.1% and 5.2%, respectively). Similar results were observed at the last value on treatment (1.6%, 1.8% and 2.0%, respectively). A low occurrence of decreases in eGFR > 50% was observed across groups, with no meaningful difference between the groups: 2 (0.1%) in the ertugliflozin 5 mg group, 9 (0.5%) in the ertugliflozin 15 mg group, and 8 (0.6%) in the non-ertugliflozin group. No subjects in the ertugliflozin 5 mg group, 3 (0.2%) in the ertugliflozin 15 mg group and 2 (0.1%) in the non-ertugliflozin group had a decrease of > 50% at the last value.

In the PBO pool, the, mean change from baseline at Week 26 in serum creatinine was not notably different between groups; in the ertugliflozin 5 mg and 15 mg groups the change was 0.00 and 0.01 mg/dL (-0.08 and 0.80 μmol/L), respectively, and was -0.01 mg/dL (-0.57 μmol/L) in the placebo group. The mean change from baseline in BUN at Week 26 was higher in the ertugliflozin 5 mg and 15 mg groups (1.5 and 1.9 mg/dL, respectively) relative to the placebo group (0.4 mg/dL). In the PBO Pool, the proportion of subjects having any occurrence meeting the PDLC criterion for BUN (≥ 50% increase and value > ULN) was numerically higher in the ertugliflozin 5 mg group and higher in the 15 mg group (7.9% and 9.8%, respectively) relative to the placebo group (5.1%). In the Broad Pool, the proportion of subjects having any occurrence meeting the PDLC criterion for BUN was higher in the ertugliflozin 5 mg and 15 mg groups (13.7% and 15.6%, respectively) relative to the placebo group (9.8%).

In the PBO pool, the incidence of renal-related AEs was low (< 1%) and similar across the ertugliflozin and placebo groups**.** None of the events was serious and only 1 subject (0.2%) in

the placebo group discontinued study medication due to an AE of renal impairment. Among these renal-related AEs events, none met the criteria for adjudication. AEs related to GFR decreased and creatinine increased were infrequent, with each being reported in ≤ 1 subject per group; none of these events were serious or led to discontinuation of study medication. One subject in the ertugliflozin 15 mg group had a non- serious event of GFR decreased which met the criteria for adjudication and was adjudicated as 'not related' In addition, 3 subjects (0.6%) in the ertugliflozin 15 mg group and no subjects in the other groups discontinued study drug due to protocol-specified creatinine or eGFR changes that did not have an associated AE.

In the Broad Pool, the incidence of AEs of eGFR decreased or creatinine increased was ≤ 1.2% in all treatment groups. Of note, 6 subjects (0.3%) in the ertugliflozin 5 mg group, 4 subjects (0.2%) in the ertugliflozin 15 mg group and 1 subject (0.1%) in the non-ertugliflozin group discontinued study drug due to protocol-specified creatinine or eGFR changes that did not have an associated AE. In the Broad pool, the incidence of renal-related AEs was low (< 1%) and not notably different across the ertugliflozin and the non-ertugliflozin groups.

Few subjects had serious renal related AEs: 2 subjects (0.1%) in the ertugliflozin 5 mg group, 1 subject (0.1%) in the ertugliflozin 15 mg group, and 1 subject (0.1%) in the non-ertugliflozin group. The proportion of subjects who discontinued study treatment due to a renal-related event was low: 2 subjects (0.1%) in the ertugliflozin 5 group, 4 (0.2%) in the ertugliflozin 15 mg group, and 2 (0.1%) in the non-ertugliflozin group. Overall, 26 events in the renal-related event SMQ were reported in 23 subjects in one or the other ertugliflozin groups (3 subjects had recurrent events) Among these events, most were mild or moderate; 7 (26.9%) were severe in intensity. In the non-ertugliflozin group, of the 6 events reported in 6 subjects, 1 (16.7%) was reported as severe and 2 (33.3%) led to discontinuation. Of note, 2 events in the ertugliflozin 5 mg group and 3 in the ertugliflozin 15 mg group (and none in the non-ertugliflozin group) were adjudicated. Subgroup analysis of renal-related AEs by baseline characteristics did not show any trends with exception of an increased occurrence of events in ertugliflozin-treated relative to non-ertugliflozin treated subjects with an eGFR < 60 mL/min/1.73 m^2 (particularly those with an eGFR < 45 mL/min/1.73 m^2). Although the incidence of renal-related events was marginally higher in subjects aged ≥ 65 years, differences related to age were likely to be associated with eGFR as higher mean age was identified in subjects with lower baseline eGFR values.

There were 11 renal events in the Broad Pool that met the criteria for adjudication as to causality: 2 in the ertugliflozin 5 mg group, 7 in the ertugliflozin 15 mg group, and 2 in the non-ertugliflozin group Among these 11 events, only 1 event was assessed as ‘very likely related’ to study medication (ertugliflozin 5 mg group). Three events were adjudicated as ‘possibly related’: 1 event in the non-ertugliflozin group and 2 events in the ertugliflozin 15 mg group. The remaining 7 events were adjudicated as not related to study medication.

In the renal impairment study (P001/1016), the eGFR decreased from baseline at Week 6 in the ertugliflozin 5 mg and 15 mg groups (-3.11 and -4.00 mL/min/1.73 m^2, respectively), followed by a slight increase, but remained below baseline through Week 26. LS mean decreases in eGFR at Week 26 were larger in the ertugliflozin 5 mg and 15 mg groups (-2.61 and -2.81 mL/min/1.73 m^2, respectively) relative to the placebo group (-0.54 mL/min/1.73 m^2). The proportion of subjects who met the PDLC criterion of eGFR decrease > 30% was higher in the ertugliflozin 5 mg and 15 mg groups relative to the placebo group. The incidence of renal-related adverse events was numerically higher in the ertugliflozin 5 mg group (4 subjects; 2.5%) and the ertugliflozin 15 mg group (2 subjects; 1.3%) compared to the placebo group (1 subject (0.6%)). Among these events, 2 events in the ertugliflozin 5 mg group were serious, with 1 subject requiring dialysis. One AE of renal impairment in the ertugliflozin 15 mg group and AEs of acute kidney injury in the ertugliflozin 5 mg group, led to discontinuation of study medication. Three subjects were reported to have AEs related to either eGFR decreased or creatinine increased: 1 subject (0.6%) in the ertugliflozin 5 mg group, 2 subjects (1.3%) in the

ertugliflozin 15 mg group, and none in the placebo group. These events were non serious. One AE of glomerular filtration rate decreased, in the ertugliflozin 15 mg group, led to discontinuation of study medication. Among the renal-related AEs and events related to eGFR decreased or creatinine increased, 2 in the ertugliflozin 5 mg treatment group, and 1 each in the ertugliflozin 15 mg and placebo group were adjudicated with regard to causality.

2.3.8. Other clinical chemistry

2.3.8.1. Integrated safety analyses

Potassium

Potassium did not increase in association with ertugliflozin treatment in the overall pooled populations or in subjects with moderate renal impairment. In the PBO Pool, there was no difference between the ertugliflozin 5 mg, 15 mg and placebo groups in terms of proportions of subjects having any occurrence of the PDLC increase of ≥ 1.0 mEq/L and value > ULN (4.3%, 4.7% and 5,1% in the ertugliflozin 5 mg, 15 mg and placebo groups, respectively). >Value > 5.4 mEq/L and a value increased by 15% above baseline (4.0%, 5.3% and 4.9%, respectively) and value ≥ 6.0 mEq/L (1.2%, 1.4% and 2.0%, respectively).

In the Broad Pool, there were no notable differences in the proportion of subjects having any occurrence of an increase in potassium meeting PDLC increase criterion of ≥ 1.0 mEq/L and value > ULN (8.5%, 9.1% and 8.0% in ertugliflozin 5 mg, 15 mg and non-ertugliflozin groups, respectively), > 5.4 mEq/L and increased by 15% above baseline (7.7%, 8.9% and 7.1%, respectively) and > 6.0 mEq/L (3.6%, 3.2% and 3.9%, respectively). In the Broad Pool, the incidence of subjects with an AE of hyperkalaemia was low and similar across treatment groups (1.0%, 0.9% and 0.8%, respectively). Similar results for potassium were observed in the moderate renal impairment Study P001/1016.

Uric acid

There were modest decreases in uric acid in ertugliflozin groups in the pooled populations. There were modest numeric decreases in uric acid in the ertugliflozin 5 mg and 15 mg groups relative to the placebo group that persisted from the first post randomisation measurement at Week 6 to Week 26; mean decrease from baseline in uric acid at Week 26 was -0.53, -0.44 and 0.09mg/dL, in the ertugliflozin 5 mg, 15 mg and placebo groups, respectively. In the PBO Pool 1.2%, 1.6% and 2.4% of subjects in the ertugliflozin 5 mg, 15 mg and placebo groups, respectively met the PDLC criteria of an increase ≥ 50% and value > ULN. In the Broad Pool, the incidence of subjects meeting the PDLC criteria for uric acid was lower in the ertugliflozin 5 mg and 15 mg groups relative to the non-ertugliflozin group (2.3%, 2.5% and 4.6%, respectively).

Serum lipids

PBO group: baseline LDL-C values were around 97mg/dl (2.5mmol/L) in all treatment groups. At Week 26, there were small dose-related least square (LS) mean percent increases in LDL-C that were numerically higher in the ertugliflozin 5 mg group and higher in the ertugliflozin 15 mg groups relative to the placebo group (percent change from baseline to Week 26 was 5.82, 8.37 and 3.21 in ertugliflozin 5 mg, 15 mg and placebo groups, respectively**.** Baseline total cholesterol values ranged from (4.56 to 4.64mmol/L) across groups. There were small dose-related LS mean percent increases in total cholesterol at Week 26 that were numerically higher in the ertugliflozin 5 mg group (2.59%) and higher in the ertugliflozin 15 mg group (5.06%) relative to the placebo group (1.06%). Baseline median triglyceride values ranged from (1.59 to 1.63 mmol/L) across groups There were small numeric non-dose dependent median percent changes in triglycerides in the ertugliflozin 5 mg group (-3.9%) and ertugliflozin 15 mg group (-1.7%) relative to the placebo group (4.5%). Baseline HDL-C values ranged from (1.22 to 1.23 mmol/L) across groups Small LS mean percent increases in HDL-C were seen in both the ertugliflozin 5 mg (6.23%) and 15 mg (7.52%) groups relative to the placebo group (1.68%).

Two studies, the monotherapy study (Study P003/1022) and the placebo controlled add-on to metformin study (Study P007/1017), included measurements of Apo B and Apo A-1 at baseline and Week 26. The apolipoprotein results were consistent with the changes noted in LDL-C and total cholesterol (that is, an increase in Apo B), and HDL-C (that is, an increase in Apo A-1).

2.3.9. Haematology and haematological toxicity

At baseline in the PBO Pool, haemoglobin values were 13.90, 14.0 and 14.0 g/dL in the ertugliflozin 5 mg, 15 mg and placebo groups, respectively. At Week 26, there were small numeric increases from baseline in haemoglobin in both the ertugliflozin 5 mg and 15 mg groups relative to a decrease in the placebo group (+0.46, +0.48 and -0.21 g/dL, respectively). In monotherapy study (Study P003/1022), haemoglobin was measured at multiple time points, but most of the increase observed was seen by the initial 6 week time-point. Mean changes over time in other haematology parameters were small, with no meaningful differences between the ertugliflozin 5 mg and 15 mg groups and placebo groups.

In the PBO Pool, the proportion of subjects having at least 1 increase in haemoglobin > 2.0 g/dL was higher in the ertugliflozin 5 mg and 15 mg groups compared to the placebo group (4.7%, 4.1% and 0.6%, respectively). The proportion of subjects having at least 1 increase > 2.0 g/dL and value > ULN was numerically higher in the ertugliflozin 5 mg groups and higher in the ertugliflozin 15 mg and relative to the placebo group (0.4%, 1.2% and 0.0%, respectively).

In the Broad Pool, the proportion of subjects having at least 1 increase in haemoglobin > 2.0 g/dL was higher in the ertugliflozin 5 mg and 15 mg groups compared to the non-ertugliflozin group (6.7%, 6.9% and 1.5%, respectively). The proportion of subjects having at least 1 increase > 2.0 g/dL and value > ULN was also higher in the ertugliflozin 5 mg and 15 mg groups (0.8%, 1.3% and 0.1%, respectively).

2.3.10. Other laboratory tests

Refer to section below for laboratory data related to bone safety and also bone biomarkers in Phase III Study P007/1017.

2.3.11. Electrocardiograph findings and cardiovascular safety

Summary statistics for mean changes over time in ECG parameters (PR interval, QRS interval, QT, QTcB, QTcF, and heart rate), including data after initiation of glycaemic rescue therapy, were described in the PBO Pool. In addition, a PDLC analysis for QTcF was examined in both the PBO and the Broad Pools. There were no clinically meaningful differences in the ECG parameters (heart rate, PR, QRS, QT, QTcB and QTcF interval) across the ertugliflozin 5 mg and 15 mg groups and placebo group.

A dedicated Thorough QTc study (Study P010/1025) conducted in healthy volunteers demonstrated that a supratherapeutic dose of ertugliflozin (100 mg) was not associated with QTc prolongation at T_{max} values around 6.5 times the mean steady state T_{max} following once-daily administration of 15 mg ertugliflozin in the fasted state. At each time point post-dose, the upper bound of the 2-sided 90% CIs (equivalent to 1-sided 95% CI) for all the time-matched mean differences between ertugliflozin 100 mg and placebo were less than the predefined cut-off of 10 ms (highest value of the upper bound was 4.30 ms).

Two Phase III studies, a cardiovascular (CV) outcomes trial (Study P004/1021) and, a 26 week Phase III Asia Pacific regional study (Study P012/1045) are still recruiting at the time of this submission with no further information presented in this submission.

Comment: A Cardiovascular Adjudication Committee adjudicated, in a blinded fashion, potential cases of CV events, venous thromboembolic events, hospitalization for heart failure, and all deaths in all Phase III studies as well as the single Phase II study with duration of at least 12 weeks. The pre-specified program-wide meta-analysis of the CV endpoint major adverse cardiac events plus (MACE+) was based

on these adjudication results. However, the sponsors have stated that to protect the integrity of the ongoing CV study, the MACE+ analysis is not presented in the submitted dossier. The Program DMC reviewed the results of the CV meta-analysis (data cut-off April 18, 2016) and reported that the upper bound of the adjusted 95% confidence interval for the hazard ratio for MACE+ was < 1.8, ruling out an 80% increase in CV risk relative to the non-ertugliflozin comparator group, and meeting the United States (US) Food and Drug Administration (FDA) requirements for a diabetes drug New Drug Application (NDA). Results based on adjudication or on data from the ongoing CVOT study were not provided in this submission.

2.3.12. Vital signs and clinical examination findings

The effects of ertugliflozin therapy on systolic and diastolic blood pressure were secondary efficacy endpoints. In this safety analysis, data obtained after initiation of glycaemic rescue therapy are included whereas the evaluation for efficacy excluded post-rescue data.

There were decreases in systolic and diastolic blood pressure and no increase in pulse rate with ertugliflozin treatment. There was also no significant effect on orthostatic blood pressure.

In the Placebo controlled Pool, the mean change from baseline in sitting SBP at Week 26 was greater in the ertugliflozin 5 mg and 15 mg groups compared with placebo group (-4.84, -4.78 and -0.78 mmHg, respectively) (Figure 43). Similar reductions were observed in sitting DBP (-1.97, -1.71 and -0.09 mmHg, respectively) (Figure 44).

Figure 43: Sitting systolic BP (mmHg); Mean change from Baseline over time (mean ± SE); All subjects as treated. pool: including rescue approach

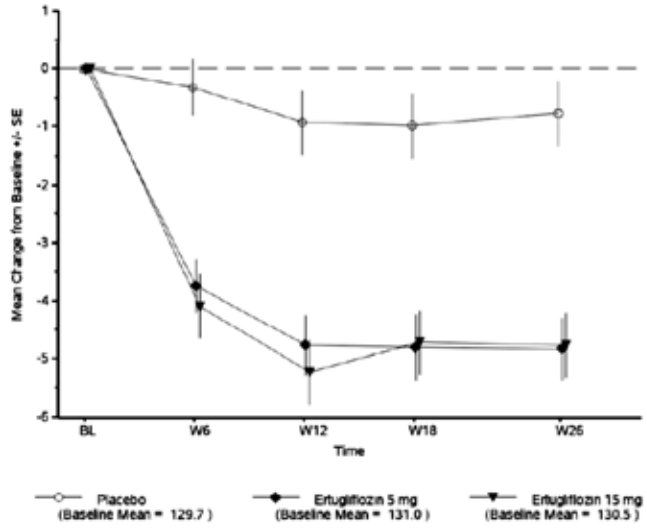
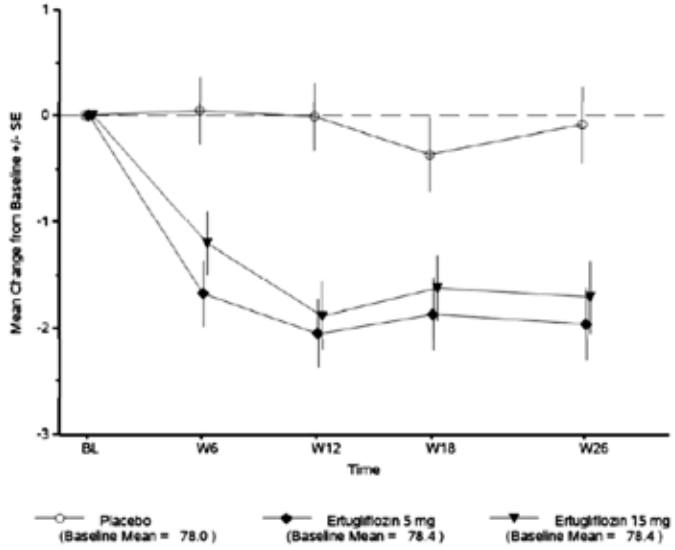


Figure 44: Sitting diastolic BP (mmHg): Mean change from baseline over time (mean ± SE). All subjects as treated. Placebo-controlled pool: including rescue approach

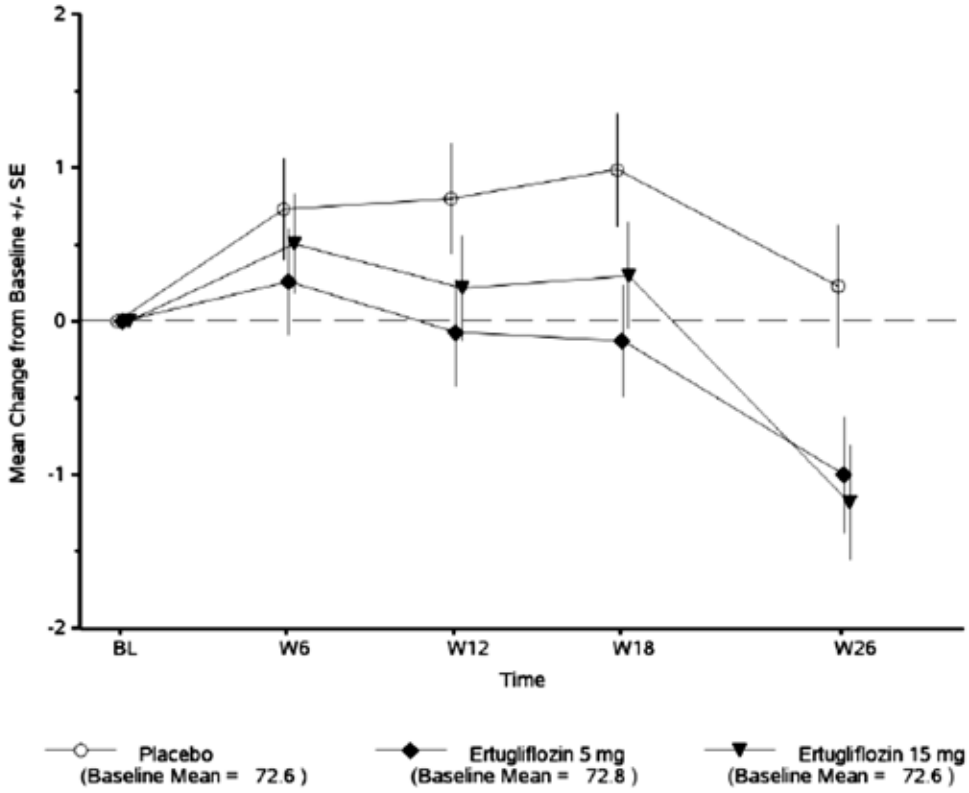


In the Placebo-controlled Pool there were small numeric differences at each time point, but there was no pattern in the proportion of subjects who met the pre-specified definition for orthostatic change in systolic and diastolic blood pressure[17] between the ertugliflozin 5 mg and 15 mg groups and the placebo group. No clinically significant pattern with regard to treatment in the proportion of subjects meeting criteria for orthostatic change by baseline status was observed. Across the groups, the majority of subjects who met the pre-specified definition for orthostatic change in systolic or diastolic blood pressure at Week 6 or Week 26 did not meet this definition at baseline.

