Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 4

Extract from the Clinical Evaluation Report for Ertugliflozin/ metformin

Proprietary Product Name: Segluromet

Sponsor: Merck Sharpe and Dohme (Australia) Pty Ltd

Date of first round report: 19 October 2017

Date of second round report: 18 January 2018

TGA Health Safety Regulation

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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

1. Submission details ____ 12
1.1. Identifying information ____ 12
1.2. Submission Type ____ 12
1.3. Drug class and therapeutic indication ____ 12
1.4. Dosage forms and strengths ____ 12
1.5. Dosage and administration ____ 12
2. Background ____ 13
2.1. Information on the condition being treated ____ 13
2.2. Current treatment options ____ 14
2.3. Clinical rationale ____ 14
2.4. Formulation development ____ 15
2.5. Related submissions ____ 15
2.6. Guidance ____ 16
2.7. Evaluator's commentary on the background information ____ 16
3. Contents of the clinical dossier ____ 16
3.1. Scope of the clinical dossier ____ 16
3.2. Paediatric data ____ 17
3.3. Good clinical practice ____ 17
3.4. Evaluator's commentary on the clinical dossier ____ 17
4. Pharmacokinetics ____ 17
4.1. Studies providing pharmacokinetic information ____ 17
4.2. Summary of pharmacokinetics ____ 18
4.3. Evaluator's overall conclusions on pharmacokinetics ____ 23
5. Pharmacodynamics ____ 24
5.1. Studies providing pharmacodynamic information ____ 24
5.2. Summary of pharmacodynamics ____ 24
5.3. Pharmacodynamic effects ____ 25
5.4. Evaluator's overall conclusions on pharmacodynamics ____ 26
6. Dosage selection for the pivotal studies ____ 26
6.1. Pharmacokinetic and pharmacodynamic dose finding studies ____ 26
6.2. Phase II dose finding studies ____ 26
6.3. Phase III pivotal studies investigating more than one dose regimen ____ 27
6.4. Evaluator's conclusions on dose finding for the pivotal studies ____ 27
7. Clinical efficacy ____ 27

7.1. Studies providing evaluable efficacy data 27
7.2. Pivotal or main efficacy studies 28
7.3. Other efficacy studies 35
7.4. Analyses performed across trials: pooled and meta-analyses 35
7.5. Evaluator's conclusions on clinical efficacy 38
8. Clinical safety 40
8.1. Studies providing evaluable safety data 40
8.2. Patient exposure 41
8.3. Adverse events 42
8.4. Evaluation of issues with possible regulatory impact 49
8.5. Other safety issues 62
8.6. Post marketing experience 63
8.7. Evaluator's overall conclusions on clinical safety 63
8.8. First round benefit-risk assessment 65
8.9. First round assessment of risks 65
8.10. First round recommendation regarding authorisation 67
9. Clinical questions 68
9.1. Pharmacokinetics 68
9.2. Pharmacodynamics 68
9.3. Efficacy 68
9.4. Safety 68
10. Second round evaluation 69
10.1. Clinical Questions 69
10.2. Second round benefit-risk assessment 70
10.3. Second round recommendation regarding authorisation 70

Abbreviation	Meaning
^{14}C-Total	Total amount of ^{14}C radioactivity recovered in urine
25-OH	25-hydroxy
A1c	Glycosylated haemoglobin (haemoglobin A1c)
AACE	American Association of Clinical Endocrinologists
ADA	American Diabetes Association
ADME	Absorption, distribution, metabolism and elimination
AE	Adverse event
Ae72%	Percent of dose recovered unchanged in urine from 0 to 72 hours post-dose
Ae96%	Percent of dose recovered unchanged in urine from 0 to 96 hours post-dose
AHA	Anti-hyperglycaemic agent
ALAG1	Absorption lag time
ALP	Alkaline phosphate
ALT	Alanine aminotransferase
ALT (SGPT)	Alanine aminotransferase
ANOVA	Analysis of variance
AST (SGOT)	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{0-24}	Area under the concentration time curve during 24 hours
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 (C_{last})
AV	Atrioventricular
BA	Bioavailability

Abbreviation	Meaning
BE	Bioequivalence
BD	Twice daily
BMI	Body mass index
BP	Blood pressure
BSAP	Bone-specific alkaline phosphatase
CA	Canadian
Cav	Average concentration
CFB	Change from baseline
CI	Confidence interval
CKD	Chronic kidney disease
CL (IV)	CL; systemic clearance
CL/F (oral)	Apparent Clearance; CL/F
cLDA	Constrained Longitudinal Data Analysis
CLr	Renal Clearance
C_{max}	Maximum Observed Plasma Concentration
C_{max}(dn)	Dose normalised (to 1 mg) C_{max}
Cmin	Lowest concentration observed during the dosing interval
CMQ	Custom MedDRA Queries
CRU	Clinical research unit
CSR	Clinical study report
CT	Computed tomography
CTX1	C-terminal telopeptides of type-1 collagen
CV	Coefficient of variation
CV	Cardiovascular
CVOT	Cardiovascular outcome trial

Abbreviation	Meaning
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
DPM	Disintegrations per minute
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
E_{max}	Maximum effect
ER	Excluding rescue
ESRD	End stage renal disease
EU	European union
F	Bioavailability
F1	Relative bioavailability
Fa	Fraction of dose absorbed
FAS	Full analysis set
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FME	Full model estimation
FOCE-I	First order conditional estimation method with interaction
FPG	Fasting plasma glucose
GAD	Glutamic acid decarboxylase
GCP	Good Clinical Practice
GMR	Geometric mean ratio

Abbreviation	Meaning
h	Hour(s)
HbA1c	Haemoglobin A1c
HCTZ	Hydrochlorothiazide
HDL-C	High-density lipoprotein-cholesterol
HPLC-MS/MS	High-performance liquid chromatography tandem mass spectrometric
HCTZ	Hydrochlorothiazide
IPTH	Intact parathyroid hormone
IR	Immediate-release
IR	Including rescue
IV	Intravenous
ka	First-order absorption rate constant
LDA	Longitudinal data analysis
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein-cholesterol
LLOQ	Lower limit of quantitation
L-PGA	L-pyroglutamic acid
L-PGA	L-pyroglutamic acid
LS	Least-squares
MACE	Major adverse cardiovascular event
MAR	Missing at random
MBMA	Model-based meta-analysis
MCAR	Missing completely at random
MedDRA	Medical Dictionary for Regulatory activities
MMTT	Mixed meal tolerance test
MR	Modified-release

Abbreviation	Meaning
MRI	Magnetic resonance imaging
nCi	Nano Curie
NDA	New Drug Application
NONMEM	Non-linear mixed effects modelling
NTX-1	N-terminal telopeptide-1
OAD	Oral anti-diabetic
OC	Osteocalcin
P1NP	Procollagen type 1 amino-terminal propeptide
PD	Pharmacodynamics(s)
PDLC	Pre-defined limit of change
PK	Pharmacokinetic(s)
PND	Postnatal day
PO	Per os
popPK	Population pharmacokinetic
PPAS	Per protocol analysis set
PPG	Post-prandial glucose
Q/F	Apparent inter-compartmental clearance
QD	Once daily
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
QTcB	QT interval corrected using the Bazett formula
QTcF	QT interval corrected using the Fridericia formula
RAAS	Renin-angiotensin-aldosterone system
Rac	Observed accumulation ratio

Abbreviation	Meaning
RNA	Ribonucleic acid
RSE	Relative standard error
RTG	Renal threshold for glucose
SA	Specific activity
SAE	Serious adverse event
SBP	Systolic blood pressure
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	Standard deviation
SGLT1	Sodium-glucose co-transporter 1
SGLT2	Sodium glucose co-transporter 2
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA query
SOC	System organ class
SOP	Standard operating procedures
$t_{1/2}$	Terminal half-life
T2DM	Type 2 diabetes mellitus
TdP	Torsades de pointes
TEAE	Treatment-emergent adverse event
T_{max}	Time for C_{max}
TRAP5	Tartrate-resistant acid phosphatase isoform 5
UGE	Urinary glucose excretion
UGE_{0-24}	Cumulative urinary glucose excretion over 24 hours
UGT	Uridine 5'-diphospho-glucuronosyltransferase
UK	United Kingdom

Abbreviation	Meaning
UKPDS	United Kingdom Prospective Diabetes Study
ULN	Upper limit of normal
US	United States
Vc/F	Apparent central volume of distribution
Vp/F	Apparent peripheral volume of distribution
Vss	Steady-state volume of distribution
Vz/F (oral)	Vz/F: apparent volume of distribution following oral administration

1. Submission details

1.1. Identifying information

Submission number	PM-2017-001330-1-5
Sponsor	Merck Sharpe and Dohme (Australia) Pty Ltd.
Trade name	Segluromet
Active substance	Ertugliflozin/metformin FDC: 2.5/500 mg; 2.5/1000 mg; 7.5/500 mg; 7.5/1000 mg.

1.2. Submission Type

This is an application to register FDC tablets containing ertugliflozin and metformin tablets for the treatment of type 2 diabetes mellitus (T2DM).

1.3. Drug class and therapeutic indication

Ertugliflozin is a new chemical entity belonging to the class of oral, sodium-glucose co-transporter 2 (SGLT2) inhibitors. Metformin is a biguanide agent approved for use in the USA, EU, Australia and several other countries throughout the world as an adjunct to diet and exercise for the treatment of T2DM.

The proposed indication is:

> *MSD-ertugliflozin-metformin or Segluromet (ertugliflozin and metformin hydrochloride) is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM when treatment with both ertugliflozin and metformin is appropriate.*

1.4. Dosage forms and strengths

FDC tablets containing ertugliflozin/metformin in the following strengths: 2.5/500 mg; 2.5/1000 mg; 7.5/500 mg; 7.5/1000 mg.

1.5. Dosage and administration

The following information was provided in the 'dosage and administration' section of the proposed PI:

General

- *Individualize the starting dose of MSD-ertugliflozin-metformin (ertugliflozin and metformin hydrochloride) based on the patient's current regimen:*
  - *In patients on metformin, switch to MSD-ertugliflozin-metformin tablets containing 2.5 mg ertugliflozin, with a similar total daily dose of metformin.*
  - *In patients on ertugliflozin, switch to MSD-ertugliflozin-metformin tablets containing 500 mg metformin, with a similar total daily dose of ertugliflozin.*
  - *In patients already treated with ertugliflozin and metformin, switch to MSD ertugliflozin-metformin tablets containing the same total daily dose of ertugliflozin and a similar daily dose of metformin.*

- *Take MSD-ertugliflozin-metformin twice daily with meals, with gradual dose escalation for those initiating metformin to reduce the gastrointestinal side effects due to metformin*
- *In patients with volume depletion not previously treated with ertugliflozin, correcting this condition prior to initiation of MSD-ertugliflozin-metformin is recommended (see Precautions).*
- *Dosing may be adjusted based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 15 mg ertugliflozin and 2,000 mg metformin HCl.*

Renal Impairment

*Assess renal function prior to initiation of MSD-ertugliflozin-metformin and periodically thereafter (see Precautions). MSD-ertugliflozin-metformin is contraindicated in patients with an eGFR less than 60 mL/min/*1.73 m^2 *or a CrCl less than 60 mL/min (see Contraindications and Precautions).*

Hepatic Impairment

Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. MSD-ertugliflozin-metformin is not recommended in patients with hepatic impairment (see Precautions).

Paediatric Population

Safety and effectiveness of MSD-ertugliflozin-metformin in paediatric patients under 18 years of age have not been established.

Elderly

No dosage adjustment of MSD-ertugliflozin-metformin is recommended based on age. Elderly patients are more likely to have decreased renal function. Because renal function abnormalities can occur after initiating ertugliflozin, and metformin is known to be substantially excreted by the kidneys, care should be taken in dose selection in the elderly. It may be useful to assess renal function in these patients prior to initiating dosing and periodically thereafter (see Precautions).

2. Background

2.1. Information on the condition being treated

The increasing worldwide prevalence of T2DM, along with its microvascular and macrovascular complications, is a major health issue and poses an increasing burden to health care systems around the world. The worldwide prevalence of diabetes in adults is expected to increase from 8.8% in 2015 (approximately 415 million people) to an estimated 10.4% (642 million people) by 2040; this represents a 55% increase in the number of people with diabetes relative to 2015. There are 1.7 million Australians with diabetes (85% of these have T2DM). Type 2 diabetes is associated with reduced life expectancy, significant morbidity due to the specific diabetes related microvascular complications (retinopathy, nephropathy and neuropathy), and the increased risk of macrovascular complications (ischemic heart disease, stroke and peripheral vascular disease). The development of these complications impacts on quality of life.

Multiple pathophysiologic deficits contribute to hyperglycaemia in patients with T2DM. Insulin resistance in muscle and liver as well as beta-cell failure represent the core pathophysiologic defects in T2DM. Approximately 85% of patients with T2DM are obese or overweight, a key factor underlying the development and maintenance of insulin resistance. In addition to muscle and liver, the kidney also plays a key role in glucose homeostasis. Under normal physiologic conditions, the kidney reabsorbs all of the glucose from the glomerular filtrate, and returns it to

the blood. The SGLT2 protein, which is primarily expressed in the renal proximal tubules, is responsible for approximately 90% of the reabsorption of glucose filtered through the glomerulus. Filtered glucose is completely reabsorbed until the transporters reach their maximum capacity, which is called the transport maximum for glucose. The plasma glucose concentration at which this occurs is referred to as the renal threshold for glucose (RTG). Above this threshold, UGE increases in proportion to plasma glucose concentrations. In healthy subjects, the RTG is approximately 10 mmol/L. Patients with diabetes have an increase in the RTG compared with healthy subjects such that glucosuria generally does not occur until plasma glucose values reach approximately 13.5mmol/L. Studies have shown that SGLT2 inhibitors lower the RTG, resulting in increased UGE, which is responsible for many of the pharmacodynamic (PD) effects seen with this class of agents. While SGLT2 inhibitors lower the RTG, the new RTG set point is above the usual threshold for hypoglycaemia suggesting that hypoglycaemia is unlikely with this mechanism.

2.2. Current treatment options

Current guidelines from the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD) and Diabetes Australia recommend a stepwise and individualised treatment approach to T2DM. These guidelines recommend metformin as the optimal first-line anti-hyperglycaemic agent (AHA), unless the patient has contraindications to metformin. Subsequently, if the A1c target is not achieved after approximately 3 months, therapy should be augmented to a 2-drug combination followed by the addition of other AHAs approximately every 3 months if the A1c goal is not achieved.

A number of systematic reviews have examined the relationship between blood glucose control and long term complications in people with T2DM. These studies concluded that improved glycaemic control can reduce retinopathy, renal disease and neuropathy in T2DM. Long term data from the United Kingdom Prospective Diabetes Study (UKPDS; Stratton, 2000) also suggests that glycaemic control reduces the risk of macrovascular complications of T2DM. Although pharmacological intervention, either in the form of a single agent or in combination, may provide effective glycaemic control for some patients, many do not achieve their target A1c levels, and glycaemic control deteriorates over time. The SGLT2 inhibitors are a new class of agents for T2DM therapy that have been shown to improve glycaemic control, reduce body weight and lower blood pressure.

Agents of this class approved for use in Australia include empagliflozin (Jardiance, approved in April 2014), dapagliflozin (Forxiga in Oct, 2012) and canagliflozin (Invokana in Sept 2013). FDCs of empagliflozin with metformin (Jardiamet in July 2015) and dapagliflozin with metformin (Xigduo XR in July 2014) are also approved in Australia.

2.3. Clinical rationale

As the pathogenesis of T2DM involves multiple metabolic defects, combination therapy with AHA agents that have different mechanisms of action can achieve robust reductions in A1c enabling patients to reach treatment goals. A FDC therapy may also help to improve treatment adherence.

The ertugliflozin/metformin FDC combines two AHAs with complementary mechanisms of action to improve glycaemic control in patients with T2DM. Ertugliflozin is a highly selective SGLT2 inhibitor that increases urinary glucose excretion (UGE) via inhibition of renal tubular urinary glucose reabsorption. In subjects with T2DM, ertugliflozin lowers plasma glucose, achieves clinically significant reductions in glycosylated haemoglobin A1c (A1c); ertugliflozin also achieves clinically significant reductions in body weight and SBP. Metformin hydrochloride is an AHA that improves glucose tolerance in patients with T2DM by lowering both basal and

post-prandial plasma glucose (PPG). It is not chemically or pharmacologically related to any other class of oral AHA. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin is approved for use in the US, EU, Australia and other countries and has an established safety and tolerability profile.

Combination therapy with ertugliflozin and metformin could also be beneficial given the findings that glucosuria produced by SGLT2 is accompanied by an increase in endogenous glucose production, which is possibly the result of an increase in glucagon, while metformin improves glycaemic control (in part) by decreasing hepatic glucose production.

Observational studies demonstrate that treatment modification or intensification in patients with inadequate glycaemic control on monotherapy is frequently delayed (Khunti L, 2013; Fu Az, 2011). Furthermore, patients with very high A1c levels are also unlikely to attain A1c treatment goals with just a single agent. Current guidelines from the ADA and the EASD state that initial combination therapy with metformin and a second agent may allow some patients with baseline A1c levels well above target to more quickly achieve their A1c goal than sequentially adding on a second agent following metformin failure. The ADA/EASD guidelines state that a reasonable threshold for initial dual combination therapy with metformin and a second agent is for subjects with an A1c > 9%. Guidelines from the American Association of Clinical Endocrinologists (AACE) recommend initiation of dual anti-hyperglycaemic therapy in patients presenting with an A1c between 7.6% to 9.0%, because monotherapy is unlikely to result in the AACE goal attainment of an A1c < 6.5% (AACE guidelines, 2002).

2.4. Formulation development

Comment: For information regarding the Formula Development of the MSD-Ertugliflozin tablets please refer the CER for Submission PM-2017-01328-1-5 (available as Attachment 2).

Six strengths of film-coated, immediate-release (IR), FDC tablets containing ertugliflozin and metformin for twice daily dosing (BD) have been developed and proposed for commercialisation: ertugliflozin 2.5 mg/metformin 500 mg; ertugliflozin 7.5 mg/metformin 500 mg; ertugliflozin 2.5 mg/metformin 850 mg; ertugliflozin 7.5 mg/metformin 850 mg; ertugliflozin 2.5 mg/metformin 1000 mg; and ertugliflozin 7.5 mg/metformin 1000 mg. The proposed FDC commercial tablet formulations are identical to the ertugliflozin/metformin FDC tablets which were used in the BE studies.

For all 6 FDC strengths, dissolution studies indicated that > 85% of the active components were released in 15 minutes and therefore the FDC tablets are classified as very rapidly dissolving. In addition, there was no pH effect on the dissolution release rate and all strengths of ertugliflozin/metformin tablets had similar release profiles.

2.4.1. Excipients

Each film-coated tablet of MSD-ertugliflozin-metformin contains the following inactive ingredients: povidone, microcrystalline cellulose, crospovidone, sodium lauryl sulphate, and magnesium stearate.

The film coating contains: hypromellose, hydroxypropyl cellulose, titanium dioxide, iron oxide red, and carnauba wax.

2.5. Related submissions

Ertugliflozin and FDCs of ertugliflozin are being co-developed by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Merck), and Pfizer Inc, with Merck serving as the regulatory sponsor. Registration of ertugliflozin (Steglatro), ertugliflozin/sitagliptin FDC (Steglujan) and

ertugliflozin/metformin FDC (Segluromet) for the treatment of T2DM are being pursued concurrently.

2.6. Guidance

Relevant guidelines for this dossier include the Guideline on Clinical development of Fixed Combination Medicinal products (CHMP/EWP/240/95/2009) and Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CPMP/EWP/1080/2012). The clinical development program was compliant with these guidelines.

2.7. Evaluator's commentary on the background information

Evaluation of background information did not raise any concerns. The stated clinical rationale is valid and acceptable.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

3.1.1. Clinical Pharmacology

The current submission comprises seven previously unevaluated, Phase I PK studies, none of which include PD data. Four of the studies examine the BE between the various strengths of the FDC proposed for marketing and the corresponding free combination. In addition, a further 3 studies examined the effect of a high-fat/high-calorie breakfast on the PKs of the active components of the FDC tablets. No new popPK or modelling studies were undertaken as part of the present submission.

3.1.2. Efficacy/ Safety

Four pivotal Phase III studies for the proposed ertugliflozin-metformin FDC were:

1. Study P007/1017: A Phase III, randomised, double-blind, placebo controlled, 26 week multicentre study with a 78 week extension to evaluate the efficacy and safety of ertugliflozin in subjects with T2DM and inadequate glycaemic control on metformin monotherapy.
2. Study P002/1013: A Phase III, multicentre, randomised, double- blind, active-comparator-controlled clinical trial to study the safety and efficacy of the addition of ertugliflozin (MK-8835/PF-04971729) compared with the addition of glimepiride in subjects with T2DM who have inadequate glycaemic control on metformin.
3. Study P005/1019: A Phase III randomised, double-blind, multicentre study to evaluate the efficacy and safety of the combination of ertugliflozin (MK- 8835/PF-04971729) with sitagliptin compared with ertugliflozin alone and sitagliptin alone, in the treatment of subjects with T2DM with inadequate glycaemic control on metformin monotherapy.
4. Study P006/1015: Phase III, multicentre, randomised, double-blind, placebo-controlled, parallel- group clinical trial to evaluate the safety and efficacy of ertugliflozin (MK-8835/PF-04971729) in the treatment of subjects with T2DM who have inadequate glycaemic control on metformin and sitagliptin.

Three other supportive Phase III studies:

5. Study P003/1022: A Phase III, randomised, double-blind, placebo- controlled, 26 week multicentre study with a 26 week extension to evaluate the efficacy and safety of ertugliflozin monotherapy in the treatment of subjects with T2DM and inadequate glycaemic control despite diet and exercise.
6. Study P017/1047: A Phase III, randomised, double-blind, placebo- controlled, parallel-group, multicentre clinical trial to evaluate the efficacy and safety of the initial combination of ertugliflozin (MK-8835/PF-04971729) with sitagliptin in the treatment of subjects with T2DM with inadequate glycaemic control on diet and exercise.
7. Study P001/1016: A Phase III, multicentre, randomised, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of ertugliflozin (mk-8835/pf-04971729) in subjects with T2DM with Stage 3 chronic kidney disease who have inadequate glycaemic control on background anti hyperglycaemic therapy.

