25 January 2018
EMA/86928/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Segluromet

International non-proprietary name: ertugliflozin / metformin hydrochloride

Procedure No. EMEA/H/C/004314/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Background information on the procedure 7
1.1. Submission of the dossier 7
1.2. Steps taken for the assessment of the product 8

2. Scientific discussion 9
2.1. Problem statement 9
2.1.1. Disease or condition 9
2.1.2. Epidemiology 9
2.1.3. Clinical presentation 9
2.1.4. Management 10
2.2. Quality aspects 12
2.2.1. Introduction 12
2.2.2. Active Substance - ertugliflozin 12
2.2.3. Active Substance - Metformin hydrochloride 15
2.2.4. Finished Medicinal Product 16
2.2.5. Discussion on chemical, pharmaceutical and biological aspects 19
2.2.6. Conclusions on the chemical, pharmaceutical and biological aspects 20
2.2.7. Recommendation(s) for future quality development 20
2.3. Non-clinical aspects 20
2.3.1. Introduction 20
2.3.2. Pharmacology 20
2.3.3. Pharmacokinetics 22
2.3.4. Toxicology 24
2.3.5. Ecotoxicity/environmental risk assessment 33
2.3.6. Discussion on non-clinical aspects 37
2.3.7. Conclusion on the non-clinical aspects 41
2.4. Clinical aspects 41
2.4.1. Introduction 41
2.4.2. Pharmacokinetics 45
2.4.3. Pharmacodynamics 50
2.4.4. Discussion on clinical pharmacology 53
2.4.5. Conclusions on clinical pharmacology 55
2.5. Clinical efficacy 55
2.5.1. Dose response studies 55
2.5.2. Main studies 56
2.5.3. Discussion on clinical efficacy 101
2.5.4. Conclusions on the clinical efficacy 108
2.6. Clinical safety 108
2.6.1. Discussion on clinical safety 137
2.6.2. Conclusions on the clinical safety 143
2.7. Risk Management Plan 144
2.8. Pharmacovigilance 148

2.9. New Active Substance 149
2.10. Product information 149
2.10.1. User consultation 149
2.10.2. Additional monitoring 149

3. Benefit-Risk Balance 149
3.1. Therapeutic Context 149
3.1.1. Disease or condition 149
3.1.2. Available therapies and unmet medical need 150
3.1.3. Main clinical studies 150
3.2. Favourable effects 151
3.3. Uncertainties and limitations about favourable effects 153
3.4. Unfavourable effects 153
3.5. Uncertainties and limitations about unfavourable effects 154
3.6. Effects Table 154
3.7. Benefit-risk assessment and discussion 155
3.7.1. Importance of favourable and unfavourable effects 155
3.7.2. Balance of benefits and risks 156
3.7.3. Additional considerations on the benefit-risk balance 157
3.8. Conclusions 157

4. Recommendations 157

List of abbreviations

Abbreviation	Definition
%AR	Applied radioactivity in percent
A1C	glycosylated haemoglobin A1c
ADA	American Diabetes Association
AHA	anti-hyperglycaemic agent
AIBN	2,2'-Azobis(2-methylpropionitrile)
ALT	alanine aminotransferase
Alu	aluminium
ANCOVA	analysis of covariance
ASaT	All Subjects as Treated
AST	aspartate aminotransferase
AUC	area under the curve
AUCinf	area under the concentration-time curve from 0 to infinity
AUClast	area under the concentration –time curve from zero to time of last measurable concentration
BCS	biopharmaceutical classification system
bid	twice daily
BMD	bone mineral density
BMI	body mass index
Broad pool	pooled safety data from all seven ertugliflozin phase III studies
BUN	blood urea nitrogen
CFU	colony forming units
CHMP	Committee for Medicinal Products for Human use
CI	confidence interval
cLDA	constrained longitudinal data analysis
CMQ	custom MedDRA query
Cmax	maximum concentration
CPP	critical process parameter
CQA	Critical Quality Attribute
CS	Control strategy
CTX	carboxy terminal cross linking telopeptides of Type I collagen
CV	cardiovascular
DMC	data monitoring committee
DOC	Dissolved Oxygen Concentration
DoE	Design of experiments
DPP-4	dipeptidyl peptidase-4
DS	Design space
DT_{50}	Time required for 50% degradation/dissipation of the initial concentration
DT_{90}	Time required for 90% degradation/dissipation of the initial concentration
DXA	dual-energy x-ray absorptiometry
E5	ertugliflozin 5 mg qd (Study P005/1019)
E5/S100	ertugliflozin 5 mg qd + sitagliptin 100 mg qd (Study P005/1019)
E15	ertugliflozin 15 mg qd (Study P005/1019)
E15/S100	ertugliflozin 15 mg qd + sitagliptin 100 mg qd (Study P005/1019)
ECHA	European Chemicals Agency
ECG	Electrocardiogram
eGFR	estimated glomerular filtration rate
ER approach	excluding rescue treatment approach
ERA	Environmental risk assessment
ertu	ertugliflozin
Ertu/Met	ertugliflozin/metformin
Ertu/Met pool	pooled safety data from placebo-controlled ertugliflozin add-on metformin phase III studies
ESFA	European Food Safety Authority
ESI-MS	electrospray positive ionization mass spectra
FA	Focus area
FAS	full analysis set

FDA	Food and Drug Administration
FDC	fixed-dose combination
$FeCl_3$	Iron (III) chloride
Fpen	Market penetration factor
FPG	fasting plasma glucose
GAD	glutamic acid decarboxylase
GC	gas chromatography
GLP 1	glucagon-like peptide 1
GMP	good manufacturing practice
HDL-C	high density lipoprotein-cholesterol
HDPE	high density polyethylene
HPLC	high performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	inductively coupled plasma mass spectrometry
IPC	in-process control
IR	infrared
IR Approach	including rescue treatment approach
J2R	jump-to-reference multiple-imputation method
Kd_{oc}	Adsorption distribution coefficient normalized to organic content in matrix
KF	Karl Fischer
KOH	potassium hydroxide
LDL-C	low density lipoprotein-cholesterol
LDPE	low density polyethylene
LOEC	Lowest Observed Effect Concentration
L-PGA	L-pyroglutamic acid
LS	Least-squares
MACE	Major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
met	metformin
mFAS	modified FAS
MNAR	missing-not-at-random assumption
NDA	New Drug Application
NIR	near infrared
NMR	nuclear magnetic resonance
NMT	not more than
NOEC	No Observed Effect Concentration
PA	polyamide
PAR	proven acceptable ranges
PAT	process analytical technology
Pbo/PBO	Placebo (PBO when referencing the Placebo Pool)
PBO-pool	pooled safety data from placebo-controlled ertugliflozin phase III studies
PDLC	Pre-defined limit of change
PEC_{SED}	Predicted environmental concentration in sediments
PEC_{SW}	Predicted environmental concentration in surface waters
Ph. Eur.	European Pharmacopoeia
PND	postnatal day
PNEC	Predicted no-effect concentration
PPG	postprandial plasma glucose
PTH	parathyroid hormone
PVC	poly vinyl chloride
PXRD	powder X-Ray diffraction
QbD	quality by design
QC	quality control
qd	once daily
QT	Time from the start of the Q wave to the end of the T wave
QTcF	QT interval corrected using the Fridericia formula
QTPP	quality target product profile
RA	risk assessment
RH	relative humidity
RQ	(Environmental) Risk Quotient
S100	sitagliptin 100 mg qd (Study P005/1019)

SAP	statistical analysis plan
SGLT1	sodium-glucose co-transporter 1
SGLT2	sodium-glucose co-transporter 2
SmPC	summary of product characteristics
SMQ	Standard MedDRA Query
SOC	System organ class
T2DM	type 2 diabetes mellitus
TAMC	total aerobic microbial count
Tmax	time to first occurrence of maximum observed concentration
TYMC	total combined yeasts/moulds count
UGE	urinary glucose excretion
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
UTI	urinary tract infection
UV	ultraviolet
UV-Vis	ultraviolet-visible

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Merck Sharp & Dohme Limited submitted on 27 January 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Segluromet, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 October 2015.

The applicant applied for the following indication:

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

- in patients not adequately controlled on their maximally tolerated dose of metformin alone
- in patients on their maximally tolerated doses of metformin along with other glucose-lowering medicinal products, including insulin, when these do not provide adequate glycaemic control (see sections 4.4, 4.5, and 5.1 for available data on different add-on therapies)
- in patients already being treated with the combination of ertugliflozin and metformin as separate tablets.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that ertugliflozin was considered to be a new active substance.

The application submitted is a new fixed combination medicinal product.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0054/2014 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

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

Applicant's request(s) for consideration

New active Substance status

The applicant requested the active substance ertugliflozin contained in the above fixed combination medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 22 September 2011, 19 December 2013 and on 21 May 2015. The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Agnes Gyurasics

- The application was received by the EMA on 27 January 2017.
- The procedure started on 23 February 2017.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 May 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 22 May 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 29 May 2017.
- During the meeting on 22 June 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 7 September 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 16 October 2017.
- During the PRAC meeting on 26 October 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 9 November 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 December 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 10 January 2018.
- During the meeting on 25 January 2018, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Segluromet on 25 January 2018.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The indication as initially proposed for Segluromet is:

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

- in patients not adequately controlled on their maximally tolerated dose of metformin alone
- in patients on their maximally tolerated doses of metformin along with other glucose-lowering medicinal products, including insulin, when these do not provide adequate glycaemic control (see sections 4.4, 4.5, and 5.1 for available data on different add-on therapies)
- in patients already being treated with the combination of ertugliflozin and metformin as separate tablets.

2.1.2. Epidemiology

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 (age 20 years to 79 years) 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. Approximately 90% of these diabetic patients have T2DM. In the United States (US), diabetes currently affects 29.1 million people or 9.3% of all adults and 26% of adults over 65 years of age. In 2015 in Europe, the estimated number of people with diabetes was 59.8 million, which is expected to increase to 71.1 million by 2040. The prevalence of diabetes in Europe was 9.1% in 2015 and expected to increase to 10.7% by 2020.

2.1.3. Clinical presentation

T2DM, the predominant type of diabetes accounting for >90% of all diabetes cases, is a progressive disease involving parallel defects of glucose metabolism in multiple tissues. Key processes leading to T2DM include peripheral insulin resistance, insulin secretory dysfunction, and hepatic glucose overproduction. The condition is associated with hypertension, hyperlipidaemia and increased body weight. The co-morbidities associated with uncontrolled diabetes are significant. Diabetes is the major cause of kidney failure, blindness, and non-traumatic leg amputations among adults in the US and the United Kingdom (UK), and is a leading cause of coronary heart disease and stroke. Cardiovascular (CV) disease is the leading cause of mortality in patients with diabetes, with life expectancy reduced by as much as 10 years in people with T2DM.

Common risk factors for T2DM include increasing age, smoking, being overweight or obese, physical inactivity and poor nutrition, family history of T2DM, race/ethnicity (eg, African American, Latino, American Indian, Asian American, and Pacific Islander), hypertension, impaired glucose metabolism ("prediabetes"), and gestational diabetes.

2.1.4. Management

Studies have found that by improving glycaemic control with pharmacological intervention, the risk of microvascular complications is significantly reduced. Long-term data from the United Kingdom Prospective Diabetes Study (UKPDS) 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.

Current guidelines from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend a stepwise and individualized 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.

Despite the availability of a broad array of AHAs, only approximately half of patients with T2DM achieve glycaemic control per treatment guidelines. Furthermore, while new classes of AHA medications have been introduced over the last decade, the percentage of patients reaching glycaemic targets has not improved. There are several factors contributing to the low attainment of A1C goals. First, patients with T2DM exhibit declining β-cell function, which influences disease progression and leads to elevated A1C levels over time. Second, increased body weight leads to worsening insulin resistance. Finally, several classes of anti-hyperglycaemic medications are associated with adverse reactions, including weight gain (which may further worsen underlying insulin resistance), hypoglycaemia, oedema, or gastrointestinal effects, which often limit their use.

The management of chronic diseases like T2DM is often limited by clinical inertia: the delay or failure to escalate or alter therapy when the therapeutic effect is not attained. One way to prevent delays in achieving the desired therapeutic effect include initiating treatment with FDC therapies, as this often achieves the desired goal without the need for alterations in therapy. In addition, use of a combination of two different classes of agents may improve the initial efficacy of the treatment. Finally, use of a FDC has been shown to improve adherence with the treatment regimen.

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.

The ertugliflozin/metformin FDC combines 2 AHAs with complementary mechanisms of action to improve glycaemic control in patients with T2DM. Metformin improves glucose tolerance in patients with T2DM, lowering both basal and PPG. Metformin improves glycaemic control mainly through a decrease in hepatic glucose production, while also decreasing intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. 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.

About the product

This is an application for the use of ertugliflozin (MK-8835, PF-04971729) administered as a fixed-dose combination (FDC) with immediate-release metformin hydrochloride. Ertugliflozin is a new chemical entity belonging to the class of oral, sodium-glucose co-transporter 2 (SGLT2) inhibitors.

The commercial formulation of the ertugliflozin/metformin FDC is a film-coated immediate-release tablet for oral administration available in 6 dose strengths to be dosed bid, four of these are proposed for the EU Market:

- Ertugliflozin 2.5 mg/metformin 850 mg FDC tablet
- Ertugliflozin 7.5 mg/metformin 850 mg FDC tablet
- Ertugliflozin 2.5 mg/metformin 1000 mg FDC tablet
- Ertugliflozin 7.5 mg/metformin 1000 mg FDC tablet.

Ertugliflozin is an oral, selective inhibitor of sodium glucose co-transporter-2 (SGLT2) which inhibits renal glucose reabsorption and results in urinary glucose excretion (UGE) and reductions in plasma glucose and haemoglobin A1c (A1C) in patients with type 2 diabetes mellitus (T2DM). It possesses a high selectivity for SGLT2 versus SGLT1 and other glucose transporters (GLUT1-4).

Ertugliflozin is a new chemical entity with a chemical name of (1S,2S,3S,4R,5S)-5-[4-Chloro-3- (4-ethoxybenzyl)phenyl]-1-hydroxymethyl-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol. Ertugliflozin is included in the drug product as a cocrystal with L-pyroglutamic acid (L-PGA), known as ertugliflozin L-PGA. Ertugliflozin is formulated as an immediate-release tablet for oral administration at 5 and 15 mg strengths. The tablets are manufactured with a conventional direct compression process, utilizing conventional excipients and common blend (5% active). Dose strengths are expressed as ertugliflozin free form.

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, Europe, and other countries and has an established safety and tolerability profile.

Type of Application and aspects on development

The development program has in all essentials followed the EMA Guideline "Clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus" (CHMP/EWP/1080/00 Rev. 1), the EMA guideline "Clinical development of fixed combination medicinal products" (CHMP/EWP/240/95 Rev. 1) and the scientific advice given on the following topics:

Design of non-clinical and clinical phase 3 development program for ertugliflozin

Update on changes to the Phase 3 clinical development plan/ planned indications for ertugliflozin in FDC

Clinical pharmacology and biopharmaceutics plans for fixed-dose combinations (FDCs) of ertugliflozin

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing a fixed dose combination of 2.5 mg or 7.5 mg ertugliflozin (as ertugliflozin L-pyroglutamic acid) with 850 or 1000 mg metformin hydrochloride as active substances;

Segluromet 2.5 mg/850 mg film-coated tablets

Segluromet 2.5 mg/1,000 mg film-coated tablets

Segluromet 7.5 mg/850 mg film-coated tablets

Segluromet 7.5 mg/1,000 mg film-coated tablets

Other ingredients are:

Tablet core: povidone K29-32 (E1201), microcrystalline cellulose (E460), crospovidone (E1202), sodium lauryl sulfate (E487), magnesium stearate (E470b).

Film-coat (2.5 mg/850 mg & 7.5 mg/850 mg): hypromellose (E464), hydroxypropyl cellulose (E463), titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172), iron oxide black (E172), carnauba wax (E903).

Film-coat (2.5 mg/1000 mg & 7.5 mg/1000 mg): hypromellose (E464), hydroxypropyl cellulose (E463), titanium dioxide (E171), iron oxide red (E172), carnauba wax (E903).

The product is available in Alu/PVC/PA/Alu blisters in packs of 14, 28, 30, 56, 60, 168, and 180 film-coated tablets as described in section 6.5 of the SmPC.

2.2.2. Active Substance - ertugliflozin

General information

The active substance is presented in the form of ertugliflozin with L-pyroglutamic acid in a 1:1 ratio. The chemical name of ertugliflozin L-pyroglutamic acid is (1S,2S,3S,4R,5S)-5-(4-chloro-3-(4-ethoxybenzyl)phenyl)-1-(hydroxymethyl)-6,8-dioxabicyclo[3.2.1]octane-2,3,4-triol, compound with (2S)-5-oxopyrrolidine-2-carboxylic acid, corresponding to the molecular formula $C_{27}H_{32}ClNO_{10.}$ It has a relative molecular mass of 566.00 g/mol.

Ertugliflozin and ertugliflozin L-pyroglutamic acid (L-PGA) have the following structures:

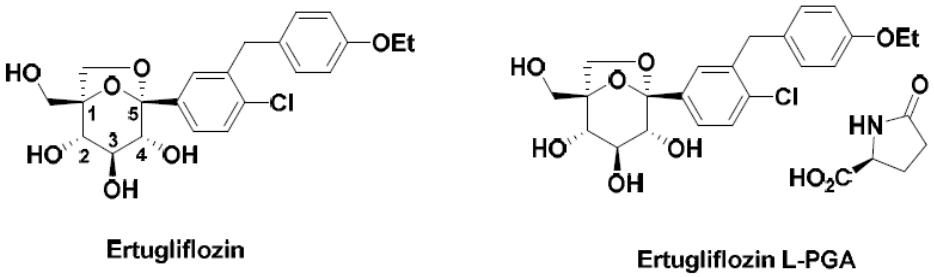


Figure 1: Ertugliflozin L-PGA structure

The chemical structure of ertugliflozin L-PGA was elucidated and confirmed by a combination of IR, ESI-MS and ESI-MS/MS, 1H NMR, 13C NMR, UV-Vis spectroscopy and crystal X-ray diffraction tests.

Solid state forms and polymorphism have been evaluated extensively by diverse crystallization techniques including slurries, solvent evaporations, grinding and thermal techniques. The ertugliflozin L-PGA co-crystal was determined to be an anhydrous crystal form with a 1:1 stoichiometry (ertugliflozin free form to L-PGA). This crystal form is non-hygroscopic, high-melting and both chemically and physically stable under normal manufacturing and storage conditions. This form was identified through extensive form screening experiments and crystallization studies and is the only form of ertugliflozin L-PGA. All batches of ertugliflozin L-PGA have been consistent. In addition, confirmation of form has been evaluated as part of the supportive and primary stability programs (36 months & 12 months at 25 °C/60% RH; respectively) using powder x-ray diffraction (PXRD) with no changes being observed.

Ertugliflozin L-PGA is a white to off-white powder. Ertugliflozin is very slightly soluble in water and aqueous media over the physiological pH range.

Ertugliflozin exhibits stereoisomerism due to the presence of five asymmetric centres (1S,2S,3S,4R,5S). Ertugliflozin L-PGA has an additional stereocentre in the L-PGA molecule (2S configuration). The risk assessment and control strategy for potential stereoisomers were adequately described in the manufacturing process development. The manufacturing process consistently produces the desired stereoisomer.

Based on the review of the data the CHMP considers that ertugliflozin could be qualified as a new active substance in itself.

Manufacture, characterisation and process controls

Ertugliflozin L-PGA is synthesized in six main steps using well defined starting materials with acceptable specifications. The manufacturing process has been developed, in parallel with the clinical development program, using a combination of conventional univariate studies and elements of QbD such as risk assessment and design of experiment (DOE) studies, in accordance with ICH Q8 and ICH Q11, to define the commercial manufacturing process of ertugliflozin L-PGA.

Development focused on building an understanding of the functional relationships between material attributes, process parameters, and the critical quality attributes (CQAs). The process understanding, developed for each step of the process, was used to define the manufacturing process and control strategy. A structured quality risk management approach was employed to identify potential critical process parameters and critical material attributes based on risk of impact to the ertugliflozin L-PGA CQAs.