There was a decrease in sitting pulse rate in the ertugliflozin 5 mg and 15 mg groups relative to the placebo group at Week 26 (Figure 45). The mean change from baseline in sitting pulse rate at Week 26 was greater in the ertugliflozin 5 mg and 15 mg groups (-1.00 bpm and -1.18 bpm, respectively) relative to the placebo group (0.23 bpm).

[17] Orthostatic change in SBP was defined as a reduction ≥ 20 mmHg, after 1 and/or 3 minutes in the standing position from the supine position (relative to the mean value from measurements taken in the supine position). Orthostatic change in DBP was defined as a reduction ≥ 10 mmHg, after 1 and/or 3 minutes in the standing position from the supine position (relative to the mean value for measurements taken in the supine position. The analyses were performed in the overall population, and separately in those with and those without orthostatic change at baseline.

Figure 45: Sitting pulse rate (bpm): Mean change from baseline over time (mean ± SE); All subjects as treated. Placebo controlled pool: including rescue approach



The effect of ertugliflozin therapy on body weight was also assessed as a secondary efficacy endpoint. In this safety analysis, data obtained after initiation of glycaemic rescue therapy are included whereas the primary evaluation for efficacy excluded post-rescue data. In each of the Phase III studies, body weight was assessed at each visit. Baseline values for body weight were comparable across the treatment groups (range: 87.3 to 88.4 kg). At each time point, weight loss was greater in the ertugliflozin 5 mg and 15 mg groups relative to the placebo group. The mean change from baseline in body weight at Week 26 was greater in the ertugliflozin 5 mg and 15 mg groups (changes of -3.1 kg in both) relative to the placebo group (-1.2 kg).

2.3.13. Immunogenicity and immunological events

The incidence of potential hypersensitivity AEs in the Broad Pool data was low overall and similar in the ertugliflozin and non-ertugliflozin groups. Hypersensitivity AEs occurred most frequently in the skin and subcutaneous tissue disorders SOC, followed by the respiratory, thoracic and mediastinal SOC. The specific AEs that occurred in greater than 3 subjects in any group were: rash, urticaria, dermatitis, dermatitis allergic, rhinitis allergic, eczema, and hypersensitivity. The incidences of these events were not notably different among the groups. Among these events, only 1 event (0.1%), angioedema in a subject in the non-ertugliflozin group, was serious. There were 5 events leading to discontinuation, 1 (0.1%) in the ertugliflozin 5 mg group, 3 (0.2%) in the ertugliflozin 15 mg group and 1 (0.1%) in the non-ertugliflozin group.

2.3.14. Serious skin reactions

There were some reports of rash, urticaria, dermatitis, dermatitis allergic, eczema, and hypersensitivity (see above). However, there were no reports of serious skin reactions such as photosensitivity, erythema multiforme, Steven Johnson syndrome (SJS), Drug reaction with eosinophilia and systemic symptoms (DRESS) or Toxic epidermal necrolysis (TEN).

2.3.15. Potential or established SGLT2 class-related safety topics

Special Safety Topics include those that are potential or established SGLT2 class-related safety topics: osmotic diuresis, volume depletion, changes in renal function, genital infection, urinary tract infection, ketoacidosis, amputations/peripheral revascularisation, bone safety/fracture, and changes in lipids.

2.3.15.1. Osmotic diuresis and volume depletion

Placebo controlled pool

The incidence of osmotic diuresis events, increased urination events, and thirst related events were higher in the ertugliflozin groups relative to the placebo group with no evident dose relationship. Polyuria and pollakiuria were the most frequently reported specific AEs in the ertugliflozin 5 mg and 15 mg groups**.** There were no serious events; only 1 subject (0.2%), in the ertugliflozin 5 mg group, discontinued study medication due to an event of pollakiuria. Overall, a total of 30 events in the osmotic diuresis CMQ were reported in 27 subjects in one of the ertugliflozin groups (3 subjects had recurrent events). Among these events, most were mild or moderate; only 1 event (3.3%) of pollakiuria in an ertugliflozin treated subject was severe. In order to further differentiate the potential symptoms of osmotic diuresis, a CMQ to identify AEs related to increased urination and a CMQ to identify AEs related to thirst were examined. The increased urination CMQ contained all the terms in the pre-specified CMQ for osmotic diuresis with the exception of 'polydipsia' (only 2 subjects were reported to have this AE). The incidence of increased urination was 2.7% and 2.4% in the ertugliflozin 5 mg and 15 mg groups, respectively, and 1.0% in the placebo group. The incidence of thirst (preferred terms: thirst and polydipsia) was low in all groups: 1.3% and 1.0% in both the ertugliflozin 5 and 15 mg groups, respectively, and 0.2% in the placebo group. None of the thirst events were serious, severe in intensity, or resulted in discontinuation from study medication.

Volume depletion events in the PBO Pool occurred with low incidence across groups, with no notable differences between the ertugliflozin groups and the placebo group with no particular preferred terms reported in more than 2 subjects. No subject in either the ertugliflozin 5 mg, ertugliflozin 15 mg or placebo group had a volume depletion event that was serious or resulted in discontinuation from study medication.

Broad pool

The results in the Broad Pool were generally consistent with those of the PBO Pool; no events were serious and few events led to discontinuation. Polyuria, pollakiuria, and nocturia were the most frequently reported specific AEs in the ertugliflozin 5 mg and 15 mg groups. . Overall, there were 93 events in the osmotic diuresis CMQ reported in 84 subjects in one or the other of the ertugliflozin groups (9 subjects had recurrent events). Among these events, 6 (6.5%) led to discontinuation of study medication. Most were mild or moderate; 1 event in the ertugliflozin 5 mg and one 1 event in the ertugliflozin 15 mg group were reported as severe in intensity. Among the 22 events in 20 subjects (2 with recurrent events) in the non-ertugliflozin group, none was severe.

Volume depletion AEs in the Broad Pool occurred with low incidence with no notable difference in the ertugliflozin 5 mg and 15 mg groups relative to the non-ertugliflozin group. Hypotension, orthostatic hypotension, syncope and dehydration were the most frequently reported preferred terms in the ertugliflozin 5 mg and 15 mg groups**.** Three subjects (0.2%) in the ertugliflozin 5 mg group had serious events (2 AEs of syncope, 1 adverse event of dehydration). One subject (0.1%) in the non-ertugliflozin group had an event of hypotension that led to discontinuation. A subgroup analysis of patients in the Broad pool showed a higher incidence of volume depletion events in the ertugliflozin groups relative to the non-ertugliflozin group among subjects with eGFR < 60 mL/min/1.73 m^2, older subjects (≥ 65 years) and in subjects on a diuretic**.**

2.3.15.2. Changes in renal function

Overall, in both the PBO and Broad Pools, the incidence of renal-related events was not notably higher in the ertugliflozin groups relative to the comparator group. There were few serious events and few subjects discontinued treatment due to an event. In the subjects with moderate renal impairment, particularly those with an eGFR < 45 mL/min/1.73 m^2, renal related events were more frequent in the ertugliflozin groups relative to the non-ertugliflozin group. Most of the subjects in the Broad Pool with renal impairment were randomised to the study in moderate renal impairment (Study P001/1016). In this study, while the incidence of renal related events was low, it was higher in the ertugliflozin 5 mg and 15 mg groups (2.5% and 1.3%, respectively) relative to the placebo group (0.6%). While the incidence of AEs related to decreased eGFR or increased creatinine was slightly higher in ertugliflozin-treated subjects in the Broad Pool, there was no notable difference in the proportion of events leading to discontinuation. Cases of persistent decrease in eGFR of ≥ 50%, doubling of creatinine, reflecting end stage renal disease or that required renal replacement therapy were adjudicated as to the causal relationship of study medication. Few cases in either the ertugliflozin or non-ertugliflozin groups were adjudicated as causally related to study medication: 1 event in the ertugliflozin 5 mg group was adjudicated as 'very likely' related and 2 events in the ertugliflozin 15 mg group and 1 event in the non-ertugliflozin group were adjudicated as 'possibly' related.

2.3.15.3. Genital infection

A prespecified CMQ was developed to identify potential AEs of genital mycotic Infections and as these event rates may differ by gender, analyses were done separately in men and women.

Placebo controlled pool

The proportion of female subjects with genital mycotic infections[18] was significantly higher (that is, Tier 1 p-value < 0.05) in the ertugliflozin 5 mg and 15 mg groups compared to the placebo group (9.1%, 12.2% and 3% in ertugliflozin 5 mg, 15 mg and placebo groups, respectively) with dose-related modestly higher incidence in the ertugliflozin 15 mg compared to the 5 mg group (Table 103); vulvovaginal candidiasis and vulvovaginal mycotic infection were most commonly reported. The proportion of male subjects with genital mycotic infections[19] was higher (that is, Tier 1 p-value < 0.05) in the ertugliflozin 5 mg and 15 mg groups compared to the placebo group (3.7%, 4.2% and 0.4%, respectively) with no notable difference between the ertugliflozin 15 mg and 5 mg groups; the most common preferred term, in the ertugliflozin and placebo groups, was balanoposthis (Table 104). In ertugliflozin-treated subjects, events of genital mycotic infection were more frequent in men who were not circumcised at baseline (5.2%) relative to those who were circumcised (1.9%). There were no serious genital mycotic infections in either gender, and few subjects (< 1% in all groups) had an event which led to discontinuation of study medication.

[18] Overall, 69 events in the genital mycotic infection CMQ were reported in 53 female subjects in one or the other ertugliflozin groups (14 subjects had recurrent events). Among these events, almost all were mild or moderate; only 1 (2.7%) event was severe. Among the 9 events reported in 7 subjects in the placebo group (1 subject had recurrent events), none was severe

[19] Overall, 24 events in the genital mycotic infections CMQ were reported in 21 male subjects in one or the other ertugliflozin groups (2 subjects had recurrent events) and all were mild or moderate.

Table 103: Subjects with genital mycotic infection AEs by SOC and PT (incidence > 0% in 1 or more treatment groups). All subjects as treated; female. Placebo controlled pool: including rescue approach

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	235		252		245		497	
with one or more adverse events of genital mycotic infections	7	(3.0)	23	(9.1)	30	(12.2)	53	(10.7)
with no adverse events of genital mycotic infections	228	(97.0)	229	(90.9)	215	(87.8)	444	(89.3)
Infections and infestations	**7**	**(3.0)**	**23**	**(9.1)**	**30**	**(12.2)**	**53**	**(10.7)**
Genital candidiasis	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.2)
Genital infection fungal	0	(0.0)	1	(0.4)	2	(0.8)	3	(0.6)
Vaginal infection	1	(0.4)	2	(0.8)	6	(2.4)	8	(1.6)
Vulvitis	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.2)
Vulvovaginal candidiasis	3	(1.3)	5	(2.0)	7	(2.9)	12	(2.4)
Vulvovaginal mycotic infection	3	(1.3)	14	(5.6)	14	(5.7)	28	(5.6)
Vulvovaginitis	0	(0.0)	1	(0.4)	1	(0.4)	2	(0.4)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Genital mycotic infection adverse events were defined by a pre-specified sponsor-generated Custom MedDRA Query.

MedDRA Version 19.0

Table 104: Subjects with genital mycotic infection AEs by SOC and PT (incidence > 0% in 1 or more treatment groups). All subjects as treated; male. Placebo controlled pool: including rescue approach

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	280		267		265		532	
with one or more adverse events of genital mycotic infections	1	(0.4)	10	(3.7)	11	(4.2)	21	(3.9)
with no adverse events of genital mycotic infections	279	(99.6)	257	(96.3)	254	(95.8)	511	(96.1)
Infections and infestations	**0**	**(0.0)**	**4**	**(1.5)**	**5**	**(1.9)**	**9**	**(1.7)**
Balanitis candida	0	(0.0)	1	(0.4)	2	(0.8)	3	(0.6)
Genital infection	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.2)
Genital infection fungal	0	(0.0)	3	(1.1)	2	(0.8)	5	(0.9)
Reproductive system and breast disorders	**1**	**(0.4)**	**6**	**(2.2)**	**6**	**(2.3)**	**12**	**(2.3)**
Balanoposthitis	1	(0.4)	6	(2.2)	6	(2.3)	12	(2.3)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Genital mycotic infection adverse events were defined by a pre-specified sponsor-generated Custom MedDRA Query.

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Broad pool

In general, the results for genital mycotic infections in the Broad Pool were consistent (Tables 105 and 106) with that in the PBO Pool. There were more events in ertugliflozin-treated male[20] and female[21] subjects than in the non-ertugliflozin treated subjects, with few discontinuations of study medication or serious events. The incidence of complicated genital infections in female subjects was low (≤ 0.3%) in all treatment groups and no events were serious. In male subjects, the incidence of complicated infections was also low (< 1%), but was higher in the ertugliflozin groups compared to the non-ertugliflozin group. Three of the complicated cases were serious and were reported in an ertugliflozin group. The most common specific AE was phimosis. Four of 8 phimosis events in ertugliflozin-treated subjects were treated with circumcision.

Subgroup analyses by intrinsic factors showed that the incidence of genital mycotic infections was higher in female than male subjects in both ertugliflozin- and non-ertugliflozin treated subjects. Subgroup analyses among all subjects (men and women combined) showed no notable between treatment differences in incidence in subgroups defined by age, eGFR, race, or ethnicity.

Table 105: Subjects with genital mycotic infection AEs by SOC and PT (incidence > 0% in 1 or more treatment groups). All subjects as treated; female. Broad pool: including rescue approach

	Non-Ertugliflozin		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	663		831		849		1,680	
with one or more adverse events of genital mycotic infections	20	(3.0)	71	(8.5)	88	(10.4)	159	(9.5)
with no adverse events of genital mycotic infections	643	(97.0)	760	(91.5)	761	(89.6)	1,521	(90.5)
Infections and infestations	**20**	**(3.0)**	**70**	**(8.4)**	**88**	**(10.4)**	**158**	**(9.4)**
Genital candidiasis	0	(0.0)	4	(0.5)	2	(0.2)	6	(0.4)
Genital infection	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)
Genital infection fungal	3	(0.5)	4	(0.5)	7	(0.8)	11	(0.7)
Vaginal infection	3	(0.5)	10	(1.2)	17	(2.0)	27	(1.6)
Vulvitis	0	(0.0)	0	(0.0)	3	(0.4)	3	(0.2)
Vulvovaginal candidiasis	11	(1.7)	14	(1.7)	24	(2.8)	38	(2.3)
Vulvovaginal mycotic infection	4	(0.6)	34	(4.1)	32	(3.8)	66	(3.9)
Vulvovaginitis	0	(0.0)	8	(1.0)	4	(0.5)	12	(0.7)
Reproductive system and breast disorders	**0**	**(0.0)**	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**
Vaginal inflammation	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)

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Genital mycotic infection adverse events were defined by a pre-specified sponsor-generated Custom MedDRA Query.
MedDRA Version 19.0

[20] Overall, 96 events in the genital mycotic infection CMQ were reported in 74 male subjects in one or the other ertugliflozin groups (14 subjects had recurrent events). Among these events all were mild or moderate; 4 events (7.5%) in the ertugliflozin 5 mg group and 1 event (2.3%) in the ertugliflozin 15 mg group led to discontinuation of study medication. Among the 3 events reported in 2 subjects in the non-ertugliflozin group, none was severe and none led to discontinuation. Almost all of the events in ertugliflozin-treated subjects occurred before Week 39.
[21] Overall, 224 events in the genital mycotic infection CMQ were reported in 159 subjects in one or the other ertugliflozin groups (42 subjects had recurrent events). Among these events almost all were mild or moderate; only 1 event (0.8%), an AE of vaginal infection, was severe. Among the 28 events in 20 subjects in the non-ertugliflozin group (4 subjects had recurrent events), all were mild or moderate

Table 106: Subjects with genital mycotic infection AEs by SOC and PT (incidence > 0% in 1 or more treatment groups). All subjects as treated; male. Broad pool: including rescue approach

	Non-Ertugliflozin		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	787		885		844		1,729	
with one or more adverse events of genital mycotic infections	2	(0.3)	41	(4.6)	33	(3.9)	74	(4.3)
with no adverse events of genital mycotic infections	785	(99.7)	844	(95.4)	811	(96.1)	1,655	(95.7)
Infections and infestations	**1**	**(0.1)**	**17**	**(1.9)**	**16**	**(1.9)**	**33**	**(1.9)**
Balanitis candida	0	(0.0)	6	(0.7)	5	(0.6)	11	(0.6)
Genital candidiasis	0	(0.0)	2	(0.2)	2	(0.2)	4	(0.2)
Genital infection	0	(0.0)	1	(0.1)	2	(0.2)	3	(0.2)
Genital infection fungal	1	(0.1)	8	(0.9)	9	(1.1)	17	(1.0)
Reproductive system and breast disorders	**1**	**(0.1)**	**26**	**(2.9)**	**18**	**(2.1)**	**44**	**(2.5)**
Balanoposthitis	1	(0.1)	26	(2.9)	18	(2.1)	44	(2.5)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Genital mycotic infection adverse events were defined by a pre-specified sponsor-generated Custom MedDRA Query.
MedDRA Version 19.0

2.3.15.4. Urinary tract infection

In the Placebo controlled Pool, the incidence of AEs of urinary tract infection[22] was similar across the 5 mg and 15 mg ertugliflozin groups and placebo group (4%, 4.1% and 3.9%, respectively) with no SAEs and only 1 discontinuation each in the ertugliflozin and placebo groups. In the Broad Pool, the incidence of AEs of urinary tract infection[23] was similar across the ertugliflozin 5 mg and 15 mg groups and the non-ertugliflozin group (6.9%, 7% and 7.9%, respectively). The incidence of SAEs (0.2%, 0.4% and 0.2%, respectively) and discontinuations due to AEs (0.3%, 0.2% and 0.1%, respectively) was low in all groups. While the overall incidence of urinary tract infections was higher in female subjects and older subjects, this was similar in both ertugliflozin- and non-ertugliflozin treated subjects suggesting no treatment effect. Complicated events were infrequent in all groups (≤ 0.6%), and the incidence was not notably different in the ertugliflozin and non-ertugliflozin groups.