3.1.3. Phase II dose-finding Studies P042/1004 and P016/1006

Integrated summary of efficacy and safety; Phase I and II Safety analyses.

3.2. Paediatric data

There is no paediatric data in the current submission. Module 1 mentions that the sponsors have submitted a PIP (Paediatric investigation plan) in the EU and the date on which the sponsors are first required to submit a report of a study conducted as part of the PIP is September2026

3.3. Good clinical practice

Studies comprising the ertugliflozin clinical development program were conducted in accordance with Guidelines for Good Clinical Practice (GCP) and the Declaration of Helsinki.

3.4. Evaluator's commentary on the clinical dossier

The submission was well-presented.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic information

Table 1: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	Bioequivalence † Single dose	P027/1041	BE between ertugliflozin 7.5 mg/metformin 1000 mg FDC tablet and the free combination (US) under fasted conditions
		P046/1054	BE between ertugliflozin 7.5 mg/metformin 850 mg FDC tablet and the free combination (EU) under fasted conditions

PK topic	Subtopic	Study ID	*
		P047/1055	BE between ertugliflozin 7.5 mg/metformin 1000 mg FDC tablet and the free combination(EU) under fasted conditions
		P050/1058	BE between ertugliflozin 2.5 mg/metformin 500 mg FDC tablet and the free combination (US) under fasted conditions
	Food effect	P028/1049	Relative BA of ertugliflozin 7.5 mg/metformin 1000 mg FDC tablet under fasted and fed conditions
		P052/1060	BE of metformin component following administration of ertugliflozin 2.5 mg/metformin 500 mg FDC tablet or the free combination (CA) under fasted and fed conditions
		P053/1061	BE of metformin component following administration of ertugliflozin 7.5 mg/metformin 850 mg FDC tablet or the free combination (CA) under fasted and fed conditions

* Indicates the primary PK aim of the study. † Bioequivalence of different formulations.

4.2. Summary of pharmacokinetics

4.2.1. Analytic Methods

A validated, specific and sensitive high-performance liquid chromatography tandem mass spectrometric (HPLC-MS/MS) method was used to determine plasma metformin levels. The lower limit of quantitation (LLOQ) was 2.00 ng/mL and the linear range of the assay was 2.00 to 1000 ng/mL.

Plasma concentrations of ertugliflozin were determined using validated, sensitive and specific HPLC-MS/MS methods with a LLOQ of 0.50 ng/mL.

4.2.2. Pharmacokinetics in healthy subjects

Comment: As previously stated, a limited number of studies examined the PKs of the ertugliflozin/metformin FDC and these primarily related to the bioequivalence between the FDC tablets and corresponding free combinations of the matching dose strengths of the individual tablets. In addition, three studies examined the effect of a high fat/high-calorie breakfast on the PKs of the FDC tablet. Where no dedicated PK studies are available for the FDC tablets, the evaluator requests that the Delegate refers to the concurrent submission (for Steglatro), which describes the studies relating to ertugliflozin (see Attachment 2 for details).

4.2.2.1. Absorption

Sites and mechanism of absorption

Ertugliflozin/metformin film-coated FDC tablets are for oral administration. For the various strengths of the FDC proposed for marketing, median ertugliflozin T_{max} values (under fasted conditions) ranged from 1.00 to 1.50 h and for metformin component were approximately 2.00 h.

4.2.2.2. Bioavailability

Bioequivalence to relevant registered products

Study P027/1041 examined the BE of ertugliflozin 7.5 mg/metformin 1000 mg FDC tablet and the free combination following a single dose under fasted conditions in 32 healthy subjects. For this study, the metformin tablets used as part of the free combination were US sourced Glucophage (metformin hydrochloride) 1000 mg.

Under these conditions the geometric mean ratios (GMRs) and 90% confidence intervals (90% CIs) for the comparison of the FDC to the free combination for ertugliflozin AUC_{inf}, AUC_{last} and C_{max} were 99.64 % (97.04%, 102.30%), 100.05% (97.31%, 102.87%) and 103.50% (97.85%, 109.47%), respectively. Median ertugliflozin T_{max} values for the FDC and free combinations were 1.03 h and 1.00 h, respectively and the mean $t_{1/2}$ values were 11.00 h and 11.19 h, respectively.

For the metformin component, the GMRs (90%CIs) comparing the FDC/free for AUC_{inf}, AUC_{last}, and C_{max} were 97.14% (89.98%, 104.87%), 97.72% (91.31%, 104.58%), and 99.20% (92.06%, 106.90%), respectively. The median metformin T_{max} for the fixed-dose and free combinations were 2.01 h and 1.98 h, respectively, and the mean $t_{1/2}$ values were 16.20 h and 16.42 h, respectively.

The results therefore indicated that the FDC and free combinations were bioequivalent.as 90% CIs for the AUC_{inf}, AUC_{last} and C_{max} GMRs for both active components were contained within the (80%, 125%) acceptance limits.

Study P047/1055 examined the BE of ertugliflozin 7.5 mg/metformin 1000 mg FDC tablet and the free combination following a single dose under fasted conditions in 34 healthy subjects. For this study, the metformin tablets used as part of the free combination were EU-sourced Glucophage (metformin hydrochloride) 1000 mg.

Under these conditions the GMRs (90% CIs) for the comparison of the FDC to the free combination for ertugliflozin AUC_{inf}, AUC_{last} and C_{max} were 98.28% (95.72%, 100.91%), 98.36% (95.54%, 101.27%) and 98.99% (93.84%, 104.42%), respectively. Median ertugliflozin T_{max} values was 1.00 h for both treatments and the mean $t_{1/2}$ values for the FDC and free combinations were 10.40 h and 11.20 h, respectively.

For the metformin component, the GMRs (90%CIs) comparing the FDC/free for AUC_{inf}, AUC_{last}, and C_{max} were 103.76% (96.43%, 111.65%), 104.66% (97.67%, 112.14%) and 110.08% (100.31%, 120.79%), respectively. The median metformin T_{max} values were 3.00 h for both treatments and the mean $t_{1/2}$ values for the fixed-dose and free combinations were 14.4 h and 11.9 h, respectively.

The results therefore indicated that as 90% CIs for the AUC_{inf}, AUC_{last} and C_{max} GMRs for both active components were contained within the (80%, 125%) acceptance limits the FDC and free combinations were bioequivalent.

Study P050/1058 examined the BE of ertugliflozin 2.5 mg/metformin 500 mg FDC tablet and the free combination following a single dose under fasted conditions in 32 healthy subjects. For this study, the metformin tablets used as part of the free combination were US-sourced Glucophage (metformin hydrochloride) 500 mg.

Under these conditions the GMRs (90% CIs) for the comparison of the FDC to the free combination for ertugliflozin AUC_{inf}, AUC_{last} and C_{max} were 98.26% (96.62%, 99.94%), 98.62% (96.82%, 100.44%) and 100.22% (94.76%, 106.00%), respectively. Median ertugliflozin T_{max} values was 1.00 h for both treatments and the mean $t_{1/2}$ values for the FDC and free combinations were 7.12 h and 7.73 h, respectively.

For the metformin component, the GMRs (90%CIs) comparing the FDC/free for AUC_{inf}, AUC_{last}, and C_{max} were 103.24% (96.16%, 110.83%), 100.36% (93.28%, 107.98%) and 101.49% (93.83%, 109.76%), respectively. The median metformin T_{max} values for the fixed-dose and free combinations were 2.00 h and 1.98 h, respectively, and the mean $t_{1/2}$ values were 13.45 h and 14.08 h, respectively.

The results therefore indicated that the FDC and free combinations were bioequivalent as 90% CIs for the AUC_{inf}, AUC_{last} and C_{max} GMRs for both active components were contained within the (80%, 125%) acceptance limits.

Although not one of the dosage strengths proposed for marketing, Study P046/1054 examined the BE of ertugliflozin 7.5 mg/metformin 850 mg FDC tablet and the free combination following a single dose under fasted conditions in 34 healthy subjects. For this study, the metformin tablets used as part of the free combination were EU sourced Glucophage (metformin hydrochloride) 850 mg.

Under these conditions the GMRs (90% CIs) for the comparison of the FDC to the free combination for ertugliflozin AUC_{inf}, AUC_{last} and C_{max} were 100.67% (97.59%, 103.84%), 100.35% (97.38%, 103.42%) and 97.21% (92.98%, 101.64%), respectively. Median ertugliflozin T_{max} values for the FDC and free combinations were 1.50 h and 1.00 h, respectively and the mean $t_{1/2}$ values were 10.30 h and 10.50 h, respectively.

For the metformin component, the GMRs (90%CIs) comparing the FDC/free for AUC_{inf}, AUC_{last}, and C_{max} were 104.96% (99.83%, 110.36%), 102.37% (98.48%, 106.42%) and 98.30% (93.04%, 103.87%), respectively. The median metformin T_{max} for the fixed dose and free combinations were 2.0 h and 3.0 h, respectively, and the mean $t_{1/2}$ values were 15.8 h and 12.8 h, respectively.

The results therefore indicated that the FDC and free combinations were bioequivalent.as 90% CIs for the AUC_{inf}, AUC_{last} and C_{max} GMRs for both active components were contained within the (80%, 125%) acceptance limits.

4.2.2.3. Influence of food

Ertugliflozin/metformin

Study P028/1049 examined the relative bioavailability (BA) of ertugliflozin 7.5 mg/metformin 1000 mg FDC tablet under fasted conditions and following a standard high-fat, high-calorie breakfast in 14 healthy subjects.

When the FDC tablet was administered with a high-fat breakfast, ertugliflozin C_{max} was approximately 40% lower compared to when it was administered following an overnight fast and the median T_{max} was delayed from 1.5 h to 2.5 h. By contrast, ertugliflozin mean AUC_{inf}, AUC_{last} and $t_{1/2}$ values were similar under both conditions. The GMR (90% CIs) comparing fed relative to fasted conditions for ertugliflozin AUC_{inf}, AUC_{last} and C_{max} were 93.81% (90.09%, 97.69%), 93.75% (90.03%, 97.63%) and 59.41% (51.06%, 69.11%), respectively. The 90% CIs for AUC_{inf} and AUC_{last} were contained within the (80%, 125%) acceptance range for bioequivalence, indicating no meaningful effect of food on ertugliflozin AUC, whereas, ertugliflozin C_{max} was significantly lower; however, this decrease is unlikely to be clinically relevant.

For the metformin component of the FDC, metformin C_{max} was approximately 30% lower in the presence of food compared to when it was administered following an overnight fast and the median T_{max} was delayed from 2.25 h to 4.00 h. The GMRs (90%CIs) comparing metformin

AUC_{inf}, AUC_{last} and C_{max} under fed relative to fasted conditions were 92.82% (85.07%, 101.26%), 94.53% (86.97%, 102.76%) and 70.68% (63.62%, 78.51%), respectively. The 90% CIs for AUC_{inf} and AUC_{last} were contained within the (80%, 125%) acceptance range for bioequivalence, indicating no meaningful effect of food on metformin AUC, whereas, metformin C_{max} was significantly lower; however, this decrease is unlikely to be clinically relevant.

Metformin

Study P052/1060 examined the BE of the metformin component of the FDC and free combination following administration of ertugliflozin 2.5 mg/metformin 500 mg FDC tablet or the free combination under fasted conditions and following a high-fat/high calorie breakfast in 32 healthy subjects. For this study, the metformin tablets used as part of the free combination were Canadian (CA)-sourced Glucophage (metformin hydrochloride) 500 mg.

Under fasted conditions, the GMRs (90% CIs) for the comparison of the FDC to the free combination for metformin AUC_{inf}, AUC_{last} and C_{max} were 98.28% (87.50%, 110.38%), 106.80% (96.17%, 118.61%) and 108.27% (95.69%, 122.50%), respectively. Median metformin T_{max} values was 2.00 h under both conditions and the mean $t_{1/2}$ values for the FDC and free combinations were 14.21 h and 8.67 h, respectively.

Following a high-fat/high-calorie breakfast, the GMRs (90%CIs) comparing the FDC/free for metformin AUC_{inf}, AUC_{last}, and C_{max} were 100.07% (87.06%, 115.03%), 98.65% (92.79%, 104.87%) and 101.46% (97.54%, 105.52%), respectively. The median metformin T_{max} values for the fixed-dose and free combinations were 3.00 h and 4.00 h, respectively, and the mean $t_{1/2}$ values were 15.44 h and 13.06 h, respectively.

The results therefore indicated that the FDC and free combinations were bioequivalent either under the fed or the fasted state as 90% CIs for the AUC_{inf}, AUC_{last} and C_{max} GMRs for both active components were contained within the (80%, 125%) acceptance limits.

Comment: Although not one of the formal objectives and therefore not examined by the sponsor, it is interesting to note that in this study, unlike Study P028/1049, it would appear that the metformin AUC and C_{max} values for the FDC are not entirely bioequivalent in the fed and fasted states. For instance, the ratio of mean metformin AUC_{inf} and C_{max} values fed versus fasted were 0.76 fold and 0.59 fold, respectively. In addition, although the sponsor states the following 'Bioequivalence of the ertugliflozin component was not evaluated because ertugliflozin meets the requirements for a waiver; it is a Biopharmaceutics Classification System (BCS) Class I drug and there is no clinical drug-drug interaction between ertugliflozin and metformin (B1521032)', given that plasma samples were already available it seems a relatively easy matter to have included the ertugliflozin PK data, especially considering the effect that food has on ertugliflozin exposure.

Study P053/1061 examined the BE of the metformin component of the FDC and free combination following administration of ertugliflozin 7.5 mg/metformin 850 mg FDC tablet or the free combination under fasted conditions and following a high-fat/high calorie breakfast in 32 healthy subjects. For this study, the metformin tablets used as part of the free combination were Canadian (CA) sourced Glucophage (metformin hydrochloride) 850 mg.

Under fasted conditions, the GMRs (90% CIs) for the comparison of the FDC to the free combination for metformin AUC_{inf}, AUC_{last} and C_{max} were 98.66% (89.42%, 108.85%), 98.87% (91.88%, 106.40%) and 101.13% (90.58%, 112.92%), respectively. Median metformin T_{max} values was 2.0 h under both conditions and the mean $t_{1/2}$ values for the FDC and free combinations were 16.7 h and 16.5 h, respectively.

Following a high-fat/high-calorie breakfast, the GMRs (90%CIs) comparing the FDC/free for AUC_{inf}, AUC_{last}, and C_{max} were 99.09% (83.74%, 117.25%), 105.80% (95.99%, 116.62%) and 98.67% (91.50%, 106.40%), respectively. The median metformin T_{max} values for the fixed dose

and free combinations were 3.53 h and 2.52 h, respectively, and the mean $t_{1/2}$ values were 16.05 h and 22.03 h, respectively.

The results therefore indicated that the FDC and free combinations were bioequivalent either under the fed or the fasted state in terms of metformin exposure as 90% CIs for the AUC_{inf}, AUC_{last} and C_{max} GMRs for both active components were contained within the (80%, 125%) acceptance limits.

Comment: As described for Study P052/1060, it would appear that the metformin AUC and C_{max} values for the FDC are not entirely bioequivalent in the fed and fasted states. For instance, the ratio of mean metformin AUC_{inf} and C_{max} values fed versus fasted were 0.89 fold and 0.74 fold, respectively.

4.2.2.4. Distribution, Metabolism and Excretion

No dedicated studies examined the distribution, metabolism or excretion of the proposed FDC tablets. However, these PK parameters are well-established for metformin (please see the Australian PI for APO-Metformin for further details) and the results for ertugliflozin are discussed in the concurrent submission for Steglatro.

4.2.3. Intra and inter individual variability of pharmacokinetics

Following a single oral administration of the highest proposed dosage strength of the FDC tablet, containing metformin 1000 mg/ertugliflozin 7.5 mg, or co-administration of the corresponding free combination(US) under fasted conditions the inter-subject variability (geometric CV%) ranged from 27% to 28% for ertugliflozin AUC_{inf}, and ranged from 23% to 24% for ertugliflozin C_{max}. For the metformin component, the geometric CV% ranged from 24% to 26% for AUC_{inf}, and ranged from 25% to 29% for C_{max}.

4.2.4. Pharmacokinetics in the target population

No dedicated PK studies examined the PKs of the FDC in the target population. However, the PI for metformin lists a number of contraindications and states the following in regards to lactic acidosis:

> *Because of the danger of lactic acidosis, metformin should not be used in the presence of the following conditions: diminished renal function; cardiovascular disease (for example coronary insufficiency, myocardial infarction, and hypertension); conditions which may be associated with tissue hypoxia (for example gangrene, circulatory shock, acute significant blood loss); pulmonary embolism; severe hepatic dysfunction; pancreatitis; excessive alcohol intake; concomitant use of diuretics*.

4.2.5. Pharmacokinetics in special populations

No dedicated PK studies examined the PKs of the FDC in special populations. However, metformin is contraindicated in several populations including patients with hepatic or renal dysfunction due to the risk of lactic acidosis (please see the preceding section of this report for further details). For ertugliflozin, there is no clinical experience in patients with Child-Pugh Class C (severe) hepatic impairment and its use is contraindicated in patients with chronic kidney disease (CKD) Stage 4 or 5 (severely impaired renal function including patients receiving dialysis; eGFR < 30 mL/min/1.73 m^2 or creatinine clearance (CrCl) < 30 mL/min) or eGFR persistently < 45 mL/min/1.73m2 or CrCl persistently < 45 mL/min (CKD Stage 3B).

4.2.6. Population pharmacokinetics

No dedicated popPK analyses were undertaken for the FDC tablets.

4.2.7. Pharmacokinetic interactions

No dedicated PK studies examined drug-drug interactions between the FDC and other drugs; however, the interaction between ertugliflozin and metformin has been examined as part of

concurrent submission for Steglatro. In summary, Study P019/1032 examined the potential for a DDI between a single dose of 15 mg ertugliflozin and 1000 mg metformin in healthy volunteers. Co-administration had no effect on ertugliflozin exposure, as reflected by the GMRs (90% CIs) for co-administration versus ertugliflozin alone of 100.34% (97.43%, 103.34%) and 97.14% (88.77%, 106.30%) for AUC_{inf} and C_{max}, respectively (submission PM-2017-01328-1-5). Similarly for metformin, co-administration with ertugliflozin had little to no effect on metformin C_{max} and AUC values and the corresponding GMRs and 90%CIs fell entirely within in the equivalence bounds (submission PM-2017-01328-1-5).

4.2.8. Clinical implications of in vitro findings

No new in vitro data was provided, which examined the potential for drug-drug interactions between the FDC and other drugs or metabolic pathways.

4.3. Evaluator's overall conclusions on pharmacokinetics

- The current submission contains four previously unevaluated studies, which examine the BE between the various strengths of the FDC proposed for marketing and the corresponding free combinations. In addition, a further 3 new studies examined the effect of a high-fat/high-calorie breakfast on the PKs of the active components of the FDC tablets.
- In regards to the tablets containing a single active component, the PKs of metformin are well-established and the PKs of ertugliflozin are described in detail in the concurrent submission for Steglatro.
- Overall, the conduct of the previously unevaluated studies was satisfactory and was compliant with existing TGA guidelines, validated analytical methods were employed and the data analyses undertaken were appropriate.
- The proposed 7.5 mg/1000 mg ertugliflozin/metformin FDC tablet was bioequivalent with the free combinations, which contained commercially available metformin tablets sourced from either the US or EU. In addition, the 2.5 mg/500 mg FDC tablet was bioequivalent with the matching dose strength of the free combination, which contained US-sourced metformin tablets. Given that the sponsor has demonstrated that the lowest and the highest dose strength of the FDC tablets are bioequivalent with the matching dose strengths of the relevant free combination tablets and the dose-adjusted AUC for the doses examined meet the criterion of ± 25% as per the Guideline On The Investigation Of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr), it can be assumed that the other proposed strengths of the FDC tablets will be bioequivalent with the relevant free combinations.
- Compared to fasted conditions, a high-fat breakfast had no effect on ertugliflozin or metformin AUC_{inf} and AUC_{last} values following a single dose of the ertugliflozin 7.5 mg/metformin 1000 mg FDC tablet. By contrast, ertugliflozin and metformin C_{max} values were ~40% and 30% lower, respectively, however, these decreases in C_{max} are unlikely to be clinically relevant.
- Overall, the PK sections of the proposed PI accurately reflect the submitted data; however, a number of limitations in the provided dataset were identified:
  - Although metformin formulations from the US, EU and CA markets have been examined, none of the BE studies included any of the approved Australia metformin formulations.
  - No dedicated PK studies examined the PKs of the FDC combinations in either the target or special populations.
  - No DDI were undertaken using the proposed FDC.

- Pharmacokinetic interactions between the FDC and other commonly administered drugs in this patient population such as diuretics, warfarin, digoxin and so on was not evaluated.
- Studies examining the effect of food on ertugliflozin PKs have not been performed in two of the previously unevaluated food studies, when plasma samples were available and this should have been a routine and relatively easy task to undertake.

Comment: The limitations regarding DDI studies are also present in the concurrent submission for Steglatro.

Question for sponsor: Metformin is also available as an extended release tablet in Australia, which requires once daily dosing; can the sponsor please explain why this formulation of metformin was not explored by the sponsors for the FDC?

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic information

Comment: None of the previously unevaluated studies directly examined the PDs of the FDC tablets; however, the PDs of ertugliflozin as a single agent are described in the concurrent submission for Steglatro, whereas, the PDs of metformin are well established.

5.2. Summary of pharmacodynamics

5.2.1. Mechanism of action

5.2.1.1. Ertugliflozin

Ertugliflozin is an orally administered selective inhibitor of SGLT2 and it possesses a high selectivity for SGLT2 versus SGLT1 and other glucose transporters (GLUT1 4). By inhibiting SGLT2, ertugliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion (UGE), which lowers fasting plasma glucose (FPG) and haemoglobin A1c levels (HbA1c) in an insulin independent manner. Additionally, UGE results in caloric loss and an associated weight loss. Ertugliflozin also causes osmotic diuresis, which may result in a reduction of blood pressure.