The study of the process led to an understanding of the functional relationships between process parameters and material attributes and ertugliflozin L-PGA CQAs, based on knowledge gained through development of ertugliflozin L-PGA, the scientific literature, and prior knowledge. A number of critical process parameters, material attributes, and in-process controls were then identified.Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The suggested GMP synthesis is considered short but is acceptable based on the additional information provided in the dossier regarding synthesis and control of starting materials, control of critical steps and intermediates and the applied control strategy.

Changes introduced during development have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in in two sealed, low density polyethylene (LDPE) anti-static liners which comply with the EC directive 2002/72/EC and EC 10/2011 as amended. The bagged material is then inserted in a high density polyethylene (HDPE) drum or equivalent secondary container.

Specification

The active substance (Ertugliflozin L-PGA) specification includes tests for appearance, particle size, identification (IR), ertugliflozin potency (HPLC), L-PGA coformer content (HPLC), water content (Ph. Eur.), residual solvents (GC), residue on ignition (Ph. Eur.) and organic impurities (HPLC).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for potency and impurities testing has been presented.

Batch analysis data from full scale batchesof the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from full scale batches of active substance from the proposed manufacturer, stored in the intended commercial package for up to 12 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, solid form (PXRD), potency, L-PGA content, impurities, water content, particle size and microbial enumeration. The analytical methods used were the same as for release and were stability indicating. All tested parameters were within the specifications.

Photostability testing following the ICH guideline Q1B was performed. Appearance, potency, L-PGA content and impurities content remained unchanged compared to the dark control.In addition, results from forced degradation / stress conditions studies were also provided.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Active Substance - Metformin hydrochloride

General information

The chemical name of metformin hydrochloride is 1,1-dimethylbiguanide hydrochloride corresponding to the molecular formula $C_4H_{11}N_1$.HCl. It has a relative molecular mass of 165.63 g/mol and the following structure:

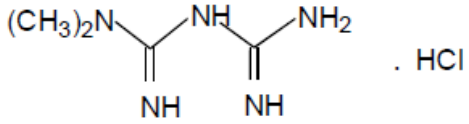


Figure 2: Metformin HCl structure

Metformin hydrochloride exists as white or almost white crystals, freely soluble in water, slightly soluble in alcohol.

As there is a monograph of metformin hydrochloride in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for metformin hydrochloride which has been provided within the current Marketing Authorisation Application.

The information from scientific literature indicates that metformin hydrochloride can exist in two polymorphic forms. Individual and combined XRPD patterns for 3 batches of metformin hydrochloride from the proposed manufacturer demonstrates that the same thermodynamically stable polymorphic form is consistently produced.

Manufacture, characterisation and process controls

The description of manufacturing process steps and in-process controls, characterisation, control of materials and of critical steps and intermediates, process validation and manufacturing process development are all covered by the CEP. The holder of the certificate has declared the absence of use of material of human or animal origin in the manufacturing of the substance.

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Specification

The active substance specification includes tests for description, identification (IR, chloride), appearance of solution (Ph. Eur.), loss on drying (Ph. Eur.), sulfated ash (Ph. Eur.), assay (Ph. Eur), impurity F (Ph.Eur.), related substances (HPLC). The specification tests and acceptance criteria ensure compliance with the Metformin Hydrochloride Ph. Eur. monograph (931) and CEP 1999-183.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from 6 commercial batches are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from production scale batches of active substance from the proposed manufacturer stored in the intended commercial package were provided under long term conditions (25ºC / 60% RH) and accelerated conditions (40ºC / 75% RH) according to the ICH guidelines. The parameters tested are the same as for release. The analytical methods used were the same as for release and were stability indicating. All tested parameters were within the specifications.

Stress /forced degradation studies to induce the formation of potential degradation products and demonstrate the stability indicating nature of the HPLC analytical procedures has been performed. The HPLC method for impurities has proved to be stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.4. Finished Medicinal Product

Description of the product and Pharmaceutical development

Segluromet 2.5 mg/850 mg film-coated tablets are presented as beige, 18 x 10 mm oval, film-coated tablet debossed with "2.5/850" on one side and plain on the other side.

Segluromet 2.5 mg/1000 mg film-coated tablets are presented as pink, 19.1 x 10.6 mm oval, film-coated tablet debossed with "2.5/1000" on one side and plain on the other side.

Segluromet 7.5 mg/850 mg film-coated tablets are presented as dark brown, 18 x 10 mm oval, film-coated tablet debossed with "7.5/850" on one side and plain on the other side.

Segluromet 7.5 mg/1000 mg film-coated tablets are presented as red, 19.1 x 10.6 mm oval, film-coated tablet debossed with "7.5/1000" on one side and plain on the other side.

The tablets are packed in non-perforated Alu/PVC/PA/Alu blisters or in perforated Alu/PVC/PA/Alu unit dose blisters.

The pharmaceutical development of the finished product followed an enhanced approach using a combination of conventional univariate studies and elements of QbD such as risk assessment, design of experiment (DOE) studies and manufacturing experience across a range of scales and equipment types, in accordance with ICH Q8. Design spaces and proven acceptable ranges (PARs) are claimed for a number of the manufacturing stepsand were acceptably justified.The quality target product profile (QTPP) was defined as an immediate release dosage form, which is bioequivalent to co-administration of corresponding monotherapy tablets, that meets compendial and other relevant quality standards. The QTPP categories were translated into product Critical Quality Attributes (CQAs).

Metformin granules were selected for development of the finished product due to poor compactibility of metformin HCl and its high drug load in the tablet formulation. Compatibility of ertugliflozin L-PGA and

metformin HCl was demonstrated by an accelerated stability assessment paradigm screen. Excipients were chosen to provide a stable formulation that would be bioequivalent to the individual monotherapy tablets when co-administered. Excipient compatibility studies for ertugliflozin were conducted and confirmed compatibility. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Both ertugliflozin and metformin monotherapy tablets and ertugliflozin / metformin fixed dose combination tablets were used throughout the clinical development programme. Two bioequivalence studies were conducted comparing ertugliflozin/metformin tablets 7.5 mg/1000 mg and 7.5 mg/850 mg strengths with respective strengths of EU sourced Glucophage® (metformin HCl) co-administered with ertugliflozin monocomonent tablets. Both strengths of ertugliflozin/metformin tablets were found to be bioequivalent to their respective monolithic tablet combinations. Dissolution results showed >85% release of ertugliflozin and metformin HCl in 15 minutes for all four strengths of ertugliflozin/metformin tablets. The very rapid dissolution over the physiological pH range along with the demonstrated BE between higher strength ertugliflozin fixed dose combinations and co-administration of the respective individual components for ertugliflozin/metformin 7.5 mg/ 850 mg and ertugliflozin/metformin 7.5 mg/1000 mg tablet strengths, supports the waiver for additional clinical bioequivalence studies of the two other strengths of ertugliflozin/metformin fixed dose combination tablets.

The sizes of the tablets are rather large, however, bioavailability for crushed tablets has been demonstrated and a comment regarding the possibility to crush the tablet to enhance swallowability has been added to the SmPC.

The manufacturing process was developed in parallel to the formulation development and clinical development programs. Formulation attributes and process parameters were categorized as either critical or non-critical, based on their impact on the product quality and the QTPP. An understanding of the relationships between formulation attributes and process parameters and the critical quality attributes (CQAs) of the finished product was developed and this process understanding was used to define the manufacturing process.

A structured, quality risk management approach was employed, for each step of the manufacturing process, to identify potentially critical process parameters and assess their impact on drug product quality and, as a result, their potential to impact product safety and/or efficacy. The risk assessment was performed based upon prior knowledge (including literature and platform understanding), as well as the knowledge gained throughout the development and scale up of the manufacturing process.

The results of the process understanding studies were analysed in order to determine if the identified parameters have the potential to significantly impact the CQAs, and to identify the ranges within which the process can be operated to produce material that meets the defined acceptance criteria for finished product quality attributes associated with in-process and release testing. Design spaces and proven acceptable ranges (PARs) are claimed for a number of the manufacturing steps and were acceptably justified.

Ertugliflozin L-PGA is a BCS Class 1 substance and metformin HCl is a BCS Class 3 substance. The combined immediate release dosage form is bioequivalent to co-administration of corresponding monocomponent tablets. Ertugliflozin and metformin HCl are highly soluble at 37 ± 0.5 °C across the physiological pH range, and the tablets are rapidly dissolving. A dissolution method with appropriate

choice of medium, apparatus and agitation rate used to release clinical batches, support development and to assess stability.

Considering a rapid tablet disintegration time (<15 minutes) and highly soluble active substances,and that disintegration testing exhibits more response to the tablets hardness, disintegration was therefore proposed and accepted, in line with ICH Q6A, as the finished product quality control method for evaluating active substance release from Segluromet tablets.

The primary packaging is Alu/PVC/PA/Alu perforated or non-perforated blisters. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The tabletting manufacturing process consists of six main steps:

1. Metformin granulation
2. Blending/Lubrication,
3. Compression,
4. Film coating,
5. Bulk packaging,
6. Primary packaging.

The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. Appropriately justified design spaces and proven acceptable ranges (PARs) are claimed for a number of the manufacturing steps.

A process validation protocol has been provided. The applicant's position that the manufacturing process can be considered as standard despite having < 2% drug load for the ertugliflozin L-PGA cocrystal all strengths, was accepted. Considering the extensive development studies which have demonstrated that there is no increased risk to meeting critical quality attributes relative to the < 2% drug load of ertugliflozin L-PGA, that development studies at the commercial manufacturing site cover the full range of commercial batch sizes that are proposed, and bracket all dose strengths, and that the manufacturing process is otherwise straightforward, this was considered acceptable. The applicant has confirmed that commercial scale process validation will be performed prior to the release of the finished product for commercial use.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form; description, identification ertugliflozin (HPLC, UV), identification metformin (HPLC, UV), assay ertugliflozin (HPLC or UPLC), assay metformin (HPLC), degradation products ertugliflozin (HPLC or UPLC), degradation products metformin (HPLC), uniformity of dosage units ertugliflozin (Ph. Eur.), uniformity of dosage units metformin (Ph. Eur.) and disintegration (Ph. Eur.).

The specification parameters and acceptance criteria have been appropriately justified in line with relevant EMA / ICH guidelines and Ph. Eur. requirements. As ertugliflozin and metformin are highly soluble, classified as BCS class 1 and BCS class 3 respectively, based on the criteria of ICH Q6A and

the development and batch data provided by the applicant, the replacement of dissolution testing by disintegration testing at release and stability is acceptable.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for batches of each strength of finished product. The results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

A bracketing approach was used for the stability studies of four tablet strengths based on minimum and maximum ertugliflozin drug load to excipient ratio.The bracketing approach was considered to be acceptable.

Stability data for finished product stored for up to 18 months under long term conditions (30ºC / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) were provided. These batches of Segluromet are identical to those proposed for marketing and were packed in the primary packaging (Al/Al blister packs) proposed for marketing.

All samples were tested in line with the finished product stability specification for appearance, assay (HPLC), degradation products (HPLC) and disintegration (Ph. Eur.). The analytical procedures used are stability indicating. In addition, the stability samples were evaluated for water content, water activity, dissolution, hardness and microbial purity.

All results comply with the proposed specification. No consistent or significant stability trends were observed for appearance, assay, individual or total degradation products, dissolution, disintegration, water activity/content, hardness or microbial purity.

One batch per strength was subjected to photostability stress testing under the conditions of ICH Q1B. The results indicated no change in assay or physical characteristics when compared with the control samples. Results of bulk hold time study were also provided.

Based on available stability data, the proposed shelf-life of 2 years with no special storage conditions as stated in the SmPC (section 6.3 & 6.4) are acceptable.

Adventitious agents

None of the components used in the manufacture of ertugliflozin/metformin tablets are of human or animal origin. The magnesium stearate used to manufacture Segluromet tablets is of vegetable origin.

2.2.5. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substances (ertugliflozin L-PGA and metformin hydrochloride) and finished product (film-coated tablets) has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.6. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.7. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Segluromet contains an active substance which was previously authorised in a medicinal product (metformin, in GLUCOPHAGE), and an active substance which was not previously authorised (ertugliflozin). Segluromet (ertugliflozin/metformin, EMEA/H/C/4314) is formulated as an immediate-release tablet for twice daily oral administration in 4 dose strengths of ertugliflozin (2.5 mg or 7.5 mg) and metformin HCl (850 mg or 1000 mg for the EU market). There are no novel excipients used in the manufacture of the Segluromet tablets. With the exception of the film coating, all excipients are compendial, and these excipients are tested and released in accordance with the specifications and methods described in the referenced pharmacopoeia.

All pivotal safety pharmacological and toxicology studies were conducted in compliance with GLP.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Primary pharmacodynamics of ertugliflozin was studied in vitro to determine potency and selectivity for inhibiting SGLT2 versus SGLT1-mediated glucose transport. In addition, the potency of ertugliflozin at physiological glucose concentration was also assessed and the mode of inhibition was determined. In vivo studies were performed in rats treated with ertugliflozin and increased UGE levels was used as an indicator of inhibition of SGLT2-mediated glucose reabsorption in the proximal tubule cells of the kidney.

In vitro, ertugliflozin was shown to be a competitive inhibitor with a Ki held constant at approximately 1 nM over the range of AMG concentrations tested (0.011 – 20 mM). The IC_{50} value for inhibiting human SGLT2 was 0.877 ± 0.369 nM, while the IC_{50} for human SGLT1 was 1960 ± 642 nM. Ertugliflozin remained potent at physiological glucose levels and was also shown to be potent against rat and dog SGLT2, with IC_{50} of 1.15 nM and 0.118 nM, respectively, with selectivity against rat and dog SGLT1. Both rat and dog were thus concluded to be relevant species to use in the toxicological studies.

The in vitro potency of the two primary circulating glucuronide metabolites M5a (PF-06685948) and M5c (PF-06481944) on SGLT1 and SGLT2 was also determined. The IC_{50} of M5a and M5c at SGLT2 were 476 nM >1000 nM, respectively (in the presence of 11.3 µM AMG) and both metabolites were

thus >500-1000 fold less potent than ertugliflozin at SGLT2. IC_{50} of both metabolites were >1000 nM at SGLT1.

The focus of the nonclinical in vivo studies was on the effect of SGLT2 inhibition by ertugliflozin on the mechanism biomarker Urinary Glucose Excretion (UGE). The effect of ertugliflozin on plasma glucose levels was not evaluated non-clinically. In pair-fed rats, ertugliflozin at a dose (30 mg/kg/d) caused a significant increase in urinary glucose excretion and decreases in plasma glucose and body weight after 8 days of dosing. A concomitant diuresis, as indicated by significant increases in urine volume, urinary volume to water intake and hematocrit was observed and was associated with an increase in urinary potassium and renin-angiotensin-aldosterone-system activation. In Sprague-Dawley rats fed ad-libitum, there was a significant increase in urinary glucose and food intake in treated rats, which resulted in no reduction in BWt when compare to vehicle-treated animals.

In Spontaneously Hypertensive Rats (SHR) a large increase in urinary glucose excretion (UGE) and a non-significant decrease in plasma glucose were seen in the pair-fed SHR treated with ertugliflozin concomitant with a 12% loss in body weight from baseline value of 307±4 g and 22% reduction in body weight compared to control SHR. Similar to the Sprague Dawley rats, ertugliflozin increased water intake, urine volume, percent of urine volume to water intake, and hematocrit, indicating a diuretic effect. Concurrent with the diuresis, ertugliflozin lowered mean systolic blood pressure by 11%, mean arterial blood pressure by 13%, and heart rate by 15% when compared with vehicle control animals. Ertugliflozin also significantly increased plasma renin activity, serum aldosterone, and plasma and urinary angiotensinogen levels, indicative of a diuretic-induced activation of the renin-angiotensin-aldosterone-system. The renin-angiotensin-aldosteronesystem activation with ertugliflozin was seen to be consistent with that observed with the diuretic, hydrochlorothiazide, when this compound was administered to the same rats after a 30-day washout period. However, the relatively large loss of body weight in the pair-fed SHR was considered to complicate translation of the results obtained with ertugliflozin in this model to the clinic.

The blood pressure lowering effects of ertugliflozin was also evaluated in SHR at doses that produce sub-maximal increases in UGE and compared to the effects of the loop diuretic furosemide given at a dose aimed to produce diuresis similar to that induced by the dose of ertugliflozin. Ertugliflozin-treatment significantly increased 24–hour UGE and resulted in 5 % reduction in body weight in pair-fed rats compared to control rats (an effect that was not significant compared to baseline values), while furosemide did not have any significant effect on body weight. Both compounds lowered mean systolic blood pressure, diastolic blood pressure and mean blood pressure to the same degree (8-10%) as compared to control rats. Although ertugliflozin increased the urine volume to water intake ratio, indicating a diuretic effect, plasma renin activity and urinary and plasma angiotensinogen were not significant altered. Unlike ertugliflozin, furosemide caused a significant increases in plasma renin activity and urinary and plasma angiotensinogen. These results thus indicate that diuresis is the predominant mechanism for blood pressure lowering with ertugliflozin in this model.

Secondary pharmacodynamic studies

Selectivity against the four major facilitative glucose transporters (GLUT 1-4), was assessed to ensure that passive and insulin mediated glucose uptake is not inhibited in cells and tissues in the body by ertugliflozin. Greater than 60 µM of ertugliflozin was needed for 50% inhibition of GLUTs 1-4, compared to an SGLT2 IC50 of 0.877 nM, indicating that the selectivity for SGLT2 versus GLUT 1-4 is greater than 60,000 fold.

Ertugliflozin was profiled in vitro against a panel of receptors, ion channels and enzymes (n=56 + 8 enzyme assays) (PD011) at a single concentration of 10 μM (4.3 μg/mL). No significant inhibition (>50%) of binding or enzyme activity was observed at this concentration, which is 250x the unbound C_{max} in humans of 0.0172 μg/mL at a dose of 15 mg once daily.

A low potential for secondary (off target) pharmacology at clinically relevant exposures is thus indicated by the studies performed.

Safety pharmacology programme

IC50 for hERG was 59 μM (25.19 μg/mL) which is approximately 1465x the human unbound $C_{max,ss}$ (0.0172 μg/mL). No test article-related effects on any hemodynamic, electrocardiographic (ECG), myocardial contractility were seen in dogs up to 5 mg/kg (total plasma concentration at 7 hours postdose 1.94 μg/mL, corresponding to an unbound plasma concentration of 0.062 μg/mL, approximately 4x greater than the human unbound $C_{max,ss}$ of 0.0172 μg/mL at a dose of 15 mg once daily). At 50 mg/kg (approximately 42x the human unbound $C_{max,ss)}$, a decrease in corrected QT interval (QTc, 6 msec) and a decrease of 489 mmHg/sec in left ventricular contractility, with a concomitant increase in PR interval (4 msec) near T_{max} (3.5 hours) was seen. An increase in systolic blood pressure (6 mmHg), and decrease in heart rate (6 bpm) were also seen between 8 and 16 hours postdose. No effects on heart rate, mean arterial pressure, systolic and diastolic pressure were seen over a 24-hour after a 25 mg/kg (p.o.) dose of ertugliflozin in rats, giving a C_{max} 7.3±0.7 μg/mL (292 ng/mL unbound, and approximately 17 x the human unbound $C_{max,ss}$).

An acute oral dose of up to 500 mg/kg ertugliflozin did not seem to induce any biologically-relevant neurofunctional or pulmonary effects in male Sprague Dawley rats.

Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies with ertugliflozin have not been conducted.

2.3.3. Pharmacokinetics

Nonclinical pharmacokinetic studies were performed in vivo in mouse, rat and dog and in vitro metabolism in rat, dog and human liver microsomes and hepatocytes. Validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods were used for the quantitation of ertugliflozin in mouse, rat, rabbit, and/or dog plasma, although non-validated methods were used for single-dose pharmacokinetic studies. Quantitative whole body autoradiography (QWBA), liquid scintillation counting and HPLC coupled to radiometric detection were used to measure [^{14}C]-ertugliflozin-derived radioactivity.

Absorption
Ertugliflozin was well absorbed and demonstrated low to moderate clearance (1.6 – 14 mL/min/kg) with a moderate volume of distribution (0.8 – 1.6 L/kg) in the nonclinical species evaluated. Mean apparent terminal half-life (t½) values for ertugliflozin ranged from approximately 2.7 to 7.6 hours in nonclinical species and oral bioavailability was moderate to high (56% to 97%). Absorption was rapid with a mean time to Cmax occurrence (Tmax) occurring at 0.5 hours postdose in mouse, 0.67 to 2.3 hours postdose in rat and 0.83 to 1.5 hours postdose in dog. Systemic exposure to ertugliflozin increased approximately proportional to dose over a dose range of 6.5 or 19.4 mg/kg in mouse and 2 to 500 mg/kg in rat.