2.3.15.5. Ketoacidosis

Ketoacidosis emerged as a safety concern for the SGLT2 class late in the Phase III development program, prompted by the identification of post-marketing cases of ketoacidosis, often with atypical presentation, in patients with type 1 and type 2 DM receiving SGLT2 inhibitors. Hence, potential cases of ketoacidosis identified in the Broad Pool based on a pre-specified ascertainment strategy were reviewed by an internal blinded case review committee separate

[22] In the ertugliflozin groups, 46 events in the urinary tract infection CMQ were reported in 42 subjects (4 subjects had recurrent events) Almost all events were mild or moderate; only 1 event (2.2%), an event of cystitis in the ertugliflozin 5 mg group, was assessed as severe In the placebo group, 22 events were reported in 20 subjects (2 subjects had recurrent events); none was severe.
[23] In the ertugliflozin groups, 294 events in the urinary tract infection CMQ were reported in 237 subjects (47 subjects had recurrent events). Among these events, more than 90% were assessed as mild or moderate; 5 events in each of the ertugliflozin 5 mg and 15 mg groups (3.4% and 3.5%, respectively) were assessed as severe. In the non-ertugliflozin group, 147 events were reported in 115 subjects (22 subjects had recurrent events), with 2 events assessed as severe

from the development team; the purpose of this committee was to assess whether these cases met a pre-specified case definition of ketoacidosis.

There were 25 potential cases of ketoacidosis in the Broad Pool that met the criteria for case review: 8 in the non-ertugliflozin group, 8 in the ertugliflozin 5 mg group, and 9 in the ertugliflozin 15 mg group. Overall, 2 (0.1%) cases in the ertugliflozin 15 mg group were determined to represent ketoacidosis with certain likelihood and 1 (0.1%) case in the ertugliflozin 15 mg group was determined to represent ketoacidosis with possible likelihood. Thus, 3 of 3,409 (0.1%) ertugliflozin-treated subjects were assessed as meeting the case definition of ketoacidosis with either certain or possible likelihood compared to no cases in the non-ertugliflozin group (1450 subjects). The rest of the cases were either determined unlikely to represent ketoacidosis (20 cases) or were unclassifiable (2 cases). Among the 3 ertugliflozin-treated subjects, 1 presented with a plasma glucose level that was lower than that typically seen with ketoacidosis (< 250 mg/dL (14 mmol/L)). This case, and one other case, occurred in the setting of sepsis. The third case occurred in the setting of a viral illness and this subject also had some features suggestive of autoimmune diabetes such as early age of onset, low BMI, and borderline positive GAD antibodies. All events of ketoacidosis resolved, 2 after discontinuation of study medication and 1 resolved on treatment. There were no significant differences between treatment groups in change from baseline in bicarbonate values (-0.8, -1.0 and -0.7 mEq/L in the ertugliflozin 5 mg, 15 mg and placebo groups, respectively). In the PBO pool, 1 (0.2%) subject in the ertugliflozin 15 mg group had an occurrence of bicarbonate < 15 mmol/L. In the Broad Pool, 6 subjects (0.4%) in the ertugliflozin 5 mg group, 5 subjects (0.3%) in the ertugliflozin 15 mg group and 2 subjects (0.1%) in the non-ertugliflozin group had a laboratory value meeting PDLC criteria for bicarbonate < 15 mmol/L. No subjects had bicarbonate levels < 10 mmol/L.

2.3.15.6. Amputation/ revascularisation

There were 10 subjects with non-traumatic limb amputations (all post-randomisation treatment analysis): 1 of 1450 (0.1%) in the non-ertugliflozin group, 1 of 1716 (0.1%) in the ertugliflozin 5 mg group and 8 of 1693 (0.5%) in the ertugliflozin 15 mg group (resulting in 9 of 3,409 (0.3%) in the all ertugliflozin group). Among these cases, the most frequently reported amputation was toe amputation; 1 subject in the ertugliflozin 15 mg group underwent 2 amputation procedures (left second toe and left third toe amputations. Baseline history revealed risk factors such as peripheral neuropathy, peripheral artery disease (including one subject with a pre-existing peripheral artery aneurysm), diabetic foot or former/current smoking to be present in all subjects. Associated AEs included those related to limb infection, peripheral artery disease, and gangrene. There were 3 subjects with peripheral revascularisation procedures: 2 of 1450 (0.1%) in the non-ertugliflozin group, no subjects in the ertugliflozin 5 mg group, and 1 of 1693 (0.1%) in the ertugliflozin 15 mg group.

In 2016, regulatory agencies described an increase in amputations, mostly affecting toes, observed with canagliflozin, another SGLT2 inhibitor, in an ongoing cardiovascular outcomes trial. This has led to regulatory evaluation of the signal of potential increased risk of lower limb amputations with all marketed SGLT2 inhibitors and all non-traumatic limb amputations identified in the Broad Pool were evaluated. In total, 12 subjects with non-traumatic limb amputation and/or peripheral revascularisation were identified in the Broad Pool, with a higher incidence in the ertugliflozin 15 mg group (8 subjects) compared to the ertugliflozin 5 mg group (1 subject) and non-ertugliflozin group (3 subjects). Amputations occurred in 1 subject in the non-ertugliflozin group, 1 in the ertugliflozin 5 mg group, and 8 in the ertugliflozin 15 mg group. There was no notable imbalance seen in cases of peripheral revascularisation. All 12 subjects had baseline risk factors for amputation (for example, peripheral neuropathy, peripheral artery disease) or peripheral revascularisation (for example, hypertension, and hyperlipidaemia). There was no evidence that volume depletion or haemoconcentration was associated with these events.

2.3.15.7. Bone safety/ fractures

Fracture events in Phase III studies were adjudicated by an independent committee which confirmed the presence of a fracture and determined the type of fracture (for example, high-trauma, low-trauma and so on). In addition to the assessment of fractures, Study 007/1017, which enrolled a study population enriched with post-menopausal women, examined BMD, biomarkers of bone metabolism, and PTH. Biomarkers of bone metabolism and PTH were further examined in the moderate renal impairment study (Study P001/1016). Changes in calcium, phosphate, and magnesium were also evaluated in the pooled populations.

Fractures

Overall, 35 subjects in the Broad Pool had an event of fracture that was sent for adjudication with similar incidence in the ertugliflozin and non-ertugliflozin groups:11 subjects in the ertugliflozin 5 mg group, 13 in the ertugliflozin 15 mg group and 11 in the non-ertugliflozin group. Most of the fractures occurred in locations other than the upper limb and incidence of fractures adjudicated as low trauma fractures was not notably different in the ertugliflozin 5 mg and 15 mg groups (4 (0.2%) and 6 (0.4%) subjects, respectively) compared to the non-ertugliflozin group (6 subjects (0.4%)).

BMD

The placebo controlled add-on to metformin study (Study P007/1017) included a higher proportion (planned per study design) of postmenopausal women; 41.1% of the 621 subjects in the study were women who had been postmenopausal for at least 3 years or women with a history of bilateral oophorectomy performed ≥ 3 years prior to screening. Ertugliflozin had no adverse impact on BMD during the 26 week treatment period; the percentage changes from baseline at all 4 anatomic sites evaluated (lumbar spine, femoral neck, total hip and distal forearm) were minimal, and the 95% CI around the between-group differences relative to placebo for changes in BMD included 0 for all sites assessed**.** In the subgroup of women who were postmenopausal, results were consistent with the results for the overall study: there was no adverse impact of ertugliflozin therapy on BMD.

Laboratory data related to bone metabolism (Calcium, magnesium and phosphate in pooled analyses)

At Week 26, the changes from baseline in calcium were small and not notably different in the ertugliflozin 5 mg and 15 mg groups (0.08 mg/dL and 0.06 mg/dL, respectively) and the placebo group (0.05 mg/dL). In the PBO Pool, there was no notable difference in the proportion of subjects having a laboratory value (at any time) meeting the PDLC criterion in the ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo groups for either a calcium increase ≥ 1.0 mg/dL and value > ULN (2.8%, 3.1%, and 2.2%, respectively) or decrease ≥ 1.0 mg/dL and value < ULN (2.0%, 0.8% and 1.6%, respectively). In the Broad Pool, there was no notable difference in the proportion of subjects having any laboratory value meeting the PDLC criterion in the ertugliflozin 5 mg, ertugliflozin 15 mg and the non-ertugliflozin groups for either a calcium increase ≥ 1.0 mg/dL and value > ULN (4.8%, 4.5%, and 3.9%, respectively) or decrease ≥ 1.0 mg/dL and value < ULN (2.3%, 1.7% and 1.8%, respectively).

In the PBO Pool, there were small increases in phosphate in the ertugliflozin 5 mg and 15 mg groups relative to the placebo group that persisted from Week 6 to Week 26: mean changes from baseline at Week 26 were 0.21 mg/dL and 0.26 mg/dL, in the ertugliflozin 5 and 15 mg groups, respectively, and 0.04 mg/dL in the placebo group. The proportion of subjects who had at least 1 increase ≥ 0.5 mg/dL and value > ULN was higher in the ertugliflozin 5 mg and 15 mg groups compared with placebo (14.1%, 15.0% and 7.3%, respectively). Additionally, at the last value on treatment, there was a higher incidence of subjects meeting this PDLC criterion in both the ertugliflozin 5 mg and 15 mg groups (5.1%, 5.3% and 1.6%, respectively). There were 3 AEs, all in the ertugliflozin 5 mg group, of either hypophosphatemia or blood phosphorus increased. In the Broad Pool, the proportion of subjects having at least 1 occurrence meeting the PDLC

criterion for phosphate (increase ≥ 0.5 mg/dL and value > ULN) was higher in the ertugliflozin 5 mg and 15 mg groups compared with the non-ertugliflozin group (18.5%, 22.9% and 11.9%, respectively). At the last value on treatment, the proportion of subjects who met the PDLC criterion for increased phosphate was numerically higher in the ertugliflozin 5 mg and 15 mg groups (3.6%, 5.7% and 2.4%, respectively). In the Broad Pool, 3 subjects in the ertugliflozin 5 mg group (all included in the PBO pool) 2 subjects in the ertugliflozin 15 mg group and 1 subject in the non-ertugliflozin group had an adverse event of either hypophosphatemia or blood phosphate increased indicating that although events meeting the PDLC criteria were relatively common, few were reported as AEs by the investigators.

Ertugliflozin led to small mean increases in magnesium, but no increases in the proportion of subjects meeting categorical PDLC analyses were observed. There was a mean increase from baseline at Week 26 in the ertugliflozin 5 mg and 15 mg groups (changes of 0.11 mEq/L and 0.14 mEq/L, respectively) relative to the a small decrease in the placebo group (-0.02 mEq/L).

Bone biomarkers in study P007/1017

Results were similar to the pooled data above with no meaningful changes in calcium and small numeric increases over time in phosphate and magnesium There was no meaningful change over time in PTH in either the ertugliflozin or placebo groups although, there were small shifts in PTH in the categorical PDLC analysis in the ertugliflozin groups which are of uncertain significance. There were 2 PDLC criteria for increases in PTH. For the first criterion, PTH increase ≥ 20% and value > ULN, the incidence was not notably different in the ertugliflozin 5 mg and 15 mg groups (6 (3.3%) and 4 (2.2%) subjects, respectively) and the placebo group (3 subjects: 1.6%).

The proportion of subjects meeting the second criterion, PTH increase ≥ 30% (regardless of whether above the ULN), was higher in the ertugliflozin 5 mg group (21.4%) and numerically higher in the 15 mg group (20.7%) relative to the placebo group (13.4%). For nearly all of the subjects who met the PDLC criteria for PTH increase ≥ 30%, the PTH level meeting the criterion remained within the reference range. CTX, a marker of bone resorption, increased over time in all groups; the magnitude of change was greater in the ertugliflozin groups relative to the placebo group (Table 107). There was no meaningful change over time in P1NP, a marker of bone formation, in the ertugliflozin or placebo groups.

Table 107: Bone biomarkers CTX and P1NP and parathyroid hormone (PTH) in P007/1017: summary statistics of change from baseline at week 26 BMD FAS: excluding bone rescue approach

	Baseline		Week 26		Change from Baseline at Week 26	
Treatment	N	Mean (SD)	N	Mean (SD)	Mean (SD)	95% CI
CTX (ng/L)						
Placebo	200	268.3 (132.9)	185	280.6 (150.4)	10.8 (106.6)	-4.7, 26.3
Ertugliflozin 5 mg	196	266.9 (129.9)	179	319.8 (154.3)	51.9 (121.9)	33.9, 69.8
Ertugliflozin 15 mg	193	272.2 (135.6)	180	353.6 (166.9)	80.2 (149.7)	58.2, 102.2
PTH (ng/L)						
Placebo	202	19.29 (8.17)	186	18.11 (7.91)	-0.98 (6.71)	-1.95, -0.01
Ertugliflozin 5 mg	194	19.52 (6.91)	182	19.60 (8.34)	0.28 (7.52)	-0.82, 1.38
Ertugliflozin 15 mg	198	19.88 (7.71)	184	20.26 (7.77)	0.14 (7.53)	-0.95, 1.24
P1NP (microgm/L)						
Placebo	200	32.0 (15.0)	186	32.7 (13.1)	0.5 (11.7)	-1.2, 2.2
Ertugliflozin 5 mg	198	32.8 (14.5)	183	33.4 (12.6)	0.8 (12.1)	-0.9, 2.6
Ertugliflozin 15 mg	196	31.5 (16.6)	183	32.3 (11.7)	0.5 (15.0)	-1.7, 2.7

Source: [Ref. 5.3.5.1: P007V01: Table 14.3.7.6.1.1.2, Table 14.3.7.6.2.1.2, Table 14.3.7.6.1.2.2]
Abbreviations: CI = confidence interval; CTX = carboxy terminal cross-linking telopeptides of Type I collagen; N = number of subjects with measurement at both baseline and time point; P1NP = procollagen type I N terminal propeptide; PTH = parathyroid hormone; SD = standard deviation.
This table contains measurements from samples collected starting with the first dose of treatment and up to 7 days after the final dose of treatment, and excludes measurements obtained after initiation of bone rescue medications, if applicable.

2.3.15.8. Change in lipids

In the PBO Pool, ertugliflozin treatment led to small increases in LDL-C and total cholesterol in a dose-related manner; small mean percent increases were also seen in HDL-C, with small median decreases in triglyceride levels.

2.3.16. Other safety topics

Other safety topics include hypoglycaemia, pancreatitis, hepatic events, hypersensitivity, malignancy and VTE.

2.3.16.1. Hypoglycaemia

Hypoglycaemia in individual Phase III studies

Most studies included a 26 week treatment period with ertugliflozin added as a single agent (Studies P003/1022, P006/1015, and P007/1017). In addition, Study P005/1019 included 2 treatment groups with ertugliflozin alone as part of the factorial design. Across the ertugliflozin treatment groups in these studies, the incidence of documented hypoglycaemia ranged from 2.0-7.8%. The incidence in the 3 placebo arms in these studies was 0.7%to 4.3% and the incidence of documented hypoglycaemia in the sitagliptin arm was 3.6% (95% CI included 0 for all of these comparisons and Tier 2 analysis was not done in Study P005/1019 to compare ertugliflozin alone groups to sitagliptin). The incidence of symptomatic events of hypoglycaemia was generally lower than that of documented hypoglycaemia. Furthermore, there was no pattern suggesting a dose relationship and the incidence of severe hypoglycaemia in each of these studies was low. In Study P002/1013 with a 52 week treatment period, the incidence of documented hypoglycaemia was lower in subjects treated with ertugliflozin 5 mg and 15 mg compared with glimepiride (a sulfonylurea agent associated with hypoglycaemia) (5.6%, 8.2% and 27.2% in ertugliflozin 5 mg, 15 mg and glimepiride, respectively) Severe hypoglycaemia (0.2%, 0.2% and 2.3%, respectively) and symptomatic hypoglycaemia was also lower in the ertugliflozin 5 mg and 15 mg groups. In 2 studies, ertugliflozin and sitagliptin were co-initiated in at least some treatment groups (Study P005/1019 as part of the factorial design and in Study P017/1047). In Study P005/1019, the incidence of documented hypoglycaemia was higher in the E15/S100 group relative to the sitagliptin group (that is, the 95% CI for the

between group difference excluded 0); the 95% CI for the comparison of the E15/S100 and E15 groups included 0. These findings were not consistent with those in Study P017/1047 in which the incidence of documented hypoglycaemia in the E5/S100 group was numerically higher than in the E15/S100 and placebo groups. The incidence of severe hypoglycaemia was low across the groups in each of these studies. In a study of subjects with moderate renal impairment (P001/1016), the use of insulin and/or an insulin secretagogue as background therapy was high (approximately 90% at randomisation) and the incidence of hypoglycaemia in this study was higher relative to the other Phase III studies, yet was similar across the ertugliflozin 5 mg and 15 mg and the placebo group(34.2%, 25.2% and 33.1%, respectively); incidence of documented and severe hypoglycaemia was also similar across treatment groups and was also similar in the large subset of subjects taking medications associated with hypoglycaemia (insulin, SU, meglitinides).

Hypoglycaemia in pooled populations

In the PBO Pool, the incidence of documented hypoglycaemia was numerically higher in the ertugliflozin 5 and 15 mg groups compared with the placebo group (5.0%, 4.5% and 2.9%, respectively). Two subjects in each group (0.4%) had an event of severe hypoglycaemia. The incidence of symptomatic hypoglycaemia was not notably different across the ertugliflozin 5 mg and 15 mg groups and placebo groups (2.9%, 2.4% and 1.9%, respectively). The proportion of subjects with 3 or more documented events was low (< 2%) across all the groups and was similar in the ertugliflozin 5 mg and 15 mg and placebo groups (1.3%, 0.8% and 0.4%, respectively). The proportion of hypoglycaemia episodes with an accompanying glucose of < 56 mg/dL (3.1mmol/L) was low and also similar across the ertugliflozin 5 mg, 15 mg and placebo groups (1.2%, 0.6% and 0.8%, respectively). In the 4 subjects having a severe event, 1 subject in the ertugliflozin 5 mg group had an accompanying glucose < 56 mg/dL (3.1 mmol/L) and 1 subject in the ertugliflozin 15 mg group had an unknown glucose. Both subjects with a severe event in the placebo group had glucose of ≤ 70 mg/dL (3.9mmol/L). Within the Broad Pool, a clinical review of accidents and injuries, including falls was conducted to identify any hypoglycaemia events that were concurrent with or immediately preceding these events. One subject had a concurrent AE of fall and hypoglycaemia, however, this occurred in the post - treatment period, 154 days after the last dose of study medication.

Overall, ertugliflozin treatment did not result in a clinically meaningful increase in the incidence of hypoglycaemia nor was there evidence of a dose relationship. This was seen in the setting of ertugliflozin used as monotherapy or in combination with diabetes medications not associated with hypoglycaemia (metformin and sitagliptin). When compared to glimepiride (a sulfonylurea agent associated with hypoglycaemia), the incidence of documented hypoglycaemia was lower in the ertugliflozin 5 mg and 15 mg groups (5.6% and 8.2%, respectively) relative to the glimepiride group (27.2%). Severe hypoglycaemia was similarly lower in the ertugliflozin 5 mg and 15 mg groups (0.2% in both groups) compared to the glimepiride group (2.3%).

2.3.16.2. Pancreatitis

Potential cases of pancreatitis were sent to a blinded adjudication committee for confirmation. There were 4 cases identified for adjudication; there was 1 case (in the ertugliflozin 5 mg group, 1 case in the ertugliflozin 15 mg group and 2 cases in the non-ertugliflozin group. Among these cases only 1, a subject in the non-ertugliflozin group, was confirmed by the adjudication committee as pancreatitis.

2.3.16.3. Hepatic events

Refer to below.

2.3.16.4. Hypersensitivity

Refer to section below.

2.3.16.5. Malignancy

The overall incidence of malignancy was low across all groups, but numerically higher in the ertugliflozin 5 mg and 15 mg group compared to the non-ertugliflozin group (0.6%, 1.2% and 0.3%, respectively). Two of the events (pancreatic neoplasm and pancreatic carcinoma) in the ertugliflozin 15 mg group were reported for the same malignancy in 1 subject in error by the investigator. Results of an analysis for subjects who reported a malignancy with onset > 6 months (180 days) after first dose of study medication was 0.3%, 0.9% and 0.4% in the ertugliflozin 5 mg, 15 mg and non-ertugliflozin groups, respectively**.** The difference in incidence in the 2 analyses reflects 5 subjects in the ertugliflozin 5 mg group and 6 subjects in the ertugliflozin 15 mg group who had malignancies diagnosed within 6 months of initiating ertugliflozin treatment.