5.2.1.2. Metformin

Metformin is an antihyperglycaemic agent which improves glucose tolerance in patients with T2DM, lowering both basal and postprandial plasma glucose, without stimulating insulin secretion. It may act via 3 mechanisms:

1. Reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis in muscle
2. Increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
3. Delay of intestinal glucose absorption.

Metformin hydrochloride stimulates intracellular glycogen synthesis by acting on glycogen synthase and increases the transport capacity of all types of membrane glucose transporters.

5.2.1.3. MSD-Ertugliflozin-Metformin

MSD-Ertugliflozin-Metformin is the fixed dose combination of the two active antihyperglycaemic agents, which are thought to have complementary mechanisms of action,

thereby improving glycaemic control in patients with type 2 diabetes over that possible with a single agent.

5.3. Pharmacodynamic effects

5.3.1. Primary pharmacodynamic effects

No dedicated studies examined the primary PD effects of the proposed FDC tablets. However, these effects are well-established for metformin and the results for ertugliflozin are discussed in the concurrent submission for Steglatro.

5.3.2. Secondary pharmacodynamic effects

No dedicated studies examined the secondary PD effects of the proposed FDC tablets. However, these effects are well-established for metformin and the results for ertugliflozin are discussed in the concurrent submission for Steglatro.

5.3.3. Time course of pharmacodynamic effects

No unevaluated studies examined the time course of PD effects for the proposed FDC tablets. However, these parameters are well-established for metformin and the results for ertugliflozin are discussed in the concurrent submission for Steglatro. However, in all of the Phase III studies in the concurrent submission, ertugliflozin was administered only once daily (QD), whereas, the proposed dosing regimen for the ertugliflozin metformin FDC is twice daily (BD).

In order to bridge the QD and BD dosing regimens a Phase I study (Study P035/1051, please see the concurrent submission for Steglatro) in healthy subjects was undertaken and demonstrated that the steady-state AUC_{0-24} and cumulative urinary glucose excretion over 24 hours (UGE_{0-24}) values were similar following QD and BD regimens at the same total daily ertugliflozin dose (2.5 mg BD versus 5 mg QD and 7.5 mg BD versus 15 mg QD). A second study, Study P040/1007 (please see the concurrent submission for Steglatro), was undertaken in subjects with T2DM to compare the effects of ertugliflozin on UGE_{0-24} and mean plasma glucose following administration of 1 mg or 2 mg BD (that is, total daily doses of 2 mg and 4 mg respectively) and QD doses of 2 mg or 4 mg. The results indicated that there was no marked difference in UGE_{0-24} across the 4 treatment arms studied, although UGE was numerically greater following the higher dose regimens (4 mg versus 2 mg total daily dose), whereas, the weighted mean plasma glucose over 24 h was similar for all treatment groups, and the mean values ranged from 169 mg/dL to 176 mg/dL. In addition, a model-based meta-analysis (MBMA), PMAR-EQDD-B152c-DP4-444 (please see the concurrent submission for Steglatro, available as Attachment 2), was undertaken in an attempt to predict the potential difference in steady-state A1c response following either BD or QD dosing in subjects with T2DM. For a typical patient with T2DM the predicted potential difference in A1c effect following BD and QD ertugliflozin was -0.025% for 2.5 mg BD versus 5 mg QD and -0.010% for 7.5 mg BD versus 15 mg QD. Moreover, the ratio of the predicted A1c effect was 1.043 for 2.5 mg BD versus 5 mg QD and was 1.016 for 7.5 mg BD versus 15 mg QD.

Overall, these results suggest that following matched total daily doses of ertugliflozin to subjects with T2DM administered either BD or QD, the effects on UGE_{0-24}, mean plasma glucose and A1c were similar.

5.3.4. Relationship between drug concentration and pharmacodynamic effects

No dedicated studies examined the relationship between drug concentration and PD effects for the proposed FDC tablets. However, these relationships are well-established for metformin and the results for ertugliflozin are discussed in the concurrent submission for Steglatro.

5.3.5. Genetic, gender and age related differences in pharmacodynamic response

No dedicated studies examined the PD effects of the proposed FDC tablets in special populations. However, these PD parameters are well-established for metformin and the results for ertugliflozin are discussed in the concurrent submission for Steglatro.

5.3.6. Pharmacodynamic interactions

No dedicated studies examined the PD interactions between the proposed FDC tablets and other drugs. However, these interactions are well-established for metformin and the results for ertugliflozin are discussed in the concurrent submission for Steglatro.

5.4. Evaluator's overall conclusions on pharmacodynamics

No studies have specifically examined the PDs of the FDC tablets. However, the results of the concurrent submission for Steglatro, indicate that following matched total daily doses of ertugliflozin alone to subjects with T2DM administered either BD or QD the effects on UGE_{0-24}, mean plasma glucose and A1c were similar.

6. Dosage selection for the pivotal studies

6.1. Pharmacokinetic and pharmacodynamic dose finding studies

The 500 mg, 850 mg, and 1000 mg tablet strengths of metformin are available and approved in different regions of the world. Therefore, a total of 6 dose strengths of the ertugliflozin/ metformin FDC (that is, 2.5 mg or 7.5 mg ertugliflozin, each in combination with metformin (500mg, 850 mg and 1000 mg), have been developed to support registration in various regions globally. However, the present submission only seeks registration of 4 dose strengths of ertugliflozin/ metformin FDC (2.5/500, 7.5/500, 2.5/1000 and 7.5/100 mg).

A food-effect study of the highest strength FDC tablet was also conducted, along with a 2-way pharmacokinetic (PK) drug-drug interaction (DDI) study between ertugliflozin and metformin.

The four Phase III studies supporting this FDC were conducted using ertugliflozin and metformin administered as separate tablets, and bridging to the FDC formulation is provided via bioequivalence (BE) studies comparing the FDC to co-administration of the individual components. The clinical studies were also supported by repeat dose toxicology studies performed with the co-administration of ertugliflozin and metformin. In addition, ertugliflozin was dosed once daily (QD) in all the Phase III studies. In order to bridge the QD dosing regimen of ertugliflozin administered in Phase III with the twice daily (bid) dosing regimen in the ertugliflozin/metformin FDC, a Phase I study (Study P035/1051) was conducted to demonstrate equivalence of steady state AUC_{0-24} and similarity in steady state PD (UGE_{0-24}) for ertugliflozin between the QD and BD regimens at the same total daily dose (2.5 mg BD versus 5 mg QD and 7.5 mg BD versus 15 mg qd). Further, a model based meta-analysis was conducted to link the PD endpoint (UGE_{0-24}) with the clinical endpoint (A1c) in T2DM patients.

6.2. Phase II dose finding studies

The doses of ertugliflozin evaluated in the Phase III clinical studies were 5 mg and 15 mg once daily (QD). Dose selection was based on dose-response modelling of efficacy endpoints (A1c, FPG, body weight) from Study P016/B1521006 (12 week Phase II dose-ranging study) as well as 24 hour UGE (mechanism biomarker) in T2DM subjects from Study P042/B1521004 (4 week Phase II dose ranging study) (refer to Steglatro report). However, the proposed 15 mg QD dose of ertugliflozin was not evaluated in both Phase II studies and the sponsors have been asked to

provide further clarification regarding choice of the 15 mg QD dose for the pivotal Phase III studies.

6.3. Phase III pivotal studies investigating more than one dose regimen

The Phase III studies of ertugliflozin in combination with metformin used ertugliflozin and metformin administered as separate tablets and not the FDC tablet. Moreover, the studies evaluated the addition of ertugliflozin QD to background metformin therapy. The metformin dosing used in Phase III was consistent with the approved doses. All 4 studies required that subjects were on a stable dose of background metformin > 1500 mg/day prior to initiating treatment with ertugliflozin.

6.4. Evaluator's conclusions on dose finding for the pivotal studies

The proposed doses of metformin used in the proposed ertugliflozin+metformin FDC are consistent with approved the metformin label. Clarification regarding choice of the 15 mg dose for ertugliflozin has been sought in the Steglatro report. The doses of ertugliflozin evaluated in the Phase III clinical studies were 5 mg and 15 mg once daily (QD), but the proposed dosing for the ertugliflozin+metformin FDC is twice daily. However, equivalence was demonstrated)) for ertugliflozin between the QD and BD regimens at the same total daily dose (2.5 mg BD versus 5 mg QD and 7.5 mg BD versus 15 mg QD) with regards to steady state PK (AUC_{0-24}) and PD (UGE_{0-24}) in the Phase I study P035/1051.

7. Clinical efficacy

7.1. Studies providing evaluable efficacy data

Four pivotal Phase III studies were submitted for the proposed ertugliflozin-metformin FDC.

1. Study P007/1017: A Phase III, Randomised, Double Blind, Placebo Controlled, 26-Week Multicentre Study with a 78 Week Extension to Evaluate the Efficacy and Safety of Ertugliflozin in Subjects with T2DM and Inadequate Glycaemic Control on Metformin Monotherapy (refer to the Steglatro evaluation report).
2. Study P005/1019: A Phase III, Randomised, Double Blind, Multicentre Study to Evaluate the Efficacy and Safety of the Combination of Ertugliflozin (MK- 8835/PF-04971729) with Sitagliptin Compared with Ertugliflozin Alone and Sitagliptin Alone, in the Treatment of Subjects with T2DM With Inadequate Glycaemic Control on Metformin Monotherapy (refer to the Steglatro evaluation report).
3. Study P002/1013: A Phase III, Multicentre, Randomised, Double Blind, Active Comparator-Controlled Clinical Trial to Study the Safety and Efficacy of the Addition of Ertugliflozin (MK-8835/PF-04971729) Compared With the Addition of Glimepiride in Subjects With T2DM Who Have Inadequate Glycaemic Control on Metformin (refer to the Steglatro evaluation report).
4. Study P006/1015: Phase III, Multicentre, Randomised, Double Blind, Placebo-Controlled, Parallel- Group Clinical Trial to Evaluate the Safety and Efficacy of Ertugliflozin (MK-8835/PF-04971729) in the Treatment of Subjects with T2DM Who Have Inadequate Glycaemic Control on Metformin and Sitagliptin (refer to the Steglatro evaluation report).

7.2. Pivotal or main efficacy studies

Comments: Study design, patient characteristics, efficacy endpoints, statistical methods, efficacy results and evaluator's comments on each individual study was discussed in the ertugliflozin report and will not be repeated here (see Attachment 2 for details). A brief summary of results across the 4 pivotal studies to support the ertugliflozin-metformin FDC is provided below.

Baseline demographic and disease characteristics: The mean age of the subjects across the four pivotal Phase III studies ranged from 55.1 to 59.1 years. Across the four studies, the proportion of subjects that were ≥ 65 years of age ranged from 15.6% to 29.9%. The majority of subjects in each study were White. The mean duration of diabetes ranged from 6.9 to 9.5 years. The mean weight of the subjects ranged from 84.9 to 88.7 kg and mean baseline BMI ranged from 30.8 to 31.9 kg/m2. Subjects with a broad range of baseline hyperglycaemia were included (mean baseline A1c ranged from 7.8% to 8.6%); Study P005/1019 had a higher mean baseline A1c compared with the other studies. Mean baseline FPG ranged from 8.9 to 10 mmol/L across the studies. Demographic and baseline characteristics were similar across the 2 studies included in the ertugliflozin/metformin pooled analysis (Studies P007/1017 and P006/1015). Overall, the demographics and baseline characteristics of the population in these studies accurately reflect the population of patients with T2DM likely to be treated with ertugliflozin and metformin combination therapy (Table 2).

Table 2: Baseline characteristics; study by study comparison. All subjects treated: ertugliflozin/metformin Studies

	P007/1017 Add-on to Metformin n (%)	P002/1013 Ertugliflozin vs. Glimepiride n (%)	P006/1015 Add-on to Metformin+Sitagliptin n (%)	P005/1019 Ertugliflozin+Sitagliptin factorial n (%)
Subjects in population	621	1325	462	1232
Baseline A1C (%)				
<8.0	304 (49.0)	847 (63.9)	249 (53.9)	363 (29.5)
8.0 to <9.0	194 (31.2)	431 (32.5)	134 (29.0)	458 (37.2)
>=9.0	115 (18.5)	46 (3.5)	76 (16.5)	390 (31.7)
Unknown [†]	8 (1.3)	1 (0.1)	3 (0.6)	21 (1.7)
Subjects with data	613	1324	459	1211
Mean	8.1	7.8	8.0	8.6
SD	0.9	0.6	0.9	1.0
Median	8.0	7.7	7.9	8.4
Range	5.7 to 11.3	5.8 to 10.9	5.7 to 11.1	5.1 to 12.3
Baseline A1C (mmol/mol)				
<63.94	304 (49.0)	847 (63.9)	249 (53.9)	363 (29.5)
63.94 to <74.86	194 (31.2)	431 (32.5)	134 (29.0)	458 (37.2)
>=74.86	115 (18.5)	46 (3.5)	76 (16.5)	390 (31.7)
Unknown [†]	8 (1.3)	1 (0.1)	3 (0.6)	21 (1.7)
Subjects with data	613	1324	459	1211
Mean	65.2	61.7	64.3	70.0
SD	9.9	6.6	9.6	11.0
Median	63.9	60.7	62.8	68.3
Range	38.8 to 100.0	39.9 to 95.6	38.8 to 97.8	32.2 to 110.9

Table 2 (continued): Baseline characteristics; study by study comparison. All subjects treated: ertugliflozin/metformin studies

	P007/1017 Add-on to Metformin n (%)	P002/1013 Ertugliflozin vs. Glimepiride n (%)	P006/1015 Add-on to Metformin+Sitagliptin n (%)	P005/1019 Ertugliflozin+Sitagliptin factorial n (%)
Baseline FPG (mg/dL)				
Subjects with data	602	1322	460	1224
Mean	168.4	161.0	169.7	180.4
SD	43.8	34.8	38.2	47.8
Median	159.0	156.0	165.0	173.5
Range	88.0 to 337.0	62.0 to 330.0	82.0 to 337.0	38.0 to 401.0
Baseline FPG (mmol/L)				
Subjects with data	602	1322	460	1224
Mean	9.3	8.9	9.4	10.0
SD	2.4	1.9	2.1	2.7
Median	8.8	8.7	9.2	9.6
Range	4.9 to 18.7	3.4 to 18.3	4.6 to 18.7	2.1 to 22.3
Baseline eGFR (mL/min/1.73m2)				
<30	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
30 to <45	1 (0.2)	4 (0.3)	0 (0.0)	2 (0.2)
45 to <60	23 (3.7)	50 (3.8)	8 (1.7)	25 (2.0)
60 to <90	290 (46.7)	713 (53.8)	257 (55.6)	588 (47.7)
>=90	307 (49.4)	557 (42.0)	197 (42.6)	616 (50.0)
Unknown [†]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Subjects with data	621	1325	462	1231
Mean	90.5	87.2	87.9	92.4
SD	19.3	18.5	16.9	20.0
Median	89.0	86.0	86.0	90.0
Range	42.0 to 178.0	28.0 to 162.0	51.0 to 145.0	35.0 to 196.0
Duration of Type 2 Diabetes Mellitus (years)				
<5	234 (37.7)	512 (38.6)	106 (22.9)	540 (43.8)
5 to <10	203 (32.7)	470 (35.5)	159 (34.4)	404 (32.8)
>=10	184 (29.6)	343 (25.9)	197 (42.6)	288 (23.4)
Subjects with data	621	1325	462	1232
Mean	8.0	7.5	9.5	6.9
SD	6.0	5.7	5.7	5.4
Median	6.8	6.3	8.8	5.7
Range	0.2 to 38.9	0.2 to 49.6	0.2 to 34.3	0.2 to 35.5
Diabetic Microvascular Complications[‡]				
Yes	124 (20.0)	264 (19.9)	116 (25.1)	213 (17.3)
No	497 (80.0)	1061 (80.1)	346 (74.9)	1019 (82.7)
AHA (alone or in combination) at Randomization[§]				
Currently on AHA therapy	621 (100.0)	1325 (100.0)	462 (100.0)	1232 (100.0)
Insulin	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Metformin	621 (100.0)	1325 (100.0)	461 (99.8)	1232 (100.0)
Sulfonylurea	2 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Thiazolidinediones	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
DPP4	1 (0.2)	1 (0.1)	460 (99.6)	0 (0.0)
Other AHA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Number of AHA therapies at Randomization				
1	618 (99.5)	1324 (99.9)	3 (0.6)	1230 (99.8)
2	3 (0.5)	1 (0.1)	459 (99.4)	2 (0.2)
3 or more	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 2 (continued): Baseline characteristics; study by study comparison. All subjects treated: ertugliflozin/metformin studies

	P007/1017 Add-on to Metformin n (%)	P002/1013 Ertugliflozin vs. Glimepiride n (%)	P006/1015 Add-on to Metformin+Sitagliptin n (%)	P005/1019 Ertugliflozin+Sitagliptin factorial n (%)
History of Hypertension				
Yes	441 (71.0)	965 (72.8)	339 (73.4)	760 (61.7)
No	180 (29.0)	360 (27.2)	123 (26.6)	472 (38.3)
Related Concomitant Medication				
Hypertensives	423 (68.1)	906 (68.4)	322 (69.7)	729 (59.2)
ACE/ARB	375 (60.4)	799 (60.3)	288 (62.3)	658 (53.4)
Dyslipidemia Medication	349 (56.2)	693 (52.3)	286 (61.9)	535 (43.4)
Statin	314 (50.6)	610 (46.0)	257 (55.6)	468 (38.0)
Diuretic	205 (33.0)	360 (27.2)	113 (24.5)	253 (20.5)
Loop Diuretic	12 (1.9)	28 (2.1)	13 (2.8)	14 (1.1)

BMI = Body Mass Index, SD = Standard Deviation.

† Not included in summary statistics.

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

§ 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.

7.2.1. Primary efficacy results

In each study, adding ertugliflozin 15 mg or 5 mg alone to the existing metformin therapy provided a clinically meaningful A1c reduction from baseline. Reductions from baseline in A1c for ertugliflozin treated subjects were larger in the studies with higher baseline A1cs. Across the studies, the reductions from baseline in A1c in the ertugliflozin arms ranged from 0.56% to 1.08%. Ertugliflozin 15 mg was non-inferior to glimepiride (Study P002/1013), but non-inferiority of the 5 mg dose was not established. In Study P005/1019 in patients on background metformin therapy, ertugliflozin 5 mg and 15 mg provided reductions in A1c that were roughly similar to sitagliptin. In all 4 studies on a background of metformin, ertugliflozin 15 mg provided numerically greater A1c reductions compared to ertugliflozin 5 mg, although the differences between the 5 mg and 15 mg ertugliflozin doses were minor (Table 3).

Table 3: A1c (%); Change from baseline at primary time point by study. FAS: Excluding rescue approach; ertugliflozin/metformin studies

	N	Baseline Mean ± SD	LS Mean Change ± SE	LS Mean Difference (95% CI)	p-value
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
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
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‡

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.

Other efficacy results: Across the 4 studies with differing mean baseline A1c values, the proportions of ertugliflozin treated subjects with an A1c < 7.0% at week 26 ranged from 26.4% to 40% with numerically greater proportion of subjects achieving A1c < 7.0% with ertugliflozin 15 mg compared with 5 mg (in all 4 studies) (Table 4).

Table 4: Analysis of subjects with A1c < 7.0% at primary time point by study; FAS: Excluding rescue approach; ertugliflozin/metformin studies

	N	Number (%) of Subjects With A1C<7.0% (Raw Proportion)	Adjusted Odds Ratio[†]	
			Point Estimate	95% CI
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)
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)
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)[§]

[†]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.

Addition of ertugliflozin 15 mg or 5 mg to the existing metformin therapy consistently resulted in clinically meaningful reductions from baseline in FPG across all 4 studies (ranging from -1.0 to 2.2mmol/L) (Table 5). The reductions in FPG following ertugliflozin were roughly similar when used as second-line therapy (2.1 and 1.5mmol/L for ertugliflozin 15 mg and 5 mg, respectively) or as third line therapy (1.7 and 1.4mmol/L for ertugliflozin 15 mg and 5 mg, respectively in Study P006/1015). The reductions from baseline in FPG were numerically greater in the ertugliflozin 15 mg and 5 mg groups compared to the glimepiride group (Study P002/1013) and sitagliptin (Study P005/1019) (Table 5).

Table 5: Changes in FPG (mmol/L) in the 4 pivotal Phase III studies for Segluromet

Study P007/1017

	Baseline		Week 26		Change from Baseline at Week 26		
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)[†]
Placebo	202	9.39 (2.312)	158	8.83 (2.213)	209	-0.21 (2.419)	-0.05 (-0.33, 0.24)
Ertugliflozin 5 mg	199	9.33 (2.525)	194	7.71 (1.570)	207	-1.42 (2.330)	-1.53 (-1.80, -1.26)
Ertugliflozin 15 mg	201	9.32 (2.463)	186	7.18 (1.414)	205	-2.22 (2.133)	-2.17 (-2.44, -1.90)
Pairwise Comparison						Difference in LS Means (95% CI)[†]	p-Value
Ertugliflozin 5 mg vs. Placebo						-1.48 (-1.83, -1.14)	<0.001
Ertugliflozin 15 mg vs. Placebo						-2.12 (-2.47, -1.78)	<0.001
Conditional Pooled SD of Change from Baseline							1.67

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, prior antihyperglycemic medication (Metformin monotherapy or Metformin + another AHA), baseline eGFR (continuous), menopausal status randomization stratum (men, premenopausal women, women who are perimenopausal or <3 years postmenopausal, women who are >=3 years postmenopausal) and the interaction of time by treatment. Time was treated as a categorical variable.