Distribution
In vitro protein binding of ertugliflozin was determined in plasma from mouse, rat, rabbit, dog, and human using equilibrium dialysis. Protein binding was high in all species and independent of drug concentration (no difference in binding between 1 and 10 µg/mL). The f_u values were 0.045, 0.040, 0.071, 0.032, and 0.064 in mouse, rat, rabbit, dog, and human plasma, respectively. Ertugliflozin distributed preferentially into plasma relative to red blood cells, with blood-to-plasma partition ratios of 0.66, 0.58, and 0.66 in rat, dog, and human, respectively.

[14C]-ertugliflozin-derived radioactivity achieved Cmax levels at 1 or 2 hours postdose in most tissues, blood, bile, and urine. Radioactivity in most tissues thereafter declined over time. Excluding bile and urine, the tissues with the highest Cmax concentrations of radioactivity were measured in the urinary bladder, liver, kidney medulla, and kidney. The radioactivity did not show affinity for pigmented tissues containing melanin and exposure in the non-circumventricular CNS tissues was lower than blood concentrations (Tissue-to-blood ratio = 0.047 to 0.094 for Cmax and 0.064 to 0.12 for AUClast).

Placental transfer of radioactivity was widespread with exposures to most fetal tissues, amniotic sac, amniotic fluid, myometrium, and placenta. Highest concentration of radioactivity was detected in the adrenal gland at all sampling times, with a mean Cmax level that was approximately 4-fold higher than fetal blood and fetal brain, blood, and eye consistently had the lowest concentrations of radioactivity. Retention of radioactivity was not observed in any maternal or fetal tissues.

Metabolism
The metabolism of ertugliflozin was evaluated in vivo after administration of a single oral dose of [14C]ertugliflozin to rats, dogs, and humans or unlabeled ertugliflozin to mice and in vitro in liver microsomes and hepatocytes from rats, dogs, and humans. The potential for in vivo chiral inversion of ertugliflozin was also assessed in pooled plasma samples and the obtained data suggest that ertugliflozin does not undergo chiral inversion in humans.

Metabolite profiles were qualitatively similar in all species with no unique human metabolites observed. Overall, glucuronidation on the hydroxy groups of the modified glucose moiety was the major metabolic pathway of ertugliflozin in the species studied, with minor contributions from oxidative metabolism. Desethylation (oxidative) was a significant metabolic pathway only in rat. Isomeric O-glucuronide metabolites of ertugliflozin (M5a, M5b, and M5c) and a glucuronide of M2 (M6a) were the primary circulating metabolites in humans, representing 12.2%, 4.1%, 24.1%, and 6.0% of total radioactivity in plasma. M5a and M5c were identified in rat, each representing 0.7% and 0.3%, respectively and M5c in dog plasma at ≤3.3%. M5c was also detected in mouse plasma but not quantified.

Due to the low levels found in plasma of the toxicological species used, exposure of the major circulating human metabolites M5a- and M5c-glucuronides has probably not reached 50% of the exposure seen in humans. M5a and M5c are thus less likely to have been adequately characterized in the toxicology studies performed. However, the M5a and M5c O-glucuronide metabolites are not considered to be of any concern and no further safety testing of these direct conjugated O-glucuronides are therefore needed. (See also Toxicology Assessment.)

Excretion
After oral administration of [14C]-ertugliflozin to rats, dogs, and humans, approximately 93.4%, 94.8%, and 91.0% of the radioactive dose was quantitatively recovered in the excreta. The predominant route of elimination of radioactivity in rats and dogs was feces and bile. In humans, radioactivity in urine and feces accounted for 50.2% and 40.9% of the dose, respectively.

Ertugliflozin-derived radioactivity was shown to pass into milk with a milk-to-plasma AUC_{24} ratio of 1.07 and milk:plasma concentration ratios ranging from 0.426 to 1.81 during 24 hours, after a single oral administration of 102 mg/kg to female rats 10 to 12 days after parturition.

Overall the non-clinical PK of ertugliflozin has been sufficiently characterized and based on this characterization the use of mice, rats and dogs as toxicological species are considered to be acceptable.

2.3.4. Toxicology

The toxicological profile of ertugliflozin was characterized in rats and dogs via single-dose intravenous (IV) injection (rat), single dose oral gavage administration (dog), and via repeat-dose oral gavage studies up to 3 months (mice), 6 months (rat) and 9 months (dog) duration. In addition, 13 weeks combination toxicity studies with ertugliflozin + sitagliptin, and ertugliflozin + metformin, were conducted in rats. The clinical route of administration is oral (immediate-release tablets). Rats and dogs were selected as toxicology species, based on pharmacodynamics and metabolism. In addition, mice and rats were used for carcinogenicity studies, and rats and rabbits for reproductive toxicology. The extent of the toxicology programme is considered sufficient for the present application.

Single dose toxicity

After single IV injection, there were no adverse effects in Sprague-Dawley (SD) rats up to 100 mg/kg bw, corresponding to exposure margins of 660-fold (C_{max}) and 485-fold (AUC) to clinical exposure (15 mg ertugliflozin once daily). In Beagle dogs administered a single oral dose, the only adverse effect was emesis at 500 mg/kg, corresponding to exposure margins of 94-fold (C_{max}) and 253-fold (AUC) to clinical exposure. Based on this data, the acute toxicity of ertugliflozin appears to be low.

Repeat dose toxicity

Most effects observed in the repeat-dose toxicity studies were related to the primary pharmacological activity of ertugliflozin, i.e. reduced renal tubular reabsorption of glucose from the glomerular filtrate, and subsequent osmotic diuresis and systemic metabolic changes. The kidney, gastrointestinal (GI) tract and bone were identified as main target organs for toxicity.

Mortalities

Preterminal mortalities occurred in five CD1 mice administered 250 mg/kg/day (14 day non-GLP study) and in two CD1 mice dosed at 100 mg/kg/day (pivotal 3-month study). In the pivotal 1-month study, five SD rats administered 500 mg/kg/day (lowered to 250 mg/kg from Day 11) were found dead or euthanized moribund, after having shown clinical signs such as soft faeces, distended abdomen, hunched posture, decreased activity/ataxia and noisy respiration. In addition, two SD rats administered 25 mg/kg/day (one in combination with metformin 200 mg/kg/day) in longer term ($\geq$ 3 months) studies were found dead on Days 74 and 80, respectively. The cause of death/moribundity in mice and rats administered ertugliflozin could not be determined; however, all preterminal mortalities occurred at exposure margins $\geq$ 100-fold the human therapeutic AUC and are thus not considered clinically relevant.

Kidney

In Tg (HRAS)2 mice treated with ertugliflozin at $\geq$ 3 mg/kg/day for 1 month, increased kidney weight,

correlated with minimal dilatation of cortical tubules, and minimal tubular basophilia in females, was observed. Similar findings were present in CD1 mice treated at ≥ 5 mg/kg/day for 3 months.

In SD rats, increased urine glucose and urine volume, usually associated with decreased urine creatinine and increased urine glucose/creatinine ratio, were observed in all studies from 7 days up to 6 months duration, at doses ≥ 5 mg/kg/day. Increased blood urea nitrogen (BUN) was also observed in all SD rat toxicity studies, at ≥ 5 mg/kg/day. Ketones in urine were present in the 6-month study. Increased kidney weight, correlated with minimal to moderate cortical and medullary tubular dilatation, was observed in the pivotal 1- and 3-month repeat-dose toxicity studies at ≥ 5 and ≥ 25 mg/kg/day, respectively. Hypertrophy of the proximal convoluted tubules was seen after 14 days treatment (non-GLP study), and in the pivotal 6-month study, at ≥ 25 mg/kg/day. Increased incidence of tubular mineralization occurred in males at ≥ 5 mg/kg/day in the 6-month study.

Dilatation of the renal pelvis was observed in males at ≥ 5 mg/kg/day in the 3- and 6-month studies, with the additional finding of pelvic inflammation at ≥ 25 mg/kg/day (3-month study). This was often associated with inflammation in the prostate gland (see further below). Pelvic inflammation was present in occasional females at ≥ 5 mg/kg/day in the 6-month study.

At high doses (≥ 250 mg/kg/day) in the 1- and 3-month repeat-dose toxicity studies, ertugliflozin caused increased severity of chronic progressive nephropathy (CPN), a spontaneously occurring background renal disease in SD rats. Additional ertugliflozin-related changes at ≥ 250 mg/kg/day included increased mineral deposition in the renal pelvis, and hyperplasia of the renal pelvic epithelium.

Reversibility was evaluated in the 6-month study, using a 2-month recovery period. All findings were fully or partly reversible except for renal tubular mineralization in males at 100 mg/kg/day and pelvic inflammation in females at ≥25 mg/kg/day. One recovery female showed inflammation in the urinary bladder (with transitional cell hyperplasia) and ureter, as well as inflammation in the renal pelvis.

In two 3-month combination studies in SD rats, with ertugliflozin + metformin or sitagliptin, respectively, glucosuria, increased urine volume and BUN, increased kidney weights and renal tubular dilatation, were observed at ≥ 5 mg/kg/day, without any exacerbation caused by co-administration of metformin (200 or 600 mg/kg/day) or sitagliptin (20 or 60 mg/kg/day).

In contrast to rats, Beagle dogs showed very few renal effects. Glucosuria, associated with increased urine volume and increased urine glucose/creatinine ratio, was observed at ≥ 1 mg/kg/day, in all pivotal repeat-dose toxicity studies from 1 to 6 months duration. Increased urine volume was not reversible after 9 months treatment, following a 2-month recovery period. Dogs did not show any increased kidney weights, or renal histopathological changes.

GI tract

In SD rats, loose stools or soft faeces were observed at high doses (≥ 250 mg/kg/day) in two repeat-dose toxicity studies (7-day and 3-months, respectively). In the 3-month study, the whole GI tract was dilated with a thickened intestinal wall, correlating with microscopic findings of increased height and width of the mucosa/villi of the small intestine. These findings occurred mainly at 250 mg/kg/day, although microscopic changes in the intestinal mucosa were observed in males at ≥ 5 mg/kg/day.

Erosions/ulcerations in the glandular stomach, sometimes associated with inflammation, were observed in all repeat-dose toxicity studies ≥ 3 months duration, at ≥ 5 mg/kg/day. In the 6-month study, additional stomach findings in the form of minimal hyperplasia of foveolar cells (mucus-producing) at 100 mg/kg, and minimal to slight crypt degeneration (pylorus) at ≥ 25 mg/kg, were present. All of the stomach findings were reversible.

Beagle dogs showed soft or watery faeces at ≥ 1 mg/kg/day, and emesis at ≥ 10 mg/kg/day, in pivotal repeat-dose toxicity studies. There were no correlating histopathological findings, and the effects were reversible following cessation of dosing.

Liver and pancreas

Non-adverse liver effects were observed in CD-1 mice (increased hepatocellular glycogen at ≥ 5 mg/kg/day in a 14-day study), SD rats (increased ALT and AST, sometimes associated with increased liver weight, at ≥ 5 mg/kg/day in studies from 14 days to 6 months duration) and Beagle dogs (decreased glycogen content at ≥ 1 mg/kg/day in the 3-month study). In the 13-week combination study with metformin, metformin alone (600 mg/kg/day) caused increased liver weight. Increased ALT and AST were partly reversible in the 6-month rat study.

In the pancreas, depletion of zymogen granules, sometimes accompanied by increased cytoplasmic basophilia in exocrine cells, was observed in all SD rat studies, from 7 days to 6 months duration, at doses ≥ 5 mg/kg/day. Zymogen granule depletion was most likely secondary to changes in food consumption. This effect was reversible and is considered non-adverse.

Adrenal gland

Increased adrenal weight without any correlating microscopic changes was observed in the CD-1 mouse 14-day study, at ≥ 5 mg/kg.

SD rats showed increased adrenal weight, associated with hypertrophy and/or vacuolation of the zona glomerulosa, at ≥ 5 mg/kg/day, in all repeat-dose toxicity studies from 1 to 6 months duration. Hypertrophy of the zona glomerulosa was fully reversible.

In the 13-week combination study with metformin, general hypertrophy of the adrenal cortex showed increased incidence in females at 25/600 mg/kg, as compared with metformin 600 mg or ertugliflozin 25 mg alone. It is possible that this may have been a stress-related effect.

Bone

In CD-1 mice, a decreased width of the physis or growth plate of the distal femur was noted at 250 mg/kg/day in the 14-day study. This change was characterized by partial or complete loss of the hypertrophic zone within the physis. Similar microscopic changes were not observed in the 3-month study at doses up to 100 mg/kg/day (NOAEL), corresponding to a 167-fold margin to human therapeutic exposure (AUC_{24} at 15 mg ertugliflozin).

In SD rats, microscopic changes in the femur/tibia and sternum were observed in the form of minimal to moderate hyperostosis of the trabeculae at ≥ 25 mg/kg/day (3-month study) or minimal to slight increase in trabecular bone at 100 mg/kg/day (6-month study; partially reversible after 8 weeks recovery). Increased serum phosphorus at 250 mg/kg/day (3-month study) and 100 mg/kg/day (6-month study) was probably related to the bone effects. Furthermore, increased excretion of calcium and phosphorus in the urine was observed at ≥ 5 mg/kg/day in the 6-month study. In other rat studies, decreased serum calcium and/or phosphorus were observed, without any corresponding changes in bone.

In the 9-month dog study, increased calcium excretion in urine (non-reversible) was observed at 150 mg/kg/day. No bone effects were seen.

Other ertugliflozin-related effects

Body weight and food consumption

Effects on bodyweight/bodyweight gain and food consumption were observed in all species tested. Usually food consumption was increased, but bodyweight and/or bodyweight gain decreased. Sometimes food consumption was decreased, and bodyweight/bodyweight gain likewise decreased.

These effects occurred in CD-1 mice at 250 mg/kg/day (14-day study), in Tg (HRAS)2 mice at ≥ 3 mg/kg/day (1-month study), in all studies in SD rats (from 7 days to 6 months) at ≥ 5 mg/kg/day, and in all pivotal repeat-dose toxicity studies in Beagle dogs at ≥ 1 mg/kg/day.

Hypoglycaemia and other serum chemistry findings
Decreased serum glucose was observed in the majority of studies in SD rats, at ≥ 5 mg/kg/day, and was reversible after 8 weeks recovery (9-month study). In the 13-week combination study with metformin, the effect on glucose was marginally more pronounced when ertugliflozin and metformin were given together as compared with ertugliflozin alone. Decreased serum glucose was also observed in the 7-day dog study (at ≥ 50 mg/kg/day), and at ≥ 1 mg/kg/day in the 3- and 9-month dog studies.

In addition to changes in serum glucose, BUN, calcium and phosphorus (discussed above) a spectrum of other serum chemistry changes were observed in the majority of studies in SD rats, at ≥ 5 mg/kg/day. These changes included lower serum sodium, potassium, and chloride, consistent with electrolyte loss via osmotic diuresis, and decreased total protein, albumin, globulin and cholesterol, considered to be secondary to changes in energy balance (lipid and protein metabolism) resulting from glucose loss and/or osmotic diuresis.

Hematology findings
In CD-1 mice treated at 250 mg/kg/day for 14 days, increased red blood cell count (RBC), haemoglobin and haematocrit were observed in males. In contrast, SD rats showed decreased RBC, haemoglobin and haematocrit in repeat-dose toxicity studies ≥ 1 month duration, at ≥ 5 mg/kg/day. Additional findings in the form of increased or decreased red cell distribution width (RDW), decreased reticulocytes, increased mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH) were noted in rats. Red blood changes in the 6-month study were not fully reversible after 8 weeks recovery, especially not RDW and reticulocyte changes in males.

In the 7-day non-GLP study, and in all pivotal repeat-dose toxicity studies ≥ 1 month duration, at ≥ 25 mg/kg/day, decreased white blood cell count (WBC), lymphocyte and monocyte counts (sometimes also eosinophil and basophil counts) were observed. White blood cell changes were fully reversible.

Mesenteric fat
Lipid depletion/atrophy was observed in the 7-day SD rat study at 500 mg/kg/day, and in the 1-month pivotal study at ≥ 5 mg/kg/day. This finding is considered to reflect catabolism of energy reserves secondary to glucosuria, i.e an adaptive, non-adverse effect.

Mandibular salivary gland
Hypertrophy of mucous cells occurred in SD rats at high doses (≥ 250 mg/kg/day) in the 1- and 3-month studies, and in the 9-month dog study at 150 mg/kg/day. In dogs it was suggested to be related to excessive salivation. Since the exposure margins to NOAELs for this effect are at least 59-fold compared to human therapeutic exposure (AUC_{24}) at a 15 mg once daily dose, it is not considered clinically relevant.

Prostate gland
Decreased secretory material was observed in the SD rat 1-month study at ≥ 250 mg/kg/day. In the 3-month study, decreased prostate weight was present at ≥ 5 mg/kg/day, being associated with mixed inflammatory cell infiltration and atrophic glands, and decreased secretory content, at ≥ 25 mg/kg/day. In the 13-week combination study with sitagliptin, mixed cell inflammation occurred in occasional animals at 5/20, 25/60 and 25/60 mg/kg/day. One animal at 5/20 mg/kg/day also showed renal pelvis and urinary bladder inflammation.

Stress-related findings
Decreased thymus weights were observed at ≥ 25 mg/kg/day in the SD rat 3-month study, most likely as a consequence of stress. Asynchrony of the estrus cycle at ≥ 250 mg/kg/day, as well as lymphoid depletion in the thymus, spleen and GALT, and hypertrophy of the adrenal zona fasciculata in preterminally dead rats at 500/250 mg/kg/day, is also considered to be stress-related.

Combination effects

Ertugliflozin in combination with metformin at 25/600 mg/kg/day caused an exacerbation of organ weight increase in the kidney, liver, and adrenal gland of females as compared with organ weight changes seen with metformin or ertugliflozin dosed separately. In addition, higher heart weight without any microscopic correlation was observed in females dosed at 25/600 mg/kg/day (> 100-fold AUC_{24} margin to clinical therapeutic exposure for ertugliflozin).

Microscopically, a marginally higher severity of metformin-related salivary gland findings was observed in males given 25/600 and 5/600 mg/kg/day than was seen with metformin alone. Likewise, an increase in incidence of general adrenal cortical hypertrophy was noted in females given 25/600 mg/kg/day as compared with metformin or ertugliflozin alone. No exacerbation of any effect of ertugliflozin or metformin given alone was noted when co-administered at 5 and 200 mg/kg/day.

No exacerbations of any effects were observed when ertugliflozin (5 or 25 mg/kg/day)was co-administered with sitagliptin (20 or 60 mg/kg/day).

Equivocal findings
A few other changes in organ weights, serum chemistry and hematology were sporadically observed in the repeat-dose toxicity studies with ertugliflozin. Since these changes were not consistently observed, and/or were not associated with any histopathological alterations, they are not considered toxicologically relevant.

Conclusion on repeat-dose toxicity
The majority of findings in the repeat-dose toxicity studies were related to the primary pharmacological activity of ertugliflozin; many findings being similar to those previously reported for other SGLT2 inhibitors (canagliflozin and dapagliflozin). These effects are to a large extent monitorable and highlighted in the RMP and SmPC.

Genotoxicity

Ertugliflozin was evaluated in a standard program of genetic toxicology assays, consisting of Ames test, *in vitro* cytogenetic test (human lymphocytes) and an *in vivo* rat micronucleus assay. The Ames test evaluation showed that ertugliflozin did not cause a positive increase in the mean number of revertants per plate with any tester strains either in the presence or absence of S9 mix. In the *in vitro* metaphase chromosome aberration test, there was no significant increase in chromosome damage at any concentration evaluated under any test condition. In addition, Ertugliflozin did not induce chromosome damage as evidenced by the absence of micronucleus formation in the polychromatic erythrocyte bone marrow cells at doses up to 500/250 mg/kg. Thus, collectively the genotoxicity testing with ertugliflozin does not indicate a genotoxic potential of the substance.

Carcinogenicity

The carcinogenic potential of ertugliflozin was evaluated in two 2-year studies in CD-1 mice and Sprague Dawley rats.