No specific preferred terms in the SMQ Malignant or unspecified tumours were reported by greater than 2 subjects in the all ertugliflozin group. However, malignancies were also manually reviewed and grouped by high-level terms to identify relevant events occurring in the same tissue or organ. High-level terms reported most often in the ertugliflozin groups included skin neoplasms malignant and unspecified[24] and breast and nipple neoplasms malignant.[25]

Malignancies were also reviewed by topics of interest to the SGLT2 class or diabetic patient population, which included bladder and pancreatic malignancies, respectively. There were 3 events of pancreatic malignancies reported in 2 subjects in the ertugliflozin 15 mg group (as noted previously, one malignancy was reported with 2 different event terms (pancreatic neoplasm and pancreatic carcinoma)). The remaining pancreatic carcinoma occurred on Day 36 of ertugliflozin treatment. There was 1 case of bladder cancer that occurred in a subject in the non-ertugliflozin group.

2.3.16.6. Venous thromboembolism

The incidence of venous thrombotic events was low and similar in the ertugliflozin and non-ertugliflozin groups (0.1% each in the ertugliflozin 5 mg, 15 mg and non-ertugliflozin groups). There were only 2 reports of pulmonary embolism (0, 1 and 1 subject in ertugliflozin 5 mg, 15 mg and non-ertugliflozin groups, respectively).

2.4. Other safety issues

2.4.1. Safety in special populations

2.4.1.1. Effect of intrinsic factors on safety of ertugliflozin

Age

There were no notable differences between the ertugliflozin (5 and 15 mg) and non-ertugliflozin treated subjects in the incidence of AE summary measures (AEs, SAEs, drug related AEs and discontinuations due to an AE) across age categories (< 65 years and ≥ 65 years)**.** Among subjects aged ≥ 65 years, but not in younger subjects, the incidence of volume depletion events was numerically higher in both ertugliflozin groups relative to the non-ertugliflozin group**.** Similarly, there were no significant differences between the ertugliflozin (5 and 15 mg) and non-ertugliflozin treated subjects across age categories < 75 years and > 75 years, with exception of incidence of overall AEs which was higher in subjects aged > 75 years in the non-

[24] Skin malignancies reported in ≥ 2 subjects in the all ertugliflozin group included basal cell carcinoma (2 subjects) and malignant melanoma (2 subjects). Basal cell carcinoma occurred at the same frequency (0.1%) in the all ertugliflozin and non-ertugliflozin groups. There were 2 events of malignant melanoma in subjects receiving ertugliflozin (1 each in the 5 and 15 mg groups) compared to none in the non-ertugliflozin group. There was also 1 skin malignancy of keratoacanthoma in a subject receiving 15 mg ertugliflozin.

[25] Breast malignancies were reported in 4 subjects in the all ertugliflozin group (2 breast cancers and 2 invasive ductal breast carcinoma) and 1 subject in the non-ertugliflozin group (breast cancer).

ertugliflozin group**.** Analysis of special interest AEs by did not show any significant differences by age category < 75 or ≥ 75 years.

Gender

Gender did not appear to have any significant effect on the incidence of AEs, SAEs, drug-related AEs and discontinuations due to AEs**.** Within both male and female subjects, genital mycotic infections were more common in the ertugliflozin groups relative to the non-ertugliflozin group.

Race

Race and ethnicity did not appear to have any significant effect on the incidence of AEs, SAEs, drug-related AEs and discontinuations due to AEs, although interpretation in the Black and Asian race subgroups was limited by smaller sample size**.** Among ertugliflozin-treated subjects, a similar increase in male and female genital mycotic infections as seen in the overall population was generally seen across race subgroups, with smaller increases seen in Black (male genital mycotic infections) and Asian (male and female genital mycotic infections) subjects**.** Among ertugliflozin-treated subjects, a similar increase in male and female genital mycotic infections as seen in the overall population was generally seen across ethnicity subgroups, with larger increases seen in the Hispanic subgroup relative to the Non-Hispanic subgroup.

eGFR

Across eGFR categories, there were no notable differences in the incidence of most AE summary measures (AEs, SAEs, drug-related AEs and discontinuations due to an AE) when comparing ertugliflozin and non-ertugliflozin treated subject**.** However, among ertugliflozin-treated subjects, but not non-ertugliflozin treated subjects, the incidence of discontinuations due to an AE was numerically higher in subjects in the lower 2 eGFR categories relative to those in the higher 2 eGFR categories (where the incidence was similar to the overall population). The event types leading to discontinuation in the lower eGFR categories were generally varied; there were several discontinuations related to changes in renal function. The incidence of volume depletion and renal-related events were higher in subgroups with lower eGFR.

2.4.2. Safety in pregnancy/ lactation

There were 2 pregnancies in the Broad Pool. One pregnancy, in the ertugliflozin 5 mg group, ended in an elective abortion. The other pregnancy, in the non-ertugliflozin group, resulted in a spontaneous abortion.

There are no adequate and well-controlled studies of ertugliflozin in pregnant women.

Ertugliflozin should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Based on results from animal studies, ertugliflozin may affect renal development and maturation, therefore ertugliflozin is not recommended during the second and third trimesters of pregnancy.

There is no information regarding the presence of ertugliflozin in human milk, the effects on the breastfed infant, or the effects on milk production. Ertugliflozin is present in the milk of lactating rats. Since human kidney maturation occurs in utero and during the first 2 years of life when locational exposure may occur, there may be risk to the developing human kidney.

2.4.3. Overdose, drug abuse, withdrawal/rebound, effects on ability to drive/ operate machinery/ impairment of mental ability

In the analyses of pooled Phase I studies, ertugliflozin was generally well tolerated when administered as a single dose of 300 mg in 7 subjects and 100 mg in 52 subjects and as multiple dose of 100 mg once daily for 14 days in 8 subjects. No new AEs were reported (that were not seen in lower dose groups (< 100 mg)) and AEs reported in more than 1 subject were generally similar to those reported at lower doses. In the Phase III program, 11 subjects in the Broad Pool

randomised to ertugliflozin had an AE of accidental overdose of study medication. None of these overdoses was reported to be associated with a clinical AE or an abnormal laboratory result.

The drug abuse and dependence potential of ertugliflozin has not been characterised, but given the mechanism of action, it is not expected to be subject to drug abuse and dependence.

There are no non-clinical or clinical data that would suggest a potential for withdrawal or rebound effects after discontinuing ertugliflozin. As with any AHA, it is expected that blood glucose levels could increase upon discontinuation of the AHA. However, based on the mechanisms of action of ertugliflozin, any increase in blood glucose levels would not be expected to be precipitous. Upon discontinuation of any AHA, patients should be advised to continue monitoring their blood glucose levels and discuss appropriate therapeutic options with their physician.

No studies on the effects of ertugliflozin on the ability to drive and use machinery have been performed. When used in combination with an insulin secretagogue or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machinery.

2.4.4. Safety related to drug-drug interactions and other interactions

Four DDI studies, P019/1032, P022/1033, P030/1036 and P032/1044, were undertaken as part of Phase I studies to examine the potential for adverse interactions between ertugliflozin and commonly co-administered drugs including metformin, sitagliptin, simvastatin and glimepiride, respectively. Overall, there was little difference in the incidence and types of AEs experienced by subjects in the presence or absence of the co-administered drugs and all AEs experienced were either mild or moderate in severity.

Risk of AEs related to volume depletion (for example, dehydration, dizziness postural, presyncope, syncope, hypotension and orthostatic hypotension) may be increased in patients on diuretics. Risk of hypoglycaemia is also increased in patients on concomitant insulin and SUs.

2.5. Post marketing experience

Not applicable as ertugliflozin is not currently marketed anywhere in the world.

2.6. Evaluator's overall conclusions on clinical safety

The safety and tolerability of ertugliflozin was evaluated in a large clinical development program comprised of subjects who are representative of the spectrum of patients with T2DM, including a wide array of background therapies including diet and exercise alone, sitagliptin, metformin, sulfonylureas and insulin. However, it is important to note that the only study which evaluated ertugliflozin in combination with insulin and SUs was the study in T2DM patients with moderate renal impairment.

The evaluation of safety primarily focused on 2 pooled datasets from the Phase III development program. The Placebo controlled (PBO) Pool contains the safety data to Week 26 from 3 similarly designed Phase III studies with a placebo comparator. The Broad Pool contains the data from 7 Phase III studies, including those in the PBO Pool, studies with active comparators, and a study in subjects with moderate renal impairment. In addition, the Broad pool includes data beyond Week 26 in the 6 studies with a total duration greater than 26 weeks. As such, this pool is suited for examination of lower incidence AEs. The non-ertugliflozin group in this pool contains subjects taking placebo (including some who switched to metformin or glimepiride after Week 26), and subjects in active comparator groups (glimepiride or sitagliptin).

Comprehensive evaluation of safety and tolerability was performed in 6068 subjects in Phase I, 2 and 3 studies and 4418 subjects were exposed to ertugliflozin.

In the PBO Pool, the incidence of subjects with AEs was similar in the ertugliflozin 5 mg and 15 mg groups and placebo group (45.5%, 50.4% and 51.1%, respectively). The only AE occurring in > 2% of subjects and at a higher incidence (that is,95% CI for the difference excluded 0) in the ertugliflozin 5 mg and 15 mg groups compared to the placebo group was vulvovaginal mycotic infection (2.7%, 2.7% and 0.6%, respectively). The findings in the Broad Pool were generally consistent with those in the PBO pool.

There were no deaths in the PBO Pool. The incidence of deaths in the Broad Pool (on treatment analysis with 14 day censoring window) was low in all groups and slightly numerically higher in the ertugliflozin groups relative to the non-ertugliflozin group: 10 (0.6%) subjects in the ertugliflozin 5 mg group, 8 (0.5%) subjects in the ertugliflozin 15 mg group, and 3 (0.2%) subjects in the non-ertugliflozin group. The incidence of death was similarly low when examined including events beyond the 14-day censoring window (the All Post-Randomisation Follow-up Period): 11 (0.6%) subjects in the ertugliflozin 5 mg group, 9 (0.5%) subjects in the ertugliflozin 15 mg group and 6 (0.4%) subjects in the non-ertugliflozin group; the most commonly reported fatal events in all groups were related to cardiovascular death.

The EMA draft reflection paper on assessment of CV risk of medicinal products for the treatment of CV and metabolic diseases was released during the conduct of the ertugliflozin Phase III program. The sponsor has initiated a CV outcome (CVOT) study to evaluate CV risk of ertugliflozin (P004/1021) but this study will remain blinded until its completion according to agreement with the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Neither the detailed results of the CV meta-analysis report nor any other results from the CVOT study have been included in this submission. The CVOT study is estimated to complete in 2019, with the exact timing dependent on the accrual of CV events.

In the PBO Pool, the incidence of non-fatal SAEs was low and not notably different in the ertugliflozin 5 mg and 15 mg groups relative to the placebo group (3.3%, 2.4% and 2.9%, respectively). Similarly, in the Broad Pool, the incidence of non-fatal SAEs was similar in the ertugliflozin 5 mg and 15 mg groups and non-ertugliflozin group (6.0%, 5.6% and 5.3%, respectively). There was no discernible pattern with regard to the type of SAEs.

The incidence of AEs leading to discontinuation of study medication was low and not notably different in ertugliflozin-treated subjects compared to comparator-treated subjects in both the PBO Pool (2.3%, 1.4% and 1.7% in ertugliflozin 5 mg, 15 mg and placebo groups, respectively) and Broad Pool (4.1%, 4.4% and 4.1% in the ertugliflozin 5 mg, 15 mg and non-ertugliflozin groups, respectively).

Among the potential or established SGLT2 class-related safety topics, ertugliflozin treatment was associated with an increased incidence of AEs for osmotic diuresis; volume depletion in subjects with moderate renal impairment, the elderly and those using diuretics. In the general population, small transient reductions in eGFR were observed that generally resolved by Week 26. In subjects with moderate renal impairment, the reductions in eGFR were slightly greater (approximately 1 mL/min/1.73m^2) compared to the general population and there was not a complete return to baseline at Week 26. The moderate renal impairment study is continuing to Week 52 and will measure eGFR 2 weeks following discontinuation of study medication. The risk of renal related AEs was increased with ertugliflozin treatment in subjects with moderate renal impairment.

An increased incidence of genital mycotic infections was observed in both women and men treated with ertugliflozin relative to comparator. However, there were very few serious or complicated events and these AEs were rarely associated with discontinuation of study medication.

Ketoacidosis was confirmed as certain or possible in 3 ertugliflozin subjects compared to none in the non-ertugliflozin group. Patients treated with ertugliflozin who present with signs and symptoms consistent with severe metabolic acidosis should be promptly assessed for

ketoacidosis regardless of presenting blood glucose levels as ketoacidosis associated with SGLT2 inhibitors may be present even if blood glucose levels are < 250 mg/dL (14 mmol/L).

A small dose related increase in LDL-C was observed following ertugliflozin treatment. Although the sponsors have stated that an assessment of CV safety based on a pre-specified cardiovascular meta-analysis (CVMA) demonstrated that ertugliflozin is not associated with an unacceptable increase in CV risk at the time of regulatory submission in accordance with US FDA recommendations for T2DM drug development, this requires confirmation.

Ertugliflozin treatment was associated with an increased risk of non-traumatic lower limb amputations; 8 of the 10 amputations reported in the Broad pool were in the ertugliflozin 15 mg group (1 subject each in the ertugliflozin 5 mg and non-ertugliflozin groups). Overall, 12 subjects reported non-traumatic limb amputation and peripheral revascularisation in the Broad pool. However, interpretation of association between ertugliflozin treatment and amputations/ peripheral revascularisation was confounded by fact that all 12 subjects had baseline risk factors for amputation (for example, peripheral neuropathy, peripheral artery disease) or peripheral revascularisation (for example, hypertension and hyperlipidaemia).

Ertugliflozin treatment was not associated with increased risk for urinary tract infection or parameters related to bone safety/fracture.. A large Phase III study (P007/1017) did not demonstrate a meaningful reduction in BMD at any anatomical region (lumbar spine, femoral neck, total hip or distal forearm). Moreover, no imbalance of fractures was observed in the overall ertugliflozin program or in the large dedicated study of subjects with moderate renal impairment.

Treatment with ertugliflozin did not result in a clinically meaningful increase in the risk of hypoglycaemia. Proportions of subjects with documented and severe hypoglycaemia were low across all groups. The incidence of hypoglycaemia may be increased when ertugliflozin is used in combination with insulin and/or insulin secretagogues. Approximately 90% of subjects in the moderate renal impairment study (P001/1016) used insulin and/or sulfonylurea as background therapy. As such, the incidence of hypoglycaemia in this study was higher relative to the other Phase III studies, yet was similar across the treatment groups.

There was no evidence for increased risk of pancreatitis, hepatic injury;[26] hypersensitivity, or venous thromboembolic events with ertugliflozin use. The overall incidence of malignancies was low in all groups, but was more frequent in the ertugliflozin groups relative to the non-ertugliflozin group. Eleven out of 31 ertugliflozin-treated subjects with a malignancy had the malignancy detected within the first 6 months of randomisation, with several events diagnosed within 1 month following randomisation. There were no specific types of malignancies for which there was any notable imbalance. The more frequent occurrence of events in ertugliflozin-treated subjects reflected a wide range of unrelated types of neoplasm, both solid and haematological, with no notable temporal pattern of onset.

Regarding laboratory parameters, small increases in haemoglobin and phosphate relative to placebo was observed in the ertugliflozin 5 mg and 15 mg groups. In both the Broad Pool and in subjects with moderate renal impairment, there was no evidence of an increased risk for

[26] No ertugliflozin-treated subject met the definition for a Hy's law case. In the Broad Pool, the percentages of subjects with increases in ALT or AST that met a PDLC ≥ 3XULN were similar (0.8-1.3% across all groups). The proportion of subjects with increases in ALT or AST that met a PDLC >5X ULN were low (0.1-0.2% across all groups). Each of these cases was adjudicated for causal association to study treatment. No cases were adjudicated as very likely or probable. Four cases in the ertugliflozin 5 mg group, 2 cases in the ertugliflozin 15 mg group, and 2 cases in the non-ertugliflozin group were adjudicated as possibly related to study medication. Among these cases, there was no pattern with regard to time of onset. Of the 6 ertugliflozin-treated subjects with an event adjudicated as possibly related to study medication, 2 subjects were using acetaminophen, 1 subject was hepatitis C antibody positive, 2 other events resolved on treatment, and the last case resolved following interruption of study medication. Only one event led to discontinuation in an ertugliflozin-treated subject.

hyperkalaemia either in the evaluation of mean changes in potassium over time or by the PDLC analyses.

2.6.1.1. Limitations

- Although the proposed indication mentions that ertugliflozin can be administered with other AHAs, it is a limitation of this submission that the safety of administration of ertugliflozin with insulin and SUs was only evaluated in a study in T2DM patients with moderate renal impairment. Furthermore, safety of ertugliflozin in combination with other less commonly used AHAs such as GLP-1 analogues, acarbose and pioglitazone has not been evaluated.
- The CV safety data (from 7 Phase III studies in nearly 5,000 subjects) were based on preferred terms from investigator AE reporting and do not reflect the results of adjudication which remain firewalled. A cardiovascular meta-analysis (CVMA) of adjudicated, confirmed CV events from the Phase II/III studies and from the CV outcome study (P004/1021) which is ongoing was not included in the dossier.

3. First round benefit-risk assessment

3.1. First round assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
Evidence to support use as monotherapy provided by pivotal Phase III placebo controlled study P003/1022 in 461 adult T2DM patients who had inadequate glycaemic control on diet and exercise. Ertugliflozin 5 mg and 15 mg once daily provided statistically significant and clinically relevant improvements in glycaemic control (HbA1c, FPG and proportion of subjects with HbA1c < 7%) and body weight at Week 26 compared with placebo.	Only data up to 26 weeks submitted. Phase B results (Week 26 to 52) to be provided when available to ascertain long term efficacy of Ertugliflozin as monotherapy in treatment of T2DM.
Evidence to support use of ertugliflozin (as adjunct to diet and exercise) with other antihyperglycaemic agents; mainly metformin and DPP-4 inhibitors (sitagliptin). Ertugliflozin 15 mg and 5 mg, as add-on to metformin (alone or in combination with sitagliptin) provides clinically meaningful improvements in glycaemic control (HbA1c, proportion of subjects with HbA1c < 7.0%, FPG, 2 h PPG), as well as body weight reduction and SBP reduction in subjects with T2DM.	Ertugliflozin in combination with sulphonylurea, insulin and GLP-I analogues was not evaluated. Results of long term maintenance of efficacy of ertugliflozin in combination with other AHAs was not provided in this submission although data from the ongoing Phase B of the pivotal studies should help to address this.
Ertugliflozin 15 mg plus metformin provides non-inferior HbA1c reduction compared to glimepiride plus metformin. Ertugliflozin 5 mg and 15 mg QD was associated with greater reduction in FPG, body weight and	Non-inferiority of ertugliflozin 5 mg and glimepiride was not established. Although these differences were not tested formally since prior hypothesis in the ordered sequence were not met.

Indication	
Benefits	**Strengths and Uncertainties**
SBP compared with glimepiride. Significantly lower incidence of hypoglycaemia with ertugliflozin compared with glimepiride.	
Simple once daily oral dosing.	
Insulin independent mechanism of action	Efficacy of ertugliflozin is dependent on renal function.
Overall, ertugliflozin 5 mg and 15 mg QD was safe and well tolerated	Dose-dependent increase in incidence of genital mycotic infections and elevated LDL-C.