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

Data cut date: 08MAR2016

PFIZER CONFIDENTIAL Source Data: ADEFF Date of Reporting Dataset Creation: 20MAY2016 Date of Table Creation: 25MAY2016 (1:12)

Table 5 (continued): Changes in FPG (mmol/L) in the 4 pivotal Phase III studies for Segluromet

Study P002/1013

	Baseline		Week 52		Change from Baseline at Week 52		
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)*
Ertugliflozin 5 mg	445	8.98 (1.899)	339	7.79 (1.629)	448	-1.16 (2.034)	-1.04 (-1.23, -0.85)
Ertugliflozin 15 mg	440	9.05 (2.013)	350	7.54 (1.701)	440	-1.40 (2.043)	-1.32 (-1.51, -1.14)
Glimepiride	437	8.77 (1.876)	351	7.88 (1.889)	437	-0.90 (2.242)	-0.90 (-1.08, -0.71)
Estimated Difference					Difference in LS Means (95% CI)*		p-Value
Ertugliflozin 5 mg vs. Glimepiride					-0.14 (-0.39, 0.10)		0.254
Ertugliflozin 15 mg vs. Glimepiride					-0.43 (-0.67, -0.18)		<0.001
Conditional Pooled SD of Change from Baseline							1.69

For baseline and Week 52, N is the number of subjects with non-missing assessments at the specific timepoint; for Change from Baseline at Week 52, 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, prior antihyperglycemic medication (monotherapy or dual therapy), 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.

Study P005/1014

	Baseline		Week 26		Change from Baseline at Week 26		
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)*
Ertugliflozin 5 mg	250	10.22 (2.899)	212	7.85 (1.628)	250	-2.02 (2.530)	-1.98 (-2.22, -1.74)
Ertugliflozin 15 mg	247	9.96 (2.537)	216	7.84 (1.869)	248	-1.97 (2.301)	-2.05 (-2.29, -1.81)
Sitagliptin 100 mg	246	9.85 (2.588)	205	8.31 (2.078)	247	-1.28 (2.394)	-1.42 (-1.66, -1.18)
Ertugliflozin 5 mg + Sitagliptin 100 mg	240	10.20 (2.458)	214	7.65 (1.803)	243	-2.57 (2.122)	-2.44 (-2.68, -2.20)
Ertugliflozin 15 mg + Sitagliptin 100 mg	241	9.83 (2.741)	217	7.23 (1.642)	244	-2.63 (2.556)	-2.70 (-2.94, -2.46)
Pairwise Comparison					Difference in LS Means (95% CI)*		p-Value
Ertugliflozin 5 mg + Sitagliptin 100 mg vs. Ertugliflozin 5 mg					-0.46 (-0.77, -0.15)		0.004
Ertugliflozin 5 mg + Sitagliptin 100 mg vs. Sitagliptin 100 mg					-1.02 (-1.33, -0.71)		<0.001
Ertugliflozin 15 mg + Sitagliptin 100 mg vs. Ertugliflozin 15 mg					-0.65 (-0.96, -0.35)		<0.001
Ertugliflozin 15 mg + Sitagliptin 100 mg vs. Sitagliptin 100 mg					-1.28 (-1.60, -0.97)		<0.001
Conditional Pooled SD of Change from Baseline							1.65

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, 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.

Study P006/1015

	Baseline		Week 26		Change from Baseline at Week 26		
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)*
Placebo	152	9.41 (2.099)	120	8.93 (2.038)	153	-0.04 (2.260)	-0.10 (-0.43, 0.23)
Ertugliflozin 5 mg	156	9.31 (2.093)	137	7.82 (1.754)	156	-1.44 (2.040)	-1.49 (-1.81, -1.18)
Ertugliflozin 15 mg	152	9.53 (2.168)	138	7.61 (1.632)	153	-1.94 (2.185)	-1.83 (-2.15, -1.52)
Pairwise Comparison					Difference in LS Means (95% CI)*		p-Value
Ertugliflozin 5 mg vs. Placebo					-1.40 (-1.82, -0.97)		<0.001
Ertugliflozin 15 mg vs. Placebo					-1.74 (-2.16, -1.31)		<0.001
Conditional Pooled SD of Change from Baseline							1.75

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, prior antihyperglycemic medication (metformin + DPP-4 inhibitor /metformin + SU), 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.

Across all 4 studies, addition of ertugliflozin 15 mg or 5 mg to the existing metformin therapy resulted in a consistent reduction from baseline in body weight (-2.69 kg to -3.74 kg). Reductions in body weight with ertugliflozin were greater than glimepiride and sitagliptin (Table 6).

Across all 4 studies, adding ertugliflozin 15 mg or 5 mg alone to the existing metformin therapy resulted in a reduction from baseline in sitting SBP (ranged from 2.25 to 5.2 mmHg) with numerically greater reductions with ertugliflozin 15 mg compared to 5 mg (Table 7).

The proportion of subjects receiving glycaemic rescue therapy in all ertugliflozin groups (either alone or co-administered with sitagliptin 100 mg) was low across all 4 studies (ranging from 0% to 6.4%) (Table 8).

Table 6: Body weight (kg); Change from Baseline at primary time point by study. FAS: Excluding rescue approach; ertugliflozin/metformin studies

	N	Baseline Mean ± SD	LS Mean Change ± SE	LS Mean Difference (95% CI)	p-value
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
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
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†

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 7: Sitting systolic BP (mmHg): Change from Baseline at primary time point by study. FAS: Excluding rescue approach; ertugliflozin/metformin studies

	N	Baseline Mean ± SD	LS Mean Change ± SE	LS Mean Difference (95% CI)	p-value
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§
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
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†

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 8: Analysis of time to glycaemic rescue at primary time point by study; All subjects treated, ertugliflozin/metformin studies

	N	Number (%) of Subjects Rescued	Time to Rescue (days)		p-value
			Minimum	Maximum	
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
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
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‡

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.

7.3. Other efficacy studies

Three other supportive Phase III studies were also included in the submitted dossier: Ertugliflozin monotherapy Study P003/1022 (refer to Steglatro evaluation report); initial ertugliflozin+sitalgliptin combination therapy Study P017/1047 (refer to Steglatro evaluation report) and Study P001/1016 in T2DM patients with Stage 3 chronic kidney disease (refer to Steglatro evaluation report, available as Attachment 2). Two Phase II studies evaluating dose-response of ertugliflozin were also evaluated in the Steglatro report.

7.4. Analyses performed across trials: pooled and meta-analyses

The ertugliflozin/metformin pool includes 2 placebo controlled studies of similar design and the same duration (P007/1017 and P006/1015). The 2 active controlled studies (P005/1019 and P002/1013) were excluded from the pooled data set because they lacked a placebo control group. Three efficacy endpoints were analysed in the pooled analysis: Change from baseline to week 26 in A1c, body weight and in proportion of subjects with A1c < 7%. To avoid the confounding effect of glycaemic rescue on efficacy comparisons, the primary approach to efficacy analyses treated data collected after the initiation of glycaemic rescue therapy as missing; these analyses are referred to as 'excluding rescue' (ER) to denote that data obtained after initiation of rescue therapy or after bariatric surgery were excluded. This approach was applied both in the individual studies and in the pooled analysis. In the pooled group (of the 2 placebo-controlled studies), mean age of the subjects was 57.7 years, 50.9% were male, the mean baseline BMI was 30.8 kg/m2, 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 A1c was 8.1%. The mean

baseline eGFR was 89.4 mL/min/1.73 m^2. The majority of subjects had mild renal impairment (eGFR > 60 to < 90 mL/min/1.73 m^2). A small proportion of subjects in the pool had a baseline eGFR > 45 to < 60 mL/min/1.73 m^2 (2.9%). Subject demographic and baseline characteristics were well balanced across the placebo, ertugliflozin 5 mg and 15 mg treatment groups (Table 9).

Table 9: Baseline disease characteristics; All subjects treated, ertugliflozin/metformin FDC Pool

	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/1.73m^2)										
<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

The mean metformin dose at randomisation was 1985.2 mg/day and 2017.9 mg/day in the ertugliflozin and placebo groups, respectively. The median metformin dose at randomisation was 2000 mg/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 (Table 10).

Table 10: Summary of metformin dose at randomisation; All subjects treated, ertugliflozin/metformin FDC pool

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	362		363		358		721	
Dose of Metformin (mg/day) at Randomization								
Subjects with data	361		362		358		720	
Mean	2017.9		1972.3		1998.2		1985.2	
SD	389.4		387.9		400.9		394.4	
Median	2000.0		2000.0		2000.0		2000.0	
Range	500 to 3000		1000 to 3000		850 to 3400		850 to 3400	
Distribution of Dose of Metformin (mg/day) at Randomization								
<1500	2	(0.6)	2	(0.6)	2	(0.6)	4	(0.6)
1500	38	(10.5)	51	(14.0)	55	(15.4)	106	(14.7)
>1500 to <2000	64	(17.7)	78	(21.5)	64	(17.9)	142	(19.7)
2000	187	(51.7)	174	(47.9)	163	(45.5)	337	(46.7)
>2000 to <3000	46	(12.7)	35	(9.6)	59	(16.5)	94	(13.0)
3000	24	(6.6)	22	(6.1)	13	(3.6)	35	(4.9)
>3000	0	(0.0)	0	(0.0)	2	(0.6)	2	(0.3)
Unknown	1	(0.3)	1	(0.3)	0	(0.0)	1	(0.1)

The LS mean reductions from baseline in A1c at Week 26 (excluding data after initiation of glycaemic rescue therapy) 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%, respectively) (Table 11).

Table 11: A1c (%); Change from Baseline at Week 2. 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 A1c 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 A1c reduction from baseline compared with ertugliflozin 5 mg across subgroup categories. The placebo-adjusted LS mean reduction from baseline in A1c was greater in subjects with a higher baseline A1c (> median (7.9) or > 9.0%) versus a lower baseline A1c (< median (7.9) or < 9.0%). The placebo-adjusted LS mean reduction from baseline in A1c was clinically meaningful across all age groups and numerically higher in younger subjects (< median (59) or < 65 years) than older subjects (> median (59) or > 65 years). Ertugliflozin demonstrated clinically meaningful A1c reductions from baseline in both male subjects and female subjects. The placebo-adjusted LS mean reduction from baseline in A1c was numerically greater in male subjects than in female subjects for both doses of ertugliflozin. The gender difference was driven by Study P006/1015. The difference cannot be explained by baseline A1c or renal function, which did not differ between male subjects and female subjects. The placebo adjusted LS mean reduction from baseline in A1c 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 3A CKD (eGFR > 45 to < 60 mL/min/1.73 m^2) Subjects with mild renal impairment had clinically meaningful reductions in A1c relative to placebo with both doses of ertugliflozin tested. No notable differences in placebo-adjusted responses were observed among the subgroups of race, ethnicity, geographic region, baseline BMI, and duration of T2DM.

The proportions of subjects meeting the A1c 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 A1c 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. No notable differences were observed among the subgroups of age, gender, race, region, baseline A1c, 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.

7.5. Evaluator's conclusions on clinical efficacy

Seven Phase III studies support the initial regulatory submission for ertugliflozin alone. Four of the 7 Phase III studies were submitted to support the ertugliflozin/metformin FDC submission, including 2 active-controlled studies (Studies P005/1019 and Study P002/1013) and 2 placebo controlled studies (Studies P006/1015 and P007/1017) that evaluated the safety and efficacy of ertugliflozin in combination with metformin in 3643 adult subjects with T2DM. Efficacy data were pooled for the 2 placebo-controlled studies to assess efficacy on a background of metformin (ertugliflozin/metformin FDC Pool).

No Phase III studies have been performed with the proposed ertugliflozin/metformin FDC tablet. The studied doses of the FDC tablets (ertugliflozin 7.5 mg/metformin 1000 mg, ertugliflozin 7.5 mg/metformin 850 mg and ertugliflozin 2.5 mg/metformin 500 mg) are bioequivalent under fasted conditions to the corresponding doses of ertugliflozin and metformin tablets (US or EU sourced Glucophage) when co-administered. The metformin component of the studied doses of the FDC tablets (ertugliflozin 7.5 mg/metformin 850 mg and ertugliflozin 2.5 mg/metformin 500 mg) is also bioequivalent to the corresponding doses of metformin tablets (Canadian sourced Glucophage) when co-administered with corresponding doses of ertugliflozin tablets under fasted and fed conditions. These clinical data, along with the in vitro multi-media dissolution data, support the bridging of pharmacokinetic, pharmacodynamic, efficacy and safety data obtained in the Phase III studies to the proposed FDC commercial tablets. Hence, data obtained from the 4 Phase III studies (Studies P006/1015, P007/1017, P002/1013 and P005/1019) that assessed the use of ertugliflozin on a background of metformin (≥ 1500 mg/day) can be bridged to the FDC tablet based on established bioequivalence.

The 4 pivotal Phase III studies included in this submission consisted of an initial 26 or 52 week treatment phase (referred to as Phase A). This key phase is completed for all of these Phase III studies, and is the focus of the efficacy results in this submission. To allow for long-term assessments of safety data, these 4 Phase III studies included a 26, 52 or 78 week, blinded (to site and subject), placebo or active controlled extension phase (Phase B). All Phase B extensions are either ongoing or have completed dosing without final analyses available at the time of this submission.

A total of 3643 subjects were randomised in the 4 Phase III studies in support of this submission, including 2597 who received ertugliflozin in combination with metformin.

Demographic and baseline characteristics were similar across the 2 studies included in the ertugliflozin/metformin FDC Pool (Studies P007/1017 and P006/1015) and was representative of the target patient population for the proposed ertugliflozin+metformin FDC (46-57% males, mean age of 55-59 years, mean BMI of 31 to 32kg/m^2), mean duration of diabetes of 7 to 9.5 years, mean baseline A1c of 7.8% to 8.6% and mean baseline eGFR of 87 to 92 mL/min/1.73m^2).

Ertugliflozin 15 mg and 5 mg as add-on to metformin (alone or in combination with sitagliptin) provides clinically meaningful improvements in glycaemic control (A1c; proportion with A1c < 7.0%, FPG, 2 hour PPG) as well as body weight reduction and SBP reduction in subjects with T2DM. Ertugliflozin 15 mg plus metformin provides non-inferior A1c reduction compared to glimepiride plus metformin.

Treatment with ertugliflozin 15 mg and 5 mg, compared with placebo, resulted in significant and clinically meaningful reductions from baseline in A1c and FPG at Week 26, as add-on therapy to metformin (Study P007/1017; add-on to metformin study), and as add-on therapy to metformin plus sitagliptin (Study P006/1015; add-on to metformin plus sitagliptin study). In both of these studies, treatment with ertugliflozin (both doses) added to metformin resulted in a higher proportion of subjects meeting the glycaemic goal of A1c < 7.0% (< 53 mmol/mol). In both the add-on to metformin study (Study P007/1017) and the add-on to metformin and sitagliptin study (Study P006/1015), treatment with both doses of ertugliflozin as add-on to metformin resulted in significant reductions from baseline in body weight and SBP at Week 26, compared with placebo. Significant reductions from baseline in diastolic blood pressure (DBP) were observed in Study P007/1017.

Efficacy of combination of ertugliflozin and metformin was also evaluated using pooled data from 2 placebo controlled studies: Studies P007/1017 (add-on to metformin study) and P006/1015 (add-on to metformin plus sitagliptin study). The reductions from baseline in A1c and body weight, and the proportions of subjects meeting the A1c goal of < 7.0% in the pool were greater in the ertugliflozin groups compared to the placebo group. In subgroup analyses of the pool, the addition of treatment with ertugliflozin 15 mg and 5 mg to metformin therapy resulted in a reduction from baseline in A1c and body weight compared with placebo across subgroups including age, gender, race, geographic region, baseline body mass index (BMI), and duration of T2DM.

7.5.1. Dose-response

Both ertugliflozin 15 mg and 5 mg have demonstrated clinical efficacy in the Phase III studies when dosed in combination with metformin. Although the studies were not powered or designed to detect between-dose differences, the A1c reductions from baseline were numerically greater for ertugliflozin 15 mg compared to 5 mg in all 4 studies and the pooled analysis. In the pooled analysis ertugliflozin 15 mg provided a numerically greater reduction in A1c (approximately 0.14%) compared to ertugliflozin 5 mg. A dose response model was used to support predictions of the efficacy of the 2 ertugliflozin doses for a typical patient on metformin background therapy. The predictions suggest that ertugliflozin 15 mg provides approximately 0.1% greater A1c reduction compared to ertugliflozin 5 mg.

In all four Phase III studies, a numerically greater proportion of subjects reached A1c < 7.0% with ertugliflozin 15 mg compared with 5 mg.

A numerically greater reduction from baseline in body weight with ertugliflozin 15 mg compared to ertugliflozin 5 mg was observed in 2 of the four Phase III studies, but was not observed in the pooled analysis.

A numerically greater reduction from baseline in SBP with ertugliflozin 15 mg compared to ertugliflozin 5 mg was observed in 3 of the 4 of the Phase III studies.

Persistence of efficacy and/or tolerance effects: The persistence of efficacy of metformin has been demonstrated in clinical practice as well as in the literature. For example, in the A Diabetes Outcome Progression Trial, although the glycaemic control with metformin monotherapy gradually deteriorated in the course of 5 years of observation, consistent with the natural progression of the disease, it was generally sustained in the first 2 or 3 years with treatment failure below 10%. Ertugliflozin used as add-on to metformin has been shown to deliver efficacy in A1c lowering over a period of 26 weeks; 3 different studies (Studies P007/1017, P005/1019, and P006/1015) demonstrated sustained clinically meaningful efficacy up to 26 weeks and 1 study (Study P002/1013) demonstrated non-inferiority for ertugliflozin 15 mg compared to SU add-on to metformin up to 52 weeks. Stable lowering of FPG was also observed over the same study periods.

7.5.2. Limitations

- The clinical efficacy of once daily versus twice daily dosing of ertugliflozin was not evaluated. Bridging data was provided by a Phase I study.
- Lack of adequate evidence to support long term efficacy (beyond 26 weeks) of co-administration of ertugliflozin+ metformin.
- Lack of adequate data to support use of ertugliflozin+metformin along with other antihyperglycaemic agents such as insulin, sulphonylureas, thiazolidiones and GLP-1 analogues. Only data available was with sitagliptin. This has not been adequately clarified by sponsors in the draft PI.

8. Clinical safety

8.1. Studies providing evaluable safety data

The 4 pivotal Phase III studies from the ertugliflozin development program which provided the main safety data for the proposed ertugliflozin-metformin FDC are summarised in Table 12.

Table 12: Phase III clinical studies supporting the ertugliflozin / metformin FDC

Protocol Number (Short Title)	Link to CSR	Short Description	Study Design	Treatments (Sample Size)	Background AHA Therapy	Key Elements of Subject Population
Studies included in the pooled dataset						
P006/1015 Add-on to Met and Sita Study	[Ref. 5.3.5.1: P006V01]	Safety and efficacy of the addition of ertugliflozin compared with the addition of placebo in subjects with T2DM on metformin and sitagliptin	Randomized, double-blind, placebo-controlled, parallel-group Phase A 26 weeks, Phase B 26 weeks	Ertu 5 mg (N=156) Ertu 15 mg (N=154[1]) Pbo (N=153)	Metformin and Sitagliptin	≥18 years A1C 7.0-10.5%, inclusive eGFR ≥60 mL/min/1.73 m^2
P007/1017 (Pbo-controlled Add-on to Met study)	[Ref. 5.3.5.1: P007V01]	Safety and efficacy of the addition of ertugliflozin compared with the addition of placebo in subjects with T2DM on metformin	Randomized, double-blind, placebo-controlled, parallel group Phase A 26 weeks, Phase B 78 weeks	Ertu 5 mg (N=207) Ertu 15 mg (N=205) Pbo (N=209)	Metformin	≥18 years A1C 7.0%-10.5%, inclusive eGFR ≥55 mL/min/1.73 m^2 Approximately 41% randomized were post-menopausal (≥3 years) women
Studies not included in the pooled dataset						
P002/1013 (Ertu vs Glim as Add-on to Met Study)	[Ref. 5.3.5.1: P002V01]	Safety and efficacy of the addition of ertugliflozin compared with the addition of glimepiride in subjects with T2DM on metformin	Randomized, double-blind, active-comparator-controlled, parallel-group Phase A 52 weeks, Phase B 52 weeks	Ertu 5 mg (N=448) Ertu 15 mg (N=441[1]) Glim (up to 6 or 8 mg)[2] (N=437)	Metformin	≥18 years A1C 7.0% -9.0%, inclusive eGFR ≥55 mL/min/1.73 m^2)
P005/1019 (Ertu+Sita Factorial Study)	[Ref. 5.3.5.1: P005V01]	Safety and efficacy of the addition of ertugliflozin and sitagliptin co-administered compared with the addition of ertugliflozin alone and sitagliptin alone, in subjects with T2DM on metformin	Randomized double-blind, parallel-group, factorial Phase A 26 weeks, Phase B 26 weeks	Ertu 5 mg + Sita 100 mg (N=243) Ertu 15 mg + Sita 100 mg (N=245[1]) Ertu 5 mg (N=250) Ertu 15 mg (N=248) Sita 100 mg (N=247)	Metformin	≥18 years A1C 7.5% - 11%, inclusive eGFR ≥60 mL/min/1.73 m^2

[1] One subject in the treatment group was randomized but never received study medication.
[2] The maximum dose of glimepiride (6 mg or 8 mg daily) was subject to the local country label.
A1C = glycosylated hemoglobin A_{1c}; eGFR = estimated glomerular filtration rate; ertu = ertugliflozin; glim = glimepiride; met = metformin; pbo = placebo; sita = sitagliptin; T2DM = type 2 diabetes mellitus

For all of the Phase III studies, for the purposes of the pooled analyses, 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), centrally-read 12-lead ECGs, and self-monitored blood glucose. For the ertugliflozin/metformin Pool, the most recent version of MedDRA (Version 19.0) was used to build the hierarchical structure of AE encoding. As a result of periodic MedDRA updates, the AE encoding in the ertugliflozin/metformin Pool was different from the adverse event encoding used in the Phase III CSRs. For the individual studies, Version 18.1 of MedDRA was used for AE term encoding, which was current at the time of database lock for data included in this submission. The analysis strategy for safety parameters in the ertugliflozin/metformin Pool are summarised in Table 13.