Mouse
Due to decreased survival observed in control and test article-treated dose groups, the mouse carcinogenicity study with ertugliflozin was terminated during week 97 for males and week 102 for females. This is not considered to have impacted substantially on the assessment of carcinogenic potential as the number of animals evaluated and study duration are still considered sufficient.

In the study, three different control groups have been used. However, while control group 1 was 0.5% methylcellulose, control groups 2 and 3 were both 0.5% methylcellulose and 10% PEG 400. It was unclear why two independent control groups were dosed with the same treatment, and why a total of three control groups were used in the study. Since this is important from a 3R perspective (to avoid the unnecessary use of animals), the Applicant was asked to clarify this issue. In the response, the Applicant explained that the underlying reason for using two PEG 400 control groups was because of limited internal experience using 10% polyethylene glycol 400 in a study of this duration. In addition, the use of an additional 0.5% methylcellulose control group was a modification of an FDA recommendation to add a saline or water control group. This rational and explanation was considered acceptable.

No test article-related neoplastic findings in male or female mice were found in the dose groups treated with ertugliflozin. The non-neoplastic changes presented which included histopathologic changes in the urinary tract and kidneys were anticipated based on findings in the repeated-dose toxicology studies and also the pharmacologically mediated increase in urine volume from SGLT2 inhibitors. While it is clear that the animals have been properly exposed, and that the exposure increased in a dose-related manner, it is unclear why the exposure has not been given as AUC. While this would not change the overall conclusion, it is considered a more useful and comprehensive way to describe the exposure. Based on extrapolation from a 3-month study, the NOEL for neoplastic findings (40mg/kg/day) corresponds to an AUC_{0-24} exposure of 87200 ngxh/ml, which is 74-fold above the human therapeutic exposure at a 15 mg dose.

Rat
Terminal necropsy of surviving male rats occurred after 104 weeks of dosing, whereas terminal necropsy of surviving female rats occurred after 92 weeks of dosing due to low survival in the female vehicle control group. Ertugliflozin exposure was associated with neoplastic and related hyperplastic findings observed in the adrenal medulla, and for benign pheochromocytoma in males administered ≥5 mg/kg/day. Based on historical control data, the statistically higher significance of benign pheochromocytoma in males administered 5 mg/kg was by the Applicant considered an aberration and not biologically meaningful. This discussion is not agreed with. The findings of benign pheocromocytoma display a clear dose-response already from the 1,5 mg/kg dose. However, considering the totality and relatedness of the study findings, the NOEL for neoplasia is considered to be 1.5mg/kg/day. The overall (both sexes) exposure in terms of AUC_{0-24} at the neoplastic NOEL was 7530 ngxh/mL, corresponding to a 6-fold margin to human therapeutic exposure at a 15 mg dose.

Reproduction Toxicity

Fertility and early embryonic development (rat)
Three animals died during the study, of which the causes of death for two animals in the 250mg/kg/day group are unclear. It can be concluded that the animals have been properly exposed, but it is unclear why the exposure has not been expressed as AUC. Nevertheless, according to the repeated-dose toxicity study in rats (tt097892) mean C_{max} and AUC_{0-24} values for ertugliflozin at 5, 25, and 250 mg/kg were 2.57, 8.11, and 51.2 µg/mL, respectively, for C_{max}, and 19.9, 89.4, 738 µg•h/mL, respectively, for AUC_{0-24} on day 91. Thus, there is sufficient exposure margin in the study.

Overall, there were ertugliflozin-related decreases in body weights in males at all dose levels, whereas the female bodyweight changes were more transient. In addition, both sexes showed increased food consumption across all dose levels, likely compensatory to caloric loss. No effects were noted on reproductive parameters, with the exception of two males at 250mg/kg/day with small testis and epididymis and correlating effects on motile sperm and sperm counts. The Applicant suggests this was a pre-existing condition. While this seems unlikely, the absence of testicular effects in the repeat-dose toxicity studies, as well as the absence of similar findings in other animals in the study, makes a direct ertugliflozin-related effect less likely.

The NOAEL for parental toxicity is considered to be 25mg/kg due to ertugliflozin associated deaths a 250mg/kg. No effects of relevance were found on reproductive endpoints, why the reproductive and early embryonic development NOAEL was 250mg/kg.

Embryofetal development

Rat

With once daily dosing of ertugliflozin, systemic exposure increased dose-dependently. Ertugliflozin induced decreased body weight and food consumption at 250mg/kg/day, why the maternal NOAEL is considered to be 100mg/kg/day. The highest dose of ertugliflozin also induced a variety of fetal effects, including an increased incidence of postimplantation loss, visceral malformations (membranous ventricular septum defect, right sided aortic arch) and skeletal malformations. In addition, one fetus had omphalocele and one fetus was malformed with ectrodactyly and short tail. Due to the low incidence and unclear etiology of these findings, the relationship to treatment with ertugliflozin is considered equivocal. Skeletal malformations (absent metacarpal, fused sternebra and hemicentric thoracic centrum) were accompanied by numerous skeletal variations in the250mg/kg/day group, and various skeletal variations were also found in the 100mg/kg/day group. These findings, while considered variations, were clearly ertugliflozin-related. The fetal NOAEL in the rat EFD study is 100 mg/kg/day, corresponding to an exposure in terms of AUC0-24 of 457 µgxh/mL. The margin to human therapeutic exposure at a 15 mg dose is 384-fold.

Rabbit
Systemic exposure of ertugliflozin increased with increasing exposure in a dose-dependent manner. Two does in the highest exposure group aborted (on GD19 and GD21, respectively) and a third doe was euthanized on GD 28 following clinical signs and tray findings suggestive of abortion. This was likely a result of maternal toxicity rather than a direct effect on the developing fetus. There was an increase in post-implantation loss at 250mg/kg/day. However, this finding was within the historical control data of the laboratory.

There were reductions in body weight (57-78% less weight gain than controls) seen at all doses, without a reduction in food intake only at the highest dose of 250mg/kg/day. No external malformations or variations were noted with the exception of a single control fetus (forelimb hyperflexion). One single high-dose embryo displayed muscular ventricular septum defect, dilated aortic arch narrowed pulmonary trunk. Since this was a single finding, the relationship to treatment with ertugliflozin cannot be determined. In addition, low incidences of minor skeletal malformations (including supernumerary cervical centrum, misshapen interparietal bone and fused rib) and variations were seen across the dose groups. While skeletal malformations are a concern, the findings seen were of low incidence (single fetuses) and occurred without obvious relation to treatment.

Based on the reductions in maternal body weight and body weight gain relative to controls at all doses, a NOEL for maternal toxicity was not identified. There were no test article-related effects on fetal

viability, growth, or morphological development; therefore, the NOEL for developmental toxicity was 250 mg/kg/day corresponding to an exposure in terms of AUC0-24 of 1150 µgxh/mL. The margin to human therapeutic exposure at a 15 mg dose is 966-fold.

Prenatal/postnatal development

No toxicokinetics was evaluated in this study. There was an increased incidence of decreased body weight, body weight gain, food consumption and clinical signs in the F0-females at doses ≥100mg/kg/day. The clinical signs were ertugliflozin-related and included dehydration (based on skin turgor), rales and urine-stained abdominal fur. Each of these signs persisted into the lactation period.

Pups to mothers exposed to 250mg/kg/day had lower survival, most likely due to decreased viability. In addition, pups exposed to ertugliflozin at doses ≥100mg/kg/day had lower pup weights. Sexual maturation (balano-preputial separation in males and later vaginal opening in females) was significantly delayed in both genders of the F1-generation exposed to 250mg/kg/day, which was also accompanied by decreases in body weight at the day of sexual maturation. Behaviour assessments did not show any effects, nor were there effects on fertility in the F1-generation.

Juvenile toxicity

Systemic exposure of ertugliflozin increased with increasing exposure in a dose-dependent manner on both PND 21 and PND 90. There were 5 unscheduled mortalities in the study, which the Applicant considers unrelated to ertugliflozin exposure. However, the cause of death for these rats was not determined. It cannot be excluded that the deaths at 250 mg/kg/day are treatment related. Since the margin to human therapeutic exposure is > 580-fold, the preterminal mortality at the high dose level is not of clinical concern.

Overall, the main ertugliflozin-related findings consisted of lower mean body weights PND 21-90 at ≥25mg/kg, with transient effects over the course of the study. There was an unclear correlation to food consumption, suggesting that the reduction in weight was correlated to ertugliflozin. In addition, apparent clinical signs including dehydration, abdominal distention, and partly closed eyes with increased severity and incidence at higher doses. Body weight and weight gain remained lower at recovery in males at 250mg/kg whereas females recovered.

There was an increase in the day of sexual maturation noted in both males (balano-preputial separation) and females (day of vaginal patency) at 250mg/kg. In addition, there were reductions in prostate weight at ≥5mg/kg, although no correlates were found microscopically.

Ertugliflozin induced changes in clinical chemistry parameters as well as urinalysis and urine chemistry parameters. After recovery, there were some remaining findings in globulin, urea nitrogen and A/G ratio.

Alterations in renal parameters (including increased organ weight, macroscopic pelvis dilatation, microscopic tubular and pelvis dilatation, and renal tubular mineralization, at doses ≥5mg/kg) was seen at PND 90. At recovery there were remaining kidney findings (of lower magnitude and incidence). However, the renal tubular mineralization was not reversible. The renal findings were by the Applicant considered an adaptive response to the pharmacology of ertugliflozin and they correlated with glucosuria. However, considering the lack of reversibility, the renal tubular mineralization is considered adverse.

Bone parameters were influenced by ertugliflozin exposure. On PND 91 there were statistically significant differences in bone formation markers in males at doses ≥ 25 mg/kg/day and also shorter femur lengths in both sexes at doses ≥25mg/kg. Increased femoral bone was noted at 250mg/kg.

There were also changes in bone geometry at doses ≥25mg/kg. At recovery, there were remaining variations in bone mass and size.

Thus, ertugliflozin administered to juvenile male and female SD rats resulted in effects of delayed puberty in both sexes, as well as irreversible effects on kidney and bone parameters. Based on the renal tubular mineralization, no NOAEL can be set for this study.

Toxicokinetic data

Toxicokinetics and exposure margins

In SD rats, exposure (C_{max} and AUC_{24}) to ertugliflozin increased with dose, with no or minimal plasma drug accumulation up to 6 months of dosing. There was no apparent gender difference, although females tended to have higher exposure at some time points. T_{max} was variable and occurred from 1 to 7 hours post dose. Co-administration with metformin or sitagliptin did not affect ertugliflozin exposure with the exception of a 37% lower AUC_{24} when 25 mg/kg/day ertugliflozin was given together with 600 mg/kg/day metformin. Since no similar effect was seen in the clinic, this finding is considered to be of low clinical relevance.

In Beagle dogs, exposure (C_{max} and AUC_{24}) to ertugliflozin increased with dose, with minimal plasma drug accumulation up to 9 months of dosing. There were no apparent gender-related differences in exposure. T_{max} occurred within 4 hours of oral administration.

Plasma exposure (AUC_{24}) achieved in the repeat-dose toxicity studies exceeded the human therapeutic exposure by up to 200-fold (mouse), 600-fold (rat) and 900-fold (dog). Exposure margins to NOAELs were generally in the range of 16- to 20-fold (rats) and 5- to 60-fold (dogs) as compared with the clinical therapeutic exposure (15 mg once daily dose). In two rat studies (13-week combination with sitagliptin; 6-month study) there were no NOAELs, mainly due to erosions/ulcerations in the glandular stomach at the low dose level (AUC_{24} exposure 18-fold above clinical therapeutic exposure).

Local Tolerance

Ertugliflozin was not a skin sensitizer in the mouse local lymph node assay, but induced corrosion in an *in vitro* human skin corrosion test, and induced eye damage in the bovine corneal opacity and permeability test. Furthermore, oral administration of ertugliflozin caused erosions/ulcerations in the glandular and non-glandular stomach of rats, inflammation and hyperplasia of the tongue (in the rat carcinogenicity study), and emesis in dogs. These findings indicate a local irritating potential of ertugliflozin.

Other toxicity studies

Metabolites

No toxicology studies were conducted on two O-glucuronide metabolites that exceed the 10% threshold in humans. Since glucuronides in general have negligible potential for systemic toxicity or genotoxicity, and both metabolites are 500-1000-fold less potent on SGLT2 and > 1000-fold less potent on SGLT1 as compared with ertugliflozin, the absence of dedicated metabolite studies is considered acceptable.

Impurities

Two 3 –month repeat-dose toxicity studies in rats were conducted to qualify impurities and

degradants. Findings in these studies were similar to those from other rat studies using ertugliflozin without the spiked degradants. A number of process related impurities and potential degradation products were toxicologically qualified in these studies. Impurity PF-06759854 is described in Module 3.2.S.4.5 as being a process related impurity present at 0.04% in the ertugliflozin batch used in study TT#13-7809 (13GR318). However, this could not be verified in the Certificate of analysis for this study (neither for study TT#15-7804). The Applicant was thus asked to clarify and to provide with the updated Certificate of analysis for study TT #15-7804 (15GR254), to confirm that impurity PF-06759854 has been toxicologically qualified. In the response, the Applicant clarified that study TT#15-7804 (15GR254) was a 3-month degradant qualification study in rats and that the batch used in this study did not contain PF-06759854. However, the impurity was included at 0.04 % in study13GR318, which has also been verified in the submitted certificate of analysis. Calculations in section 3.2.S.4.5 (added above) supports that the rats used in the 13 week oral toxicity study were properly exposed to the impurity at a level that exceeds the human clinical exposure. It can thus be concluded that impurity PF-06759854 has been toxicologically qualified.

2.3.5. Ecotoxicity/environmental risk assessment

Ertugliflozin

The environmental risk assessment (ERA) is based on ertugliflozin which has a molecular weight of 436.88 g/mol and is hydrophilic with a water solubility of 0.64 mg/mL (pH 6.5) and a log K_{OW} = 2.47 (pH 7). The surface water predicted environmental concentration PEC (PEC_{SW}) was calculated to 0.075µg/L using the default Fpen (0.01) and the maximum dose of 15mg. Based on the OECD TG314B, ertugliflozin seems also to have a high primary degradation in sludge. Ertugliflozin is also degraded in surface water to several transformation products, demonstrating a DT_{50} of 0.55d. Based on OECD TG308, aerobic degradation testing in combined fresh water-sediment systems gives DT_{50} 45.3d – 56.8d (12°C) with the water-specific and sediment specific values falling below the persistence (P) criterion ($DT_{50,water}$ < 40d, $DT_{50,sediment}$, < 120d). Together, the data indicates that ertugliflozin is not persistent in water-sediment systems. Ertugliflozin has a tendency to sediment accumulation (21.6-35.5% AR >10% after 14d). The organic content solid adsorption coefficients for ertugliflozin were below 10000L/kg for sediment, sludge and soil (Kd_{oc} 198-967L/kg).

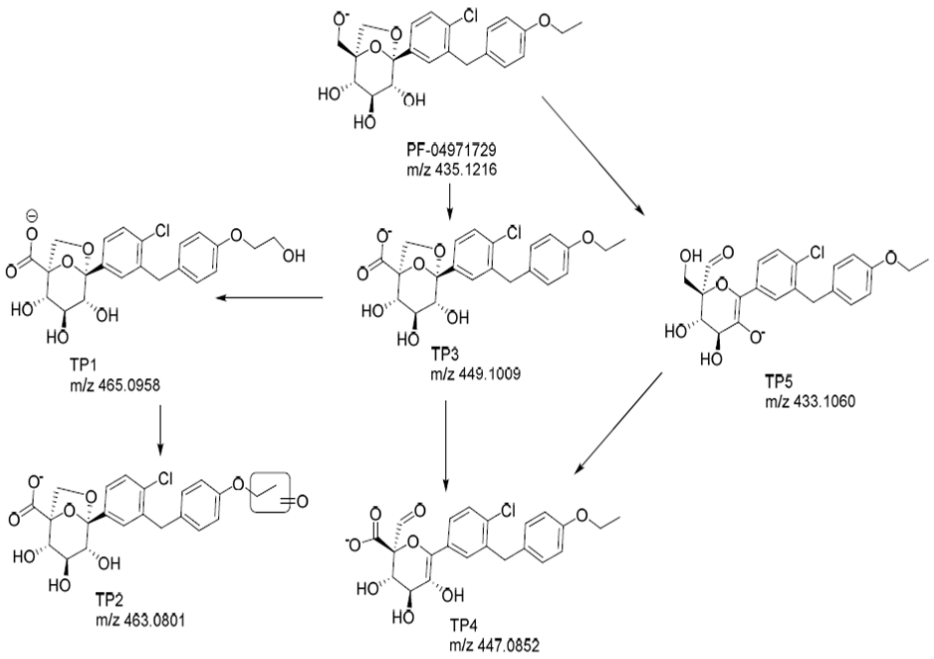


Figure 3: Overview of proposed transformation product/degradation pathway for ertugliflozin (PF-04971729, m/z 435.1216). Transformation product 5 (TP5, m/z 433.1060) was found in all environmental compartments (sludge, surface water and sediment systems).

A range of transformation products were detected in surface waters, sediment and sludge samples. One of the products ("TP5") present in all compartments was a more lipophilic aldehyde-compound (the result of dehydrogenation and a ring opening of the dioxolane ring). The applicant proposed the following structure for TP5: (2R,3S,4S)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)-3,4,5-trihydroxy-2-(hydroxymethyl)-3,4-dihydro-2H-pyran-2-carbaldehyde (see also **Figure 3**). The NOEC for aquatic toxicity was only found at the maximum doses tested, setting aquatic invertebrates (*D. magna*) with the most sensitive NOEC of 2.14mg/L. For sediment-dwelling chironomid larvae, the NOEC and LOEC (midge emergence) was 87mg/L and 249mg/L respectively. The ERA table is included below **(Table 1)**:

Table 1: The ERA table

Substance (INN/Invented Name): Ertugliflozin			
CAS-number (if available): 1210344-57-2			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD TG107	2.47	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	2.47	Not B.
	BCF	NA	B/not B
Persistence	DT50 or ready biodegradability	$DT_{50,\ water}$ = ~24-32d $DT_{50,\ sediment}$ = ~15-56d $DT_{50,\ whole\ system}$ = ~45-57d	Overall, unlikely to be persistent.
Toxicity	NOEC or CMR	NOEC > 0.01mg/L No genotoxicity but the test substance caused hyperplasia in male	Not T based on aquatic toxicity results. Possibly CMR.

		adrenal medulla and benign pheochromo-cytoma in a 2 year rat study (TT #13-7800).	
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surface\ water}$, default or refined (e.g. prevalence, literature)	0.075	µg/L	> 0.01 threshold (Y). Triggers Phase IIA.
Other concerns (e.g. chemical class)			No
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD TG106	K_{doc} sed .1 = 967 L/kg K_{doc} sed. 2 = 927 L/kg K_{doc} sludge 1 = 198 L/kg K_{doc} sludge 2 = 250 L/kg K_{doc} soil 1 = 755 L/kg K_{doc} soil 2 = 490 L/kg	K_{doc} sludge < 10 000 L/kg.
Biodegradability Simulation Test	OECD TG314B	<u>*Ertugliflozin*</u> DT_{50} = 0.695h Mineralization 28d: 40.8% High primary degradation in sludge <u>*Transformation products*</u> DT_{50} ("TP3.7") = 24.4h DT_{50} ("TP8") = 1.59h AR at 1h >10%	Sludge from Easton WWTP, 28d incubation.
28d Surface water biodegradation Test	OECD TG309	<u>*Ertugliflozin*</u> $DT_{50,\ water}$ = 0.55d $DT_{90,\ water}$ = 1.83d CO_2-mineralization = 36.7% <u>*Transformation products*</u> $DT_{50,\ water}$ ("TP5") = 4.66d $DT_{90,\ water}$ ("TP5") = 15.56d	Most of ertugliflozin degraded within 24h.
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD TG308	$DT_{50,\ water}$ = ~24 - 32d $DT_{50,\ sediment}$ = ~15 - 56d $DT_{50,\ whole\ system}$ = ~45 - 57d % shifting to sediment = 21.6-35.5% AR after 14d.	Uses DT_{50} (12°C) %AR(14d) > 10 Triggers an OECD TG218 test.