3.2. First round assessment of risks

Risks	Strengths and Uncertainties
Incidence of deaths was low, but numerically higher in ertugliflozin groups.	Deaths occurred in 10 (0.6%), 8 (0.5% and 3 (0.2%) of subjects in ertugliflozin 5 mg, 15 mg and non-ertugliflozin groups, respectively; majority of fatal events were related to CV deaths.
The CV safety data (from 7 Phase III studies in nearly 5,000 subjects) were based on preferred terms from investigator AE reporting and do not reflect the results of adjudication which remain firewalled.	The sponsor has initiated a CV outcome study (P004/1021) to assess CV risks and has already randomised 8000 patients. This CVOT study is expected to complete in 2019.
Increased risk of lower limb amputations; of the 10 reported amputations in the Broad pool with highest incidence in the ertugliflozin 15 mg group; 8 subjects in the ertugliflozin 15 mg group and 1 subject each in the ertugliflozin and non-ertugliflozin groups. This is especially important in light of current findings of increased risk of lower limb amputations associated with another SGLT2 inhibitor-canagliflozin.	12 subjects with non-traumatic limb amputation and peripheral revascularisation reported in the Broad pool; all 12 subjects had baseline risk factors for amputation (for example, peripheral neuropathy, peripheral artery disease) or peripheral revascularisation (for example, hypertension and hyperlipidaemia).
Reduction in eGFR observed following ertugliflozin treatment with greater reduction in patients with moderate renal impairment. Incidence of renal-related AEs also higher.	
The incidence of volume depletion events was numerically higher in both ertugliflozin groups relative to the non-ertugliflozin group especially among subjects aged > 65 years, with renal impairment and those on diuretics.	Incidence of volume depletion AEs in subgroup of subjects aged > 65 years was 2.2%, 2.6% and 1.1% in the ertugliflozin 5 mg, 15 mg and non-ertugliflozin groups, respectively.
The incidence of genital mycotic infections was	Incidence of complicated infections was low

Risks	Strengths and Uncertainties
higher in the ertugliflozin groups than in the non-ertugliflozin groups in both men and women. In female subjects, there was a modest dose-relationship.	(< 1%) but still higher in the ertugliflozin groups.
Lack of evaluation of efficacy/ safety of ertugliflozin in combination with insulin, SUs and GLP-1 analogues.	
None of the Phase II dose ranging studies evaluated the proposed 15 mg dose of ertugliflozin.	
Lack of evidence to support long term maintenance of efficacy of ertugliflozin beyond 26 weeks with exception of one study (P002/1013) comparing ertugliflozin with glimepiride in patients with inadequate glycaemic control on metformin monotherapy which provided data up to 52 weeks	Phase B of most of the studies (except the initial combination therapy study (P017/1047) with ertugliflozin+sitalgliptin) should provide data on long term efficacy and these results should be made available for evaluation in order to confirm long term maintenance of efficacy in proposed indication.

3.3. First round assessment of benefit-risk balance

The ertugliflozin Phase III program was designed to support the use of ertugliflozin, ertugliflozin/metformin FDC, and ertugliflozin/sitagliptin FDC in 3 respective marketing applications.

Ertugliflozin 15 mg and 5 mg provided clinically important reductions in HbA1c (Table 108), FPG (Table 109) and greater proportion of patients with HbA1c < 7% (Table 110) across the wide range of study populations examined, including use as monotherapy, as add-on to metformin (dual combination therapy), or as add-on to metformin and sitagliptin (triple combination therapy). Consistent reductions from baseline in 2 h PPG at Week 26 were demonstrated with ertugliflozin 15 mg and 5 mg as monotherapy or in combination with sitagliptin (with and without metformin background therapy). Consistent reductions from baseline in body weight at Week 26 or Week 52 (Study P002/1013) were observed with ertugliflozin 15 mg and 5 mg across the Phase III studies regardless of background medication and duration of T2DM (Table 111). A generally consistent trend of reduction from baseline in sitting SBP at Week 26 or Week 52 (Study P002/1013) was observed with ertugliflozin 15 mg and 5 mg across the Phase III studies regardless of between-study differences in background medication and study designs (Table 112). In all Phase III studies in the general T2DM population, the proportion of subjects receiving glycaemic rescue therapy in all ertugliflozin groups (either alone or co-administered with sitagliptin 100 mg) was low, ranging from 0% to 6.4%, and the proportion of subjects rescued was higher in the placebo groups, ranging from 16.3% to 32.0% (Table 113).

Table 108: A1c (%) Change from baseline at primary time-point by study FAS excluding rescue approach

	N	Baseline Mean ± SD	LS Mean Change ± SE	LS Mean Difference (95% CI)	p-value
P003/1022 (Week 26) Monotherapy					
Placebo	153	8.1 ± 0.92	0.20 ± 0.089		
Ertugliflozin 5 mg	156	8.2 ± 0.88	-0.79 ± 0.081	-0.99 (-1.22,-0.76)	<0.001
Ertugliflozin 15 mg	151	8.4 ± 1.12	-0.96 ± 0.082	-1.16 (-1.39,-0.93)	<0.001
P007/1017 (Week 26) Add-on to Metformin					
Placebo	209	8.2 ± 0.90	-0.03 ± 0.065		
Ertugliflozin 5 mg	207	8.1 ± 0.89	-0.73 ± 0.062	-0.70 (-0.87,-0.53)	<0.001
Ertugliflozin 15 mg	205	8.1 ± 0.93	-0.91 ± 0.063	-0.88 (-1.05,-0.71)	<0.001
P002/1013 (Week 52) Ertugliflozin vs. Glimepiride					
Glimepiride	437	7.8 ± 0.60	-0.74 ± 0.045		
Ertugliflozin 5 mg	448	7.8 ± 0.60	-0.56 ± 0.045	0.18 (0.06,0.30)	N/A
Ertugliflozin 15 mg	440	7.8 ± 0.60	-0.64 ± 0.045	0.10 (-0.02,0.22)	N/A
P005/1019 (Week 26) Ertugliflozin+Sitagliptin factorial					
Sitagliptin 100 mg	247	8.5 ± 1.03	-1.05 ± 0.062		
Ertugliflozin 5 mg	250	8.6 ± 1.05	-1.02 ± 0.061		
Ertugliflozin 15 mg	248	8.6 ± 1.01	-1.08 ± 0.062		
Ertugliflozin 5 mg + Sitagliptin 100 mg	243	8.6 ± 0.99	-1.49 ± 0.062	-0.43[†] (-0.60,-0.27)	<0.001[†]
				-0.46[‡] (-0.63,-0.30)	<0.001[‡]
Ertugliflozin 15 mg + Sitagliptin 100 mg	244	8.6 ± 0.97	-1.52 ± 0.062	-0.47[†] (-0.63,-0.30)	<0.001[†]
				-0.49[‡] (-0.66,-0.33)	<0.001[‡]
P006/1015 (Week 26) Add-on to Metformin+Sitagliptin					
Placebo	153	8.0 ± 0.93	-0.09 ± 0.070		
Ertugliflozin 5 mg	156	8.1 ± 0.86	-0.78 ± 0.067	-0.69 (-0.87,-0.50)	<0.001
Ertugliflozin 15 mg	153	8.0 ± 0.83	-0.86 ± 0.068	-0.76 (-0.95,-0.58)	<0.001
P017/1047 (Week 26) Ertugliflozin+Sitagliptin					
Placebo	96	8.9 ± 0.86	-0.44 ± 0.127		
Ertugliflozin 5 mg + Sitagliptin 100 mg	98	8.9 ± 0.87	-1.60 ± 0.110	-1.16 (-1.49,-0.84)	<0.001
Ertugliflozin 15 mg + Sitagliptin 100 mg	96	9.0 ± 0.87	-1.68 ± 0.112	-1.24 (-1.57,-0.91)	<0.001
P001/1016 (Week 26) Renal Impairment Overall Cohort					
Placebo	154	8.1 ± 0.89	-0.26 ± 0.076		
Ertugliflozin 5 mg	158	8.2 ± 1.02	-0.29 ± 0.074	-0.03 (-0.23,0.18)	0.807
Ertugliflozin 15 mg	155	8.2 ± 0.87	-0.41 ± 0.075	-0.15 (-0.35,0.06)	0.155
P001/1016 (Week 26) Renal Impairment Overall Cohort Post-hoc Analysis					
Placebo	128	8.0 ± 0.86	-0.14 ± 0.082		
Ertugliflozin 5 mg	134	8.2 ± 1.00	-0.28 ± 0.079	-0.14 (-0.36,0.08)	
Ertugliflozin 15 mg	127	8.2 ± 0.91	-0.47 ± 0.082	-0.33 (-0.55,-0.11)	

LS means and p-value are based on the cLDA model for the primary analysis.

For the P001/1016 post-hoc analysis, the analysis population is the subjects without positive metformin assays.

[†]For the comparison to Sitagliptin alone.

[‡]For the comparison to the Ertugliflozin alone.

Table 109: FPG (mg/dL) Change from baseline at primary time-point by study FAS excluding rescue approach

	N	Baseline Mean ± SD	LS Mean Change ± SE	LS Mean Difference (95% CI)	p-value
P003/1022 (Week 26) Monotherapy					
Placebo	153	180.2 ± 45.76	0.57 ± 3.353		
Ertugliflozin 5 mg	155	180.9 ± 48.55	-33.96 ± 2.998	-34.53 (-42.76,-26.29)	<0.001
Ertugliflozin 15 mg	152	179.1 ± 48.21	-43.44 ± 3.026	-44.01 (-52.28,-35.74)	<0.001
P007/1017 (Week 26) Add-on to Metformin					
Placebo	209	169.1 ± 41.66	-0.85 ± 2.589		
Ertugliflozin 5 mg	207	168.1 ± 45.49	-27.54 ± 2.453	-26.69 (-32.90,-20.48)	<0.001
Ertugliflozin 15 mg	205	167.9 ± 44.38	-39.10 ± 2.479	-38.25 (-44.50,-31.99)	<0.001
P002/1013 (Week 52) Ertugliflozin vs. Glimepiride					
Glimepiride	437	157.9 ± 33.79	-16.17 ± 1.718		
Ertugliflozin 5 mg	448	161.8 ± 34.22	-18.74 ± 1.734	-2.57 (-6.98,1.84)	0.254[§]
Ertugliflozin 15 mg	440	163.2 ± 36.27	-23.86 ± 1.722	-7.70 (-12.09,-3.30)	<0.001[§]
P005/1019 (Week 26) Ertugliflozin+Sitagliptin factorial					
Sitagliptin 100 mg	247	177.4 ± 46.64	-25.56 ± 2.229		
Ertugliflozin 5 mg	250	184.1 ± 52.23	-35.73 ± 2.198		
Ertugliflozin 15 mg	248	179.5 ± 45.71	-36.91 ± 2.192		
Ertugliflozin 5 mg + Sitagliptin 100 mg	243	183.8 ± 44.28	-43.96 ± 2.205	-18.40[†] (-24.03,-12.77)	<0.001[†]
				-8.23[‡] (-13.82,-2.65)	0.004[‡]
Ertugliflozin 15 mg + Sitagliptin 100 mg	244	177.2 ± 49.38	-48.70 ± 2.196	-23.14[†] (-28.76,-17.53)	<0.001[†]
				-12.97[‡] (-18.54,-7.40)	<0.001[‡]
P006/1015 (Week 26) Add-on to Metformin+Sitagliptin					
Placebo	153	169.6 ± 37.82	-1.76 ± 3.022		
Ertugliflozin 5 mg	156	167.7 ± 37.72	-26.91 ± 2.883	-25.15 (-32.76,-17.54)	<0.001
Ertugliflozin 15 mg	153	171.7 ± 39.06	-33.04 ± 2.888	-31.28 (-38.90,-23.66)	<0.001
P017/1047 (Week 26) Ertugliflozin+Sitagliptin					
Placebo	96	207.5 ± 44.94	-9.30 ± 4.714		
Ertugliflozin 5 mg + Sitagliptin 100 mg	98	198.0 ± 47.73	-48.25 ± 3.997	-38.94 (-49.93,-27.96)	<0.001
Ertugliflozin 15 mg + Sitagliptin 100 mg	96	187.7 ± 46.67	-55.36 ± 4.031	-46.05 (-57.09,-35.02)	<0.001
P001/1016 (Week 26) Renal Impairment (eGFR ≥45 to <60 mL/min/1.73m^2)					
Placebo	99	158.4 ± 56.04	-4.95 ± 5.123		
Ertugliflozin 5 mg	105	160.1 ± 52.56	-11.76 ± 4.731	-6.81 (-19.47,5.85)	0.291[§]
Ertugliflozin 15 mg	97	157.5 ± 49.65	-20.47 ± 4.948	-15.51 (-28.50,-2.53)	0.019[§]

LS means and p-value are based on the cLDA model for the primary analysis.

[†]For the comparison to Sitagliptin alone.

[‡]For the comparison to the Ertugliflozin alone.

[§]Nominal p-value.

Table 110: Analysis of subjects with A1c < 7.0% at primary time-point by study FAS excluding rescue approach

	N	Number (%) of Subjects With A1C<7.0% (Raw Proportion)	Adjusted Odds Ratio[†]	
			Point Estimate	95% CI
P003/1022 (Week 26) Monotherapy				
Placebo	153	20 (13.1)		
Ertugliflozin 5 mg	156	44 (28.2)	3.59	(1.85, 6.95)
Ertugliflozin 15 mg	151	54 (35.8)	6.77	(3.46, 13.24)
P007/1017 (Week 26) Add-on to Metformin				
Placebo	209	33 (15.8)		
Ertugliflozin 5 mg	207	73 (35.3)	3.03	(1.81, 5.06)
Ertugliflozin 15 mg	205	82 (40.0)	4.48	(2.64, 7.62)
P002/1013 (Week 52) Ertugliflozin vs. Glimepiride				
Glimepiride	437	190 (43.5)		
Ertugliflozin 5 mg	448	154 (34.4)	0.68	(0.50, 0.91)
Ertugliflozin 15 mg	440	167 (38.0)	0.79	(0.59, 1.05)
P005/1019 (Week 26) Ertugliflozin+Sitagliptin factorial				
Sitagliptin 100 mg	247	81 (32.8)		
Ertugliflozin 5 mg	250	66 (26.4)		
Ertugliflozin 15 mg	248	79 (31.9)		
Ertugliflozin 5 mg + Sitagliptin 100 mg	243	127 (52.3)	2.95[‡]	(1.92, 4.54)[‡]
			4.14[§]	(2.68, 6.40)[§]
Ertugliflozin 15 mg + Sitagliptin 100 mg	244	120 (49.2)	2.56[‡]	(1.69, 3.89)[‡]
			2.53[§]	(1.68, 3.83)[§]
P006/1015 (Week 26) Add-on to Metformin+Sitagliptin				
Placebo	153	26 (17.0)		
Ertugliflozin 5 mg	156	50 (32.1)	3.16	(1.74, 5.72)
Ertugliflozin 15 mg	153	61 (39.9)	4.43	(2.44, 8.02)
P017/1047 (Week 26) Ertugliflozin+Sitagliptin				
Placebo	96	8 (8.3)		
Ertugliflozin 5 mg + Sitagliptin 100 mg	98	35 (35.7)	6.88	(2.81, 16.83)
Ertugliflozin 15 mg + Sitagliptin 100 mg	96	30 (31.3)	7.39	(2.98, 18.31)
P001/1016 (Week 26) Renal Impairment (eGFR ≥45 to <60 mL/min/1.73m^2)				
Placebo	99	12 (12.1)		
Ertugliflozin 5 mg	105	17 (16.2)	1.16	(0.53, 2.56)
Ertugliflozin 15 mg	97	11 (11.3)	1.06	(0.44, 2.55)

[†]Adjusted odds ratio based on a logistic regression model. Missing data imputed using the cLDA model fitted with fixed effects as in the primary analysis.
[‡]For the comparison to Sitagliptin alone.
[§]For the comparison to the Ertugliflozin alone.

Table 111: Body weight (kg) Change from baseline at primary time-point by study FAS excluding rescue approach

	N	Baseline Mean ± SD	LS Mean Change ± SE	LS Mean Difference (95% CI)	p-value
P003/1022 (Week 26) Monotherapy					
Placebo	153	94.2 ± 25.16	-1.42 ± 0.308		
Ertugliflozin 5 mg	156	94.0 ± 25.39	-3.18 ± 0.278	-1.76 (-2.57,-0.95)	<0.001
Ertugliflozin 15 mg	152	90.6 ± 18.27	-3.58 ± 0.282	-2.16 (-2.98,-1.34)	<0.001
P007/1017 (Week 26) Add-on to Metformin					
Placebo	209	84.5 ± 17.06	-1.33 ± 0.208		
Ertugliflozin 5 mg	207	84.9 ± 17.17	-3.01 ± 0.199	-1.67 (-2.24,-1.11)	<0.001
Ertugliflozin 15 mg	205	85.3 ± 16.46	-2.93 ± 0.202	-1.60 (-2.16,-1.03)	<0.001
P002/1013 (Week 52) Ertugliflozin vs. Glimepiride					
Glimepiride	437	86.8 ± 20.73	0.91 ± 0.176		
Ertugliflozin 5 mg	448	87.9 ± 18.93	-2.96 ± 0.177	-3.87 (-4.36,-3.38)	<0.001[§]
Ertugliflozin 15 mg	440	85.6 ± 19.05	-3.38 ± 0.177	-4.29 (-4.77,-3.80)	<0.001
P005/1019 (Week 26) Ertugliflozin+Sitagliptin factorial					
Sitagliptin 100 mg	247	89.8 ± 23.46	-0.67 ± 0.229		
Ertugliflozin 5 mg	250	88.6 ± 22.19	-2.69 ± 0.225		
Ertugliflozin 15 mg	248	88.0 ± 20.33	-3.74 ± 0.227		
Ertugliflozin 5 mg + Sitagliptin 100 mg	243	89.5 ± 20.85	-2.52 ± 0.228	-1.85[†] (-2.48,-1.22)	<0.001[†]
Ertugliflozin 15 mg + Sitagliptin 100 mg	244	87.5 ± 20.48	-2.94 ± 0.228	-2.27[†] (-2.90,-1.64)	<0.001[†]
P006/1015 (Week 26) Add-on to Metformin+Sitagliptin					
Placebo	153	86.5 ± 20.82	-1.32 ± 0.229		
Ertugliflozin 5 mg	156	87.6 ± 18.62	-3.35 ± 0.221	-2.03 (-2.65,-1.40)	<0.001
Ertugliflozin 15 mg	153	86.6 ± 19.48	-3.04 ± 0.223	-1.72 (-2.35,-1.09)	<0.001
P017/1047 (Week 26) Ertugliflozin+Sitagliptin					
Placebo	97	95.0 ± 20.53	-0.94 ± 0.386		
Ertugliflozin 5 mg + Sitagliptin 100 mg	98	90.8 ± 20.72	-2.94 ± 0.334	-2.00 (-2.99,-1.01)	<0.001
Ertugliflozin 15 mg + Sitagliptin 100 mg	96	91.2 ± 22.47	-3.04 ± 0.338	-2.10 (-3.10,-1.11)	<0.001
P001/1016 (Week 26) Renal Impairment (eGFR ≥45 to <60 mL/min/1.73m^2)					
Placebo	99	89.3 ± 18.90	0.46 ± 0.295		
Ertugliflozin 5 mg	105	89.0 ± 22.28	-1.31 ± 0.280	-1.77 (-2.57,-0.96)	<0.001[§]
Ertugliflozin 15 mg	97	84.6 ± 17.96	-1.39 ± 0.294	-1.84 (-2.66,-1.02)	<0.001[§]

LS means and p-value are based on the cLDA model for the primary analysis.

[†]For the comparison to Sitagliptin alone.

[§]Nominal p-value.