Table 13: Analysis strategy for safety parameters in the ertugliflozin / metformin pool

Tier	Safety Endpoint	p-Value	95% CI for Between-group Difference	Descriptive Statistics
Tier 1[†]	Urinary tract infection	X	X	X
	Genital mycotic infection (gender specific)	X	X	X
	Volume depletion[‡]	X	X	X
	Symptomatic hypoglycemia[§]	X	X	X
Tier 2	Adverse event summary measures		X	X
	AEs by SOC, Specific AEs, and PDLCs		X	X
	Hypoglycemia categories		X	X
	Percent change from baseline at Week 26 in lipids		X	X
	Change from baseline at Week 26 in eGFR, serum creatinine		X	X
Tier 3	AEs by SOC, specific AEs, and PDLCs that do not qualify for Tier 1 or Tier 2			X
	Change from baseline results (labs, ECGs, vital signs not in Tier 2)			X

Adverse Events refer to both Clinical and Laboratory AEs; X = results will be provided.
[†]Urinary tract infection, genial mycotic infection, and volume depletion were defined by CMQs. The specific terms included in these definitions are provided in Appendix 2.
[‡]Referred to in the CSRs as hypovolemia.
[§]All symptomatic hypoglycemia episodes were classified by the investigator as adverse events and, thus, any episodes that were not classified as AEs were asymptomatic episodes.
AE= adverse event; CI = confidence interval; CMQ = custom MedDRA query; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; Ertu/Met Pool = ertugliflozin/metformin pool; PDLC=Pre-Defined Limit of Change; SOC=System Organ Class,

Comment: No Phase III studies have been performed with the proposed ertugliflozin/metformin FDC tablet; however, data obtained from the 4 Phase III studies (Studies P006/1015, P007/1017, P002/1013 and P005/1019), that assessed the use of ertugliflozin on a background of metformin (≥ 1500 mg/day) can be bridged to the FDC tablet based on established bioequivalence. Two of the studies (Studies P006/1015 and P007/1017) were placebo-controlled and had a common study design that allowed the data to be pooled (ertugliflozin/metformin Pool) for review of safety.

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

None.

8.1.2. Pivotal and/or main efficacy studies

The 4 pivotal Phase III studies from the ertugliflozin development program which provided the main safety data for the proposed ertugliflozin-metformin FDC are summarised in Table 12.

8.1.3. Studies that assessed safety as the sole primary outcome

None.

8.2. Patient exposure

The ertugliflozin/metformin Pool includes 1083 subjects who were randomised and received at least 1 dose of study medication; 363, 358 and 362 received ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, respectively. The mean observation period on study medication was similar in the ertugliflozin 5 mg and 15 mg groups (177.7 days and 174.2 days, respectively) and the placebo group (174.4 days), with 665 subjects receiving ertugliflozin in combination with

metformin for > 26 weeks (Table 14). The proportion of subjects who discontinued study medication within 26 weeks was numerically lower in the ertugliflozin 5 mg and 15 mg groups (5.2% and 7.8%, respectively) compared to the placebo group (8.6%). The most common reason for discontinuation in all groups was withdrawal by subject (Table 15). Demographic and baseline characteristics were generally similar across groups.

Table 13: Observation period on study medication; All subjects as treated

Treatment	< 11 wks	≥ 11 to <25 wks	≥ 25 wks	Total Subjects	Duration Range	Mean Duration
Placebo	14	24	324	362	1 to 245 days	174.4 days
Ertugliflozin 5 mg	9	15	339	363	2 to 239 days	177.7 days
Ertugliflozin 15 mg	17	15	326	358	1 to 238 days	174.2 days
All Ertugliflozin	26	30	665	721	1 to 239 days	176.0 days

Observation Period = last Phase A dose date - first Phase A dose date + 1(in days).
Observation Period does not account for incorrect dosing or missed doses.

Table 14: Disposition of subjects; ertugliflozin/metformin FDC pool, Phase A

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All-Ertugliflozin		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Entered Screening									2,522	
Screening Ongoing									0	
Not Randomized									1,438	
Run-in Period									0	
Randomized	362		363		359		722		1,084	
Treated	362		363		358		721		1,083	
Trial Disposition										
Completed	342	(94.5)	359	(98.9)	340	(94.7)	699	(96.8)	1,041	(96.0)
Discontinued	20	(5.5)	4	(1.1)	19	(5.3)	23	(3.2)	43	(4.0)
Adverse Event	1	(0.3)	1	(0.3)	2	(0.6)	3	(0.4)	4	(0.4)
Lost To Follow-Up	4	(1.1)	0	(0.0)	4	(1.1)	4	(0.6)	8	(0.7)
Non-Compliance With Study Drug	2	(0.6)	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.2)
Protocol Violation	1	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)
Screen Failure	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.1)	1	(0.1)
Withdrawal By Subject	12	(3.3)	3	(0.8)	12	(3.3)	15	(2.1)	27	(2.5)
Subject Study Medication Disposition										
Completed	331	(91.4)	344	(94.8)	330	(91.9)	674	(93.4)	1,005	(92.7)
Did Not Take Study Medication	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.1)	1	(0.1)
Discontinued	31	(8.6)	19	(5.2)	28	(7.8)	47	(6.5)	78	(7.2)
Adverse Event†	6	(1.7)	7	(1.9)	4	(1.1)	11	(1.5)	17	(1.6)
Creatinine/eGFR	0	(0.0)	0	(0.0)	3	(0.8)	3	(0.4)	3	(0.3)
Excluded Medication	2	(0.6)	0	(0.0)	1	(0.3)	1	(0.1)	3	(0.3)
Hypoglycemia	0	(0.0)	0	(0.0)	1	(0.3)	1	(0.1)	1	(0.1)
Lost To Follow-Up	3	(0.8)	0	(0.0)	4	(1.1)	4	(0.6)	7	(0.6)
Non-Compliance With Study Drug	3	(0.8)	2	(0.6)	0	(0.0)	2	(0.3)	5	(0.5)
Physician Decision	1	(0.3)	1	(0.3)	1	(0.3)	2	(0.3)	3	(0.3)
Protocol Violation	1	(0.3)	1	(0.3)	1	(0.3)	2	(0.3)	3	(0.3)
Subject Moved	1	(0.3)	1	(0.3)	1	(0.3)	2	(0.3)	3	(0.3)
Withdrawal By Subject	14	(3.9)	7	(1.9)	12	(3.3)	19	(2.6)	33	(3.0)

Each subject is counted once for Trial Disposition, Subject Study Medication Disposition
For the calculation of percentage, the denominator is the number of randomized subjects.
† Two subjects in placebo group were discontinued in Phase A due to pre-existing AEs.

8.3. Adverse events

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

8.3.1.1. Integrated safety analyses (ertugliflozin/metformin pool)

The incidence of AEs was similar in the ertugliflozin and placebo groups (49.2%, 42.4% and 48% in placebo, ertugliflozin 5 mg and 15 mg groups, respectively). AEs in the Infection and infestations SOC were the most frequently reported in all groups (21%, 17.1% and 20.1%,

respectively). Ertugliflozin-treated subjects showed higher incidence of AEs in Renal and urinary disorders SOC (1.7%, 3% and 4.5%, respectively; pollakiuria, polyuria, and dysuria most common) and Reproductive system and breast disorders SOC (0.8%, 3% and 2.5%, respectively; balanoposthitis and vulvovaginal pruritus most common). Among AEs that occurred in > 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 the vulvovaginal mycotic infection Among the AEs that occurred in < 2% of subjects in all groups, those that occurred at a higher incidence in the ertugliflozin groups were balanoposthitis, dysuria, polyuria and dry mouth (Table 15).

Table 15: Subjects with AEs (incidence ≥ 2% in 1 or more treatment groups); All subjects as treated. Ertugliflozin/metformin FDC pool including rescue approach

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		All Ertugliflozin	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	362		363		358		721	
with one or more adverse events	178	(49.2)	154	(42.4)	172	(48.0)	326	(45.2)
with no adverse events	184	(50.8)	209	(57.6)	186	(52.0)	395	(54.8)
Cardiac disorders	**3**	**(0.8)**	**5**	**(1.4)**	**7**	**(2.0)**	**12**	**(1.7)**
Gastrointestinal disorders	**26**	**(7.2)**	**29**	**(8.0)**	**24**	**(6.7)**	**53**	**(7.4)**
Diarrhoea	9	(2.5)	4	(1.1)	4	(1.1)	8	(1.1)
General disorders and administration site conditions	**13**	**(3.6)**	**8**	**(2.2)**	**9**	**(2.5)**	**17**	**(2.4)**
Infections and infestations	**76**	**(21.0)**	**62**	**(17.1)**	**72**	**(20.1)**	**134**	**(18.6)**
Influenza	9	(2.5)	4	(1.1)	7	(2.0)	11	(1.5)
Nasopharyngitis	8	(2.2)	7	(1.9)	6	(1.7)	13	(1.8)
Upper respiratory tract infection	20	(5.5)	8	(2.2)	16	(4.5)	24	(3.3)
Urinary tract infection	4	(1.1)	7	(1.9)	7	(2.0)	14	(1.9)
Vulvovaginal mycotic infection	1	(0.3)	7	(1.9)	8	(2.2)	15	(2.1)
Injury, poisoning and procedural complications	**11**	**(3.0)**	**12**	**(3.3)**	**17**	**(4.7)**	**29**	**(4.0)**
Investigations	**15**	**(4.1)**	**14**	**(3.9)**	**16**	**(4.5)**	**30**	**(4.2)**
Weight decreased	5	(1.4)	4	(1.1)	11	(3.1)	15	(2.1)
Metabolism and nutrition disorders	**40**	**(11.0)**	**26**	**(7.2)**	**23**	**(6.4)**	**49**	**(6.8)**
Hypoglycaemia	15	(4.1)	15	(4.1)	12	(3.4)	27	(3.7)
Musculoskeletal and connective tissue disorders	**27**	**(7.5)**	**20**	**(5.5)**	**35**	**(9.8)**	**55**	**(7.6)**
Back pain	8	(2.2)	7	(1.9)	12	(3.4)	19	(2.6)
Nervous system disorders	**19**	**(5.2)**	**24**	**(6.6)**	**23**	**(6.4)**	**47**	**(6.5)**
Headache	5	(1.4)	12	(3.3)	8	(2.2)	20	(2.8)
Renal and urinary disorders	**6**	**(1.7)**	**11**	**(3.0)**	**16**	**(4.5)**	**27**	**(3.7)**
Reproductive system and breast disorders	**3**	**(0.8)**	**11**	**(3.0)**	**9**	**(2.5)**	**20**	**(2.8)**
Respiratory, thoracic and mediastinal disorders	**13**	**(3.6)**	**8**	**(2.2)**	**6**	**(1.7)**	**14**	**(1.9)**
Skin and subcutaneous tissue disorders	**9**	**(2.5)**	**7**	**(1.9)**	**9**	**(2.5)**	**16**	**(2.2)**

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.

MedDRA Version 19.0

8.3.1.2. Pivotal and/or main efficacy studies

Study P002/1013

The overall incidence of AEs was similar across the glimepiride and ertugliflozin treatment groups. The incidence of genital mycotic infections in both men and women in the ertugliflozin 5 mg and 15 mg groups was significantly higher than those in the glimepiride group. The incidence of urinary tract infections and hypovolemia AEs was not meaningfully different between the ertugliflozin and glimepiride groups. Analyses of documented and symptomatic hypoglycaemia performed excluding data after initiation of glycaemic rescue therapy showed that the incidence of documented and symptomatic hypoglycaemia was lower in the ertugliflozin groups than in the glimepiride group for both hypoglycaemia categories (Table 16).

Table 16: Analysis of subjects with AEs by SOC (incidence ≥ 4 subjects in 1 or more treatment groups); All subjects as treated, Phase A: excluding rescue approach

			Difference in % vs Glimepiride
Treatment	n	(%)	Estimate (95% CI)[1]
Subjects in population			
Ertugliflozin 5 mg	448		
Ertugliflozin 15 mg	440		
Glimepiride	437		
with one or more adverse events			
Ertugliflozin 5 mg	263	(58.7)	-2.9 (-9.3, 3.6)
Ertugliflozin 15 mg	262	(59.5)	-2.0 (-8.5, 4.5)
Glimepiride	269	(61.6)	
with no adverse events			
Ertugliflozin 5 mg	185	(41.3)	2.9 (-3.6, 9.3)
Ertugliflozin 15 mg	178	(40.5)	2.0 (-4.5, 8.5)
Glimepiride	168	(38.4)	
Blood and lymphatic system disorders			
Ertugliflozin 5 mg	5	(1.1)	-0.0 (-1.7, 1.6)
Ertugliflozin 15 mg	7	(1.6)	0.4 (-1.3, 2.2)
Glimepiride	5	(1.1)	
Cardiac disorders			
Ertugliflozin 5 mg	10	(2.2)	-0.5 (-2.8, 1.7)
Ertugliflozin 15 mg	6	(1.4)	-1.4 (-3.5, 0.5)
Glimepiride	12	(2.7)	
Ear and labyrinth disorders			
Ertugliflozin 5 mg	8	(1.8)	1.1 (-0.4, 2.9)
Ertugliflozin 15 mg	8	(1.8)	1.1 (-0.4, 2.9)
Glimepiride	3	(0.7)	
Eye disorders			
Ertugliflozin 5 mg	9	(2.0)	0.4 (-1.5, 2.4)
Ertugliflozin 15 mg	7	(1.6)	-0.0 (-1.9, 1.8)
Glimepiride	7	(1.6)	
Gastrointestinal disorders			
Ertugliflozin 5 mg	60	(13.4)	2.4 (-1.9, 6.8)

Table 16 (continued): Analysis of subjects with AEs by SOC (incidence ≥ 4 subjects in 1 or more treatment groups); All subjects as treated, Phase A: excluding rescue approach

Ertugliflozin 15 mg	53	(12.0)	1.1 (-3.2, 5.3)
Glimepiride	48	(11.0)	
General disorders and administration site conditions			
Ertugliflozin 5 mg	13	(2.9)	-0.3 (-2.7, 2.1)
Ertugliflozin 15 mg	14	(3.2)	-0.0 (-2.5, 2.4)
Glimepiride	14	(3.2)	
Hepatobiliary disorders			
Ertugliflozin 5 mg	8	(1.8)	1.1 (-0.4, 2.9)
Ertugliflozin 15 mg	5	(1.1)	0.4 (-1.0, 2.0)
Glimepiride	3	(0.7)	
Infections and infestations			
Ertugliflozin 5 mg	142	(31.7)	2.2 (-3.9, 8.2)
Ertugliflozin 15 mg	119	(27.0)	-2.5 (-8.4, 3.5)
Glimepiride	129	(29.5)	
Injury, poisoning and procedural complications			
Ertugliflozin 5 mg	14	(3.1)	0.2 (-2.3, 2.6)
Ertugliflozin 15 mg	16	(3.6)	0.7 (-1.8, 3.2)
Glimepiride	13	(3.0)	
Investigations			
Ertugliflozin 5 mg	21	(4.7)	-1.5 (-4.6, 1.5)
Ertugliflozin 15 mg	37	(8.4)	2.2 (-1.2, 5.8)
Glimepiride	27	(6.2)	
Metabolism and nutrition disorders			
Ertugliflozin 5 mg	41	(9.2)	-17.4 (-22.4, -12.5)
Ertugliflozin 15 mg	56	(12.7)	-13.8 (-19.0, -8.6)
Glimepiride	116	(26.5)	
Musculoskeletal and connective tissue disorders			
Ertugliflozin 5 mg	44	(9.8)	1.1 (-2.7, 5.0)
Ertugliflozin 15 mg	43	(9.8)	1.1 (-2.8, 5.0)

Table 16 (continued): Analysis of subjects with AEs by SOC (incidence ≥ 4 subjects in 1 or more treatment groups); All subjects as treated, Phase A: excluding rescue approach

Treatment	n	(%)	Difference in % vs Glimepiride Estimate (95% CI)[†]
Musculoskeletal and connective tissue disorders			
Glimepiride	38	(8.7)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ertugliflozin 5 mg	7	(1.6)	0.6 (-1.0, 2.4)
Ertugliflozin 15 mg	7	(1.6)	0.7 (-0.9, 2.4)
Glimepiride	4	(0.9)	
Nervous system disorders			
Ertugliflozin 5 mg	35	(7.8)	-2.3 (-6.1, 1.5)
Ertugliflozin 15 mg	30	(6.8)	-3.3 (-7.0, 0.4)
Glimepiride	44	(10.1)	
Psychiatric disorders			
Ertugliflozin 5 mg	13	(2.9)	0.8 (-1.3, 3.1)
Ertugliflozin 15 mg	9	(2.0)	-0.0 (-2.1, 2.0)
Glimepiride	9	(2.1)	
Renal and urinary disorders			
Ertugliflozin 5 mg	24	(5.4)	1.9 (-0.8, 4.8)
Ertugliflozin 15 mg	33	(7.5)	4.1 (1.1, 7.3)
Glimepiride	15	(3.4)	
Reproductive system and breast disorders			
Ertugliflozin 5 mg	24	(5.4)	3.5 (1.1, 6.2)
Ertugliflozin 15 mg	22	(5.0)	3.2 (0.8, 5.8)
Glimepiride	8	(1.8)	
Respiratory, thoracic and mediastinal disorders			
Ertugliflozin 5 mg	15	(3.3)	-1.5 (-4.2, 1.2)
Ertugliflozin 15 mg	22	(5.0)	0.2 (-2.8, 3.2)
Glimepiride	21	(4.8)	
Skin and subcutaneous tissue disorders			
Ertugliflozin 5 mg	18	(4.0)	0.6 (-2.0, 3.2)
Ertugliflozin 15 mg	21	(4.8)	1.3 (-1.3, 4.1)
Glimepiride	15	(3.4)	
Vascular disorders			
Ertugliflozin 5 mg	18	(4.0)	1.5 (-0.9, 4.0)
Ertugliflozin 15 mg	12	(2.7)	0.2 (-2.0, 2.5)
Glimepiride	11	(2.5)	

[†] Based on Miettinen & Nurminen method.

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

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

Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

MedDRA Version 19

Study P005/1019

The overall incidence of AEs was similar across the treatment groups. In both men and women, the incidence of genital mycotic infections in the E5/S100 and E15/S100 groups was similar to that of the E5 and E15 groups. However, genital mycotic infections occurred more commonly in the 4 ertugliflozin treated groups than in the S100 group. The incidence of AEs of hypoglycaemia in the E15/S100 group (7.0%) was higher than in the S100 group (2.4%) and was numerically higher than in the 3 other treatment groups (2.9% to 3.6%). No notable between-group differences were observed urinary tract infections and hypovolaemia (Table 17). AEs of dizziness occurred more frequently in the 4 ertugliflozin treatment groups than in the S100 group. AEs of dizziness were reported for 11 subjects among the 4 ertugliflozin treated groups, including 8 subjects in the E5 and E15 groups combined and 3 subjects in the E5/S100 and E15/S100 groups combined. No AEs of dizziness were reported in the S100 group. Among the 11 subjects with an AE of dizziness, none had more than 1 event. Among the AEs of dizziness, 10 were mild and 1 was severe ([patient ID redacte] in the E5 group). Five events

were considered related to study medication by the investigator, and 3 led to discontinuation of study medication.

Table 17: Study P005/1019 Analysis of AE summary measures; All subjects as treated, Phase A: excluding rescue approach

Treatment	n	(%)	Difference in % vs Ertugliflozin 5 mg Estimate (95% CI)†	Difference in % vs Ertugliflozin 15 mg Estimate (95% CI)†	Difference in % vs Sitagliptin 100 mg Estimate (95% CI)†
with drug-related‡ adverse events					
Sitagliptin 100 mg	12	(4.9)			
Ertugliflozin 5 mg + Sitagliptin 100 mg	27	(11.1)	-5.7 (-11.9, 0.5)		6.3 (1.5, 11.3)
Ertugliflozin 15 mg + Sitagliptin 100 mg	39	(16.0)		3.9 (-2.3, 10.1)	11.1 (5.9, 16.7)
with serious adverse events					
Ertugliflozin 5 mg	8	(3.2)			
Ertugliflozin 15 mg	3	(1.2)			
Sitagliptin 100 mg	3	(1.2)			
Ertugliflozin 5 mg + Sitagliptin 100 mg	6	(2.5)	-0.7 (-4.0, 2.5)		1.3 (-1.4, 4.2)
Ertugliflozin 15 mg + Sitagliptin 100 mg	4	(1.6)		0.4 (-2.1, 3.1)	0.4 (-2.1, 3.1)
with serious drug-related adverse events					
Ertugliflozin 5 mg	0	(0.0)			
Ertugliflozin 15 mg	0	(0.0)			
Sitagliptin 100 mg	0	(0.0)			
Ertugliflozin 5 mg + Sitagliptin 100 mg	1	(0.4)			
Ertugliflozin 15 mg + Sitagliptin 100 mg	0	(0.0)			
who died					
Ertugliflozin 5 mg	0	(0.0)			
Ertugliflozin 15 mg	0	(0.0)			
Sitagliptin 100 mg	0	(0.0)			
Ertugliflozin 5 mg + Sitagliptin 100 mg	0	(0.0)			
who died					
Ertugliflozin 15 mg + Sitagliptin 100 mg	0	(0.0)			
discontinued study medication due to an adverse event					
Ertugliflozin 5 mg	6	(2.4)			
Ertugliflozin 15 mg	3	(1.2)			
Sitagliptin 100 mg	1	(0.4)			
Ertugliflozin 5 mg + Sitagliptin 100 mg	3	(1.2)	-1.2 (-4.1, 1.5)		0.8 (-1.1, 3.2)
Ertugliflozin 15 mg + Sitagliptin 100 mg	7	(2.9)		1.7 (-1.0, 4.7)	2.5 (0.3, 5.4)
discontinued study medication due to a drug-related adverse event					
Ertugliflozin 5 mg	6	(2.4)			
Ertugliflozin 15 mg	3	(1.2)			
Sitagliptin 100 mg	0	(0.0)			
Ertugliflozin 5 mg + Sitagliptin 100 mg	1	(0.4)	-2.0 (-4.8, 0.1)		0.4 (-1.1, 2.3)
Ertugliflozin 15 mg + Sitagliptin 100 mg	5	(2.0)		0.8 (-1.7, 3.6)	2.0 (0.5, 4.7)
discontinued study medication due to a serious adverse event					
Ertugliflozin 5 mg	0	(0.0)			
Ertugliflozin 15 mg	0	(0.0)			
Sitagliptin 100 mg	0	(0.0)			
Ertugliflozin 5 mg + Sitagliptin 100 mg	2	(0.8)			
Ertugliflozin 15 mg + Sitagliptin 100 mg	0	(0.0)			
discontinued study medication due to a serious drug-related adverse event					
Ertugliflozin 5 mg	0	(0.0)			
Ertugliflozin 15 mg	0	(0.0)			
Sitagliptin 100 mg	0	(0.0)			
Ertugliflozin 5 mg + Sitagliptin 100 mg	0	(0.0)			
Ertugliflozin 15 mg + Sitagliptin 100 mg	0	(0.0)			

† Based on Miettinen & Nurminen method.
‡ Determined by the investigator to be related to the drug.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

8.3.2. Treatment related adverse events (adverse drug reactions)

8.3.2.1. Integrated safety analyses (ertugliflozin/metformin pool)

The incidence of treatment-related AEs was numerically higher in the ertugliflozin groups compared with placebo (7.5%, 13.1% and 12.3% in placebo, ertugliflozin 5 mg and 15 mg groups, respectively). This was primarily due to a numerically increased incidence of AEs related to genital mycotic infections and osmotic diuresis in ertugliflozin treated subjects. Incidence of hypoglycaemia was also higher in ertugliflozin groups, but this is discussed in detail in below.