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD TG201	NOEC EC_{50}	50 000 63 000	µg/L	*P. subcapitata*
Daphnia sp. Reproduction Test	OECD TG211	NOEC	2140	µg/L	*D. magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD TG210	NOEC	1000	µg/L	*P. promelas*
Activated Sludge, Respiration Inhibition Test	OECD TG209	NOEC	1000	mg/L	Easton WWTP sludge
Phase IIb Studies					
Sediment dwelling organism	OECD TG218	$NOEC_{OC10}$	511 800	µg/ kg	*C. riparius*

Metformin

The ERA is based on metformin which has a molecular weight of 165.63g/mol, is freely water soluble at 286mg/mL in water at pH 7.0-7.5 and 20°C and has a log K_{OW} = -2 (pH 7). The default Phase I

PEC_{SW} was calculated to 5.0µg/L using the default Fpen (0.01) and the maximum dose of 1000mg. Based on the OECD TG314B, metformin seems also to have a high primary degradation in sludge. The aerobic degradation in whole fresh water-sediment systems corresponds to a $DT_{50,water}$ 5.3d to 20.3d (20°C) and a $DT_{50,sediment}$ around 14d with a moderate partitioning to the sediment within 17d (29-30% AR >10%). The half-lives at 12°C were calculated per Focus (2014) to be 43.3d and 12.0d in the water phases and 38.8d for the sediment.

Metformin had a sludge biodegradation DT_{50} and DT_{90} of 2h and 6.6h in an OECD TG314B test. The organic content solid adsorption coefficients (Kd_{oc}) for metformin were Kd_{oc} > 10 000L/kg for soil (~64-19645L/kg; geometric mean of 838L/kg) but not sludge (8L/kg). Fish (*P. promelas*) demonstrated the most sensitive aquatic toxicity NOEC (9.77mg/L with LOEC >9.77mg/L). For sediment-dweller organisms, male developmental rate in chironomid larvae (*C. riparius*) was found to be the most sensitive endpoint (NOEC 62.5mg/L with LOEC 125mg/L). The ERA table for metformin is included below

Table 2**)**:

Table 2: The ERA table for metformin

Substance (INN/Invented Name): Metformin			
CAS-number (if available): 657-24-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD TG107	-2	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	-2	Not B.
	BCF	NA	B/not B
Persistence	DT50 or ready biodegradability	$DT_{50,water}$ = 5.3-20.3d $DT_{50,sediment}$ = 14d	DT_{50} not corrected for temperature at 12C.
Toxicity	NOEC or CMR	NOEC > 0.01mg/L	Not T based on aquatic toxicity results.
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surface\ water}$, default or refined (e.g. prevalence, literature)	5.0	µg/L	> 0.01 threshold (Y). Triggers Phase IIA.
Other concerns (e.g. chemical class)			No
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD TG106	K_{doc} soil 1 = 1693 L/kg K_{doc} soil 2 = 64 L/kg K_{doc} soil 3 = 159 L/kg K_{doc} soil 4 = 19645 L/kg K_{doc} soil 5 = 1221 L/kg K_{doc} sludge 1 = 8 L/kg	K_{doc} sludge < 10 000 L/kg. The soil with the highest Kdoc was a loam soil (Horn, Switzerland).
Biodegradability Simulation Test	OECD TG314B	DT_{50} = 2h DT_{90} = 6.7h Likely high primary degradation in sludge.	Sludge from Wareham WWTP (MA, US). 28d incubation.
Aerobic and Anaerobic	OECD TG308	$DT_{50,\ water}$ (20C)= 5.3 – 20.3d	Triggers an OECD

Transformation in Aquatic Sediment systems		$DT_{50,\ sediment}$ (20C) = 14d $DT_{50,\ water}$ (12C)= 12-43.3d $DT_{50,\ sediment}$ (12C) = 38.8d % shifting to sediment = 50.8-59.5% AR after 17d.			TG218 test. Metformin can be considered persistent in water according to PBT criteria (DT_{50}>40d).
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD TG201	NOEC	104	mg/L	*P. subcapitata*
Daphnia sp. Reproduction Test	OECD TG211	NOEC	40.9	mg/L	*D. magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD TG210	NOEC	10	mg/L	*P. promelas*
Activated Sludge, Respiration Inhibition Test	OECD TG209	NOEC	10	mg/L	Sludge from Romanshorn WWTP (Switzerland).
Phase IIb Studies					
Sediment dwelling organism	OECD TG218	NOEC $NOEC_{OC10}$	62.5 329	mg/kg	*C. riparius*

2.3.6. Discussion on non-clinical aspects

Pharmacology

Ertugliflozin was shown to be a competitive inhibitor of SGLT2 with a Ki of ~1 nM. The IC_{50} value for inhibiting human SGLT2 was 0.877 $\pm$ 0.369 nM, with high selectivity for human SGLT1. Potent and selective SGLT2 inhibition was also shown in rat and dog and these species are thus concluded to be relevant to use in toxicological studies. The two primary circulating glucuronide metabolites M5a and M5c were shown not to have any significant activity at SGLT2 or SGLT1.

In vivo, ertugliflozin caused a significant increase in urinary glucose excretion and decreases in plasma glucose and body weight in pair fed rats after 8 days of dosing. A concomitant diuresis was observed and was associated with an increase in urinary potassium and renin-angiotensin-aldosterone-system activation. In animals fed ad libitum a significant increase in urinary glucose was also seen, concomitant with an increased food intake and no reduction in body weight. Ertugliflozinin was also given to Spontaneously Hypertensive Rats and the effects were compared to that of hydrochlorothiazide and furosemide. The results obtained indicate that diuresis is the primary mechanism for blood pressure lowering with ertugliflozin in this model.

A low potential for secondary (off target) pharmacology at clinically relevant exposures is indicated by studies performed on GLUT 1-4 and a panel of receptors, ion channels and enzymes. No significant inhibition was seen in any of the assays performed.

No significant effects were seen on hERG in vitro or cardiovascular effects in vivo after a single 25 mg/kg (p.o.) dose of ertugliflozin to rats, giving a C_{max} 7.3±0.7 µg/mL (292 ng/mL unbound, and approximately 17 x the human unbound $C_{max,ss}$). No test article-related effects on any hemodynamic, electrocardiographic (ECG), myocardial contractility were either seen in dogs up to 5 mg/kg (approximately 4x greater than the human unbound $C_{max,ss}$ of 0.0172 µg/mL at a dose of 15 mg once daily). No biologically-relevant neurofunctional or pulmonary effects were seen in male Sprague

Dawley rats at doses up to 500 mg/kg ertugliflozin. No safety pharmacology issues were thus revealed at clinically relevant exposure levels in the non-clinical studies performed.

Pharmacokinetics

Ertugliflozin was well absorbed and demonstrated low to moderate clearance with a moderate volume of distribution. Mean apparent terminal half-life (t½) values ranged from approximately 2.7 to 7.6 hours. Plasma protein binding was high (~95%) in all species investigated.

[14C]-ertugliflozin-derived radioactivity achieved C_{max} levels at 1 or 2 hours post dose in most tissues, blood, bile, and urine. Radioactivity in most tissues thereafter declined over time. The radioactivity did not show affinity for pigmented tissues and no retention was seen, suggesting that no accumulation is to be expected after repeat dosing. Placental transfer of radioactivity was widespread with exposures to most fetal tissues and excretion to milk was also seen. Metabolite profiles were qualitatively similar in all species with no unique human metabolites observed. Isomeric O-glucuronide metabolites of ertugliflozin were the primary circulating metabolites in humans with two metabolites (M5a and M5c) reaching levels >10% of total plasma exposure. The predominant route of elimination of radioactivity in rats and dogs was feces and bile, while in humans, radioactivity in urine and feces accounted for 50.2% and 40.9% of the dose, respectively.

In many studies both with ertugliflozin alone and in combination with metformin or sitagliptin, the exposure appeared to be lower in males than in females. However, there was no consistent trend across dose groups and studies.

Due to the low levels found in plasma of the toxicological species used, exposure of the major circulating human metabolites M5a- and M5c-glucuronides has probably not reached 50% of the exposure seen in humans. M5a and M5c are thus less likely to have been adequately characterized in the toxicology studies performed. However, the M5a and M5c O-glucuronide metabolites are not considered to be of any concern and no further safety testing of these direct conjugated O-glucuronides are therefore needed.

The Applicant was asked to provide clarification regarding the chemical structures of M1, M3 and M8. In their response, the Applicant submitted a new study report (PK077MK8835) wherein the chemical structures of the most abundant oxidative metabolites of ertugliflozin formed in incubations with recombinant CYP3A4 and human liver microsomes were discussed. Two of the metabolites were hydroxyl derivatives of ertugliflozin with an OH-group between the two phenyl rings; one of the metabolites was the hydroxyl derivative of ertugliflozin with OH-group in ethoxyphenyl ring at ortho position to benzylic carbon. However, the definitive chemical structures of M1 and M3 could not be established. The structure of M8 was assigned as the glucuronide conjugate of M3.

Overall the non-clinical PK of ertugliflozin has been sufficiently characterized and based on this characterization the use of mice, rats and dogs as toxicological species is considered to be acceptable.

Toxicology

The primary pharmacologic effect of ertugliflozin is to cause a reduced renal tubular reabsorption of glucose from the glomerular filtrate, leading to glucosuria. This effect was evident in both rats and dogs administered ertugliflozin in repeat-dose toxicity studies. As a consequence of glucosuria, an increased fluid load developed in the nephrons (osmotic diuresis), leading to tubular dilatation and increased urine volumes. Tubular dilatation as such is considered to be an adaptive effect and non-adverse. Increases in BUN occurred in the absence of any increase in creatinine and probably reflected increased water loss associated with diuresis (prerenal azotemia).

Tubular mineralization, pelvic inflammation and exacerbation of CPN in SD rats are considered to be adverse effects. Tubular mineralization was suggested by the Applicant to be due to increased calcium and phosphorus excretion, linked to rat-specific inhibition of SGLT1. This seems plausible. Exacerbation of CPN occurred only at high dose levels, at an exposure > 500-fold the human therapeutic AUC, and is thus not of clinical concern. Pelvic inflammation, sometimes associated with inflammation in the prostate gland and (occasionally) in the urinary bladder/ureter may be a consequence of glucosuria, which increases the risk for bacterial ascending infections. Urinary tract infections have not been observed in the clinic (see Clinical Safety). Genital infections are included in section 4.8 of the SmPC. From a non-clinical perspective, no further action is needed.

A number of GI findings occurred in rats, including a slightly trophic effect on the intestinal villi. The Applicant suggested that these effects were due to high local intestinal concentrations of ertugliflozin, causing inhibition of SGLT1, which in turn resulted in a reduced intestinal absorption of glucose. Fermentation of unabsorbed glucose in the large intestine was proposed to lead to gas formation, causing luminal dilatation and a slight trophic effect on the villi. Although no experimental data was produced to support this theory, the explanation seems plausible.

The Applicant further speculated that inhibition of SGLT1 in the gut may have been at the root of the GI symptoms (watery faeces, emesis) in dogs. However, since the selectivity against SGLT1 in dogs is > 2000-fold this seems unlikely. A local irritating effect appears more plausible. No adverse GI effects have been reported in the clinic. Although not discussed by the Applicant, it seems likely that a higher selectivity against SGLT2 versus SGLT1 in humans as compared with rats and dogs may explain the absence of GI effects in patients treated with ertugliflozin.

Liver effects in rats in the form of increased transaminases (ALT, AST) and increased liver weight, and in dogs in the form of decreased glycogen content, may have been related to increased hepatic gluconeogenesis to compensate for urinary glucose losses. The Assessor has reviewed AST, ALT and ALP on an individual level in all pivotal dog studies, concluding that there were no ertugliflozin-related effects on these parameters suggesting liver toxicity.

Increased adrenal weight, associated with hypertrophy of the zona glomerulosa, was observed in rats. Cells of the zona glomerulosa produce aldosterone, which regulates the body’s concentration of sodium and potassium by acting on the distal convoluted renal tubules to increase sodium and water reabsorption, and increase potassium excretion. This finding is considered to be an adaptive, non-adverse response to ertugliflozin-related osmotic diuresis.

The bone effects in rodents would appear to be secondary to SGLT1 inhibition in the GI tract, leading to increased levels of intestinal glucose, which in turn promotes bacterial fermentation. As a consequence of this, a more acidic environment increases ionized calcium, and, subsequently, increased calcium absorption from the gut into the blood. Increased systemic calcium would result in decreased levels of parathyroid hormone (PTH) and decreased bone resorption, and would also serve as a substrate for increased calcium deposition. Similar bone effects in rats have been observed with canagliflozin and dapagliflozin and may be regarded as a class effect.

The exposure margin to the lowest NOAEL for ertugliflozin-induced bone effects (5 mg/kg/day in the 3-month study) is 16-fold based on human therapeutic AUC_{24} at a 15 mg once daily dose. It should be taken into consideration that ertugliflozin is > 2000-fold selective for human SGLT2 versus SGLT1, while the selectivity in rat is only 300-fold. In view of this, the clinical relevance of the bone effects in rodents appears to be limited.

The effects on food consumption and bodyweight are considered to be due to a catabolic state associated with ertugliflozin-induced glucosuria and osmotic diuresis. Hypoglycaemia was probably secondary to ertugliflozin-induced glucosuria. From a non-clinical perspective, no further action is needed.

The Applicant speculated that the changes in red blood cell parameters might be a consequence of negative energy balance, similar to what has been reported in feed-restricted rats. This seems plausible. The margins to human clinical exposure for these effects, as well as for the changes in white blood cell parameters, are relatively large; thus their clinical relevance is considered low.

Inflammation in the prostate gland of rats was likely the consequence of an ascending urinary infection, secondary to glucosuria. 'Genital infections' are included in section 4.8 of the SmPC. From a nonclinical perspective, no further action is needed.

The observed exacerbations of some organ weight and microscopic findings when ertugliflozin was administered together with metformin in rats are not considered adverse, due to the changes being of an adaptive nature and/or showing large exposure margins to clinical exposure.

The Applicant suggests that the mechanism for tumour development in rats is carbohydrate malabsorption, which may lead to glucose shortage in the organism, which along with the energy dependent need to excrete high amounts of calcium, induces a high adrenergic tone in the animal. However, it is likely that the basis for the mechanism is the poor absorption of ertugliflozin in the rat, which leads to increased local concentrations in the gut capable of inhibiting SGLT1, which in turn impacts SGLT1- dependent glucose absorption.

The data provided by the Applicant indicates that 81.4% and 76.3% of the orally administered ertugliflozin is absorbed in male and female rats respectively. It was thus unclear if this absorption rate for ertugliflozin still can give high enough local concentrations in the gut to significantly inhibit intestinal SGLT1. The Applicant was therefore asked to further clarify and discuss the relation between local ertugliflozin concentrations in the 2-year rat carcinogenicity study and intestinal SGLT1-inhibition. The Applicant has provided data that there would still be a high enough local gastrointestinal concentration of ertugliflozin to provide sufficient inhibition of SGLT1 in the gastrointestinal tract. This conclusion is agreed with.

Relevance of developmental toxicology findings for recommendations in section 4.6 of the SmPC: The findings regarding ertugliflozin-induced effects on renal development and function are reflected in the SmPC section 4.6. Data suggests that ertugliflozin may affect renal development and maturation; therefore, ertugliflozin should not be used during pregnancy.

While it is unknown whether ertugliflozin is excreted in human breast milk, available data in rats show excretion in milk, as well as pharmacologically-mediated effects in nursing offspring in the prenatal/postnatal development study. Since a risk to breast-feeding infants cannot be excluded, ertugliflozin should not be used while breast-feeding (see SmPC).

The Applicant was asked to discuss the local irritating potential of ertugliflozin. The *in vitro* human skin corrosion test and the bovine corneal opacity and permeability test were conducted with high concentrations more relevant for a worker safety situation. In rats, erosions/ulcerations were observed in the glandular and non-glandular stomach; however, the histopathological grading was from minimal to slight and no similar findings were present in dogs. Hyperplasia of the tongue, which was observed

in the rat carcinogenicity study, could possibly be related to increased food and water intake for an extended time period. Since the frequency of gastrointestinal disorders does not appear to be significantly higher in patients treated with ertugliflozin as compared with placebo it is not considered necessary to include gastrointestinal irritation in the product information.

ERA: Regarding the environmental impact of ertugliflozin, it seems to be non-persistent in water-sediment systems and biodegradable in sludge but with a low sludge adsorption potential - indicating that there is little risk for terrestrial effects from agricultural sludge usage. The main entry into the environment is into surface waters via the effluent. In a similar manner, metformin demonstrated high primary degradation in sludge and a low sludge adsorption potential. Based on the overall data, neither ertugliflozin nor metformin are classified as a PBT or vPvB candidates. Both active substances shift partly from surface water to the sediment at >10% after 14d (metformin more than ertugliflozin). Metformin can be considered persistent in water according to PBT criteria (DT_{50} = 43.3d > 40d).

The ERAs for both ertugliflozin and metformin have been updated. The applicant has updated the predicted environmental concentration (PEC) calculation for ertugliflozin by using a more appropriate prevalence Fpen (type II diabetes prevalence 8.3%), giving an surface water PEC (PEC_{SW}) of 0.62ug/L, a groundwater PEC (PEC_{GW}) of 0.16ug/L, and wet and dry sediment PECs of 0.013mg/kg ($PEC_{W,SED}$) and 0.060mg/kg ($PEC_{D,SED}$). All dependent risk quotient (RQ) values were well below 1, supporting the applicant argument that ertugliflozin is unlikely to be an environmental risk. The PEC values for metformin were also recalculated, based on existing consumption data (using the sales of metformin in Luxembourg) – giving an Fpen of 0.014. This resulted in a PEC_{SW} of 7ug/L, a PEC_{GW} of 1.75ug/L and sediment PEC (PEC_{SED}) of 440ug/kg. All dependent risk quotient (RQ) values were well below 1, supporting the applicant argument that metformin is unlikely to be an environmental risk.

In response to previous other concerns, some minor metformin ERA issues have been addressed (regarding temperature adjustment for water/sediment DT50 and issues around soil Kdoc determination). Overall, the available data plus the responses from the applicant indicate that ertugliflozin is unlikely to pose environmental risks to aquatic/sediment compartments and that metformin exposure by this product is unlikely to pose an additional environmental risk to the aquatic/sediment compartment to that already present in the environment resulting from other products containing the active substance.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical dossier is sufficient and all concerns were addressed.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 3: Overview of Phase 3 Studies Contributing to Efficacy of the Ertugliflozin/Metformin FDC

Study	Randomized Population	N	Study Design	Treatment Groups and Number of Subjects Randomized	Treatment Duration
Placebo-controlled studies					
P007/1017 Add-on to metformin	Adult subjects ≥18 years of age with T2DM and inadequate glycaemic control (A1C 7.0% to 10.5%, inclusive) on background of metformin	621	Multicenter, randomized (1:1:1), double-blind, placebo-controlled	Placebo (n=209) Ertugliflozin 15 mg (n=205) Ertugliflozin 5 mg (n=207) Subjects receiving placebo who did not receive glycaemic rescue therapy in Phase A were switched to glimepiride in Phase B	104 weeks Phase A: 26 weeks Phase B: 78 weeks **Ongoing**
P006/1015 Add-on to metformin plus sitagliptin	Adult subjects ≥18 years of age with T2DM and inadequate glycaemic control (A1C 7.0% to 10.5%, inclusive) on background of metformin and sitagliptin	463	Multicenter, randomized (1:1:1), double-blind, placebo-controlled	Placebo (n=153) Ertugliflozin 15 mg (n=154) Ertugliflozin 5 mg (n=156)	52 Weeks Phase A: 26 weeks Phase B: 26 weeks **Completed**
Active controlled studies					
P002/1013 Ertugliflozin vs glimepiride as add-on to metformin	Adult subjects ≥18 years of age with T2DM and inadequate glycaemic control (A1C 7.0% to 9.0%, inclusive) on background of metformin	1326	Multicenter, randomized (1:1:1), double-blind, active-controlled	Glimepiride up to 8 mg (n=437) Ertugliflozin 15 mg (n=441) Ertugliflozin 5 mg (n=448)	104 weeks Phase A: 52 weeks Phase B: 52 weeks **Completed**

Study	Randomized Population	N	Study Design	Treatment Groups and Number of Subjects Randomized	Treatment Duration
P005/1019 Ertugliflozin plus sitagliptin factorial	Adult subjects ≥18 years of age with T2DM and inadequate glycaemic control (A1C 7.5% to 11.0%, inclusive) on background of metformin	1233	Multicenter, randomized (1:1:1:1:1), double-blind, factorial	Sitagliptin 100 mg (n=247) Ertugliflozin 15 mg (n=248) Ertugliflozin 5 mg (n=250) Ertugliflozin 15 mg/ sitagliptin 100 mg (n=245) Ertugliflozin 5 mg/ sitagliptin 100 mg (n=243)	52 Weeks Phase A: 26 weeks Phase B: 26 weeks **Completed**
Abbreviations: A1C=glycosylated haemoglobin A1c; n=number of subjects randomly assigned to study medication; N=overall number of subjects randomly assigned to study medication; T2DM=type 2 diabetes mellitus					

Table 4: Overview of Phase 2 Studies

Study Number	Randomized Population	N	Study Design	Treatment Groups and Number of Subjects Randomized	Treat-ment Duratio n	Primary and Secondary Efficacy Endpoints
P016/1006	Adults (18 to 70 years) with T2DM and inadequate glycaemic control; currently receiving metformin, A1C of 6.5% to 11.0%	328	Randomized (1:1:1:1:1:1), double-blind, double-dummy, placebo- and active-controlled, parallel-group, 2-period study	Placebo (n=54) Sitagliptin 100 mg (n=55) Ertugliflozin 1 mg (n=54) Ertugliflozin 5 mg (n=55) Ertugliflozin 10 mg (n=55) Ertugliflozin 25 mg (n=55)	12 weeks	Primary: change from baseline in A1C Secondary: change from baseline in body weight, SBP, DBP, and FPG; proportion of subjects achieving A1C <7.0% as well as <6.5%.
P042/1004	Adults (18 to 65 years) with T2DM and history of mild to moderate hypertension, on stable antidiabetic medication(s), A1C ≥7% and ≤10%.	194	Randomized (1:1:1:1:1), double-blind, double-dummy, placebo- and active-controlled, parallel-group study.	Placebo (n=39)† HCTZ 12.5 mg (n=39) Ertugliflozin 1 mg (n=39) Ertugliflozin 5 mg (n=38) Ertugliflozin 25 mg (n=39)	4 weeks	Primary: change from baseline in average, 24-hour SBP Secondary: change from baseline in daytime and night-time average SBP; 24-hour, and daytime and night-time average DBP and heart rate; trough seated SBP, DBP, and pulse rate; UGE0-24; and FPG.