Table 112: Sitting systolic BP (mmHg) Change from baseline at primary time-point by study FAS excluding rescue approach

	N	Baseline Mean ± SD	LS Mean Change ± SE	LS Mean Difference (95% CI)	p-value
P003/1022 (Week 26) Monotherapy					
Placebo	152	129.8 ± 14.46	-2.22 ± 1.058		
Ertugliflozin 5 mg	156	130.5 ± 13.51	-5.54 ± 0.904	-3.31 (-5.98,-0.65)	0.015
Ertugliflozin 15 mg	152	129.7 ± 14.21	-3.93 ± 0.922	-1.71 (-4.40,0.98)	0.213
P007/1017 (Week 26) Add-on to Metformin					
Placebo	209	129.3 ± 15.43	-0.70 ± 0.896		
Ertugliflozin 5 mg	207	130.5 ± 13.77	-4.38 ± 0.831	-3.68 (-5.96,-1.39)	0.002
Ertugliflozin 15 mg	204	130.2 ± 11.87	-5.20 ± 0.848	-4.50 (-6.81,-2.19)	<0.001
P002/1013 (Week 52) Ertugliflozin vs. Glimepiride					
Glimepiride	437	129.9 ± 12.04	0.95 ± 0.561		
Ertugliflozin 5 mg	448	130.2 ± 12.80	-2.25 ± 0.567	-3.20 (-4.73,-1.67)	<0.001[‡]
Ertugliflozin 15 mg	440	130.8 ± 12.36	-3.81 ± 0.561	-4.77 (-6.29,-3.25)	<0.001[‡]
P005/1019 (Week 26) Ertugliflozin+Sitagliptin factorial					
Sitagliptin 100 mg	247	128.3 ± 12.21	-0.66 ± 0.721		
Ertugliflozin 5 mg	250	129.7 ± 12.48	-3.89 ± 0.709		
Ertugliflozin 15 mg	248	128.9 ± 12.51	-3.69 ± 0.708		
Ertugliflozin 5 mg + Sitagliptin 100 mg	243	130.2 ± 12.63	-3.42 ± 0.711	-2.76[†] (-4.69,-0.83)	0.005[†]
Ertugliflozin 15 mg + Sitagliptin 100 mg	244	129.1 ± 13.27	-3.67 ± 0.707	-3.01[†] (-4.94,-1.09)	0.002[†]
P006/1015 (Week 26) Add-on to Metformin+Sitagliptin					
Placebo	153	130.2 ± 13.31	-0.88 ± 0.926		
Ertugliflozin 5 mg	156	132.1 ± 12.45	-3.81 ± 0.871	-2.93 (-5.36,-0.49)	0.019
Ertugliflozin 15 mg	153	131.6 ± 13.16	-4.82 ± 0.880	-3.94 (-6.39,-1.50)	0.002
P017/1047 (Week 26) Ertugliflozin+Sitagliptin					
Placebo	97	127.4 ± 14.05	2.41 ± 1.392		
Ertugliflozin 5 mg + Sitagliptin 100 mg	98	130.7 ± 12.74	-2.04 ± 1.115	-4.44 (-7.87,-1.01)	0.011
Ertugliflozin 15 mg + Sitagliptin 100 mg	96	129.2 ± 12.17	-3.98 ± 1.119	-6.39 (-9.83,-2.95)	<0.001
P001/1016 (Week 26) Renal Impairment (eGFR ≥45 to <60 mL/min/1.73m^2)					
Placebo	99	134.1 ± 12.41	-0.90 ± 1.435		
Ertugliflozin 5 mg	105	132.5 ± 13.10	-2.33 ± 1.350	-1.42 (-5.13,2.29)	0.451[‡]
Ertugliflozin 15 mg	97	133.2 ± 12.39	-4.36 ± 1.393	-3.46 (-7.24,0.31)	0.072[‡]

LS means and p-value are based on the cLDA model for the primary analysis.
[†]For the comparison to Sitagliptin alone.
[‡]Nominal p-value.

Table 113: Analysis of time to glycaemia rescue at primary time-point by study All subjects treated

	N	Number (%) of Subjects Rescued	Time to Rescue (days)		p-value
			Minimum	Maximum	
P003/1022 (Week 26) Monotherapy					
Placebo	153	39 (25.5)	9	162	
Ertugliflozin 5 mg	156	3 (1.9)	46	131	<0.001
Ertugliflozin 15 mg	152	4 (2.6)	69	153	<0.001
P007/1017 (Week 26) Add-on to Metformin					
Placebo	209	37 (17.7)	15	183	
Ertugliflozin 5 mg	207	6 (2.9)	23	151	<0.001
Ertugliflozin 15 mg	205	3 (1.5)	127	145	<0.001
P002/1013 (Week 52) Ertugliflozin vs. Glimepiride					
Glimepiride	437	14 (3.2)	91	327	
Ertugliflozin 5 mg	448	25 (5.6)	110	325	0.068
Ertugliflozin 15 mg	440	16 (3.6)	82	337	0.691
P005/1019 (Week 26) Ertugliflozin+Sitagliptin factorial					
Sitagliptin 100 mg	247	16 (6.5)	53	191	
Ertugliflozin 5 mg	250	16 (6.4)	5	156	
Ertugliflozin 15 mg	248	7 (2.8)	1	133	
Ertugliflozin 5 mg + Sitagliptin 100 mg	243	6 (2.5)	50	196	0.036† 0.042‡
Ertugliflozin 15 mg + Sitagliptin 100 mg	244	0 (0.0)	N/A	N/A	<0.001† 0.009‡
P006/1015 (Week 26) Add-on to Metformin+Sitagliptin					
Placebo	153	25 (16.3)	26	212	
Ertugliflozin 5 mg	156	2 (1.3)	135	141	<0.001
Ertugliflozin 15 mg	153	3 (2.0)	43	147	<0.001
P017/1047 (Week 26) Ertugliflozin+Sitagliptin					
Placebo	97	31 (32.0)	9	166	
Ertugliflozin 5 mg + Sitagliptin 100 mg	98	6 (6.1)	79	148	<0.001
Ertugliflozin 15 mg + Sitagliptin 100 mg	96	0 (0.0)	N/A	N/A	<0.001
P001/1016 (Week 26) Renal Impairment					
Placebo	99	8 (8.1)	43	183	
Ertugliflozin 5 mg	105	8 (7.6)	22	144	0.799
Ertugliflozin 15 mg	97	3 (3.1)	17	137	0.117

P-values are based on the Log-Rank Test for time to glycemic rescue.
†For the comparison to Sitagliptin alone.
‡For the comparison to the Ertugliflozin alone.

Overall, clinically meaningful reductions from baseline in HbA1c have been demonstrated with ertugliflozin 15 mg and 5 mg in the monotherapy study, the add-on to metformin studies, the add-on to metformin plus sitagliptin study, and in the co-administration with sitagliptin studies. In these 6 studies, other glycaemic parameters, such as FPG, proportion of subjects to reach the HbA1c goal of < 7.0% and proportion of subjects receiving glycaemic rescue therapy, were consistent with the HbA1c result. In addition, reductions in body weight and SBP have also been consistently demonstrated.

The safety and tolerability of ertugliflozin was evaluated in a large clinical development program comprised of subjects who are representative of the spectrum of patients with T2DM,

including a wide array of background medications. Comprehensive evaluation of safety and tolerability was performed in the 6068 subjects treated in Phase I, II, and III studies with ertugliflozin. Overall, ertugliflozin was safe and well tolerated at both the 5 mg and 15 mg doses, which demonstrated generally similar safety profiles. Evidence for a dose response was observed for increases in LDL-C and genital mycotic infections in female subjects. Ertugliflozin treatment led to a higher incidence of adverse events of genital mycotic infections, increased urination, thirst, and vulvovaginal pruritus. Ertugliflozin treatment also led to a higher incidence of volume depletion related events relative to comparators in subjects with moderate renal impairment, elderly subjects, or subjects on diuretics. Ertugliflozin treatment led to small, transient, early mean decreases in eGFR that largely returned to baseline by Week 26. In subjects with moderate renal impairment, there was a slightly larger mean decrease in eGFR which did not completely resolve at Week 26, and a higher incidence of renal-related events. Ketoacidosis was confirmed in 3 ertugliflozin treated subjects and no non-ertugliflozin-treated subjects. Ertugliflozin treatment led to small increases in LDL-C. The incidence of hypoglycaemia was increased when ertugliflozin was used in combination with insulin and/or insulin secretagogues. The clinical significance of amputation/ peripheral revascularisation events as they relate to ertugliflozin is uncertain. Ertugliflozin treatment did not appear to be associated with an increased risk of and urinary tract infection, fracture, venous thromboembolism, hepatic injury, pancreatitis, hypersensitivity, or malignancy.

A limitation of this submission was the lack of data on CV safety of ertugliflozin as results of the CV meta-analysis (based on data from Phase III studies) was not submitted for evaluation. This is especially important in light of the slightly higher incidence of deaths (mainly CV deaths) and lower limb amputations in T2DM patients treated with ertugliflozin compared to the non-ertugliflozin group. It is noted that the sponsor has initiated two large studies to address this deficiency although no data was submitted in the current dossier.

There is lack of adequate data on long-term maintenance of efficacy beyond 6 months. This submission only included results from Phase A (up to 26 weeks in all Phase III studies except study P002/1013 (Phase A was at 52 weeks for this study which compared ertugliflozin with glimepiride in T2DM patients with inadequate glycaemic control on metformin therapy). Hence results from the ongoing Phase B of all 7 Phase III studies should be submitted for evaluation as soon as it is available to enable assessment of long term maintenance of efficacy and safety of ertugliflozin in the proposed indications.

Although the proposed indication mentions that ertugliflozin can be used as adjunct to diet and exercise with other anti-hyperglycaemic agents, it is important to note that the pivotal Phase III studies only evaluated efficacy/ safety of ertugliflozin in combination with metformin and DPP-4 inhibitors (sitagliptin). Combination of ertugliflozin with sulphonylureas, insulin and GLP-1 analogues was not evaluated.

Overall, the benefit-risk profile of ertugliflozin (5 mg and 15 mg once daily) is not favourable for the following proposed indication: 'Steglatro (ertugliflozin) is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus as monotherapy when metformin is considered inappropriate due to intolerance or in combination with other anti-hyperglycaemic agents.'

However, the benefit risk profile may become favourable if the changes recommended below are adopted.

3.4. First round recommendation regarding authorisation

It is recommended that approval for the following indication cannot be granted at this stage:

> *Steglatro (ertugliflozin) is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus as monotherapy when metformin*

is considered inappropriate due to intolerance or in combination with other anti-hyperglycaemic agents.

However, approval could be granted for a slightly modified wording of the above indication:

Indications: MSD-Ertugliflozin (ertugliflozin) is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus as:

- *Monotherapy when metformin is considered inappropriate due to intolerance.*
- *or in combination with other antihyperglycaemic drugs (see CLINICAL TRIALS and Precautions for available data on different add-on combination therapies).*

Approval for above modified indication is also subject to the following:

- Incorporation of suggested changes to proposed PI.
- Satisfactory response to Clinical questions below.
- Results from the ongoing Phase B of all 7 Phase III studies should be submitted for evaluation as soon as it is available to enable assessment of long term maintenance of efficacy and safety of ertugliflozin in the proposed indications.
- Provision of results of the CV meta-analysis of Phase III studies in this submission. Furthermore, results of the ongoing CVOT study should be submitted for evaluation on completion.

4. Clinical questions

4.1. Pharmacokinetics

4.1.1. Question 1

Could the sponsors clarify why the bioequivalence of the 5 mg tablet used in the pivotal Phase III studies and the 5 mg tablet proposed for marketing not evaluated?

4.2. Pharmacodynamics

4.2.1. Question 2

It is not clear how the results shown in the Table summarising the 'Estimated percent maximum response for various endpoints' (please refer to Table 114 below) were calculated. For instance, the two modelling studies, PMAR-EQDD-B152a-DP4-407 and ASR-EQDD-B152a-DP3-253 provided estimates of the ED_{50} values for HbA1c and UGE_{0-24} of 1.30 mg and 0.75 mg, respectively, which do not match the values shown in Table 114. In addition, although the reported maximum percent response for UGE is correct in this Table, which appears to be calculated from the predicted dose response divided by the predicted E_{max} as reported in ASR-EQDD-B152a-DP3-253, the maximum response values for HbA1c for a 5 and 15 mg dose in this Table do not correspond with the results of PMAR-EQDD-B152a-DP4-407. Finally the evaluator has not been able to trace the results for FPG to any of the modelling studies provided that they were undertaken in subjects with T2DM.

Can the sponsor therefore please clarify how the results as shown in Table 114 of this report were calculated and also provide the source of the data used as a basis for these calculations?

Table 114: Estimated percent maximum response for various endpoints

Ertugliflozin Dose	UGE - T2DM (ED_{50}=0.78 mg)	A1C (ED_{50}=1 mg)	FPG (ED_{50}=1.1 mg)
5 mg	87%	83%	82%
15 mg	95%	94%	93%

Abbreviations: A1C = hemoglobin A_{1c}; ED_{50} = dose producing half (50%) of the maximal response; FPG = fasting plasma glucose; T2DM = type 2 diabetes mellitus; UGE = urinary glucose excretion.

4.3. Efficacy

4.3.1. Question 3

There are a few questions related to the Phase II Study P016/1006 as listed below:

- The incidence of protocol deviations in each of the treatment groups was not provided. The link to one source table listed in the CSR did not work. Could the sponsors provide this information and confirm if these deviations had any effect on interpretation of results from the study.
- Could the sponsors clarify lack of any dose-response for ertugliflozin for both the composite endpoints: proportion of subjects with HbA1c < 7%, no hypoglycaemic episodes, no weight gain at Week 12 and proportion of subjects with HbA1c < 7%, blood pressure < 130/80 mmHg, and no weight gain at Week 12 (ertugliflozin 5 mg showed higher response rates compared to both ertugliflozin 10 mg and 25 mg).
- The proposed 15 mg dose of ertugliflozin was not evaluated in this Phase II study. It appears that the ertugliflozin 10 mg dose showed numerically lesser improvement compared to the 5 mg dose for the primary efficacy endpoint of change from baseline to week 12 in HbA1c, while both 10 and 25 mg doses had numerically fewer proportion of subjects with HbA1c < 7% (and < 6.5%) at week 12 compared with the 5 mg dose. It is noted that FPG, body weight and reduction in SBP/DBP appeared to be numerically greater with the 10 mg and 25 mg doses compared with the 5 mg dose. However, considering the fact that the proposed 15 mg dose of ertugliflozin was not evaluated in this pivotal dose ranging Phase II study, the selection of the ertugliflozin 15 mg dose for the Phase III studies appears to be arbitrary. Could the sponsors provide clarification on this.

4.3.2. Question 4

In the other Phase II dose-ranging study P042/1004, ertugliflozin results in clinically meaningful lowering in BP (primary endpoint) with magnitude of effect being at least comparable to HCTZ with no clear evidence of a dose response beyond the 5 mg dose. Although the 5 mg dose also showed significant increase in UGE and decrease in FPG (secondary endpoints), there was only minimal further improvement with the ertugliflozin 25 mg dose. The proposed 15 mg dose of ertugliflozin was not evaluated in this study either selection of the ertugliflozin 15 mg dose for the Phase III studies appears to be arbitrary. Could the sponsor please provide clarification on this?

4.3.3. Question 5

In the pivotal Phase III monotherapy Study P003/1022, it is noted that the ertugliflozin 15 mg group had numerically greater proportion of patients with baseline HbA1c $\geq$9% compared to the other 2 treatment groups (16.3%, 16.7% and 25.7% in placebo, ertugliflozin 5 mg and 15 mg groups, respectively). Furthermore, the proportion of patients with baseline eGFR >90 mL/min/1.73m^2 were numerically greater in both ertugliflozin groups compared with placebo (34.6%, 46.2% and 44.7%, respectively). The sponsors have been asked to clarify if this affected interpretation of efficacy results, especially considering that subgroup analyses based on baseline eGFR was not evaluated.

4.3.4. Question 6

The CSR of Phase III study P002/1013 mentions that besides the 14 subjects from study site 0855 that discontinued another 3 subjects from study site 0042 were also discontinued. However, it is mentioned that these 17 subjects were still included in analyses. Could the sponsors confirm if inclusion of these subjects from study sites which were non-compliant with GCP guidelines had any impact on interpretation of results from this pivotal study. Could the sponsors also clarify if the 6 subjects who discontinued from study sites 0035 and 0559 due to non-GCP related reasons were included in the efficacy analyses?

4.3.5. Question 7

In the Phase III pivotal Study P017/1047, it is noted that the proportion of patients on beta-blockers and diuretics was numerically higher in the E5/S100 and E15/S100 groups compared with placebo. This could have confounded interpretation of effects of proposed combination therapy on blood pressure. Could the sponsors please comment on this?

4.3.6. Question 8

In pivotal Phase III Study P006/1015, 41 (8.9%) randomised subjects were incorrectly stratified across the 3 treatment groups, including 33 (7.1%) subjects who were reported as taking an SU at screening but who were not, and 8 (1.7%) subjects who were reported as not taking an SU at screening but who were. Subjects were analysed according to their intended stratum. The sponsors have been requested to clarify if the incidence of incorrect stratification based on SU use prior to screening was similar across all treatment groups and if this could have confounded interpretation of efficacy results.

4.4. Safety

4.4.1. Question 9

There appears to be an error in the following sponsor paragraph: '*In the Broad Pool, the proportion of subjects having at least 1 occurrence meeting the PDLC criterion for phosphate (increase ≥ 0.5 mg/dL and value > ULN) was higher in the ertugliflozin 5 mg and 15 mg groups (18.5% and 22.9%, respectively), relative to the non ertugliflozin group (11.9%). At the last value on treatment, the proportion of subjects who met the PDLC criterion for increased phosphate was numerically higher in the ertugliflozin 5 mg group (3.6%) and higher in the ertugliflozin 15 mg group (5.7%) relative to the placebo group (2.4%).*'

Comment: The comparisons were between the ertugliflozin and non-ertugliflozin groups in the Broad Pool. Could the sponsors clarify if the last sentence refers to all 'non-ertugliflozin' group or 'placebo' group?

4.4.2. Question 10

A limitation of this submission was the lack of data on CV safety of ertugliflozin. Although, the sponsor has initiated two large studies to address this deficiency, no data was submitted in the current dossier. Could the sponsors clarify the following statement: '*Cardiovascular (CV) outcomes trial (P004/1021) is ongoing and remains blinded per the data access plan. CV meta-analysis related documents were submitted to the US FDA by a firewalled team*.'
Is there are any CV safety data that has not been submitted to the TGA?

5. Second round evaluation

5.1. Clinical questions

The sponsor has responded to the request. The evaluator's questions, sponsors response and evaluators comments are summarised below.

5.1.1. Pharmacokinetics

5.1.1.1. Question 1

Could the sponsors clarify why the bioequivalence of the 5 mg tablet used in the pivotal Phase III studies and the 5 mg tablet proposed for marketing not evaluated?

Sponsor's response

Two doses of ertugliflozin, 5 mg and 15 mg, have been evaluated in Phase III studies and both doses are submitted for registration. Ertugliflozin is formulated as an immediate release tablet for oral administration at 5 mg and 15 mg strengths using a common blend with 5% drug loading. The tablets are manufactured by a conventional direct compression process, utilizing precedented excipients. The complete compositional and processing information was included in the New Drug Application.