8.3.2.2. Pivotal and/or main efficacy studies

Study P002/1013

The incidence of treatment-related AEs was similar across the ertugliflozin and glimepiride groups (17.8%, 18.3% and 21.6% with glimepiride, ertugliflozin 5 mg and 15 mg, respectively); UTI, dysuria, pollakiuria, polyuria, balanoposthitis, and vulvovaginal pruritus were more common in the ertugliflozin groups while hypoglycaemia was more common in the glimepiride group.

Study P005/1019

The incidence of treatment-related AEs was higher in the E5/S100 and E15/S100 groups than in the S100, but was not notably different than those in the E5 and E15 groups. The most commonly reported drug related AEs in the 4 ertugliflozin treated groups were those associated with genital mycotic infections. The numerically higher incidences of AEs in the 4 ertugliflozin treated groups relative to the S100 group were not due to an excess of any particular drug related AE, but rather to a slightly higher incidence of several AEs dispersed throughout the SOC. An exception, however, was in the E15/S100 group, in which 7 (2.9%) subjects had a drug related AE of hypoglycaemia. In comparison, 1 to 3 subjects (0.8% to 1.2%) in the 4 other treatment groups experienced drug related hypoglycaemia.

8.3.3. Deaths and other serious adverse events (SAEs)

8.3.3.1. Integrated safety analyses (ertugliflozin/metformin pool)

There were no deaths in the 26-week ertugliflozin/metformin Pool, and the incidence of non-fatal SAEs was low with no significant differences between the placebo, ertugliflozin 5 mg and 15 mg groups (3.6%, 2.8% and 2.8%, respectively). Non-fatal SAEs occurred across multiple SOCs with no obvious event pattern. Only 1 specific non-fatal SAE (acute myocardial infarction in the placebo group) occurred in more than 1 subject.

8.3.3.2. Pivotal and/or main efficacy studies

Study P002/1013

Five (1.1%) subjects in the ertugliflozin 5 mg group, 1 (0.2%) in the ertugliflozin 15 mg group, and none in the glimepiride group died due to AEs occurring in the Phase A treatment period. None of the AEs resulting in death was considered to be related to study medication and there was no pattern with regard to specific AE terms.

The incidence of SAEs (including fatal and non-fatal events combined) was higher in the ertugliflozin 5 mg group and numerically higher in the ertugliflozin 15 mg group than in the glimepiride group. Across the 3 treatment groups, SAEs were distributed across multiple SOCs, and only 2 SAEs occurred in > 1 subject in a treatment group, including pneumonia (2 subjects in the ertugliflozin 5 mg group and 1 in the glimepiride group) and cerebrovascular accident (2 subjects in the ertugliflozin 5 mg group and 1 in the glimepiride group).The higher incidence of SAEs in the ertugliflozin groups was not due to an excess of any specific AEs or of AEs within a particular SOC. The proportion of subjects who died due to an AE occurring in Phase A was higher in the ertugliflozin 5 mg group (5 subjects) than in the glimepiride group (0 subjects). One subject in the ertugliflozin 15 mg group died. One additional subject in the glimepiride group died due to an adverse event that started during the post-treatment period; this subject is not included in the Phase None of the AEs leading to death was considered to be drug related by the investigator and there was no pattern for these specific AEs.

Study P005/1019

No deaths were reported. SAEs occurred at a low incidence across groups (< 4%), and small numeric differences in the incidence of SAEs was not due to an increased incidence in any particular SAE term. The only SAE that occurred in > 1 subject in a treatment group was acute

myocardial infarction, which occurred in 2 subjects in the E15/S100 group. Only 1 SAE was considered by the investigator to be related to study medication (pyelonephritis in a (information redacted) treated with E5/S100).

8.3.4. Discontinuations due to adverse events

8.3.4.1. Integrated safety analyses (ertugliflozin/metformin pool)

The incidence of AEs resulting in discontinuation from study medication in the ertugliflozin/metformin Pool was low overall and similar in the placebo, ertugliflozin 5 and 15 mg groups (1.1%, 2.2% and 1.1%, respectively). The only discernible pattern was a low incidence of discontinuations in ertugliflozin treated subjects due to adverse events related to genital mycotic infections with no specific AEs that resulted in discontinuation from study medication in greater than 1 subject in any group.

8.3.4.2. Pivotal and/or main efficacy studies

Study P002/1013

The incidence of discontinuations due to AEs was similar in the ertugliflozin 5 mg and glimepiride groups but was numerically higher in the ertugliflozin 15 mg group (3.9%, 4% and 5.7% in glimepiride, ertugliflozin 5 mg and 15 mg groups, respectively); the higher incidence of discontinuations in the ertugliflozin 15 mg group was mainly due to genital mycotic infection-related AEs and renal and urinary disorders (decreased eGFR, acute kidney injury (2 subjects) and pollakiuria (2 subjects). Eight subjects including 2 (0.4%) in the ertugliflozin 5 mg group, 5 (1.1%) in the ertugliflozin 15 mg group and 1 (0.2%) in the glimepiride group discontinued study medication due to SAEs.

Study P005/1019

Discontinuation of study medication due to an AE, which occurred at a low incidence across groups, had a higher incidence in the E15/S100 group (2.9%) relative to the S100 group (0.4%); incidences in the 3 other groups (1.2 to 2.4%) were not notably different relative to the E15/S100 group. The only AEs that led to discontinuation of study medication in > 1 subject were dizziness and balanoposthitis (each resulted in discontinuation of 2 subjects in the E5 group) and AEs leading to discontinuation of study medication were dispersed across multiple SOCs.

8.4. Evaluation of issues with possible regulatory impact

8.4.1. Liver function and liver toxicity

8.4.1.1. Integrated safety analyses (ertugliflozin/metformin pool)

In the ertugliflozin/metformin pool, baseline ALT ranged from 26.5 to 28.3 IU/L and baseline AST ranged from 21.2 to 23.2 IU/L across groups respectively). There were decreases in ALT and AST in the ertugliflozin 5 mg and 15 mg groups relative to the placebo group which persisted from Week 6 until Week 26. Mean decreases in ALT at Week 26 were larger in the ertugliflozin 5 mg and 15 mg groups (-4.4 IU/L and -5.9 IU/L, respectively) than in the placebo group (-1.0 IU/L). Mean decreases in AST were also seen at Week 26 in the ertugliflozin 5 mg and 15 mg groups (-1.7 IU/L and -3.5 IU/L, respectively) relative to essentially no change in the placebo group (-0.3 IU/L). Ertugliflozin was not associated with a greater incidence of PDLCs for ALT and AST (≥ 3 x ULN). One (0.3%) and 2 (0.6%) subjects in the ertugliflozin 5 mg and 15 mg groups, respectively, compared to 4 (1.1%) subjects in the placebo group had at least 1 ALT value ≥ 3 x ULN; no subject in the ertugliflozin/metformin Pool had an ALT value > 5 x ULN. No subject in the ertugliflozin groups and 1 subject in the placebo group had an AST value ≥ 3 x ULN. Elevations in ALT or AST were also infrequent in the active comparator studies not

included in the ertugliflozin/metformin pool. In the ertugliflozin/metformin pool, there were no adverse events of ALT or AST increased in the ertugliflozin groups.

8.4.1.2. Pivotal and/or main efficacy studies

Study P002/1013

Five subjects had elevations in ALT or ALT and AST that met criteria for adjudication (value ≥ 5 x ULN). For 1 of the 5 adjudicated cases, the CAC considered the causal relationship with study medication to be doubtful (ertugliflozin 15 mg group); the 4 others (1 in the ertugliflozin 5 mg group, 2 in the ertugliflozin 15 mg group, and 1 in the glimepiride group) were considered possibly related to study medication by the CAC. None of the ALT or AST elevations were associated with > 2 x ULN increase in bilirubin. None of the AEs of ALT or AST increased led to study medication discontinuation and all resolved on treatment.

Study P005/1019

No subjects had a hepatic event that met criteria for adjudication. Mean reductions in ALT (with baseline values ranging from 26.6 to 28.9 IU/L) were observed in all 5 treatment groups at Week 26, with numerically greater decreases seen in the 4 ertugliflozin treated groups (4.4 to 5.1 IU/L) than in the S100 group (1.7 IU/L).

8.4.2. Renal function and renal toxicity

8.4.2.1. Integrated safety analyses (ertugliflozin/metformin pool)

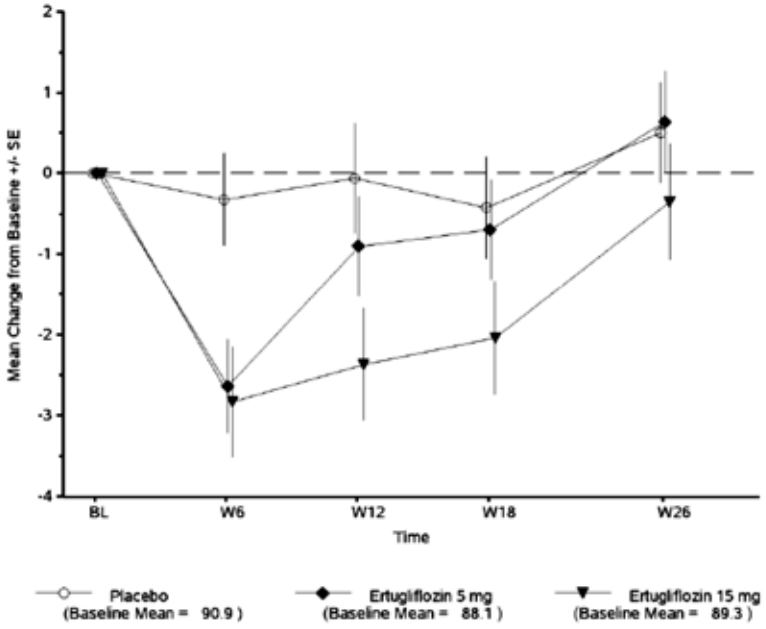
In the Phase III ertugliflozin development program, ertugliflozin treatment led to a transient decrease in eGFR. Metformin is known to be substantially excreted by the kidney and, as such, metformin has dosing considerations based on renal function.

For all Phase III studies in the ertugliflozin program, including the 4 Phase III studies specific to the proposed FDC, changes in renal function were evaluated in several ways: (1) examination of laboratory measures of renal function (examination of mean changes in renal related laboratory parameters and categorical PDLC analyses of changes from baseline); (2) evaluation of renal related events identified from the narrow SMQ for Acute Renal Failure, as well as AEs of GFR decreased and blood creatinine increased; (3) evaluation of adjudicated events meeting pre-specified criteria.

eGFR change from Baseline

In the ertugliflozin/metformin pool, baseline eGFR values were approximately 90 mL/min/1.73 m^2 in each group. There was slightly greater reduction in the ertugliflozin groups compared to placebo at Week 6 (-0.3, -2.6 and -2.8mL/min/1.73 m^2 in the placebo, ertugliflozin 5 mg and 15 mg groups, respectively) with a subsequent return of eGFR to or towards baseline by Week 26 such that there was no notable differences at Week 26 between either the ertugliflozin 5 mg or 15 mg groups and the placebo group (Figure 1).

Figure 1: eGFR (mL/min/1.73m²); Mean change from Baseline over time (mean ± SE); All subjects as treated ertugliflozin/metformin FDC pool: including rescue approach



The proportion of subjects who had any occurrence of a decrease in eGFR of > 30% from baseline was similar in the placebo and ertugliflozin groups (3.4%, 3.1% and 3.7% in the placebo, ertugliflozin 5 mg and 15 mg groups, respectively). Only 1 (0.3%) subject in the ertugliflozin 15 mg group and 1 (0.3%) subject 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%.

Serum creatinine and blood urea nitrogen (BUN)

There were small increases in serum creatinine at week 6 in the ertugliflozin groups compared to no change in the placebo groups (+0.34, +2.49 and +2.63umol/L), although there was subsequent return to or towards baseline with no change between treatment groups by Week 26. In the ertugliflozin/metformin Pool, the baseline values for BUN ranged from 14.7 mg/dL to 15.1 mg/dL across groups. There were small increases from baseline in BUN at Week 6 in the ertugliflozin 5 mg and 15 mg groups (1.4 mg/dL and 1.9 mg/dL, respectively) and in the placebo group (0.2 mg/dL). The mean change from baseline in BUN at Week 26 was higher in the ertugliflozin 5 mg and 15 mg groups (1.4 mg/dL and 2.2 mg/dL, respectively) relative to the placebo group (0.3 mg/dL).The proportion of subjects who met the PDLC criteria for BUN (≥ 50% increase and value > ULN) for at least 1 occurrence was higher in the ertugliflozin 15 mg group (12.4%) and numerically higher in the ertugliflozin 5 mg group (8.0%) relative to the placebo group (4.9%).

Renal related AEs

The incidence of renal related events was low and similar across the ertugliflozin 5 mg (2 subjects; 0.6%) and 15 mg groups (1 subject; 0.3%) and the placebo group (1 subject; 0.3%). None of the events was serious or led to discontinuation. One subject, in the ertugliflozin 15 mg group (in Study P007/1017), who had an AE of renal failure, met criteria for renal adjudication that was adjudicated as 'not related' to study medication. In the ertugliflozin/metformin Pool, adverse events related to decreased eGFR and increased creatinine were infrequent, with each being reported in ≤ 1 subject per group None of these events was serious or led to discontinuation of study medication. In addition, 3 (0.8%) subjects in the ertugliflozin 15 mg group and none in the other groups discontinued study medication due to protocol specified criteria for eGFR or creatinine criteria. None of these subjects reported an associated AE.

It is important to note that the among the 4 Phase III studies submitted for the proposed ertugliflozin-metformin FDC, 6 renal events, all in ertugliflozin 15 mg treated subjects, were adjudicated. Among these 6 events, 2 were adjudicated as 'possibly' related to study medication and 4 were considered 'not related.

While metformin is not associated with a decrease in eGFR, it is cleared renally, has dosing considerations based on renal function, and in the presence of severe renal impairment, has been reported to be associated with lactic acidosis. Treatment with ertugliflozin in combination with metformin, as with ertugliflozin, led to transient, modest decreases in eGFR at Week 6 that returned to or towards baseline at Week 26. In a longer term study (Study P002/1013) on metformin background, eGFR in both ertugliflozin dose groups was above baseline between Week 26 and Week 52. In the ertugliflozin/metformin pool, the incidence of renal related events was low (< 1%) and not notably higher in the ertugliflozin groups relative to the placebo group. None of the events was serious or led to discontinuation.

As with initiation of the individual agents, monitoring of renal function should be performed prior to initiation of ertugliflozin and metformin combination therapy and periodically thereafter and this has been adequately covered in the proposed PI.

8.4.2.2. Pivotal and/or main efficacy studies

A similar pattern of eGFR change over time was noted in the 2 active comparator studies not included in the ertugliflozin/metformin Pool (Studies P002/1013 and P005/1019) with eGFR values in both ertugliflozin groups above baseline between Week 26 and Week 52 in Study P002/1013.

8.4.3. Other clinical chemistry

Phosphate, magnesium, calcium: In the ertugliflozin/metformin Pool, baseline phosphate values were 3.6 mg/dL in each group. 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 0.2, 0.3 and 0.0 mg/dL in the ertugliflozin 5 mg, 15 mg and placebo groups, respectively. The active comparator studies not included in the ertugliflozin/metformin pool, Studies P002/1013 and P005/1019, showed similar, small increases in phosphate in the ertugliflozin groups relative to the comparator group. In the ertugliflozin/metformin Pool, 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 relative to the placebo group (16.3%, 15.9% and 8.6% , respectively). These results are similar to the other studies and pools in the ertugliflozin development program, indicating no increased risk when ertugliflozin is used with metformin.

In the ertugliflozin/metformin Pool, the baseline magnesium value was approximately 1.5 mEq/L in each group. There were small increases in magnesium 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 0.11, 0.14 and 0.01 mEq/L in the ertugliflozin 5 mg, 15 mg and placebo groups, respectively. In the ertugliflozin/metformin Pool, no subjects in either the ertugliflozin 5 mg and 15 mg groups or the placebo group met the PDLC criterion of increase ≥ 1.0 mEq/L and value > ULN for serum magnesium. There was 1 AE of blood magnesium decreased in the ertugliflozin 15 mg group, but no AE related to an increase in serum magnesium. The active comparator studies (Studies P002/1013 and P005/1019) showed similar, small increases in magnesium in the ertugliflozin groups relative to the comparator group.

In the ertugliflozin/metformin Pool, there was no meaningful change in calcium in the ertugliflozin or the placebo group with no meaningful increases in the events meeting PDLC criteria. The active comparator studies not included in the ertugliflozin/metformin pool, Studies P002/1013 and P005/1019, also showed no findings related to change in calcium with ertugliflozin treatment.

In the ertugliflozin/metformin Pool, the proportion of subjects who had at least 1 occurrence of PDLC increase of ≥ 1.0 mEq/L in serum potassium and value > ULN were similar in the ertugliflozin 5 mg and 15 mg and placebo groups (4.56%, 4.3% and 4.9%, respectively). With similar results for the proportion of subjects who had at least 1 occurrence of a value > 5.4 mEq/L and a value increased by 15% above baseline (4.6%, 4.9% and 5.1%, respectively) and proportion of subjects who had at least 1 occurrence of a value > 6.0 mEq/L (1.7%, 1.7% and 2.0%, respectively). One subject in the ertugliflozin 5 mg group, 3 in the ertugliflozin 15 mg group, and 4 in the placebo group had an AE of either blood potassium increased or hyperkalaemia. These results are similar to those in the 2 active comparator studies on metformin background not included in the ertugliflozin/metformin Pool.

There were no meaningful changes in bicarbonate levels in the ertugliflozin/metformin Pool or in the 2 active comparator studies included in the ertugliflozin/metformin FDC dossier. One subject, in the ertugliflozin 15 mg group, had at least 1 bicarbonate value < 15 mmol/L. No subject had a bicarbonate value < 10 mmol/L.

In the ertugliflozin/metformin Pool, baseline uric acid values were approximately 5.4 mg/dL in each group. There were modest decreases in uric acid 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 -0.50, -0.39 and 0.12 mg/dL in the ertugliflozin 5 mg, 15 mg and placebo groups, respectively. Few subjects in the ertugliflozin/metformin pool (1.7%, 2.3% and 2.6%, respectively met PDLC criteria of an increase ≥ 50% and value > ULN In the ertugliflozin/metformin pool, there were no AEs related to changes in uric acid. The active comparator studies not included in the ertugliflozin/metformin pool, Studies P002/1013 and P005/1019, similarly showed decreases in uric acid in the ertugliflozin treated groups relative to the non-ertugliflozin treated groups.

Serum lipids

The data in the ertugliflozin/metformin pool and the individual active comparator studies on a background of metformin showed that ertugliflozin treatment relative to placebo led to small changes from baseline in the serum lipid profile including increased LDL-C, total cholesterol, and HDL-C; with decreases in triglycerides (Table 18).

Table 18: LDL-C (mg/dL); % change from Baseline at Week 26 cLDA: individual doses versus placebo. All subjects as treated; ertugliflozin/metformin FDC pool including rescue approach

	Baseline		Week 26		Percent Change from baseline at Week 26		
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)[†]
Placebo	352	97.05 (35.72)	334	96.15 (33.57)	334	5.10 (35.73)	4.98 (1.33, 8.63)
Ertugliflozin 5 mg	353	96.07 (35.01)	339	98.42 (34.66)	338	7.16 (38.05)	6.65 (3.03, 10.28)
Ertugliflozin 15 mg	344	94.46 (34.27)	327	99.05 (33.88)	324	8.78 (33.19)	8.50 (4.80, 12.20)
Estimated Difference					Difference in LS Means (95% CI)[†]		
Ertugliflozin 5 mg vs. Placebo					1.67 (-3.31, 6.66)		
Ertugliflozin 15 mg vs. Placebo					3.53 (-1.51, 8.57)		
Conditional Pooled SD of Percent Change from Baseline							32.57

For baseline and Week 26, N is the number of subjects with non-missing assessments at the specific time point; for Percent Change from Baseline at Week 26, N is the number of subjects in the ASaT population (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. The Mean and SD for the Percent Change from baseline are based on non-missing values.