† In total, 39 subjects were randomly assigned to the placebo group; however, one of these subjects did not receive study medication.

Abbreviations: A1C=glycosylated haemoglobin A_{1c}; DBP=diastolic blood pressure; FPG=fasting plasma glucose; HCTZ=hydrochlorothiazide; n=number of subjects randomly assigned to study medication; N=overall number of subjects randomly assigned to study medication; SBP=systolic blood pressure; T2DM=type 2 diabetes mellitus; UGE_{0-24}=24-hour urinary glucose excretion

Source: [Ref. 5.3.5.1: P042] [Ref. 5.3.5.1: P016]

2.4.2. Pharmacokinetics

The majority of the clinical pharmacology support for the FDC ertugliflozin/metformin (Segluromet) comes from the clinical pharmacology program for ertugliflozin as mono-component Steglarto. Three additional clinical studies have been performed to support the FDC ertugliflozin/metformin **(Table 5)**.

Table 5: Overview of further clinical pharmacology studies to support the FDC ertugliflozin/metformin (Segluromet), in addition to clinical pharmacology package of the mono-component ertugliflozin (Steglatro)

Description	Phase	Subject	n	Dose	Reference
BE - ertu 7.5 mg/met 850 mg vs individual components	1	HV	34	7.5 mg	P046 (B1521054)
BE - ertu 7.5 mg/met 1000 mg vs individual components	1	HV	34	7.5 mg	P047 (B1521055)
Food effect, FDC ertu 7.5 mg/met 1000 mg	1	HV		7.5 mg	P028 (B1521049)

The clinical pharmacokinetic (PK) data on ertugliflozin are provided based on phase 1, 2 and 3 studies but also on a number of *in vitro* studies. **Table 6** shows an overview of the phase 1 studies supporting both ertugliflozin as mono-component product and as a FDC.

Table 6: Overview of studies included in the clinical pharmacology package of ertugliflozin

Description	Phase	Subject	n	Dose	Reference
SAD	1	HV	24	- placebo, 0.5, 2.5, 10, 30, 100, 300 mg fasted - 100 mg fed	P036 (B1521001)
MAD 2 weeks	1	Obese HV	40	Placebo, 1, 5, 25, 100 mg	P037 (B1521002)
Repeated dosing 6 days PD - od *versus* bid dosing	1	HV	40	5 mg qd, 2.5 mg bid, 15 mg qd, 7.5 mg bid for 6 days	P035 (/B1521051)
Absolute F Fraction absorbed	1	HV	8	- 15 mg oral ertugliflozin - 100 µg iv 14C-ertugliflozin - 100 µg oral 14C-ertugliflozin	P020 (B1521043)
Relative F - tablet	1	HV	16	15 mg	P011

Description	Phase	Subject	n	Dose	Reference
amorphous vs cocrystal					(B1521034)
BE - commercial tablet *vs* phase 3 dose	1	HV	16	15 mg	P023 (B1521037)
Food effect, therapeutic (162655dose, commercial tablet	1	HV	14	15 mg	P024 (B1521048)
Mass balance	1	HV	6	- 25 mg oral solution - 100 µCi 14C-ertugliflozin	P038 (B1521003)
Renal impairment	1	HV T2DM pats T2DM RI	8 6 22-24	15 mg	P009 (B1521023)
Hepatic impairment	1	HV HI CP7-9	8 8	15 mg	P014 (B1521024)
Japanese	1	HV		- 1, 5, 25 mg single - 25 mg qd for 7 days	P041 (B1521009)
PD - od *versus* bid dosing	1	T2DM	26	- 2 mg od *vs* 1 mg bid - 4 mg od *vs* 2 mg bid	P040 (B1521007)
DDI metformin	1	HV	18	15 mg	P019 (B1521032)
DDI sitagliptin	1	HV	12	15 mg	P022 (B1521033)
DDI glimepiride	1	HV	18	15 mg	P032 (B1521044)
DDI simvastatin	1	HV	18	15 mg	P030 (B1521036)
DDI rifampicin	1	HV	12	15 mg	P021 (B1521040)

The basic pharmacokinetics of metformin are based on the Glucophage SmPC and literature.

Bioanalysis

HPLC-MS/MS methods for determination of ertugliflozin in plasma have been developed, pre- and within study validated. HPLC-MS/MS methods for simultaneous determination of ertugliflozin and M2 or ertugliflozin and M5c and M5a have also been developed and validated.

LC-MS/MS methods for determination of ertugliflozin in the urine or for simultaneous determination of ertugliflozin, M5c and M5a in the urine were developed and validated.

HPLC-MS/MS methods for determination of metformin, sitagliptin, simvastatin/simvastatin acid and glimepiride were developed and validated.

Ertugliflozin

Absorption

Ertugliflozin is characterized as a BCS I compound. *In vitro* ertugliflozin was a Pgp and BCRP substrate.

The F_a (fraction absorbed) of ertugliflozin following an oral dose was calculated to 111% and the absolute bioavailability (F) to 105%, by the use of the microdose approach.

A relative fast absorption of ertugliflozin, t_{max} ≈1h, is seen following oral administration.

Dose proportional increase in systemic exposure has been shown following single doses of 0.5-300 mg and repeated dosing of 1-100 mg od.

Steady state was reached at day five following repeated od administration. The steady state exposure increased *ca* 30% compared to after the first dose, with a R_{AC} varying between 1.2-1.4.

The total exposure of ertugliflozin after a total daily dose of 5 mg is comparable independently if administered a single dose qd or divided in two doses bid. The same applies for a total daily dose of 15 mg *ie* the total exposure is comparable following 7.5 mg bid and 15 mg qd.

Steglatro® is a cocrystal consisting of 1:1 ertugliflozin and L-pyroglutamic acid (L-PGA), in the absence of L-PGA, the active moiety is an amorphous solid. The relative F of ertugliflozin of tablets containing the amorphous form relative to the cocrystal form was 99% with 90%CI for both C_{max} and AUC within 80-125%. Thus any dissociation of the cocrystal to the amorphous form will not have any impact on the oral availability of ertugliflozin.

The commercial 15-mg tablet is BE to the phase-3 15-mg dose, administered as one 10-mg and one 5-mg tablet, with 90%CI for the ratios, commercial/phase 3, of AUC, AUC_{last} and C_{max} within the BE criteria of 80-125.

A decrease in exposure, C_{max} and AUC, of ca 30 and 10%, respectively, was seen following administration of 15 mg ertugliflozin together with food. The decrease in exposure is not considered clinically relevant and ertugliflozin may be dosed without any food restrictions.

Distribution

The V_{ss} (volume of distribution at steady state) estimated to 85 L. The f_u (unbound fraction) of ertugliflozin is determined to be 6.4%.

No clinically meaningful difference was seen in *ex vivo* protein binding of ertugliflozin between healthy subjects and T2DM patients with normal renal function and with varying degree of RI and in subjects with moderate HI However, f_u was slightly lower than determined *in vitro* 3.5%.

The blood/plasma ratio was 0.66.

Elimination

The terminal $t_{1/2}$ was calculated to about 14h and CL was estimated to *ca* 190 ml/min.

Following 25 mg 14C-ertugliflozin orally 41 and 50% of the radioactivity was excreted in the faeces and urine, respectively. *Ca* 1.5% of the dose was excreted unchanged in the urine. Thirty-four percent of the dose was excreted unchanged in faeces, and as the absolute F is 100%, it can be concluded that biliary excretion is responsible for *ca* 35% of the elimination of ertugliflozin.

A total of eight metabolites were detected, seven in the urine and three in faeces. The major metabolic pathway was direct glucuronidation (M5a, M5b, M5c) but also glucuronidation of M2 (M6a, M6b).

CYP3A4 was predominantly responsible in the formation of M1, M2, and M3. Minor contributions by CYP2C8, 3A5 and 2D6 were also seen.

UGT1A9 and 2B7 were involved in the glucuronidation of ertugliflozin to form M5a and M5c. M5a was mainly formed by UGT2B7 and the major enzyme contributing to the formation of M5c was UGT1A9. No clinically relevant differences in ertugliflozin exposure were seen between different UGT1A9 genotypes in healthy volunteers.

Dose proportionality and time dependencies

No signals of time-dependent PK of ertugliflozin have been identified *in vitro* or following repeated dosing of ertugliflozin.

Pharmacokinetic data from 15 clinical studies (nine Phase 1, two Phase 2, and four Phase 3 studies) were included in the popPK analysis. The final model was a 2-compartment model with lag time, first-order absorption, and first-order elimination. Baseline body weight was included using an allometric relationship, with the exponent fixed to 0.75 and 1.0 for apparent clearances and volumes, respectively. Covariates included in the model were eGFR, gender, race and patient status on CL/F, and age, gender and race on Vc/F. Based on the final model, the mean elimination half-life was 15.3 hr for healthy subjects and 16.6 hr for T2DM patients with normal renal function (eGFR ≥90 mL/min/1.73 m^2).

Special populations

An increase in AUC of *ca* 60% was seen in all subjects with RI independently if diagnosed with mild, moderate or severe decreased renal function. The f_u of ertugliflozin determined *ex vivo* increased slightly from 3.4% in healthy subjects to 4.1% in T2DM patients with severe RI. AUC of M5c and M5a increased 2- to 3-fold in subjects with decreased renal function.

The systemic exposure, AUC and C_{max}, of ertugliflozin was slightly lower by 13 and 21%, respectively, in subjects with moderate HI than in healthy subjects. The total exposure of M5c was *ca* 50% higher and M5a was c*a* 25-30% lower in HI compared to in healthy subjects. The $t_{1/2}$ of M5c and M5a was unchanged in HI compared to healthy subjects.

Age, weight, sex and gender effects on exposure are not anticipated to be clinically relevant.

Pharmacokinetic interaction studies

The PK interaction potential of ertugliflozin has been evaluated in a number of *in vitro* studies and in five *in vivo* studies. The enzymes and transporters with potential clinical relevance are summarized below.

Table 7: Enzymes with potential clinical relevance

Enzyme	Substrate	Inhibitor *in vitro*	IC50 (µM)	Clinical relevance	Induction Clinical relevance
CYP1A2	(Yes)				No
CYP2B6		Yes	21% @30	No	No
CYP2C8	(Yes)	Yes	27% @30	No	
CYP2C9		Yes	43% @30	No	
CYP2C19		Yes	10% @30	No	
CYP2D6	(Yes)	Yes	19% @30	No	
CYP3A	Yes	Yes	24% @30	No	No
UGT1A1		?	?	No	
UGT1A4		?	?	No	
UGT1A6					
UGT1A9	Yes	?			
UGT2B7	Yes				

(Yes) - minor contribution

Table 8: Transporters with potential clinical relevance

Transporter	Substrate	Inhibitor *in vitro*	IC50 (µM)	Clinical relevance
Efflux transporters				
Pgp	Yes	Yes	176	No
BCRP	Yes	Yes	*Ca* 60% @100	No
Uptake transporters				
OATP1B1		Yes	35	No
OATP1B3		Yes	141	No
OAT1				
OAT3		Yes	70	No
OCT1		Yes	53	No
OCT2		Yes	917	No

No clinically relevant difference in systemic exposure was seen of ertugliflozin or of metformin and sitagliptin, glimepiride and simvastain when co-administered with ertugliflozin compared to when administered alone.

Metformin

Absorption

Metformin absorption is saturable and incomplete after oral administration. The absolute bioavailability is approximately 50-60% in healthy subjects.

A decrease in C_{max} of ca 25% was reported following a dose of 850 mg taken together with food, which is deemed not clinical relevant and dose recommendation is taken without or with simultaneous food intake.

Distribution

Plasma protein binding of metformin is negligible. The mean volume of distribution (Vd) of metformin ranged between 63-276L.

Elimination

Plasma protein binding of metformin is negligible. The mean volume of distribution (Vd) of metformin ranged between 63-276L.

Dose proportionality and time dependencies

It is assumed that the PK of metformin absorption is non-linear.

Special populations

Renal CL decreased in proportion to that of creatinine in subjects diagnosed with renal impairment. The elimination $t_{1/2}$ was prolonged in RI, leading to increased levels of metformin in plasma. Metformin is contraindicated in patients with renal failure or renal dysfunction (CLcr <60 ml/min).

Metformin is contraindicated in patients with hepatic insufficiency due to the increased risk of lactic acidosis.

Pharmacokinetic interaction studies

No PK DDIs are listed in the metformin SmPC.

FDC ertugliflozin/metformin

Bioequivalence (BE) of the FDC ertugliflozin 7.5 mg/metformin 850 mg compared to co-administration of ertugliflozin 7.5 mg and metformin 850 mg was shown for both compounds, with the 90% CI of the ratio test/reference within the criteria for BE [80, 125%] for both AUC_{inf} and C_{max}.

BE of the FDC ertugliflozin 7.5 mg/metformin 1000 mg compared to co-administration of ertugliflozin 7.5 mg and metformin 1000 mg was shown for both compounds, with the 90% CI of the ratio test/reference within the criteria for BE [80, 125%] for both AUC_{inf} and C_{max}.

A delayed C_{max} for both ertugliflozin and metformin resulting in a decrease with *ca* 40 and 30%, respectively, was seen when the FDC ertugliflozin 7.5 mg/metformin 1000 mg was administered with food.

2.4.3. Pharmacodynamics

Mechanism of action

Ertugliflozin

Ertugliflozin is an oral, highly selective SGLT2 inhibitor with greater than 2000-fold higher selectivity for SGLT2 compared to sodium-glucose co-transporter 1 (SGLT1).

Under conditions of normoglycaemia, glucose is filtered in the glomerulus, with essentially all the filtered glucose being reabsorbed into the circulation in the early and late portion of the proximal tubule via the action of SGLT2 and SGLT1, respectively. Under conditions of hyperglycaemia, when the transporters reach their maximum reabsorptive capacity (referred to as the transport maximum for

glucose) glycosuria ensues. Ertugliflozin inhibits renal glucose reabsorption, resulting in a lowering of the renal threshold for glucose and increased UGE, thereby reducing plasma glucose and A1C in subjects with T2DM. Ertugliflozin improves glycaemic control via a mechanism independent of insulin and pancreatic β-cell function and its durability is not dependent on β-cell function. Because the extent of UGE is dependent on ambient glucose levels, as glucose levels decrease to normal, UGE also decreases, making hypoglycaemia unlikely.

Metformin

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.

Primary and Secondary pharmacology

Primary pharmacology

UGE in Healthy Subjects

In the single and multiple escalating dose studies of ertugliflozin in healthy subjects (Studies P036/1001 and P037/1002), 24-hour UGE increased in a dose-related manner and median 24-hour UGE values appeared to plateau at doses ≥25 mg. The 24-hour UGE values were generally similar on Day 1 and at steady state for the respective ertugliflozin dose groups. The median 24-hour UGE values at steady state after administration of 25 mg qd in healthy Japanese subjects (69.9 g) were similar to those observed in healthy subjects in other Phase 1 studies, supporting no meaningful ethnic difference in UGE between Japanese and Western healthy subjects.

In Study P035/1051, the 24-hour UGE values were 58.58 g, 57.63 g, 57.09 g, and 52.46 g for the 7.5 mg bid, 15 mg qd, 2.5 mg bid, and 5 mg qd doses, respectively, indicating no meaningful differences for the bid vs corresponding qd doses.

UGE in T2DM Subjects

In Study P040/1007, the 24-hour UGE values in T2DM subjects administered 1 mg bid, 2 mg qd, 2 mg bid, and 4 mg qd ertugliflozin doses were 69.45 g, 70.43 g, 78.29 g, and 80.54 g, respectively, indicating no meaningful differences in UGE for the bid vs corresponding qd doses.

Ertugliflozin, at a dose of 15 mg, induced higher median change from baseline 24-hour UGE in T2DM subjects with normal renal function (68.1 g) compared to healthy subjects (45.8 g) as expected with higher circulating glucose levels in T2DM subjects (Study P009/1023). Consistent with the mechanism of action of SGLT2 inhibitors, 24-hour UGE was dependent on renal function, with UGE decreasing with increase in degree of renal impairment despite increased ertugliflozin exposures in subjects with renal impairment. Compared to the median value of UGE in T2DM subjects with normal renal function, the UGE was approximately 53% to 69% of normal in subjects with mild renal impairment, and 42% to 48% of normal in subjects with moderate renal impairment.

Table 9: Summary Statistics for Change from Baseline in 24-hour UGE (g) by Renal Function

Renal Function Group	eGFR	N	Geometric Mean (%CV)	Median	Minimum	Maximum
T2DM, normal renal function	≥90 mL/min	6	72.31 (30)	68.1	51.5	120.5
	≥90 mL/min/1.73m^2	3	79.84 (37)	69.3	60.9	120.5
T2DM, mild RI	60-89 mL/min	8	35.98 (113)	36.4	6.3	119.9
	60-89 mL/min/1.73m^2	9	46.84 (47)	45.8	20.4	119.9
T2DM, moderate RI	30-59 mL/min	8	27.55 (68)	28.8	13.1	77.2
	30-59 mL/min/1.73m^2	8	30.65 (108)	33.4	6.3	89.7
T2DM severe RI	<30 mL/min	6	10.09 (57)	10.3	4.9	20.7
	<30 mL/min/1.73m^2	8	11.24 (53)	12.5	4.9	20.7
Healthy, normal renal function	≥90 mL/min	8	46.33 (31)	45.8	27.4	70.0
	≥90 mL/min/1.73m^2	4	48.75 (45)	55.2	27.4	70.0

Source: [Ref. 5.3.3.3: P009].
Abbreviations: %CV= percent coefficient of variation; eGFR=estimated glomerular filtration rate; RI=renal impairment; T2DM=type 2 diabetes mellitus; UGE=urinary glucose excretion.

A regression model-predicted mean 24-hour UGE with ertugliflozin for a T2DM subject with a BSA-unnormalized eGFR of 52.5 mL/min was 25.3 g, and for a T2DM subject with a BSA-normalized eGFR of 52.5 mL/min/1.73m^2 was 29.5 g.

Secondary pharmacology

Study P010/1025 was a single-dose, randomized, 3-treatment, 6-sequence, 3-period crossover, placebo- and active-controlled study in 42 healthy subjects to demonstrate a lack of effect of a supratherapeutic dose of ertugliflozin on the QTc interval. The ertugliflozin dose administered was 100 mg. The observed LS mean difference in QTcF between ertugliflozin and placebo ranged from 0.09 milliseconds to 2.99 ms. At the median time of peak ertugliflozin concentrations (1.5 hours post dose), the LS mean difference was 1.47 milliseconds.