The rationale for not conducting a bioequivalence study for the 5 mg tablet used in the pivotal Phase III studies and the 5 mg tablet proposed for marketing are as follows:

1. A pivotal bioequivalence study (Study P023/1037), performed using the higher strength (15 mg) commercial tablets, and demonstrated that the ertugliflozin 15 mg commercial tablet is bioequivalent to the ertugliflozin 15 mg Phase III dose (administered as one 10 mg tablet and one 5 mg tablet).
2. Ertugliflozin meets the requirements of a BCS Class 1 drug based on its high solubility (highest strength of 15 mg is soluble in 250 mL or less of aqueous media over the pH range of 1.2 to 6.8) and high permeability (absolute bioavailability ~100%).
3. Ertugliflozin pharmacokinetics is dose-proportional and linear over the therapeutic dose range.
4. The 5 mg commercial tablet is proportionally similar in its active and inactive ingredients to the 15 mg commercial tablet.
5. Multimedia dissolution profiles comparing the 5 mg Phase III tablets to the 5 mg commercial tablets, and the 5 mg + 10 mg Phase III tablets compared to the 15 mg commercial formulation tablets demonstrated very rapid dissolution of ertugliflozin for all tablet strengths (≥ 85% dissolved in 15 minutes).

Evaluator's comment

The evaluator is satisfied with the sponsor's response.

5.2. Pharmacodynamics

5.2.1. Question 2

It is not clear how the results shown in the Table summarising the 'Estimated percent maximum response for various endpoints' (please refer to Table 114 of this report) were calculated. For instance, the two modelling studies, PMAR-EQDD-B152a-DP4-407 and ASR-EQDD-B152a-DP3-253, provided estimates of the ED_{50} values for HbA1c and UGE_{0-24} of 1.30 mg and 0.75 mg, respectively, which do not match the values shown in Table 114. In addition, although the reported maximum percent response for UGE is correct in this Table,

which appears to be calculated from the predicted dose response divided by the predicted E_{max} as reported in ASR-EQDD-B152a-DP3-253, the maximum response values for HbA1c for a 5 and 15 mg dose in this Table do not correspond with the results of PMAR-EQDD-B152a-DP4-407. Finally the evaluator has not been able to trace the results for FPG to any of the modelling studies provided that they were undertaken in subjects with T2DM.

Can the sponsor therefore please clarify how the results as shown in Table 114 of this report were calculated and also provide the source of the data used as a basis for these calculations?

Sponsor's response

Results in Table 114 of the report were calculated using the model predicted values provided in Table 'Model-predicted placebo adjusted change from baseline responses for key endpoints based on phase 2 studies' presented. To calculate the estimated percent maximum response for the key endpoints (HbA1c, FPG and UGE), as reported in Table 6.3, only data from the Phase II studies P016/B1521006 (HbA1c and FPG) and P042/B1521004 (UGE) were used. In the PMAR-EQDD-B152a-DP4-407, both Phase III as well as Phase II data were used to estimate the dose response relationship. Therefore, the percent maximum response values for HbA1c for the 5 and 15 mg doses presented in Table 6.3 do not correspond with the results of PMAR-EQDD-B152a-DP4-407. As mentioned by the reviewer, the reported percent maximum response is calculated from the predicted response for the dose divided by the predicted E_{max} from the model.

The sponsors have provided tables for HbA1c, body weight and FPG respectively, from Study P016/B1521006 summarising the results from the E_{max} dose response model for HbA1c, FPG and body weight (Table 115).

Table 115: Model-predicted placebo adjusted change from baseline responses for key endpoints based on Phase II studies

Ertugliflozin Dose (mg)	A1C (%) ED_{50}=1.0 mg E_{max}=-0.77%	FPG (mg/dL) ED_{50}=1.1 mg E_{max}=-34.8 mg/dL	Body weight (%) ED_{50}=0.8 mg E_{max}=-2.11%	UGE_{24} (g) ED_{50}=0.75 mg E_{max}=71.5 g
5	-0.64	-28.4	-1.81	62.5
15	-0.72	-32.4	-2.00	68.9

Source: [Ref. 5.3.5.1: P016], [Ref. 5.3.5.3: 04J9DB].
Abbreviations: $A1_C$=glycosylated hemoglobin A_{1c}; ED_{50}=dose producing 50% of the maximal response; E_{max}= maximum effect; FPG=fasting plasma glucose; UGE_{24}=24-hour urinary glucose excretion.

Evaluator's comment

The sponsor's response is satisfactory.

1.1.1 Efficacy

5.2.2. Question 3

There are a few questions related to the Phase II study P016/1006 as listed below:

- ***The incidence of protocol deviations in each of the treatment groups was not provided. The link to the source table in the CSR did not work. Could the sponsors provide this information and confirm if these deviations had any effect on interpretation of results from the study.***
- ***Could the sponsors clarify lack of any dose-response for ertugliflozin for both the composite endpoints: proportion of subjects with HbA1c < 7%, no hypoglycaemic episodes, no weight gain at Week 12 and proportion of subjects with HbA1c < 7%, blood pressure < 130/80 mm Hg, and no weight gain at Week 12 (ertugliflozin 5 mg showed higher response rates compared to both ertugliflozin 10 mg and 25 mg).***

- ***The proposed 15 mg dose of ertugliflozin was not evaluated in this Phase II study. It appears that the ertugliflozin 10 mg dose showed numerically lesser improvement compared to the 5 mg dose for the primary efficacy endpoint of change from baseline to week 12 in HbA1c, while both 10 and 25 mg doses had numerically fewer proportion of subjects with HbA1c < 7% (and < 6.5%) at Week 12 compared with the 5 mg dose. It is noted that FPG, body weight and reduction in SBP/DBP appeared to be numerically greater with the 10 mg and 25 mg doses compared with the 5 mg dose. However, considering the fact that the proposed 15 mg dose of ertugliflozin was not evaluated in this pivotal dose ranging Phase II study, the selection of the ertugliflozin 15 mg dose for the Phase III studies appears to be arbitrary. Could the sponsors provide clarification?***

Sponsor's response

- The complete list of protocol deviations from the 12 week Phase II study (Study P016/1006) is included and the sponsor has provided an active link to it. The most common protocol deviations were minor infractions involving the informed consent process, such as incomplete contact information of the witness or incomplete name of the subject on the document. Protocol deviations related to entry criteria were reported for only 6 subjects, and dispersed across 3 different criteria. As such, none of the deviations in this category occurred in a large enough number of subjects to have a meaningful effect on interpretation of study results. Similarly, as only 1 subject had a randomization-related deviation (Vitamin D stabilization incomplete), there is no effect on study results for deviations in this category. Other deviations in the study were primarily procedural (for example, visit conducted outside visit window), generally occurred in small numbers of subjects, and are not expected to affect the interpretation of study results.
- These composite endpoints were exploratory in nature. One composite endpoint combined efficacy and safety information (proportion of subjects with HbA1c < 7%, no hypoglycaemic episodes, no weight gain) while the other composite consisted of HbA1c < 7%, blood pressure < 130/80 mm Hg, and no weight gain. The sponsor believes that it is inappropriate to evaluate these composite endpoints from the perspective of dose-responsiveness given the mix of endpoints included in the composite outcome. As just one example, body weight could be favourably impacted by the effects of glucosuria while at the same time also influenced by improvement in glycaemic control over time leading to a lower amount of glucosuria. Effects on plasma volume could also confound assessments on body weight. Dose response information for selection of Phase III doses was based on model-based analysis from both Phase II studies with a focus on glycaemic endpoints as this was the targeted indication. More importantly, the efficacy and safety results from the large Phase III program of nearly 5,000 subjects provide the most comprehensive set of dose response information for evaluation of efficacy and safety.
- The ertugliflozin doses selection for Phase III were based on a comprehensive analysis of data from the 2 dose-ranging Phase II studies. The focus for Phase III dose selection was on the endpoints of HbA1c and FPG from the 12 week study and UGE data from the 4 week Phase II study given the targeted indication for improved glycaemic control in T2DM. These data were utilised in the developed model-based analysis to aid in Phase III dose selection. The model based analysis of the comprehensive dataset provides a more robust assessment than examining endpoints in isolation, which due to stochastic tendencies, could be subject to variability. With a sample size typical of Phase II dose-ranging studies and examining various endpoints, some variability is to be expected, which is the rationale for a quantitative, model-based approach based on the totality of available data. The 5 mg and 15 mg doses were selected for Phase III as they were expected to provide responses that were > 80% and >90% of the E_{max}, respectively for glycaemic endpoints. There was a predicted difference of 0.1% in HbA1c between 5 mg and 15 mg doses of ertugliflozin (Table 115). The model based analysis supported that 15 mg would thus provide additional

HbA1c lowering relative to 5 mg, and that no further efficacy was to be expected from the 25 mg dose evaluated in Phase II. In the pool of placebo controlled Phase III studies, including data from > 1500 subjects, the placebo adjusted LS mean changes from baseline in HbA1c were -0.76% and -0.91% for the ertugliflozin 5 mg and 15 mg groups, respectively. Thus, ertugliflozin 15 mg resulted in an incremental HbA1c-lowering of 0.15% relative to ertugliflozin 5 mg. Furthermore, in all Phase III trials, there was a trend for a larger effect on glycaemic endpoints with ertugliflozin 15 mg versus 5 mg. These results, along with the safety data from the Phase III program, support the dose selection for ertugliflozin.

Evaluator's comments

- The sponsor's response is satisfactory.
- The sponsor's response is satisfactory.
- Although the proposed 15 mg dose of ertugliflozin was not evaluated in the dose-ranging Phase II studies, data from these studies was used for the model-based analysis which suggested that a 15 mg dose would provide additional HbA1c lowering relative to 5 mg, and that no further efficacy was to be expected from the 25 mg dose. Overall, the sponsor's response to the queries regarding the Phase II dose-ranging studies and selection of 5 mg and 15 mg doses for the pivotal Phase III studies was satisfactory.

5.2.2.1. Question 4

In the other Phase II dose-ranging study P042/1004, ertugliflozin results in clinically meaningful lowering in BP (primary endpoint) with magnitude of effect being at least comparable to HCTZ with no clear evidence of a dose response beyond the 5 mg dose. Although the 5 mg dose also showed significant increase in UGE and decrease in FPG (secondary endpoints), there was only minimal further improvement with the ertugliflozin 25 mg dose. The proposed 15 mg dose of ertugliflozin was not evaluated in this study either selection of the ertugliflozin 15 mg dose for the Phase III studies appears to be arbitrary. Could the sponsors provide clarification on this?

Sponsor's response

The rationale for the ertugliflozin doses selected for the Phase III program is discussed in the response to Question 3c. As described above, the focus for the Phase III dose selection was based on endpoints of HbA1c, FPG, and UGE. Given the potential of multiple contributors (UGE and the corresponding osmotic diuresis; weight loss) to blood pressure lowering with SGLT2 inhibitors, the sponsor did not taken into account blood pressure changes with ertugliflozin for Phase III dose selection.

Evaluator's comments

The sponsor's response is satisfactory.

5.2.2.2. Question 5

In the pivotal Phase III monotherapy study P003/1022, it is noted that the ertugliflozin 15 mg group had numerically greater proportion of patients with baseline HbA1c ≥9% compared to the other 2 treatment groups (16.3%, 16.7% and 25.7% in placebo, ertugliflozin 5 mg and 15 mg groups, respectively). Furthermore, the proportion of patients with baseline eGFR >90 mL/min/1.73m^2 were numerically greater in both ertugliflozin groups compared with placebo (34.6%, 46.2% and 44.7%, respectively). The sponsors have been asked to clarify if this affected interpretation of efficacy results, especially considering that subgroup analyses based on baseline eGFR was not evaluated.

Sponsor's response

Glycemic efficacy of all SGLT2 inhibitors is dependent on baseline HbA1c and renal function. The reviewer notes that there was a numerically greater proportion of subjects in the

ertugliflozin 15 mg group with baseline HbA1c > 9%, and numerically greater proportion of subjects in the ertugliflozin groups with baseline eGFR > 90 mL/min/1.73 m^2. The statistical model used for analysis of HbA1c change from baseline was a cLDA model. This model estimated a common mean HbA1c across treatment groups at baseline and treatment group-specific mean changes from baseline were estimated relative to that common baseline mean. Accordingly, the small numerical difference in the proportion of subjects at baseline with HbA1c > 9% had no effect on the primary results of change from baseline in HbA1c.

With respect to renal function, the most complete summary statistics to describe the baseline eGFR distribution between treatment groups in an individual study is a comparison of means and SD. For Study P003/1022, mean baseline eGFR (mL/min/1.73 m^2) was nearly identical between groups: placebo (86.2 ± 19.4); ertugliflozin 5 mg (88.5 ± 18.4); ertugliflozin 15 mg (88.3 ± 18.0). The overall mean baseline for the entire study population was 87.7 mL/min/1.73 m^2. The individual categorical distributions slightly differed at baseline between treatment groups. However, as with many other categorical groupings, these are often less informative than the mean when evaluating continuous endpoints. For example, a subject with an eGFR of 60.0 mL/min/1.73 m^2 and a subject with an eGFR of 89.9 mL/min/1.73 m^2 are summarized in the same categorical grouping despite recognition of the marked difference in these values. Therefore, given that the mean baseline eGFR values were nearly identical across groups, the reported efficacy results provide an accurate representation of the effects of ertugliflozin in the monotherapy treatment setting. In summary, the small numerical proportional differences at baseline in HbA1c and eGFR did not have any impact on the conclusions from the ertugliflozin monotherapy study (P003/1022).

Evaluator's comments

The sponsor's response is satisfactory.

5.2.2.3. Question 6

The CSR of Phase III Study P002/1013 mentions that besides the 14 subjects from study site 0855 who discontinued another 3 subjects from study 0042 were also discontinued. However, it is mentioned that these 17 subjects were still included in analyses. Could the sponsors confirm if inclusion of these subjects from study sites which were non-compliant with GCP guidelines had any impact on interpretation of results from this pivotal study. Could the sponsors also clarify if the 6 subjects who discontinued from study sites 0035 and 0559 due to non-GCP related reasons were included in the efficacy analyses?

Sponsor's response

All subjects randomised at the 2 sites closed for GCP findings (0855 and 0042) at the 2 sites closed for non-GCP related reasons (0035 and 0559) were included in the efficacy and safety analyses. With regard to the 2 sites closed for GCP findings (0855 and 0042), the potential effect on the interpretation of study results is limited for the following reasons. Many of the findings at both sites were due to suboptimal record keeping practices, as well as poor investigator oversight. While the poor performance of both sites led to protocol deviations, the findings identified were not the result of fraudulent behaviour. For this reason, the integrity of the data from these subjects was not considered compromised. In addition, the process of randomization distributed the 23 subjects randomized across both sites nearly evenly among the 3 groups (6, 8, and 9 subjects in the ertugliflozin 5 mg, 15 mg, and glimepiride groups, respectively). As a result, the number of subjects from these sites in each group was small relative to the individual group sizes (approximately 440 subjects per group), with limited potential to effect the interpretation of study results.

Evaluator's comments

The sponsor's response is satisfactory.

5.2.2.4. Question 7

In the Phase III pivotal Study P017/1047, it is noted that the proportion of patients on beta-blockers and diuretics was numerically higher in the E5/S100 and E15/S100 groups compared with placebo. This could have confounded interpretation of effects of proposed combination therapy on blood pressure. Could the sponsors please comment on this?

Sponsor's response

While a higher proportion of ertugliflozin-treated subjects were taking a beta-blocker or diuretic, several other classes of antihypertensive medications were used concomitantly by subjects in the study. Overall, use of antihypertensive medications was balanced across groups, with approximately 50% of subjects in each group taking at least 1 medication for blood pressure control at baseline and Week 26. RAAS blockers were the most commonly used antihypertensive agents, and taken by a slightly lower proportion of subjects in the E15/S100 group (37.5%) relative to the placebo group (42.3%)(Table 116). These data suggest that even though small differences in usage exist between groups for certain classes of antihypertensive agents, one cannot infer that subjects in the placebo group received more or less intensive blood pressure therapy than subjects in the combination groups. Subjects were to be treated according to standard of care for blood pressure management, and it is possible that they were using more than 1 antihypertensive agent. Therefore, the sponsor believes that any differences in beta-blocker or diuretic use are unlikely to have confounded the blood pressure analyses.

Table 116: Ertugliflozin Protocol MK-8835-017/B1521047 Subjects with BP and lipid lowering medication at baseline and Week 26 All subjects treated

	Placebo		Ertugliflozin 5 mg + Sitagliptin 100 mg		Ertugliflozin 15 mg + Sitagliptin 100 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Baseline								
Subjects in population at Baseline	97		98		96		291	
Blood Pressure								
Subjects with one or more medications	47	(48.5)	49	(50.0)	51	(53.1)	147	(50.5)
Antihypertensives	1	(1.0)	3	(3.1)	2	(2.1)	6	(2.1)
Agents acting on the RAS	41	(42.3)	43	(43.9)	36	(37.5)	120	(41.2)
Beta blocking agents	15	(15.5)	13	(13.3)	21	(21.9)	49	(16.8)
Calcium channel blockers	12	(12.4)	14	(14.3)	15	(15.6)	41	(14.1)
Diuretics	11	(11.3)	16	(16.3)	19	(19.8)	46	(15.8)
Lipid Modifying Agents								
Subjects with one or more medications	34	(35.1)	28	(28.6)	31	(32.3)	93	(32.0)
Fibrates	9	(9.3)	3	(3.1)	5	(5.2)	17	(5.8)
HMG CoA reductase inhibitors	29	(29.9)	24	(24.5)	26	(27.1)	79	(27.1)
Other lipid modifying agents	0	(0.0)	1	(1.0)	2	(2.1)	3	(1.0)
Week 26								
Subjects in population at Week 26	90		96		94		280	
Blood Pressure								
Subjects with one or more medications	48	(53.3)	50	(52.1)	51	(54.3)	149	(53.2)
Antihypertensives	1	(1.1)	3	(3.1)	2	(2.1)	6	(2.1)
Agents acting on the RAS	42	(46.7)	43	(44.8)	36	(38.3)	121	(43.2)
Beta blocking agents	14	(15.6)	14	(14.6)	21	(22.3)	49	(17.5)
Calcium channel blockers	11	(12.2)	13	(13.5)	15	(16.0)	39	(13.9)
Diuretics	10	(11.1)	15	(15.6)	19	(20.2)	44	(15.7)
Lipid Modifying Agents								
Subjects with one or more medications	33	(36.7)	31	(32.3)	32	(34.0)	96	(34.3)
Fibrates	9	(10.0)	6	(6.3)	5	(5.3)	20	(7.1)
HMG CoA reductase inhibitors	28	(31.1)	26	(27.1)	27	(28.7)	81	(28.9)
Other lipid modifying agents	0	(0.0)	2	(2.1)	2	(2.1)	4	(1.4)

Every subject is counted a single time for each applicable specific medication. A subject with multiple medications within a medication category is counted a single time for that category.

Data Source: [ADSL, ADCM] Date of Reporting Dataset Creation: 23MAR2016 Date of Table Creation: 25MAR2016 (10:11)

Evaluator's comments

The sponsor's response is satisfactory.

5.2.2.5. Question 8

In pivotal Phase III Study P006/1015, 41 (8.9%) randomised subjects were incorrectly stratified across the 3 treatment groups, including 33 (7.1%) subjects who were reported as taking an SU at screening but who were not, and 8 (1.7%) subjects who were reported as not taking an SU at screening but who were. Subjects were analysed according to their intended stratum. The sponsors have been requested to clarify if the incidence of incorrect stratification based on SU use prior to screening was similar across all treatment groups and if this could have confounded interpretation of efficacy results.

Sponsor's response

The incidence of incorrect stratification was similar across the treatment Groups (Table 117). Across the treatment groups, 5.2% to 8.3% of subjects were not using SUs at Visit 1, but were mis-stratified as being SU users. Conversely, across treatment groups, 1.3% to 1.9% of subjects were using SUs at Visit 1, but were mis-stratified as being non-SU users. Given that similar proportions of subjects across groups were mis-stratified and the fact that a modest number of subjects were involved the mis-stratification errors for SU use did not confound the interpretation of efficacy results.