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

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

These findings were consistent with those in the ertugliflozin Phase III development program including the 2 active comparator studies not included in the ertugliflozin/metformin pool. Changes over time in lipid levels have been observed with other SGLT2 inhibitors. In particular, increased LDL-C is described in the labels of SGLT2 inhibitors. Ertugliflozin treatment in the

Phase III development program led to small changes in the lipid profile, including increased LDL-C, total cholesterol, and HDL-C; there were decreases in triglycerides.

8.4.4. Haematology and haematological toxicity

8.4.4.1. Integrated safety analyses (ertugliflozin/metformin Pool)

In the ertugliflozin/metformin Pool, baseline haemoglobin values ranged from 13.77 g/dL to 13.94 g/Dl across groups. At Week 26, there were small increases from baseline in haemoglobin in both the ertugliflozin 5 mg and 15 mg groups (0.43 g/dL and 0.44 g/dL, respectively) relative to a decrease in the placebo group (-0.22 g/dL). There were no AEs related to haemoglobin increase. 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 (4.6% and 3.5%, respectively) relative to the placebo group (0.6%). Few subjects in the ertugliflozin 5 mg group (2 subjects; 0.6%) and ertugliflozin 15 mg group (3 subjects; 0.9%), and none in the placebo group, had at least 1 increase in haemoglobin > 2.0 g/dL and value > ULN.

8.4.4.2. Pivotal and/or main efficacy studies

The active comparator studies not included in the ertugliflozin/metformin pool, Studies P002/1013 and P005/1019, showed similar, small increases in haemoglobin in the ertugliflozin groups relative to the non-ertugliflozin groups. In Study P002/1013, in the ertugliflozin groups, a small mean increase in haemoglobin (≤ 0.58 g/dL, from a baseline of approximately 13.8 g/dL), initially seen at Week 12 and remained stable through Week 52. Mean haemoglobin levels were essentially unchanged from baseline in the glimepiride group. In Study P003/1019, small increases in haemoglobin (≤ 0.63 g/dL, from baseline values of approximately 14 g/dL) were observed at Weeks 12 and 26 in the co-administration and individual ertugliflozin treatment groups, relative to a slight decline (≤ 0.28 g/dL) in the sitagliptin group.

The results in the Phase III studies with metformin background were consistent with those seen in the broad Phase III ertugliflozin program. The small changes in haemoglobin seen with the addition of therapy with ertugliflozin (on the background of metformin or in other clinical settings) are unlikely to be of clinical relevance.

A decrease to subnormal levels of previously normal serum vitamin B12 levels has been seen in patients taking metformin and measurement of hematologic parameters on an annual basis is advised. Metformin therapy should be discontinued in patients having surgical procedures, intravascular contrast studies, or experiencing hypoxic states.

8.4.5. Other laboratory tests

Not applicable.

8.4.6. Electrocardiograph findings and cardiovascular safety

In the ertugliflozin/metformin pool, no clinically meaningful changes from baseline in ECG parameters were observed in the ertugliflozin groups relative to the placebo group, or between groups in the 2 active comparator studies not included in the ertugliflozin/metformin pool, Studies P002/1013 and P005/1019. In the ertugliflozin/metformin Pool, no subjects met the criteria for a QTcF value ≥ 500 ms or an increase ≥ 60 ms and value above gender-specific ULN. The number of subjects meeting QTcF criteria for increase ≥ 30 ms and value above gender-specific ULN was similar in the ertugliflozin 5 mg and 15 mg groups (1.3% in both groups) and the placebo group (1.0%).

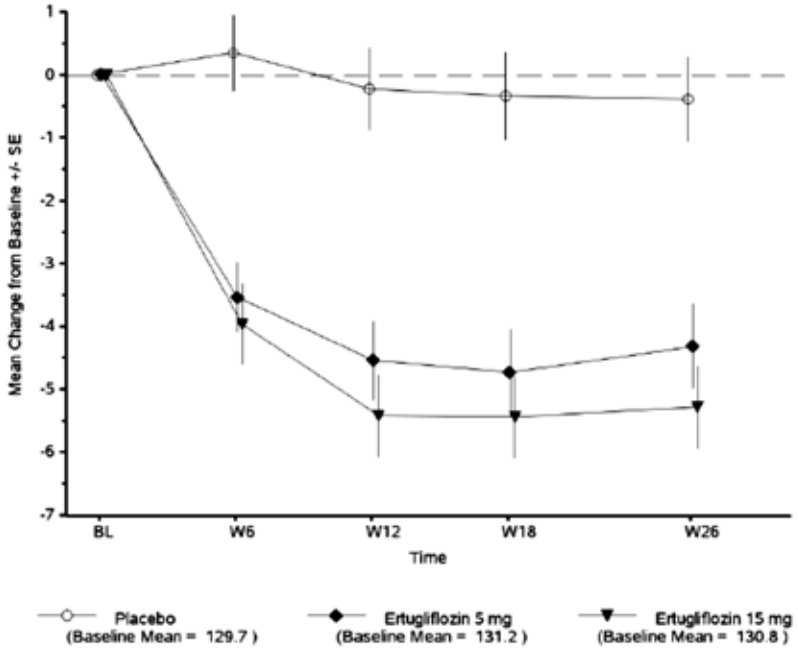
The EMA draft reflection paper on assessment of CV risk of medicinal products for the treatment of CV and metabolic diseases was released during the conduct of the ertugliflozin Phase III program. The sponsor has initiated two studies to evaluate CV risk of ertugliflozin (a CVOT study P004/1021 and an Asia Pacific regional study P012/1045). However, recruitment in these studies is ongoing and limited (CVOT) or no data (Asia Pacific) from these studies are

currently available. These CV outcomes studies will remain blinded until its completion according to agreement with the US FDA and the EMA. The CVOT study is estimated to complete in 2019, with the exact timing dependent on the accrual of CV events. Results of the CV meta-analysis were not provided in the submitted dossier.

8.4.7. Vital signs and clinical examination findings

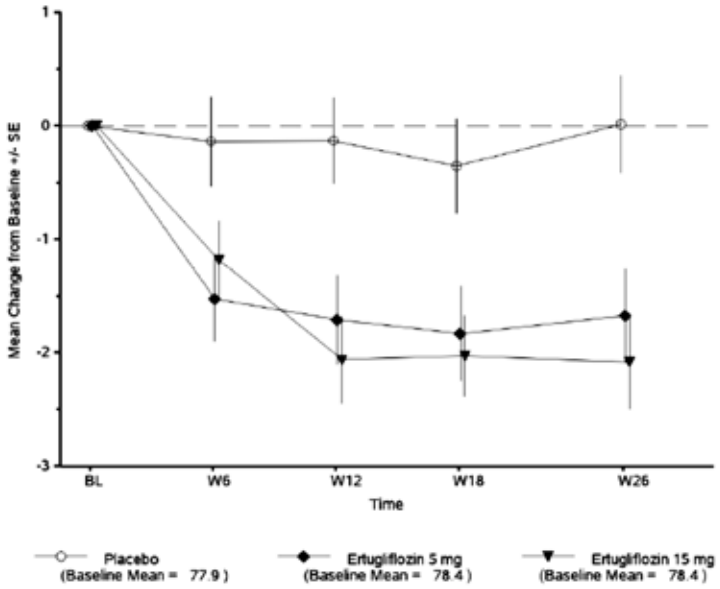
In the ertugliflozin/metformin pool, baseline SBP values were approximately 130 mmHg across groups. There was a decrease in SBP at each time point in the ertugliflozin 5 mg and 15 mg groups relative to the placebo group (Figure 2). The mean change from baseline in sitting SBP at Week 26 was greater in the ertugliflozin 5 mg and 15 mg groups (-4.32 mmHg and -5.29 mmHg, respectively) relative to the placebo group (-0.39mmHg). Similar results were observed in the 2 active comparator studies not included in the ertugliflozin/metformin pool (Studies P002/1013 and P005/1019).

Figure 2: Sitting systolic BP (mmHg); Mean change from baseline over time (mean ± SE), All subjects as treated. Ertugliflozin/metformin FDC pool: including rescue approach



In the ertugliflozin/metformin pool, baseline DBP values were approximately 78 mmHg across groups. There was a decrease in DBP at each time point in the ertugliflozin groups relative to the placebo group (Figure 3). The mean change from baseline in DBP at Week 26 was greater in the ertugliflozin 5 mg and 15 mg groups (-1.68 mmHg and -2.09 mmHg, respectively) relative to the placebo group (0.01 mmHg) Generally similar results were observed in the 2 active comparator studies not included in the ertugliflozin/metformin pool, Studies P002/1013 and P005/1019.

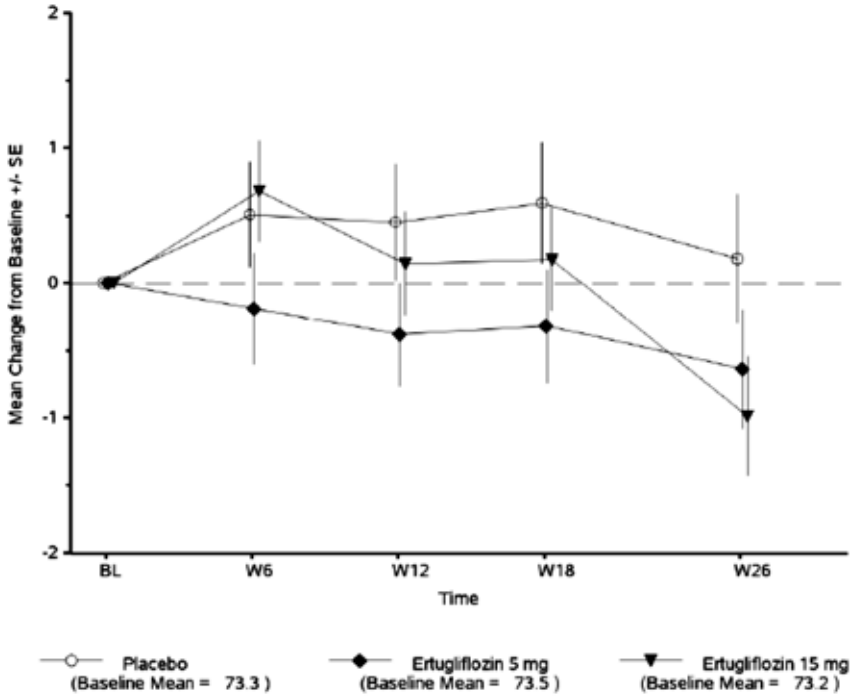
Figure 3: Sitting diastolic BP (mmHg); Mean change from Baseline over time (mean ± SE), All subjects as treated; ertugliflozin / metformin FDC pool: including rescue approach



While there were small numeric differences at each time point, there was no distinguishable pattern in the proportion of subjects who met the pre-specified definition for orthostatic change in systolic or diastolic blood pressure between the ertugliflozin 5 mg and 15 mg groups and placebo group. There was also no discernible pattern in the proportions of subjects meeting systolic or diastolic orthostatic change criteria in the 2 active comparator studies not included in the ertugliflozin/metformin Pool.

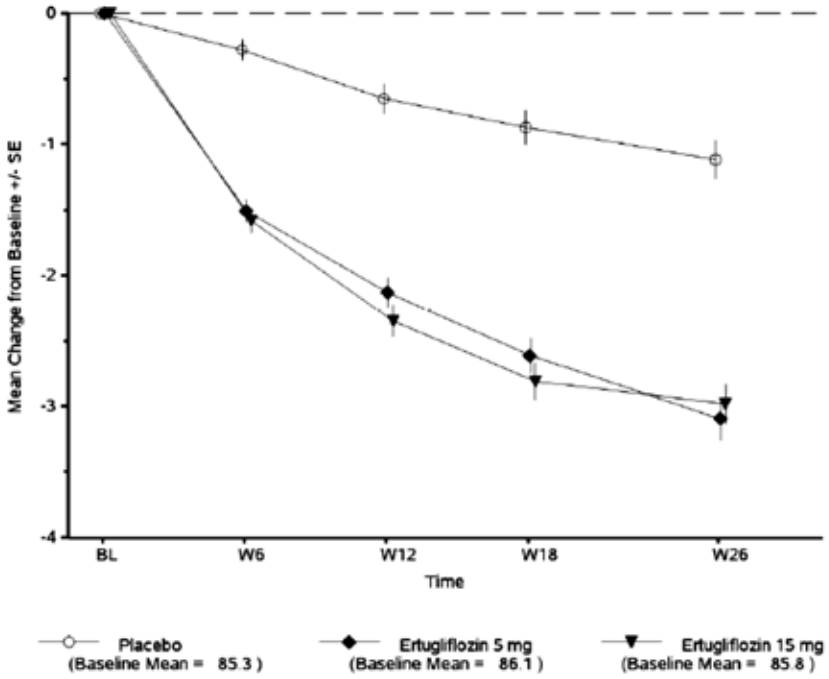
In each of the Phase III studies, sitting pulse rate was assessed at each visit. No meaningful differences in sitting pulse rate were observed over time in the ertugliflozin groups relative to the placebo group (Figure 4) or between groups in the 2 active comparator studies not included in the ertugliflozin/metformin pool.

Figure 4: Sitting pulse rate (bpm); Mean change from Baseline over time (mean ± SE). All subjects as treated; ertugliflozin/metformin FDC pool including rescue approach



In both of the studies in the ertugliflozin/metformin pool, the effect of ertugliflozin therapy on body weight was assessed as a secondary efficacy endpoint. In this safety analysis, data obtained after initiation of glycaemic rescue therapy were included whereas the primary evaluation for efficacy excluded post-rescue data. In the ertugliflozin/metformin pool, baseline values for body weight ranged from 85.3 to 86.1 kg (Figure 5). There was a decrease in body weight at each time point 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 (–3.1 kg and -3.0 kg, respectively) relative to the placebo group (-1.1 kg). Reductions from baseline in body weight were also observed in the ertugliflozin treated subjects in the 2 active comparator studies not included in the ertugliflozin/metformin pool.

Figure 5: Body weight (kg) Mean change from baseline over time (mean ± SE) All subjects as treated. Ertugliflozin / metformin FDC pool: including rescue approach



8.4.8. Immunogenicity and immunological events

The incidence of potential hypersensitivity AEs in the ertugliflozin broad pool (which included > 75% of patients on background metformin treatment) 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 with similar incidences across treatment 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.

8.4.9. Serious skin reactions

There were some reports of rash, urticaria, dermatitis, dermatitis allergic, eczema, and hypersensitivity in the ertugliflozin broad pool (which included > 75% of patients on background metformin treatment). 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).

8.4.10. Special safety topics for the Ertugliflozin/metformin FDC

Changes in renal function and ketoacidosis are 2 of the Special Safety Topics for ertugliflozin. Metformin has dosing considerations based on renal function and has a risk for lactic acidosis, particularly in subjects with significant renal impairment. Hence, changes in renal function and metabolic acidosis, along with hypoglycaemia, an important safety concern for all AHAs, were designated as Special Safety Topics for the proposed ertugliflozin/metformin FDC. Other Special Safety Topics identified for ertugliflozin were discussed in detail in the Steglatro report. Of these safety topics, osmotic diuresis, volume depletion, genital infection (specifically genital mycotic infection), urinary tract infection and changes in lipids were evaluated in the ertugliflozin/metformin pool.

8.4.10.1. Changes in renal function

Refer to *Renal function and renal toxicity* above.

8.4.10.2. Metabolic acidosis

Overall, 3 of 3409 (0.1%) ertugliflozin treated subjects were assessed to have met the case definition of ketoacidosis with either 'certain' or 'possible' likelihood compared to no cases in the non-ertugliflozin group (0 of 1450 subjects). Although the 3 cases assessed as 'certain' or 'possible' ketoacidosis were all in subjects on background metformin enrolled in the 4 FDC studies, approximately 75% of the studies in the ertugliflozin Phase III program evaluated subjects on background metformin, and therefore, this result may not reflect an increased risk of metabolic acidosis with ertugliflozin and metformin combination therapy relative to that of the individual agents. No events of lactic acidosis or related events (blood lactic acid abnormal, blood lactic acid increased, urine lactic acid, urine lactic acid increased, and hyperlactacidaemia) were reported in the Phase III development program. In the ertugliflozin/metformin Pool, there were no meaningful differences between groups in mean change from baseline in bicarbonate concentrations or events meeting PDLC criteria for decreases in bicarbonate.

8.4.10.3. Hypoglycaemia

As background therapy and initiation of glycaemic rescue therapy could confound the frequency and severity of hypoglycaemia, primary analyses for hypoglycaemia in the ertugliflozin Phase III program were in the excluding rescue population in the 4 individual studies contributing to this submission (Studies P007/1017, P006/1015, P002/1013 and P005/1019).

In the placebo controlled add-on to metformin Study P007/1017, there were no notable differences in the incidence of documented hypoglycaemia (symptomatic and asymptomatic together). The incidence of severe hypoglycaemia was low (Table 19). One subject in the ertugliflozin 5 mg group and 1 subject in the placebo group had events of severe hypoglycaemia. The incidence of symptomatic hypoglycaemia at Week 26 in the ertugliflozin 5 mg and the ertugliflozin 15 mg groups was numerically higher than in the placebo group (Table 20).

Table 19: Documented (symptomatic and asymptomatic) and severe hypoglycaemia events in the individual Phase III studies (ertugliflozin / metformin)

P007/1017 (26 weeks) Placebo-controlled Add-on to Metformin	Placebo (N=209)	Ertugliflozin 5 mg (N=207)	Ertugliflozin 15 mg (N=205)		
Documented, n (%) Severe, n (%)	9 (4.3) 1 (0.5)	15 (7.2) 1 (0.5)	16 (7.8) 0 (0)		
P006/1015 (26 weeks) Add-on to Metformin and Sitagliptin	Placebo (N=153)	Ertugliflozin 5 mg (N=156)	Ertugliflozin 15 mg (N=153)		
Documented, n (%) Severe, n (%)	5 (3.3) 1 (0.7)	7 (4.5) 1 (0.6)	3 (2.0) 0 (0)		
P002/1013 (52 weeks) Ertugliflozin vs Glimepiride as Add-on to Metformin	Glim (N=437)	Ertugliflozin 5 mg (N=448)	Ertugliflozin 15 mg (N=440)		
Documented, n (%) Severe, n (%)	119 (27.2) 10 (2.3)	25 (5.6) 1 (0.2)	36 (8.2) 1 (0.2)		
P005/1019 (26 weeks) Ertugliflozin + Sitagliptin Factorial	Sitagliptin (N=247)	Ertugliflozin 5 mg (N=250)	Ertugliflozin 15 mg (N=248)	Ertugliflozin 5 mg + Sitagliptin 100 mg (N=243)	Ertugliflozin 15 mg + Sitagliptin 100 mg (N=244)
Documented, n (%) Severe, n (%)	9 (3.6) 0 (0)	14 (5.6) 0 (0)	13 (5.2) 1 (0.4)	13 (5.3) 0 (0)	22 (9.0) 1 (0.4)

N = number of subjects in the ASaT population, n = number of subjects with one or more events

Table 20: Symptomatic hypoglycaemia AEs by study (ertugliflozin / metformin)

P007/1017 (26 weeks) Placebo-controlled Add-on to Metformin Study	Placebo (n=209)	Ertugliflozin 5mg (n=207)	Ertugliflozin 15mg (n=205)		
Symptomatic Hypoglycemia, n (%)	4 (1.9)	7 (3.4)	7 (3.4)		
P006/1015 (26 weeks) Add-on to Metformin and Sitagliptin Study	Placebo (n=153)	Ertugliflozin 5mg (n=156)	Ertugliflozin 15mg (n=153)		
Symptomatic Hypoglycemia, n (%)	4 (2.6)	6 (3.8)	1 (0.7)		
P002/1013 (52 weeks) Ertugliflozin vs Glimepiride as Add-on to Metformin Study	Glimepiride (n=437)	Ertugliflozin 5mg (n=448)	Ertugliflozin 15mg (n=440)		
Symptomatic Hypoglycemia, n (%)	84 (19.2)	14 (3.1)	23 (5.2)		
P005/1019 (26 weeks) Ertugliflozin + Sitagliptin Factorial Study	Sitagliptin 100 mg (n=247)	Ertugliflozin 5mg (n=250)	Ertugliflozin 15mg (n=248)	Ertugliflozin 5 mg + Sitagliptin 100 mg (n=243)	Ertugliflozin 15 mg + Sitagliptin 100 mg (n=244)
Symptomatic Hypoglycemia, n (%)	6 (2.4)	6 (2.4)	6 (2.4)	6 (2.5)	12 (4.9)
N = number of subjects in the ASaT population, n = number of subjects with one or more events					

In the add-on to metformin and sitagliptin Study P006/1015, the incidence of documented hypoglycaemia was low and not notably different between the ertugliflozin dose groups and the placebo group. Two subjects, 1 in the ertugliflozin 5 mg group and 1 in the placebo group, had an AE of severe hypoglycaemia. Compared with placebo, the incidence of symptomatic hypoglycaemia at Week 26 was similar in the ertugliflozin 5 mg group, and numerically lower in the ertugliflozin 15 mg group (Table 20).

In the ertugliflozin versus glimepiride as add-on to metformin Study P002/1013, the incidence of documented hypoglycaemia was lower in the ertugliflozin dose groups relative to the glimepiride group (5.6%, 8.2% and 27.2% in the ertugliflozin 5 mg, 15 mg and glimepiride groups, respectively). The incidence of severe hypoglycaemia was also lower in the ertugliflozin dose groups compared to glimepiride. There were 2 ertugliflozin treated subjects, 1 each in the ertugliflozin 5 mg and 15 mg groups, compared with 10 glimepiride treated-subjects with severe hypoglycaemia reported. The incidence of symptomatic hypoglycaemia at Week 52 was lower in both the ertugliflozin 5 mg and 15 mg groups relative to the glimepiride group (3.1%, 5.2% and 19.2%, respectively).

In the ertugliflozin + sitagliptin factorial Study P005/1019, the incidence of documented hypoglycaemia was low and similar in the E5 and E15 groups, with a numerically lower incidence seen in the S100 group. One subject in the E15 group, and none in the E5 or S100 groups, had a severe event of hypoglycaemia. The incidence of symptomatic hypoglycaemia was the same in the E5, E15, and S100 groups (Table 20).