Relationship between plasma concentration and effect

The relationship between 24-hour UGE and ertugliflozin dose in T2DM subjects was characterized using data from the phase 2 dose-ranging Study P042/1004. In this study, the 24-hour UGE was assessed in an outpatient setting at baseline (Day 0) and after 28-day dosing with ertugliflozin 1 mg, 5 mg, or 25 mg, placebo, or hydrochlorothiazide in subjects with T2DM with inadequate glycaemic and blood pressure control. An E_{max} model was fitted to the observed 24-hour UGE data as a function of administered dose. The model estimated a maximal baseline-adjusted 24-hour UGE response of 71.5 (95% CI: 57.9, 87.3) g and an ED50 of 0.752 (95% CI: 0.299, 1.58) mg. The predicted mean 24-hour UGE following administration of ertugliflozin 5 mg and 15 mg doses for 28 days were 62.5 (90% CI: 54.9, 69.7) and 68.9 (90% CI:58.9, 78.7) g. The dose-response modelling indicated that ertugliflozin 5 mg and 15 mg result in near maximal UGE, with the 15 mg dose providing incrementally greater UGE relative to the 5 mg dose.

2.4.4. Discussion on clinical pharmacology

This application concerns a combination of the NCE ertugliflozin, with the MAA procedure for Steglatro® ongoing in parallel, and the well-known substance metformin. The Applicant has provided a solid clinical pharmacology program for ertugliflozin and very well presented.

The MAA for Segluromet® contains the complete ertugliflozin clinical pharmacology program submitted for Steglatro® and three additional phase 1 studies in support of the FDC tablets. This assessment report focuses on the assessment of Steglatro® and the additional studies submitted. The presented PK on metformin are based on the Glucophage® SmPC.

The absolute F of ertugliflozin is 100% following oral administration of clinical relevant doses and a dose-proportional increase in systemic exposure has been seen after repeated dosing up to 100 mg od.

Bioequivalence of the FDC ertugliflozin 7.5 mg/metformin 850 mg compared to co-administration of ertugliflozin 7.5 mg and metformin 850 mg was shown for both compounds. BE was also shown for the FDC with ertugliflozin 7.5 mg/metformin 1000 mg compared to co-administration of the single components.

Decreased C_{max} for both ertugliflozin and metformin (*ca* 40 and 30%, respectively) were seen when the FDC ertugliflozin 7.5 mg/metformin 1000 mg was administered with food. These decreases are consistent with the decreases seen following administrations of the single components. No clinical relevant change in total exposure was seen compared when administered in fasted condition, thus there is no restrictions for concomitant food intake with Segluromet®.

Ertugliflozin is mainly eliminated *via* metabolism with <2% excreted unchanged in the urine. *Ca* 12% is excreted as oxidative metabolites (in urine+faeces), *ca* 46% as glucuronides (main drug related component in the urine) and 34% as parent compound (in faeces). UGT mediated, UGT1A9 and UGT2B7, metabolism is responsible for >85% of elimination. No *in vivo* data confirming the proposed elimination pathways are available. However, clinical consequences of potential increase in systemic exposure of ertugliflozin, following inhibition of the main elimination pathway *ie* UGT inhibition, are not expected. The PBPK platform was not deemed qualified to predict UGT inhibition.

Both UGT1A9 and UGT2B7 are expressed in the liver and the kidney. *In vitro* measurements of the formation of M5a and M5c were performed using human liver and human kidney microsomes to understand the role of the liver and the kidney. Taking into account tissue specific microsomal protein expressions, the $f_{m,UGT}$ in the liver and the kidney was calculated to 0.89 and of 0.11, respectively.

About 50% increase in exposure was seen in subjects diagnosed with RI independently of degree of renal function. The f_u of ertugliflozin determined *ex vivo* increased slightly from 3.4% in healthy subjects compared to 4.1% in T2DM patients with severe renal function. The exposure of the main metabolites, the direct glucuronidated metabolites, was increased 2- to 3-fold. The increases in exposure in RI patients are not considered clinically relevant.

The exposure of ertugliflozin was slightly lowered, AUC and C_{max}, 13 and 21%, respectively, in subjects with moderate HI compared to healthy subjects. This is not considered clinically relevant.

It is not clear how age influences the use of Segluromet, a FDC of ertugliflozin/metformin, in elderly patients. The SmPC has been updated with information that there is limited experience in subjects >75 years.

No clinically relevant difference in systemic exposure of ertugliflozin was seen when co-administered metformin, sitagliptin, glimepiride and simvastatin when co-administered compared to when administered alone.

Based on an extensive *in vitro* evaluation, it can be concluded that ertugliflozin is not characterized as an OATP substrate.

The total exposure of ertugliflozin decreased *ca* 40% when co-administered with rifampicin. Rifampicin is a known inducer but also a known OATP inhibitor. However, it can be concluded that the seen decrease in exposure when co-administered is a consequence of induction as ertugliflozin is not an OATP substrate.

No difference in exposure of metformin, sitagliptin or glimepiride was seen when co-administered with ertugliflozin compared when dosed alone.

Ertugliflozin is claimed not to inhibit UGTs *in vitro* at clinical relevant concentration. There are specificity limitations in the study design considering used substrates and inhibitors but it can be concluded that ertugliflozin is not an inhibitor of UGT1A6 and 2B7. The conclusion on no inhibition of UGT1A1, 1A4 and 1A9 are more ambiguous, but as no signals were observed in any of the assays the issue will not be further pursued.

An increase in exposure of simvastatin/simvastatin acid was seen when co-administered with ertugliflozin but not considered clinically relevant. Simvastatin is characterized as CYP3A4, OATP1B1 and BCRP substrate. The mechanism behind the increase in plasma levels is unknown as ertugliflozin is not an inhibitor of OATP, BCRP or CYP3A4.

Ertugliflozin is an oral, highly selective SGLT2 inhibitor with greater than 2000-fold higher selectivity for SGLT2 compared to sodium-glucose co-transporter 1 (SGLT1). The primary mechanism of action is well known by now, as ertugliflozin is the fourth SGLT2-inhibitor to reach this stage of development in the EU. The mechanism of action for metformin is well known.

Both single and multiple escalating dose studies in healthy volunteers showed an increase in UGE by dose. No additional increase was observed at doses higher than 25 mg ertugliflozin in any of the studies.

In Phase 3 studies, ertugliflozin was administered qd. The ertugliflozin/metformin FDC contains an immediate-release formulation of metformin. Given that metformin immediate-release is recommended to be administered bid, ertugliflozin/metformin FDC will also be dosed bid. In order to bridge the qd dosing regimen of ertugliflozin administered in the phase 3 studies with the bid dosing regimen in the ertugliflozin/metformin FDC, the effect of qd and bid dosing was investigated in healthy volunteers. No meaningful difference in the UGE was observed between the two different dosing regimens. The effect of qd and bid dosing was also investigated in subjects with T2DM. No meaningful difference in the UGE was observed between the two different dosing regimens. Notably, in both studies the difference between the two dose levels (5 vs 15 mg daily and 2 vs 4 mg daily, respectively) was small.

Study P009/1023 was an open-label, single oral dose study which included T2DM patients with either normal renal function or mild, moderate or severe renal impairment. In addition healthy volunteers were included. The HbA1c was higher in the T2DM group with normal renal function than in the groups with renal impairment (7.9% vs 7.1%). This may have affected the result to some extent, but considering that the effect of ertugliflozin on UGE in patients with T2DM and mild renal impairment was comparable to that observed in healthy volunteers, the data provide evidence that the effect of ertugliflozin declines with declining renal function.

No firm connection has been established between the plasma levels and the pharmacodynamic effects. This is understandable because the drug acts extracellularly and pharmacological and therapeutic effects depend on the drug concentration in the tubular lumen. Therefore studying the relationship

between the excreted ertugliflozin amount (Ae24) and UGE allows drawing conclusions about the PK/PD. The relationship between eGFR and the excreted amount is close to linear.

The definitive QTc study showed no effect of ertugliflozin on QTc.

The Applicant has not provided any data on pharmacodynamic interactions. The SmPC includes information on interactions with diuretics which may increase the risk of dehydration and hypotension and on interactions with insulin and insulin secretagogues which may increase the risk of hypoglycaemia. This is relevant and sufficient.

Studies performed in Japanese subjects showed no apparent differences in the effect of ertugliflozin compared to the outcome in studies performed in Western healthy subjects.

2.4.5. Conclusions on clinical pharmacology

Overall the clinical pharmacology properties of the FDC ertugliflozin/metformin have been appropriately described and are reflected in the SmPC.

2.5. Clinical efficacy

Seven Phase 3 studies support the initial regulatory submission for ertugliflozin alone. Four of the seven Phase 3 studies also 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 adult subjects with T2DM **(Table 3).** Efficacy data were pooled for the 2 placebo-controlled studies to assess efficacy on a background of metformin.

The following three studies from the ertugliflozin program are considered supportive; P003/1022 (Monotherapy) and P017/1047 (Ertugliflozin plus sitagliptin initial combination). Study P001/1016 was a special populations study in moderate renal impairment.

2.5.1. Dose response studies

Ertugliflozin

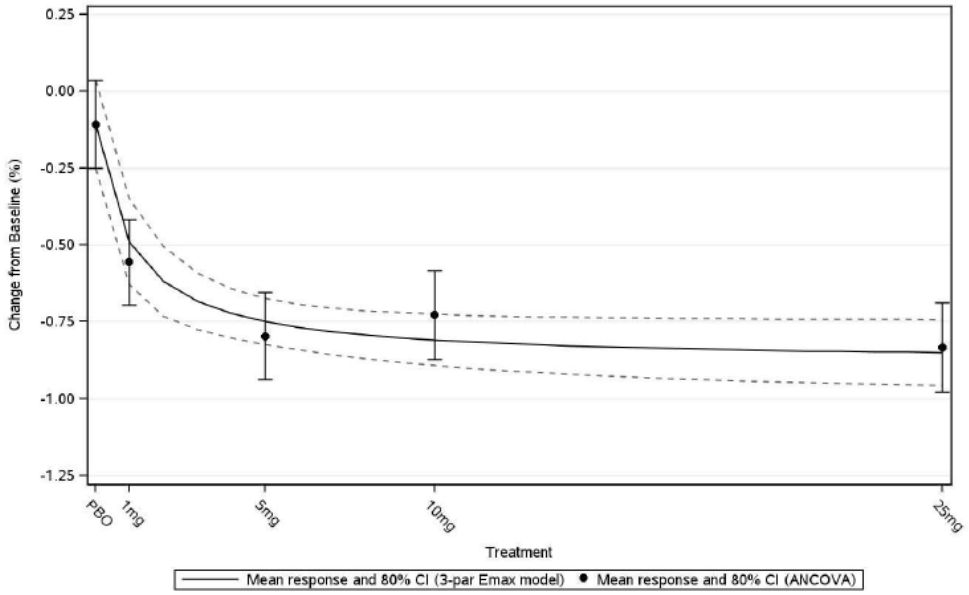
The dose response studies discussed in the following were conducted to support the doses for ertugliflozin as monocomponent.

Ertugliflozin doses of 5 mg and 15 mg qd were evaluated in all phase 3 studies (dosed in the morning without regard to food). The primary driver for dose selection was the dose-response modelling for the change from baseline in A1C, FPG, body weight, and the mechanistic biomarker 24 hour UGE in subjects with T2DM (based on Phase 2 Studies P016/1006 and P042/1004). For these endpoints, the 5 mg and 15 mg doses consistently elicited a response that was >80% and >90% of the maximum response, respectively.

Study P016/1006 was a randomized, double-blind, double-dummy, placebo- and active-controlled, 6-treatment group, parallel-group, 2-period study in subjects with T2DM. In total, 328 subjects were randomly assigned to study medication (ertugliflozin 1 mg, 5 mg, 10 mg and 25 mg, sitagliptin 100 mg or placebo). Demographic characteristics (gender, age, weight, and race) were similar across treatment groups. Treatment groups were well balanced in baseline disease characteristics.

Figure 4 presents the result of the primary efficacy endpoint: change from baseline in A1C at Week 12. At Week 12, there was a significant reduction in A1C for each ertugliflozin group vs placebo. The magnitude of the placebo-adjusted least squares (LS) mean change from baseline ranged from a decrease of 0.45% to 0.72%. At Week 12, there was also a significant reduction in A1C for sitagliptin vs placebo where the magnitude of placebo-adjusted LS mean change was a decrease of 0.76% from baseline.

Figure 4: Dose-Response Analysis (3-Parameter E_{max}) of Percent Change From Baseline in HbA1c at Week 12 (FAS LOCF)



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

Study P042/1004 was a randomized, double-blind, double-dummy, placebo- and active-controlled, 5-treatment, parallel-group study in subjects with a history of mild to moderate hypertension and a diagnosis of T2DM. In total, 194 subjects were randomly assigned to study medication (ertugliflozin 1 mg, 5 mg and 25 mg, hydrochlorothiazide 12.5 mg or placebo). Demographic and baseline characteristics were well balanced at baseline across treatment groups.

There was a significant decrease from baseline in the primary efficacy endpoint, average 24-hour SBP at Week 4 for all doses of ertugliflozin (1 mg, 5 mg, and 25 mg) vs placebo. The average decreases were approximately 3 to 4 mm Hg. There was also a significant decrease from baseline in the average 24-hour SBP at Week 4 for HCTZ vs placebo. The mean decrease from baseline was approximately 3 mm Hg. There was a dose-dependent change from baseline (increase) in UGE_{0-24} at Week 4 for all doses of ertugliflozin (1 mg, 5 mg, and 25 mg) vs placebo. In contrast, there was no change from baseline in UGE_{0-24} at Week 4 for HCTZ or placebo.

2.5.2. Main studies

The phase 3 program evaluating efficacy and safety of 5 mg and 15 mg ertugliflozin once daily was designed to support ertugliflozin as an adjunct to diet and exercise for the treatment of patients with

T2DM as monotherapy and combination therapy, add-on or co-initiation, with other anti-hyperglycaemic agents. A total of seven phase 3 studies have been submitted.

The focus of the ertugliflozin/metformin registration dossier is on the four studies where ertugliflozin and metformin were co-administered; P002/1013, P005/1019, P006/1015 and P007/1017 **(Table 3)**.

A total of 4863 subjects were randomly assigned to treatment in the Phase 3 studies supporting registration of ertugliflozin, with 2597 of these subjects randomly assigned to treatment with ertugliflozin on a background of metformin.

Methods

Four Phase 3 studies are included in this registration dossier. All were randomized, double-blind, parallel-group studies. Two were placebo-controlled studies and 2 were active-controlled studies **(Table 3)**.The primary assessment of efficacy was generally performed after 26 weeks or after 52 weeks (only applicable in the study comparing ertugliflozin with glimepiride as an add-on to metformin; Study P002/1013).

Placebo-controlled studies examined the efficacy of ertugliflozin at doses of 15 mg and 5 mg as add-on to background metformin (Study P007/1017) and add-on to background metformin plus sitagliptin (Study P006/1015).

Active-controlled studies evaluated the efficacy of ertugliflozin at doses of 15 mg and 5 mg administered as add-on to metformin compared to glimepiride (Study P002/1013) and as an add-on to metformin when administered alone or co-administered with sitagliptin in a factorial study design (Study P005/1019).

All studies had a 2-week placebo run-in period prior to randomization. Each study had 2 treatment periods: a Phase A period and a Phase B period. Phase A represents the primary time period for evaluation of hypotheses. The duration of Phase A was 26 weeks for all studies except Study P002/1013, which was 52 weeks.

The Phase B periods for these studies will provide longer-term safety and efficacy data for ertugliflozin. The Phase B periods of these 4 studies are either ongoing (Studies P007/1017 and P002/1013) or have completed dosing (Studies P005/1019 and P006/1015).

Study Participants

The primary inclusion and exclusion criteria were harmonized across the Phase 3 studies. Subjects were diagnosed with T2DM in accordance with the ADA guidelines; all subjects had inadequate glycaemic control at baseline. The entry A1C range differed based on study design and was slightly higher in the study that included co-administration treatment arms, Study P005/1019 (7.5%-11.0%, inclusive), relative to the other studies . Subjects were ≥18 years of age with no history of other type of diabetes, ketoacidosis, CV event within 3 months of screening, or hepatic impairment. For those studies requiring specific background anti-hyperglycaemic therapy, subjects needed to be receiving stable dose(s) that reflected near or maximal efficacy for the background anti-hyperglycaemic treatment prior to randomization.

In all studies, subjects needed to be receiving background treatment with a stable metformin dose of ≥1500 mg/day. For Study P006/1015, background AHA therapy consisted of metformin ≥1500 mg/day and sitagliptin 100 mg. For Studies P007/1017 and P002/1013, subjects with screening

eGFR<55 mL/min/1.73 m^2 or a serum creatinine ≥1.3 mg/dL (men) or ≥1.2 mg/dL (women) were excluded. For Studies P005/1019 and P006/1015, subjects with a screening eGFR <60 mL/min/1.73 m^2 were excluded.

Treatments

Placebo-controlled studies examined the efficacy of ertugliflozin at doses of 15 mg and 5 mg as add-on to background metformin (Study P007/1017) and add-on to background metformin plus sitagliptin (Study P006/1015).

Active-controlled studies evaluated the efficacy of ertugliflozin at doses of 15 mg and 5 mg administered as add-on to metformin compared to glimepiride (Study P002/1013) and as an add-on to metformin when administered alone or co-administered with sitagliptin in a factorial study design (Study P005/1019).

Thus the combination of ertugliflozin and metformin was compared both to placebo and to active control. In addition the triple combination of ertugliflozin, metformin and sitagliptin was compared to placebo and active control.

Outcomes/endpoints

The primary assessment of efficacy was generally performed after 26 weeks or after 52 weeks (only applicable in the study comparing ertugliflozin with glimepiride as an add-on to metformin; Study P002/1013).

The following endpoints were evaluated in all studies: change from baseline in A1C, fasting plasma glucose (FPG), body weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP), and the proportion of subjects with A1C <7.0% (<53 mmol/mol). Two-hour post-prandial glucose (PPG) and the β-cell responsivity static component (Φ_s) was measured in Study P005/1019.

Sample size

In study P007/1017 the planned total sample size was approximately 600 subjects, 200 per arm, and was to provide at least 99% power to detect a difference of 0.5% between each ertugliflozin dose and placebo assuming a standard deviation (SD) of 1.0%. Although a smaller sample size would provide sufficient study power, the sample size was chosen to provide additional safety exposure for subjects with T2DM and inadequate glycaemic control on metformin in monotherapy, and also to enable BMD endpoints to be estimated with a pre-specified degree of precision.

In study 006/1015 the planned total sample size was approximately 405 subjects, 135 subjects per arm, and was chosen to provide adequate exposure data to assess safety for 52 weeks. An effective sample size, accounting for e.g. information loss due to missing data, of 120 per arm was to provide 97% power to detect a true difference in HbA1c of 0.5% between a given ertugliflozin dose and placebo.

In study P002/1013 the planned total sample size was 1230 subjects (410 per arm) and was estimated using a non-inferiority margin of 0.3% and the assumption of a true mean difference in HbA1C of 0%.

In study P005/1019 the planned total sample size was 1250 subjects where a sample size of 250 subjects per arm were to provide 94% power to declare superiority and detect a difference in HbA1C of

0.4% for each of the pairwise comparisons at a given ertugliflozin dose level assuming a standard deviation (SD) of 1.2%.

Randomisation

In all studies an equal allocation ratio was used (i.e. 1:1:1 or, in study P005/1019, 1:1:1:1:1). All the studies had a 2-week single-blind placebo run-in period prior to randomisation. To be eligible for randomisation subjects had to meet all entry criteria that also included being at least 80% compliant with the single-blind placebo run-in medication. Randomisation was performed through the use of an interactive voice response system/integrated web response system (IVRS/IWRS).

In study P007/1017, randomisation was stratified based on geographical region and postmenopausal status (4 levels). In study P006/1015 randomisation was stratified according to use of sulfonylurea (SU) at screening (yes/no). In study P005/1019 randomisation was stratified by participation in the mixed meal tolerance test (MMTT) (yes/no).