Table 117: Ertugliflozin Protocol MK-8835-006/B1521015 Summary of incorrectly stratified subjects All subjects randomised

	Placebo n (%)	Ertugliflozin 5 mg n (%)	Ertugliflozin 15 mg n (%)	Total n (%)
Subjects in population	153	156	154	463
Subjects mis-stratified	14 (9.2)	16 (10.3)	11 (7.1)	41 (8.9)
Mis-stratified to sulfonylurea use at Visit 1/Screening: Yes (Actually No)	12 (7.8)	13 (8.3)	8 (5.2)	33 (7.1)
Mis-stratified to sulfonylurea use at Visit 1/Screening: No (Actually Yes)	2 (1.3)	3 (1.9)	3 (1.9)	8 (1.7)

Data Source: [ADSL] Date of Reporting Dataset Creation: 06JUN2016 Date of Table Creation: 07JUN2016 (7:26)

Evaluator's comments

The sponsor's response is satisfactory.

1.1.2 Safety

5.2.2.6. Question 9

There appears to be an error in the following paragraph of the SCS: '*In the Broad Pool, the proportion of subjects having at least 1 occurrence meeting the PDLC criterion for phosphate (increase ≥ 0.5 mg/dL and value > ULN) was higher in the ertugliflozin 5 mg and 15 mg groups (18.5% and 22.9%, respectively), relative to the non ertugliflozin group (11.9%) At the last value on treatment, the proportion of subjects who met the PDLC criterion for increased phosphate was numerically higher in the ertugliflozin 5 mg group (3.6%) and higher in the ertugliflozin 15 mg group (5.7%) relative to the placebo group (2.4%).'*

Comment: ***The comparisons were between the ertugliflozin and non-ertugliflozin groups in the Broad Pool. Could the sponsors clarify if the last sentence refers to all 'non-ertugliflozin' group or 'placebo' group?***

Sponsor's response

The sponsor confirms that the last sentence in the paragraph noted above contains an error, and that it should refer to the 'non-ertugliflozin group' instead of the 'placebo group.'

Evaluator's comments

The sponsor's response is satisfactory.

5.2.2.7. Question 10

A limitation of this submission was the lack of data on CV safety of ertugliflozin. Although, the sponsor has initiated two large studies to address this deficiency, no data was submitted in the current dossier. Could the sponsors clarify the following statement mentioned: '*Cardiovascular (CV) outcomes trial (P004/1021) is ongoing and remains blinded per the data access plan. CV meta-analysis related documents were submitted to the US FDA by a firewalled team*.'

Is there are any CV safety data that has not been submitted to the TGA?

Sponsor's response

The sponsor notes that CV safety data from 7 Phase III studies in nearly 5,000 subjects was provided to the TGA as part of the overall assessment of safety for ertugliflozin and was described in the Summary of Clinical Safety in the original registration dossier. To provide updated safety information, the sponsor is attaching the 4-month Safety Update Report (SUR), which provides a substantial increase in long-term exposure relative to the original submission (approximately 2 times the number of subjects with ≥ 76 weeks to 102 weeks exposure, and approximately 5 times the number of subjects with ≥ 102 weeks exposure), and summarizes complete or nearly complete cumulative Phase A+B data for 4 of the 6 studies with Phase A+B designs. The CV safety data included in the submission and the 4-month SUR were based on preferred terms from investigator AE reporting and do not reflect the results of adjudication which remain firewalled.

The SUR presented in this response is a cumulative review of ertugliflozin safety data from the Broad Pool through the established SUR data cut-off dates listed in Table 118. Deaths, non-fatal serious adverse events, adverse events leading to discontinuation from study medication, as well as Special Safety Topics were reviewed in this SUR. Review of the 4-month SUR revealed 4 AEs resulting in death (myocardial infarction, death, sudden death, hepatic cancer), all of which occurred in the non-ertugliflozin group. No additional deaths were reported during the post-treatment follow-up period. The cumulative incidence of adverse events resulting in death in the All Post-randomization Follow-up period was 0.6% in the ertugliflozin 5 mg group, 0.5% in the ertugliflozin 15 mg group, and 0.7% in the non-ertugliflozin group (Table 119). The cumulative incidence of non-fatal SAEs related to cardiac disorders was low and similar across treatment groups (1%, 1.5% and 1.4% in non-ertugliflozin, ertugliflozin 5 mg and 15 mg groups, respectively) with similar results observed for nervous system disorders (0.6%, 0.8% and 0.2%, respectively) (Table 120).

Table 118: Last data analysed cut-off dates for studies in pooled analysis of the original ertugliflozin application and in the SUR

Protocol Number	Application LDA Date	SUR LDA Date
P001/1016	15 May 2016	01 Oct 2016
P002/1013	31 May 2016	01 Oct 2016
P003/1022	15 May 2016	16 Aug 2016
P005/1019	01 May 2016	18 Jul 2016
P006/1015	01 May 2016	13 Jul 2016
P007/1017	31 May 2016	01 Oct 2016
P017/1047	NA (study complete)	NA (study complete)
Abbreviations: NA = not applicable; LDA = last data analyzed; SUR = safety update report		

Table 119: Subjects with AEs resulting in death (incidence > 0% in any column) Individual doses versus non-ertugliflozin All subjects as treated. Broad pool: Including rescue approach

	Non-Ertugliflozin						Ertugliflozin 5 mg						Ertugliflozin 15 mg					
	Application		SUR		Cumulative		Application		SUR		Cumulative		Application		SUR		Cumulative	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	1,450		674		1,450		1,716		710		1,716		1,693		718		1,693	
with one or more adverse events	3	(0.2)	4	(0.6)	7	(0.5)	10	(0.6)	0	(0.0)	10	(0.6)	8	(0.5)	0	(0.0)	8	(0.5)
with no adverse events	1,447	(99.8)	670	(99.4)	1,443	(99.5)	1,706	(99.4)	710	(100.0)	1,706	(99.4)	1,685	(99.5)	718	(100.0)	1,685	(99.5)
Cardiac disorders	**1**	**(0.1)**	**1**	**(0.1)**	**2**	**(0.1)**	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**	**3**	**(0.2)**	**0**	**(0.0)**	**3**	**(0.2)**
Acute myocardial infarction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)	3	(0.2)	0	(0.0)	3	(0.2)
Cardiogenic shock	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Myocardial infarction	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
General disorders and administration site conditions	**1**	**(0.1)**	**2**	**(0.3)**	**3**	**(0.2)**	**6**	**(0.3)**	**0**	**(0.0)**	**6**	**(0.3)**	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**
Cardiac death	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Death	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Multiple organ dysfunction syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Sudden cardiac death	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Sudden death	1	(0.1)	1	(0.1)	2	(0.1)	3	(0.2)	0	(0.0)	3	(0.2)	1	(0.1)	0	(0.0)	1	(0.1)
Infections and infestations	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**
Pneumonia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Septic shock	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)
Injury, poisoning and procedural complications	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Injury	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**(0.0)**	**1**	**(0.1)**	**1**	**(0.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**
Hepatic cancer	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Plasma cell myeloma	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)
Nervous system disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(0.1)**	**0**	**(0.0)**	**2**	**(0.1)**
Haemorrhagic stroke	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)
Ischaemic stroke	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)
Psychiatric disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Depression	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Chronic obstructive pulmonary disease	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Table 120: Subjects with non-fatal SAEs (incidence > 0% in any column) Individual doses versus non-ertugliflozin All subjects as treated. Broad pool: including rescue approach

	Non-Ertugliflozin						Ertugliflozin 5 mg						Ertugliflozin 15 mg					
	Application		SUR		Cumulative		Application		SUR		Cumulative		Application		SUR		Cumulative	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	1,450		674		1,450		1,716		710		1,716		1,693		719		1,693	
with one or more adverse events	77	(5.3)	12	(1.8)	88	(6.1)	103	(6.0)	15	(2.1)	117	(6.8)	94	(5.6)	11	(1.5)	101	(6.0)
with no adverse events	1,373	(94.7)	662	(98.2)	1,362	(93.9)	1,613	(94.0)	695	(97.9)	1,599	(93.2)	1,599	(94.4)	708	(98.5)	1,592	(94.0)
Blood and lymphatic system disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.1)**	**0**	**(0.0)**	**1**	**(0.1)**	**2**	**(0.1)**	**0**	**(0.0)**	**2**	**(0.1)**
Iron deficiency anaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Lymph node haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)
Lymphadenopathy	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)
Cardiac disorders	**13**	**(0.9)**	**1**	**(0.1)**	**14**	**(1.0)**	**23**	**(1.3)**	**3**	**(0.4)**	**25**	**(1.5)**	**22**	**(1.3)**	**2**	**(0.3)**	**24**	**(1.4)**
Acute coronary syndrome	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)	2	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Acute myocardial infarction	3	(0.2)	0	(0.0)	3	(0.2)	4	(0.2)	0	(0.0)	4	(0.2)	3	(0.2)	0	(0.0)	3	(0.2)
Angina pectoris	0	(0.0)	0	(0.0)	0	(0.0)	3	(0.2)	0	(0.0)	3	(0.2)	5	(0.3)	0	(0.0)	5	(0.3)
Angina unstable	2	(0.1)	1	(0.1)	3	(0.2)	2	(0.1)	1	(0.1)	3	(0.2)	1	(0.1)	0	(0.0)	1	(0.1)
Atrial fibrillation	1	(0.1)	0	(0.0)	1	(0.1)	2	(0.1)	0	(0.0)	2	(0.1)	2	(0.1)	0	(0.0)	2	(0.1)
Bradycardia	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Bundle branch block left	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac failure	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)	2	(0.1)	1	(0.1)	3	(0.2)
Cardiac failure chronic	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac failure congestive	1	(0.1)	0	(0.0)	1	(0.1)	2	(0.1)	0	(0.0)	2	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiomyopathy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Coronary artery disease	3	(0.2)	0	(0.0)	3	(0.2)	4	(0.2)	1	(0.1)	5	(0.3)	3	(0.2)	0	(0.0)	3	(0.2)
Cardiac disorders	**13**	**(0.9)**	**1**	**(0.1)**	**14**	**(1.0)**	**23**	**(1.3)**	**3**	**(0.4)**	**25**	**(1.5)**	**22**	**(1.3)**	**2**	**(0.3)**	**24**	**(1.4)**
Coronary artery stenosis	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)	2	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Microvascular coronary artery disease	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Myocardial infarction	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	1	(0.1)	2	(0.1)	2	(0.1)	1	(0.1)	3	(0.2)
Myocardial ischaemia	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)	3	(0.2)	0	(0.0)	3	(0.2)
Sinus node dysfunction	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)	2	(0.1)
Nervous system disorders	**8**	**(0.6)**	**1**	**(0.1)**	**9**	**(0.6)**	**12**	**(0.7)**	**2**	**(0.3)**	**14**	**(0.8)**	**4**	**(0.2)**	**0**	**(0.0)**	**4**	**(0.2)**
Carotid arteriosclerosis	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Carotid artery stenosis	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Cerebral haemorrhage	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)
Nervous system disorders	**8**	**(0.6)**	**1**	**(0.1)**	**9**	**(0.6)**	**12**	**(0.7)**	**2**	**(0.3)**	**14**	**(0.8)**	**4**	**(0.2)**	**0**	**(0.0)**	**4**	**(0.2)**
Cerebral infarction	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.1)	2	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Cerebrovascular accident	1	(0.1)	0	(0.0)	1	(0.1)	3	(0.2)	0	(0.0)	3	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)
Encephalopathy	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)
Epilepsy	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hemiplegia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)
Ischaemic stroke	5	(0.3)	0	(0.0)	5	(0.3)	1	(0.1)	1	(0.1)	2	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Sciatic nerve palsy	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Sciatica	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.1)
Syncope	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.1)	0	(0.0)	2	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Transient ischaemic attack	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.1)	1	(0.1)	0	(0.0)	1	(0.1)

In addition to the above data, the sponsor also conducted a cardiovascular meta-analysis (CVMA) of adjudicated, confirmed CV events from the Phase II/III studies in the submission and from the CV outcome study (P004/1021) which is ongoing and not included in the dossier. Access to the CVMA data including Study P004/1021 data and results is governed by a Data Access Plan and limited to a small firewalled team as was agreed with US FDA and discussed with the CHMP before submission of the NDA/MAA.

On 26 February 2016, US FDA advised the sponsor to use interim information from the CVOT only to evaluate premarket CV-risk:

- US FDA also recommended that the general safety information from the CVOT or efficacy sub-studies embedded in the CVOT should not be analysed at the time of the CVMA, and should not be part of the regulatory submission.
- US FDA believes that widespread early interim unblinding of the CVOT would jeopardize the integrity of the data for the remaining portion of the trial, and potentially affect the reliability of the final CV-risk analysis.
- The US FDA strongly believes that the number of individuals (including those employed by the sponsor) with access to the interim analysis results and unblinded treatment allocation numbers for study subjects should be minimised.

For the above reasons, data from the CVMA were submitted only to the US FDA by a separate firewalled team in order to not jeopardize the ongoing CVOT trial by disclosure of the interim results from this study. In April 2016, the sponsor requested scientific advice from the EMA/SAWP/CHMP, informing them that there will be no safety data from the ongoing CVOT included in the registration dossier. The CHMP agreed that submission of unblinded interim

data from the CVOT could give rise to concerns over trial integrity, and therefore, CHMP did not require that the CVMA (which includes the interim data from the ongoing CVOT) be submitted. CHMP agreed to evaluate the overall data package of nonclinical and clinical data for a conclusion on CV safety, considering also the scientific knowledge and clinical experience on the whole substance class, and how similar the mechanism of action and receptor specificity are relative to other SGLT2 inhibitors.

Over 8,000 subjects have been randomised in the CVOT (P004/1021). Per clinicaltrials.gov, the completion date for this study is anticipated to be October 2019. This event-driven study is being conducted in T2DM subjects with established vascular disease. By design, at completion, this study is expected to accrue >714 subjects with a MACE event and > 300 subjects with CV death. The ertugliflozin DMC has reviewed the CVMA and reviews safety data, including CV safety data, on an ongoing basis. They have provided an attestation that the Stage 1 CV risk assessment criterion has been met. The goal of this pre-specified Stage 1 meta-analysis was to rule out an 80% increase in CV risk based on the time to first occurrence of MACE+ (composite endpoint of confirmed CV death, nonfatal MI, nonfatal stroke, or unstable angina requirement hospitalization). The DMC meets twice per year (approximately every 6 months) and as of the last DMC meeting in July 2017 has not recommended any changes to the conduct of the CVOT. The sponsor believes that the data provided in the original submission, including the DMC attestation letter, provided adequate information on CV safety to support the initial registration of ertugliflozin. For additional information on CV safety, the sponsor commits to provide the results of the CV outcome study (Study P004/1021) upon completion. A final CSR is expected in fourth quarter 2020; however, as this is an event-driven study, this is an estimated timeframe. The updated safety information including mortality data through the 4-month SUR continue to support the overall safety profile of ertugliflozin.

Evaluator's comments

The CV safety data included in the submission and the 4 month SUR were based on preferred terms from investigator AE reporting and do not reflect the results of adjudication which remain firewalled. The SUR provides a substantial increase in long-term exposure relative to the original submission (approximately 2 times the number of subjects with ≥ 76 weeks to 102 weeks exposure, and approximately 5 times the number of subjects with ≥ 102 weeks exposure), and summarises complete or nearly complete cumulative Phase A+B data for 4 of the 6 studies with Phase A+B designs. A CV outcome study P004/1021 is ongoing (Final CSR expected in 2020) and the sponsor has committed to provide the results of this study upon completion. Overall, the sponsor's response is satisfactory.

6. Second round benefit-risk assessment

6.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of ertugliflozin in the proposed usage are unchanged from those identified in the first round evaluation.

6.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of ertugliflozin in the proposed usage are:

Table 121: Second round assessment of risks

Risks	Strengths and Uncertainties
Incidence of deaths was low, but numerically higher in ertugliflozin groups.	Deaths occurred in 10 (0.6%), 8 (0.5%) and 3 (0.2%) of subjects in ertugliflozin 5 mg, 15 mg and non-ertugliflozin groups, respectively; majority of fatal events were related to CV deaths.
The CV safety data (from 7 Phase III studies in nearly 5,000 subjects) included in the original submission and the 4-month SUR (provided in the S31 response) were based on preferred terms from investigator AE reporting and do not reflect the results of adjudication which remain firewalled.	The sponsor also conducted a cardiovascular meta-analysis (CVMA) of adjudicated, confirmed CV events from the Phase II/3 studies in the submission and from the CV outcome study (P004/1021) which is ongoing and not included in the dossier. Access to the CVMA data including Study P004/1021 data and results is governed by a Data Access Plan and limited to a small firewalled team as was agreed with US FDA and discussed with the CHMP before submission of the NDA/MAA.
Increased risk of lower limb amputations; of the 10 reported amputations in the Broad pool with highest incidence in the ertugliflozin 15 mg group; 8 subjects in the ertugliflozin 15 mg group and 1 subject each in the ertugliflozin and non-ertugliflozin groups. This is especially important in light of current findings of increased risk of lower limb amputations associated with another SGLT2 inhibitor-canagliflozin.	12 subjects with non-traumatic limb amputation and peripheral revascularisation reported in the Broad pool; all 12 subjects had baseline risk factors for amputation (for example, peripheral neuropathy, peripheral artery disease) or peripheral revascularisation (for example, hypertension and hyperlipidaemia).
Reduction in eGFR observed following ertugliflozin treatment with greater reduction in patients with moderate renal impairment. Incidence of renal-related AEs also higher.	
The incidence of volume depletion events was numerically higher in both ertugliflozin groups relative to the non-ertugliflozin group especially among subjects aged > 65 years, with renal impairment and those on diuretics.	Incidence of volume depletion AEs in subgroup of subjects aged > 65 years was 2.2%, 2.6% and 1.1% in the ertugliflozin 5 mg, 15 mg and non-ertugliflozin groups, respectively.
The incidence of genital mycotic infections was higher in the ertugliflozin groups than in the non-ertugliflozin groups in both men and women. In female subjects, there was a modest dose-relationship.	Incidence of complicated infections was low (< 1%) but still higher in the ertugliflozin groups.
Lack of evaluation of efficacy/ safety of ertugliflozin in combination with insulin, SUs and GLP-1 analogues.	
None of the Phase II dose ranging studies evaluated the proposed 15 mg dose of	Data from the 2 Phase II dose-ranging studies was used for the model-based analysis which suggested that a 15 mg dose would provide

Risks	Strengths and Uncertainties
ertugliflozin.	additional HbA1c lowering relative to 5 mg, and that no further efficacy was to be expected from the 25 mg dose.
Lack of evidence to support long term maintenance of efficacy of ertugliflozin beyond 26 weeks with exception of one study (P002/1013) comparing ertugliflozin with glimepiride in patients with inadequate glycaemic control on metformin monotherapy which provided data up to 52 weeks	Phase B of most of the studies (except the initial combination therapy study (P017/1047)with ertugliflozin+sitalgliptin) should provide data on long term efficacy and these results should be made available for evaluation in order to confirm long term maintenance of efficacy in proposed indication.

6.3. Second round assessment of benefit-risk balance

The benefit-risk balance of ertugliflozin (Steglatro), given the proposed usage is favourable.

All the clinical questions raised in the first round report have been addressed satisfactorily. Furthermore, all changes recommended by the evaluators to the draft PI in the first round report have been incorporated.

6.4. Second round recommendation regarding authorisation

Approval of ertugliflozin (Steglatro) is recommended for the following indication:

Steglatro (ertugliflozin) is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus as:

- *Monotherapy when metformin is considered inappropriate due to intolerance.*
- *or in combination with other antihyperglycaemic drugs (see Clinical Trials and Precautions for available data on different add-on combination therapies).*

Approval for the above indication is subject to the following:

- Results from the ongoing Phase B of all 7 Phase III studies should be submitted to enable assessment of long-term efficacy and safety of ertugliflozin.
- Submission of results of the cardiovascular meta-analysis (CVMA) of adjudicated, confirmed CV events from the Phase II/3 studies and from the ongoing CV outcome study (P004/1021) upon completion.

7. References

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