In the ertugliflozin/metformin FDC Pool, the incidence of documented hypoglycaemia (symptomatic and asymptomatic) was similar in the placebo and ertugliflozin groups (3.9%, 6.1% and 5.3%, in the placebo, ertugliflozin 5 mg and 15 mg groups, respectively). In addition, the incidence of severe hypoglycaemia was low (< 1%) and similar across the ertugliflozin dose groups and placebo group. Among the subjects having an episode of documented hypoglycaemia, most had only 1 event. The incidence of subjects having 3 or more events of documented hypoglycaemia was not notably different (0.6%, 1.7% and 0.8%, respectively). Finally, the incidence of subjects with an episode of documented hypoglycaemia associated with a glucose of < 3.1 mmol/L was low and similar in placebo and ertugliflozin groups (1.1%, 1.4% and 0.8%, respectively). Among the subjects having a severe event, only 1 subject in the ertugliflozin 5 mg group had a glucose < 3.1 mmol/L). There were no notable differences in the incidence of subjects having symptomatic hypoglycaemia events (2.2%, 3.6% and 2.2%, respectively). A clinical review of accidents and injuries, including falls, as determined by a CMQ determined that there were no subjects in the ertugliflozin/metformin Pool with hypoglycaemia events that were concurrent with or immediately preceding these events.

8.4.11. Urinary tract infections

In the ertugliflozin/metformin pool, the incidence of urinary tract infections was significantly higher in the ertugliflozin 15 mg group (4.2%; p = 0.044) and numerically higher in the ertugliflozin 5 mg group (2.8%) and the all ertugliflozin groups (3.5%) compared to the placebo group (1.7%). There was 1 event of urinary tract infection in the ertugliflozin 15 mg group that resulted in discontinuation of study medication. There were no serious events of urinary tract infections. In Study P002/1013, the incidence of urinary tract infections was similar across the ertugliflozin 5 mg and 15 mg treatment groups (6.7% and 6.4%, respectively) and the glimepiride group (6.9%). In Study P005/1019, the incidence of urinary tract infections was numerically higher in the E5 and E15 groups (6.0% and 5.6%, respectively) relative to the S100 group (3.2%) (no formal comparisons were performed). Of note, the incidence of urinary tract infections in the E5/S100 and E15/S100 groups (3.3% and 3.7%, respectively) was similar to that of the S100 group.

Comment: While the incidence of urinary tract infection was higher in ertugliflozin treated subjects in the ertugliflozin/metformin pool, this was not typical of the other larger pooled analyses reviewed for the ertugliflozin SCS (PBO and broad pools). The sponsors propose that as there is no mechanism to suggest a risk from the concurrent use of ertugliflozin and metformin and urinary tract infection is not considered a meaningful risk for the combination. Furthermore, 'urinary tract infections' has been included as a potential risk in the proposed pharmacovigilance activities.

8.4.12. Genital mycotic infection

In the ertugliflozin/metformin pool, the incidence of genital mycotic infection in men was significantly higher in the ertugliflozin 5 mg group (3.9%; p = 0.005), ertugliflozin 15 mg group (3.4%; p = 0.009), and the all ertugliflozin group (3.7%; p = 0.006) relative to the placebo group (none reported). None of the events was serious. One subject in the ertugliflozin 5 mg group discontinued study medication due to an event of balanoposthitis. The incidence of genital mycotic infection in women was significantly higher in the ertugliflozin 5 mg group (6.5%; p = 0.015), ertugliflozin 15 mg group (8.7%; p = 0.002), and the all ertugliflozin group (7.6%; p = 0.004) relative to the placebo group (1.2%). The incidence of genital mycotic infection was numerically higher in the ertugliflozin 15 mg group relative to the ertugliflozin 5 mg group. Two subjects in the ertugliflozin 5 mg group (vulvovaginal mycotic infection and vulvovaginal candidiasis) discontinued study medication as a result of genital mycotic infections. The incidence of genital mycotic infections in both male and female subjects was also greater in ertugliflozin subjects in the 2 active comparator studies (Studies P002/1013 and P005/1019). In the overall ertugliflozin Phase III development program, the incidence of complicated infections was low in all groups (< 1% in men and ≤ 0.3% in women). Overall, the data in the ertugliflozin/metformin Pool and the individual active controlled studies on a background of metformin identified no additional safety or tolerability concerns with regard to genital mycotic infections, for the combination relative to the two agents given alone.

8.4.13. Volume depletion and osmotic diuresis

The incidence of volume depletion events in the ertugliflozin/metformin pool was similar across the ertugliflozin 5 mg and 15 mg groups and the placebo group. The incidence of AEs related to osmotic diuresis in the ertugliflozin/metformin pool was low across all groups but numerically higher in the ertugliflozin 5 mg and 15 mg groups (2.2% and 2.0%, respectively) relative to the placebo group (0.6%). None of these events was serious or led to discontinuation of study medication. One subject, in the ertugliflozin 15 mg group, had a severe event (pollakiuria); all other events were mild or moderate in intensity. Results for AEs related to increased urination were similar to those seen for osmotic diuresis. The incidence of events related to thirst was low, but numerically higher in the ertugliflozin 5 mg and 15 mg groups

(0.8% and 0.6%, respectively) compared to the placebo group (0.3%)). None of the thirst AEs was of a serious or severe nature or resulted in discontinuation from study medication. No formal analysis of osmotic diuresis was performed in individual CSRs. However, in a post hoc analysis for the ertugliflozin+sitagliptin factorial Study P005/1010, the incidence of osmotic diuresis was low (≤ 2.1% in each group), without any notable pattern of occurrence across groups.

8.4.14. Other safety topics in the ertugliflozin Phase III program

In the Phase III ertugliflozin development program, there was no increased risk associated with ertugliflozin treatment and fracture, venous thromboembolism, hepatic injury, pancreatitis, hypersensitivity or malignancy. Non-traumatic limb amputations and peripheral revascularisations were reported with low incidence overall; amputations, particularly involving toes, occurred more frequently in ertugliflozin treated subjects. The clinical significance of the amputation/peripheral revascularisation data as related to ertugliflozin is uncertain.

8.5. Other safety issues

8.5.1. Safety in special populations

No specific analyses to assess intrinsic factors were performed for subjects taking the combination of ertugliflozin and metformin. Formal subgroup analyses for safety were not performed in the ertugliflozin/metformin pool given the smaller subgroup sizes limiting the precision of the estimates. However, genital mycotic infections were assessed by gender (refer above). Subgroup analyses for age, gender, race, ethnicity, and renal function were performed in the 7 study ertugliflozin broad pool (refer to the Steglatro evaluation report (see Attachment 2)).

8.5.1.1. Pregnancy/lactation

There are no adequate and well-controlled studies in pregnant women with the ertugliflozin/metformin FDC or its individual components. The FDC should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Metformin did not adversely affect developmental outcomes when administered to rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about 2 and 6 times the maximum recommended human dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of foetal concentrations demonstrated a partial placental barrier to metformin. Based on results from animal studies, ertugliflozin may affect renal development and maturation, therefore the ertugliflozin/metformin FDC is not recommended during the second and third trimesters of pregnancy.

No studies in lactating animals have been conducted with the combined components of the ertugliflozin/metformin FDC. In studies performed with the individual components, both ertugliflozin and metformin are secreted in the milk of lactating rats. It is not known whether ertugliflozin is excreted in human milk. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney, based on data with ertugliflozin. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from the ertugliflozin/metformin FDC, a decision should be made whether to discontinue nursing or to discontinue the FDC, taking into account the importance of the drug to the mother.

8.5.1.2. Overdose, drug abuse, withdrawal/ rebound

In 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 adverse events were reported (that

were not seen in lower dose groups (< 100 mg)) and adverse events reported in more than 1 subject were generally similar to those reported at lower doses. There is no specific antidote for overdose with ertugliflozin. Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 g. Hypoglycaemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases. Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, haemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

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.

No risk for drug abuse is contained in the metformin label. 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 metformin and ertugliflozin, any increase in blood glucose levels would not be expected to be precipitous.

Upon discontinuation of any AHA agent, patients should be advised to continue monitoring their blood glucose levels and discuss appropriate therapeutic options with their health care professional.

8.5.1.3. Effects on ability to drive or operate machinery or impairment of mental ability

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

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

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulphonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

No DDI studies were undertaken using the proposed FDC tablets. When administered as single agents, the DDIs for metformin are well established and the DDIs for ertugliflozin are discussed in the concurrent submission for Steglatro. It should be noted however that the PK interactions between ertugliflozin and other drugs commonly administered to the target population such as diuretics, warfarin, digoxin and so on was not evaluated in the concurrent submission. In addition, a limited number of DDI studies were undertaken with drugs that are known to interact with the pathways via which ertugliflozin is metabolised. For instance, although ertugliflozin is in part metabolised by CYP3A4, no studies have examined the effects of a strong CYP3A-inhibitor on ertugliflozin PKs or safety.

8.6. Post marketing experience

Not applicable as the ertugliflozin/metformin FDC has not been approved for use in any country.

8.7. Evaluator's overall conclusions on clinical safety

The safety and tolerability profile of ertugliflozin, 5 mg QD and 15 mg QD, has been presented in a separate submission (refer to the Steglatro report, submission PM-2017-01328-1-5, available as Attachment 2). Metformin, including the proposed daily doses, has an established safety and

tolerability profile. The main AEs associated with metformin use are diarrhoea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, metallic taste and headache. Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment. The following conditions and situations can result in lactic acidosis: impaired renal function, concomitant medication(s) that may affect renal function, impaired hepatic function, excessive alcohol intake, poorly controlled diabetes, ketosis, prolonged fasting, and any condition associated with hypoxia. Therefore, patients experiencing these conditions should avoid taking metformin. Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Hypoxic states, including CV collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterised by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia.

All the above know AEs associated with metformin use have been adequately covered in the proposed PI for the FDC of ertugliflozin metformin.

Ertugliflozin treatment, in the overall Phase III program and in the ertugliflozin/metformin pool, led to small mean changes from baseline in the serum lipid profile including increased LDL-C, total cholesterol, and HDL-C and decreases in triglycerides. There were small increases in phosphate and magnesium, but not calcium, with ertugliflozin treatment. This was similar to the findings in the broader Phase III ertugliflozin program. The clinical significance of these findings is unknown given there was no increase in fractures or decrease in bone mineral density (BMD) at 26 weeks in ertugliflozin treated groups in the placebo-controlled add-on to metformin Study (P007/1017). There were no meaningful changes noted in potassium level. There were no meaningful changes in potassium, bicarbonate, or sodium associated with ertugliflozin treatment in the ertugliflozin/metformin Pool and the 2 active comparator studies on metformin background therapy not included in the Pool. Ertugliflozin treatment in the ertugliflozin/metformin Pool was associated with decreases in systolic and diastolic blood pressure and body weight. There was no noted increase in heart rate or measures of orthostatic hypotension. There were no clinically meaningful differences in ECG parameters (heart rate, PR, QRS, QT, QTcB, and QTcF interval) across the ertugliflozin 5 mg and 15 mg groups and placebo group. These results are consistent with those in the full ertugliflozin development program.

Overall, the combination of ertugliflozin and metformin was generally safe and well tolerated, for both the 5 mg and 15 mg doses of ertugliflozin. The use of an FDC of ertugliflozin and metformin is supported by these Phase III clinical data that evaluate the combination of ertugliflozin and metformin administered as separate tablets, with the demonstrated BE of the FDC to the individual components when co-administered and equivalence of ertugliflozin area under the curve over 24 hours at steady state of once daily (QD) and twice daily (BD) dosing regimen. Overall, no safety concerns were identified that were unique to the combination of ertugliflozin and metformin and safety of the proposed FDC is adequately described by experience with the individual agents.

8.8. First round benefit-risk assessment

8.8.1. First round assessment of benefits

Table 21: First round assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
Ertugliflozin 15 mg and 5 mg, as add-on to metformin (alone or in combination with sitagliptin) provides clinically meaningful improvements in glycaemic control (A1c, proportion of subjects with A1c < 7.0%, FPG, 2 hour PPG), as well as body weight reduction and SBP reduction in subjects with T2DM.	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 A1c reduction compared to glimepiride plus metformin. Ertugliflozin 5 mg and 15 mg od was associated with greater reduction in FPG, body weight and SBP compared with glimepiride. Significantly lower incidence of hypoglycaemia with ertugliflozin compared with glimepiride.	Non-inferiority of ertugliflozin 5mg and glimepiride was not established.
No safety concerns were identified that were unique to the combination of ertugliflozin and metformin and safety of the proposed FDC is adequately described by experience with the individual agents.	Dose-dependent increase in incidence of genital mycotic infections and elevated LDL-C.
FDC has the potential to improve treatment compliance.	However, proposed FDC uses immediate release metformin and so requires twice daily dosing. Use of extended release metformin which requires only once daily dosing was not explored by the sponsors.

8.9. First round assessment of risks

Table 22: 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.
Although CV meta-analysis of confirmed/adjudicated CV events in the Phase III studies was conducted, results were	The sponsor has initiated a CV outcome Study P004/1021 which is expected to complete in 2019.

Risks	Strengths and Uncertainties
not presented.	
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 5mg, 15mg 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.
None of the Phase II dose ranging studies evaluated the proposed 15mg 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.

8.9.1. First round assessment of benefit-risk balance

No Phase III studies have been performed with the proposed ertugliflozin/metformin FDC tablet. The studied doses of the FDC tablets (ertugliflozin 7.5 mg/metformin 1000 mg, ertugliflozin 7.5 mg/metformin 850 mg and ertugliflozin 2.5 mg/metformin 500 mg) are bioequivalent under fasted conditions to the corresponding doses of ertugliflozin and metformin tablets (US or EU-sourced Glucophage) when co-administered. The metformin component of the studied doses of the FDC tablets (ertugliflozin 7.5 mg/metformin 850 mg and ertugliflozin 2.5 mg/metformin 500 mg) is also bioequivalent to the corresponding doses of metformin tablets (Canadian sourced Glucophage) when co-administered with corresponding doses of ertugliflozin tablets under fasted and fed conditions. These clinical data, along with the in vitro multi-media dissolution data, support the bridging of pharmacokinetic,

pharmacodynamic, efficacy and safety data obtained in the Phase III studies to the proposed FDC commercial tablets. Hence, data obtained from the 4 Phase III studies (P006/1015, P007/1017, P002/1013 and P005/1019) that assessed the use of ertugliflozin on a background of metformin (≥ 1500 mg/day) can be bridged to the FDC tablet based on established bioequivalence.

In all 4 studies, clinically meaningful A1c reductions were observed when ertugliflozin 5 mg or 15 mg was added on to metformin (second line use) or metformin and sitagliptin (third line use). On a background of metformin, ertugliflozin 5 mg and 15 mg resulted in reductions in A1c that were generally greater than the results in the placebo group at Week 26, irrespective of gender, age, sex, race, ethnicity, geographic region, baseline BMI, baseline A1c, baseline eGFR, and duration of T2DM.The results of Study P002/1013 demonstrate that ertugliflozin offers several clinically relevant advantages to glimepiride as an add-on to metformin with regards to safety/ tolerability (that is, lower rates of hypoglycaemia) and reductions in SBP and body weight.

In the ertugliflozin/metformin FDC pool, ertugliflozin 15 mg provided a numerically greater reduction in A1c (approximately 0.14%) compared to ertugliflozin 5 mg. In all 4 Phase III studies, a numerically greater proportion of subjects reached A1c < 7.0% with ertugliflozin 15 mg compared with 5 mg. The small but consistently greater A1c reduction from baseline with ertugliflozin 15 mg over ertugliflozin 5 mg may have an impact on the ability of patients to reach their A1c goal.

The mechanism of action of ertugliflozin and metformin and the safety profiles of each agent do not suggest significant safety or tolerability risks related to the combination of the 2 agents. The safety data from the 4 Phase III studies are entirely consistent with the safety data from the overall ertugliflozin program (7 Phase III studies). Overall, studies on a background of metformin identified no additional safety or tolerability risk for the combination relative to the 2 agents administered alone.

The ertugliflozin/metformin FDC will contain an immediate-release formulation of metformin, which requires twice daily dosing. Therefore, the ertugliflozin/metformin FDC also requires twice daily dosing. Bridging of the once daily ertugliflozin dosing regimen used in the Phase III studies to the proposed BD regimen for the FDC was shown through a Phase I PK/PD study (P035/1051) which showed equivalence of steady-state ertugliflozin AUC_{0-24} on Day 6, and similarity in steady state PD (UGE_{0-24} after the morning dose on Day 6), between the QD and BD regimens at the same total daily dose (2.5 mg BD versus 5 mg QD and 7.5 mg BD versus 15 mg QD). This study supports BD dosing of the ertugliflozin-metformin FDC. However, it is important to note that there was no clinical study to compare the clinical efficacy/safety of once versus twice daily ertugliflozin dosing. Furthermore, two FDCs containing a SGLT-2 inhibitor and metformin are already available in Australia: Xigduo-XR: FDC of dapagliflozin+metformin which requires once daily dosing, and Jardiamet: FDC containing empagliflozin and metformin which requires twice daily dosing. It is important to note that empagliflozin has added advantage of being approved in adults with type 2 diabetes mellitus and established cardiovascular disease to reduce the risk of cardiovascular death. This is especially important in light of the fact that no CV data was submitted for ertugliflozin. There is also lack of adequate evidence for LT efficacy/safety of ertugliflozin (refer to Steglatro report).

Overall, the benefit-risk profile Segluromet (FDC of ertugliflozin+metformin) in the proposed usage is not currently favourable, but may become favourable if the changes recommended in section 8.6 are adopted.

8.10. First round recommendation regarding authorisation

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

> *Segluromet (ertugliflozin and metformin hydrochloride) is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and metformin is appropriate*.

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

> *Indications: Segluromet (ertugliflozin and metformin hydrochloride) is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and metformin is appropriate. (refer Clinical Trials, Dosage and Administration).*

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

- Resolution of outstanding issues of the ertugliflozin submission (refer to Steglatro report (see Attachment 2)).
- Incorporation of suggested changes to proposed PI.
- Satisfactory response to Clinical questions.

9. Clinical questions

9.1. Pharmacokinetics

9.1.1. Question 1:

Can the sponsor please confirm that the compositions of the proposed Segluromet and MSD-ertugliflozin-metformin FDC tablets of matching dose strengths are identical?

9.1.2. Question 2:

Metformin is also available as an extended-release tablet in Australia, which requires once daily dosing; can the sponsor please explain why this formulation of metformin was not explored by the sponsors for the FDC?

9.2. Pharmacodynamics

None.

9.3. Efficacy

None.

9.4. Safety

9.4.1. Question 3

In the SCS the following is mentioned:

> *4.1.1 Sitting Systolic Blood Pressure In the ertugliflozin/metformin Pool, baseline systolic blood pressure values were approximately 130 mmHg across groups. There was a decrease in systolic blood pressure at each time point in the ertugliflozin 5 mg and 15 mg groups relative to the placebo group (Figure 4). The mean change from baseline in sitting systolic blood pressure at Week 26 was greater in the ertugliflozin 5 mg and 15 mg groups (-4.32 mmHg and -5.29 mg/dL, respectively) relative to the placebo group (-0.39 mg/dL)*.

There appears to be a typographical error in terms of units for SBP. Could the sponsors please confirm that the values are accurate although the units are not?

10. Second round evaluation

10.1. Clinical Questions

The clinical questions in the first round report are stated first followed by a summary of the sponsor's response and then the evaluator's comments on the sponsor's response.

10.1.1. Pharmacokinetics

10.1.1.1. Question 1

Can the sponsor please confirm that the compositions of the proposed Segluromet and MSD-ertugliflozin-metformin FDC tablets of matching dose strengths are identical?

Sponsor's response

The sponsor confirms that the composition of the proposed Segluromet and MSD-ertugliflozin-metformin fixed-dose combination (FDC) of matching dose strengths are identical.

Evaluator's comments

The evaluator is satisfied with the sponsor's response.

10.1.1.2. Question 2

Metformin is also available as an extended-release tablet in Australia, which requires once daily dosing; can the sponsor please explain why this formulation of metformin was not explored by the sponsors for the FDC?

Sponsor's response

Both an immediate release as well as an extended-release formulation was evaluated by the sponsor for the FDC. The results showed that only the immediate release metformin FDC formulation is commercially viable as immediate release metformin is available globally while the extended-release metformin is only available in specific markets.

Evaluator's comments

The evaluator is satisfied with the sponsor's response.

10.1.2. Safety

10.1.2.1. Question 3

In the SCS the following is mentioned:

> *4.1.1 Sitting Systolic Blood Pressure In the ertugliflozin/metformin Pool, baseline systolic blood pressure values were approximately 130 mmHg across groups. There was a decrease in systolic blood pressure at each time point in the ertugliflozin 5 mg and 15 mg groups relative to the placebo group (Figure 4). The mean change from baseline in sitting systolic blood pressure at Week 26 was greater in the ertugliflozin 5 mg and 15 mg groups (-4.32 mmHg and -5.29 mg/dL, respectively) relative to the placebo group (-0.39 mg/dL).*

There appears to be a typographical error in terms of units for SBP. Could the sponsor please confirm that the values are accurate although the units are not?

Sponsor's response

The sponsor confirms that the blood pressure units for the ertugliflozin 15 mg and placebo groups are incorrect and that all other results in the paragraph are accurate.

Evaluator's comments:

The sponsor's response is satisfactory.

10.2. Second round benefit-risk assessment

10.2.1. Second round assessment of benefits

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

10.2.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of ertugliflozin + metformin FDC in the proposed usage are unchanged from those identified in the first round evaluation of Segluromet.

10.2.3. 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.

10.3. Second round recommendation regarding authorisation

Approval of Segluromet (ertugliflozin and metformin FDC) is recommended for the following indication:

> *Segluromet (ertugliflozin and metformin hydrochloride) is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and metformin is appropriate. (refer Clinical Trials, Dosage and Administration).*

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 component of the proposed FDC.
- Submission of results of the cardiovascular meta-analysis (CVMA) of adjudicated, confirmed CV events from the Phase II/III studies and from the ongoing CV outcome study (Study P004/1021) upon completion.

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