Blinding (masking)

After randomisation, all the studies were double-blind. Masking was achieved and maintained in each study through the use of a double-dummy approach with a placebo tablet matching the ertugliflozin 5 mg tablet and another placebo tablet matching the ertugliflozin 10 mg tablet, with, in addition in the two active-controlled studies, placebo matching glimepiride (study P002/1013) and placebo matching sitagliptin (study P005/1019), respectively.

All these studies had two post-randomisation treatment periods, Phase A and Phase B. Phase A represented the primary time period for evaluation of hypotheses and at the completion of the Phase A portion (defined as database lock) subjects' treatment assignments were unblinded to permit authoring of CSRs. Personnel associated with the conduct of the study as well as trial site personnel and subjects, were to remain blinded and were not to be unblinded until after the Phase B portion had been completed.

Statistical methods

Statistical methods were generally similar across the individual Phase 3 studies. All tests were to be conducted at a two-sided significance level of $\alpha=0.05$ using pre-specified multiplicity strategies taking into account multiple testing (documented in the SAPs and protocols).

The analysis population for all efficacy analysis was the Full Analysis Set (FAS), which was to consist of all randomised subjects who received at least one dose of study medication and had at least one measurement for the analysis endpoint (baseline or post-randomisation). Subjects were to be included in the treatment group to which they were randomly assigned. A per-protocol (PP) population was also defined as a secondary population for analyses of primary and key secondary efficacy endpoints.

Data obtained after the initiation of rescue therapy or after bariatric surgery were to be censored (i.e., treated as missing) to avoid the confounding influence of rescue therapy. These analyses were referred to as "excluding rescue" (ER). Supplemental efficacy analyses that included measurements collected after the start of glycaemic rescue therapy were also performed and were referred to as "including rescue approach" (IR). The extent and timing of the use of rescue therapy were to be compared across treatment groups by the number and percentage of subjects rescued with an analysis also of time to rescue.

Two main analysis approaches were used for the efficacy endpoints. The estimand for all of the primary hypotheses was the difference in mean A1C improvement at the primary timepoint, in the target population defined by the inclusion / exclusion criteria, if all subjects adhered to therapy without use of rescue medication

Continuous endpoints (including the primary endpoint)

Continuous endpoints were analysed using a constrained LDA (cLDA) model (as proposed by Liang and Zeger) with treatment, time, and treatment-by-time interaction along with additional covariates as pre-specified for each study included in the model. Time was treated as a categorical variable so that no restriction was imposed on the trajectory of the means over time. An unstructured covariance matrix was used to model the correlation among repeated measurements. Baseline eGFR values >120 ml/min/1.73 m^2 were set to 120 in these analyses. The treatment difference in terms of mean change from baseline to a given time point was estimated and tested from the cLDA model.

In study P001/1016, P006/1015, P007/1017 and P017/1047, data from any subject incorrectly stratified at randomization were analyzed according to the intended stratum rather than the actual stratum. An accounting of all incorrectly stratified subjects was provided.

Within the constrained longitudinal data analysis (cLDA) model framework, no explicit imputation of missing assessments is performed. To assess the robustness of the primary analyses to departures from the MAR assumption, two sensitivity analyses using the tipping-point approach and a jump-to-reference multiple-imputation (J2R) method were to be performed. In the J2R analysis, missing values were imputed based on the missing-at-random (MAR) assumption for the reference (control) group and based on the missing-not-at-random (MNAR) assumption for the ertugliflozin groups using the reference group profile for time points after withdrawal. These sensitivity analyses were performed under both rescue therapy data handling scenarios; in primary sensitivity analyses, A1C measurements collected after the start of glycaemic rescue therapy were considered as missing data and in supplemental sensitivity analyses, A1C measurements collected after the start of glycaemic rescue therapy were included as reported.

For study P002/1013, only the tipping point sensitivity analysis was performed because the primary efficacy endpoint of change from baseline in A1C at Week 52 was assessed with a non-inferiority hypothesis. In addition, primary and key secondary efficacy endpoints at Week 52 were to be repeated based on the Per-Protocol (PP) population. The PP population included all randomised subjects who took at least one dose of study medication, had a measurement of the analysis endpoint at both baseline and in the day range for the time point of interest (Week 52), without any of a number of pre-defined violations. Also, a modified FAS (mFAS) population, defined as all subjects in the FAS who did not have any of the protocol violations as defined for the PP population, was to be an additional secondary population. Subjects who discontinued prematurely without a protocol violation were to be included in the mFAS. Analyses were to be performed in this population only if its size differed from that of the PP population by more than 2% of patients in any arm.

Binary endpoints

For the proportions of subjects with A1C <7.0% (<53 mmol/mol), a subject was categorised as having met the goal or not having met the goal at the analysis time point based on the observed A1C value or an imputed estimate. For subjects in the FAS population with missing A1C values at the analysis time point, the cLDA model described above was used to impute the missing A1C value and, therefore, categorisation as at or not at the A1C goal at the analysis time point. A logistic regression model including terms for treatment and baseline A1C as well as other covariates pre-specified for each study was used to estimate the odds ratio for comparison of each ertugliflozin group to the comparator for

each imputed dataset. The parameter estimates from the log odds ratios from 10 imputed data sets were combined using Rubin's rules to yield an overall estimate of the log odds ratio. The log odds ratio was back-transformed into the odds ratio for final reporting.

An additional analysis of the proportion of subjects with A1C at goal was performed where all subjects with missing A1C at the analysis time point were counted as not being at goal.

Results

Participant flow

Placebo-controlled studies:

Table 10: Disposition of subjects – study P007/1017 (phase A, 26 weeks)

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Entered Screening							1535	
Not Randomized							914	
Subjects Randomized	209		207		205		621	
Subject Study Medication Disposition								
Completed	190	(90.9)	201	(97.1)	190	(92.7)	581	(93.6)
Discontinued	19	(9.1)	6	(2.9)	15	(7.3)	40	(6.4)
Adverse Event	5	(2.4)	2	(1.0)	3	(1.5)	10	(1.6)
Excluded Medication	2	(1.0)	0	(0.0)	1	(0.5)	3	(0.5)
Hypoglycemia	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.2)
Lost to Follow-Up	3	(1.4)	0	(0.0)	3	(1.5)	6	(1.0)
Non-Compliance with Study Drug	1	(0.5)	1	(0.5)	0	(0.0)	2	(0.3)
Physician Decision	1	(0.5)	0	(0.0)	0	(0.0)	1	(0.2)
Protocol Violation	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.2)
Subject Moved	1	(0.5)	0	(0.0)	1	(0.5)	2	(0.3)
Withdrawal by Subject	6	(2.9)	2	(1.0)	6	(2.9)	14	(2.3)

Source: Table 14.1.1.6
Abbreviations: n = number of subjects
Each subject is counted once for Trial Disposition, Subject Study Medication Disposition based on the latest corresponding disposition record.
For the calculation of percentage, the denominator is the number of randomized subjects.
Completed refers to the number of subjects completing Phase A.
One screening failure subject PPD took the study medication during the screening period due to a dispensing error.
Since the subject is not randomized, he/she is not counted in the 'treated' category, and excluded from all efficacy and safety analyses based on the statistical analysis plan.

The discontinuation rate was highest in the placebo group (9%) followed by the ertugliflozin 15 mg group (7%), the overall discontinuation rate being 6%. The discontinuation rates were generally low.

Table 11: Disposition of subjects – study P006/1015 (phase A, 26 weeks)

	Placebo		Ertugliflozin 5 mg		Ertugliflozin 15 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Entered Screening							987	
Not Randomized							524	
Subjects Randomized	153		156		154		463	
Subject Study Medication Disposition								
Completed	141	(92.2)	143	(91.7)	140	(90.9)	424	(91.6)
Did Not Take Study Medication	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.2)
Discontinued	12	(7.8)	13	(8.3)	13	(8.4)	38	(8.2)
Adverse Event	1	(0.7)	5	(3.2)	1	(0.6)	7	(1.5)
Creatinine/eGFR	0	(0.0)	0	(0.0)	3	(1.9)	3	(0.6)
Lost To Follow-Up	0	(0.0)	0	(0.0)	1	(0.6)	1	(0.2)
Non-Compliance with Study Drug	2	(1.3)	1	(0.6)	0	(0.0)	3	(0.6)
Physician Decision	0	(0.0)	1	(0.6)	1	(0.6)	2	(0.4)
Protocol Violation	1	(0.7)	0	(0.0)	1	(0.6)	2	(0.4)
Subject Moved	0	(0.0)	1	(0.6)	0	(0.0)	1	(0.2)
Withdrawal By Subject	8	(5.2)	5	(3.2)	6	(3.9)	19	(4.1)

Each subject is counted once for Subject Study Medication Disposition, based on the latest corresponding disposition record.
For the calculation of percentage, the denominator is the number of randomized subjects.

Data Source: Table 14.1.4.2 Date of Reporting Dataset Creation: 06JUN2016 Date of Table Creation: 07JUN2016 (7:20)

The discontinuation rates were low and balanced between groups, the overall discontinuation rate being 8.2%. Discontinuations due to adverse events were most common in the ertugliflozin 5 mg group (3.2%) compared to the other treatment groups.

Active-controlled studies:

Table 12: Disposition of subjects – study P002/1013 (phase A, 52 weeks)

	Ertugliflozin 5 mg		Ertugliflozin 15 mg		Glimepiride		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Entered Screening							2985	
Not Randomized							1659	
Subjects Randomized	448		441		437		1326	
Subject Study Medication Disposition								
Completed	340	(75.9)	357	(81.0)	348	(79.6)	1045	(78.8)
Did Not Take Study Medication	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Discontinued	108	(24.1)	83	(18.8)	89	(20.4)	280	(21.1)
Adverse Event	15	(3.3)	22	(5.0)	13	(3.0)	50	(3.8)
Death	4	(0.9)	0	(0.0)	1	(0.2)	5	(0.4)
Excluded Medication	2	(0.4)	1	(0.2)	4	(0.9)	7	(0.5)
Hyperglycemia	24	(5.4)	13	(2.9)	10	(2.3)	47	(3.5)
Hypoglycemia	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.1)
Lack of Efficacy	0	(0.0)	0	(0.0)	3	(0.7)	3	(0.2)
Lost To Follow-Up	16	(3.6)	8	(1.8)	14	(3.2)	38	(2.9)
Non-Compliance with Study Drug	10	(2.2)	2	(0.5)	3	(0.7)	15	(1.1)
Physician Decision	3	(0.7)	2	(0.5)	3	(0.7)	8	(0.6)
Pregnancy	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.1)
Protocol Violation	2	(0.4)	4	(0.9)	3	(0.7)	9	(0.7)
Study Terminated By Sponsor	6	(1.3)	4	(0.9)	10	(2.3)	20	(1.5)
Subject Moved	5	(1.1)	4	(0.9)	6	(1.4)	15	(1.1)
Withdrawal By Subject	20	(4.5)	23	(5.2)	18	(4.1)	61	(4.6)

Each subject is counted once for Subject Study Medication Disposition, based on the latest corresponding disposition record.
For the calculation of percentage, the denominator is the number of randomized subjects.
The Study Terminated By Sponsor category includes any subject who was discontinued from study drug because the site was closed by Merck.

Data Source: Table 14.1.4.2 Date of Reporting Dataset Creation: 11JUN2016 Date of Table Creation: 19JUN2016 (7:17)

The discontinuation rates were balanced between groups, the overall discontinuation rate being 21%. Hyperglycaemia was twice as common in the ertugliflozin 5 mg group (5.4%) compared to the ertugliflozin 15 mg group and the glimepiride group.

Table 13: Disposition of subjects – study P005/1019 (phase A, 26 weeks)

	Ertugliflozin 5 mg		Ertugliflozin 15 mg		Sitagliptin 100 mg		Ertugliflozin 5 mg + Sitagliptin 100 mg		Ertugliflozin 15 mg + Sitagliptin 100 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Entered Screening											2582	
Not Randomized											1349	
Subjects Randomized	250		248		247		243		245		1233	
Subject Study Medication Disposition												
Completed	233	(93.2)	226	(91.1)	221	(89.5)	226	(93.0)	221	(90.2)	1127	(91.4)
Did Not Take Study Medication	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.1)
Discontinued	17	(6.8)	22	(8.9)	26	(10.5)	17	(7.0)	23	(9.4)	105	(8.5)
Adverse Event	3	(1.2)	3	(1.2)	1	(0.4)	3	(1.2)	6	(2.4)	16	(1.3)
Creatinine/eGFR	3	(1.2)	0	(0.0)	1	(0.4)	1	(0.4)	1	(0.4)	6	(0.5)
Excluded Medication	0	(0.0)	0	(0.0)	2	(0.8)	0	(0.0)	0	(0.0)	2	(0.2)
Hyperglycemia	0	(0.0)	0	(0.0)	2	(0.8)	0	(0.0)	0	(0.0)	2	(0.2)
Lost To Follow-Up	3	(1.2)	6	(2.4)	4	(1.6)	2	(0.8)	1	(0.4)	16	(1.3)
Non-Compliance with Study Drug	1	(0.4)	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)	3	(0.2)
Physician Decision	1	(0.4)	1	(0.4)	1	(0.4)	2	(0.8)	2	(0.8)	7	(0.6)
Protocol Violation	1	(0.4)	1	(0.4)	0	(0.0)	1	(0.4)	1	(0.4)	4	(0.3)
Subject Moved	1	(0.4)	0	(0.0)	1	(0.4)	1	(0.4)	1	(0.4)	4	(0.3)
Withdrawal By Subject	4	(1.6)	10	(4.0)	14	(5.7)	6	(2.5)	11	(4.5)	45	(3.6)

Each subject is counted once for Subject Study Medication Disposition, based on the latest corresponding disposition record.
For the calculation of percentage, the denominator is the number of randomized subjects.

Data Source: Table 14.1.4.2 Date of Reporting Dataset Creation: 26FEB2016 Date of Table Creation: 04MAR2016 (5:25)

The discontinuation rates were low and balanced between groups, the overall discontinuation rate being 8.5%. Discontinuations due to adverse events were twice as common in the ertugliflozin 15 mg + sitagliptin 100 mg group (2.4%) compared to the other treatment groups given ertugliflozin. The lowest rate (0.4%) was observed in the sitagliptin 100 mg group.

Recruitment

The ertugliflozin development program was global in scope, with subjects participating from North America, Europe, Latin America, Asia, and South Africa.

Conduct of the study

Major protocol deviations were reported for between 24 and 33% of subjects across the studies except for the renal impairment study (P001/1016) where major protocol deviations were reported for 48% of subjects. Across the studies, the most common deviations were "failure to conduct major/significant evaluations" and "subjects who did not give appropriate Informed Consent". Multiple enrolments were discovered in all studies, mostly in the US.

Baseline data

The mean age of the subjects across the four metformin Phase 3 studies ranged from 55.1 to 59.1 years. Across the four studies, the proportion of subjects ≥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/m^2.

Subjects with a broad range of baseline hyperglycaemia were included (mean baseline A1C ranged from 7.8% to 8.6%) so as to provide an assessment of ertugliflozin efficacy in a population representative of the typical patient likely to receive ertugliflozin/metformin FDC. Study P005/1019 had a higher mean baseline A1C compared with the other studies. Mean baseline FPG ranged from 161.0 mg/dL to 180.4 mg/dL.

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.

Numbers analysed

The analysis population for all efficacy analysis was the Full Analysis Set (FAS), which was to consist of all randomised subjects who received at least one dose of study medication and had at least one measurement for the analysis endpoint (baseline or post-randomisation).

Outcomes and estimation

Primary endpoint - Change from Baseline in A1C

Change from baseline in A1C was the primary efficacy endpoint in all studies. Results are presented in **Table 14** and **Figure 5**, excluding data after initiation of glycaemic rescue therapy.

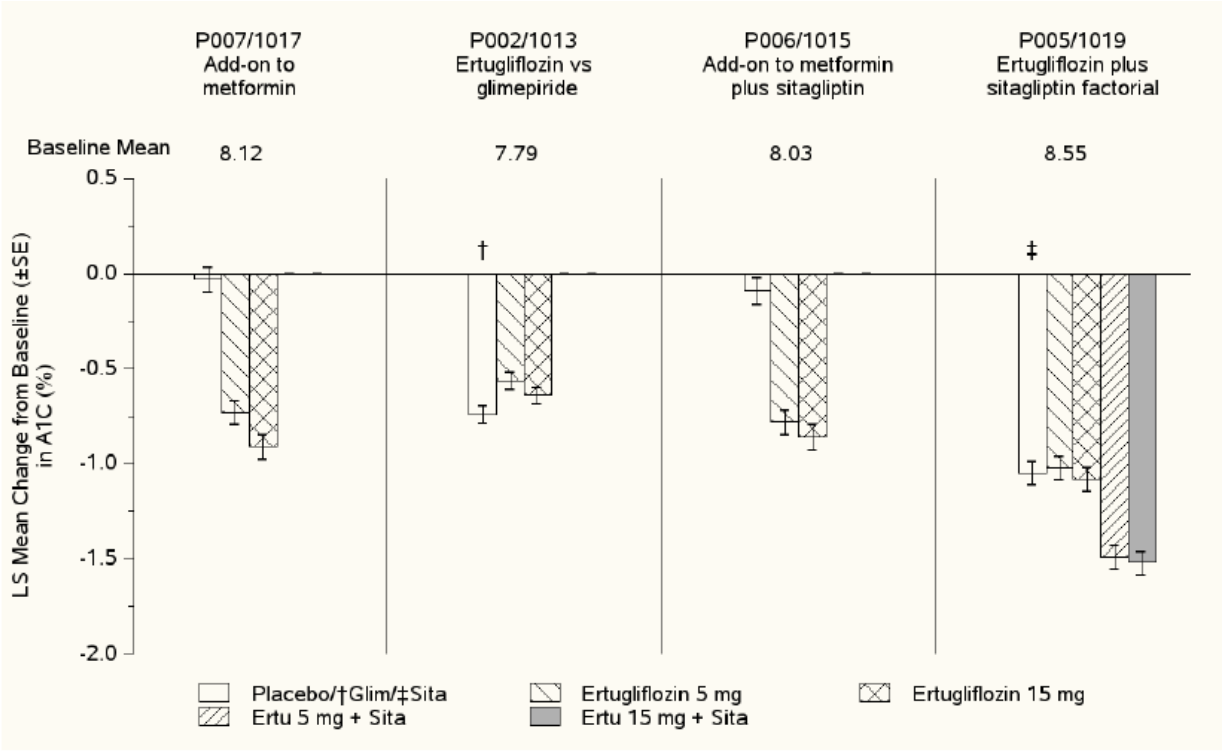
Table 14: A1C (%): Change from Baseline at Primary Timepoint by Study - Full Analysis Set: Excluding Rescue Approach - Ertugliflozin/Metformin Studies

	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
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
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

	N	Baseline Mean ± SD	LS Mean Change ± SE	LS Mean Difference (95% CI)	p-value
Ertugliflozin 15 mg	440	7.8 ± 0.60	-0.64 ± 0.045	0.10 (-0.02,0.22)	N/A
P005/1019 (Week 26) Ertugliflozin+Sitagliptin factorial					
Sitagliptin 100 mg	247	8.5 ± 1.03	-1.05 ± 0.062		
Ertugliflozin 5 mg	250	8.6 ± 1.05	-1.02 ± 0.061		
Ertugliflozin 15 mg	248	8.6 ± 1.01	-1.08 ± 0.062		
Ertugliflozin 5 mg + Sitagliptin 100 mg	243	8.6 ± 0.99	-1.49 ± 0.062	-0.43[†] (-0.60,-0.27)	<0.001[†]
				-0.46[‡] (-0.63,-0.30)	<0.001[‡]
Ertugliflozin 15 mg + Sitagliptin 100 mg	244	8.6 ± 0.97	-1.52 ± 0.062	-0.47[†] (-0.63,-0.30)	<0.001[†]
				-0.49[‡] (-0.66,-0.33)	<0.001[‡]
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.					

Source: [P002V01: analysis-adeff] [P005V01: analysis-adeff] [P006V01: analysis-adeff] [P007V01: analysis-adeff]

Figure 5: A1C (%): Change from Baseline at Primary Timepoint by Study - Full Analysis Set: Excluding Rescue Approach - Ertugliflozin/Metformin Studies



Primary timepoint is Week 52 for P002/1013, and Week 26 for the other studies.
Source: [P002V01: analysis-adeff] [P005V01: analysis-adeff] [P006V01: analysis-adeff] [P007V01: analysis-adeff]

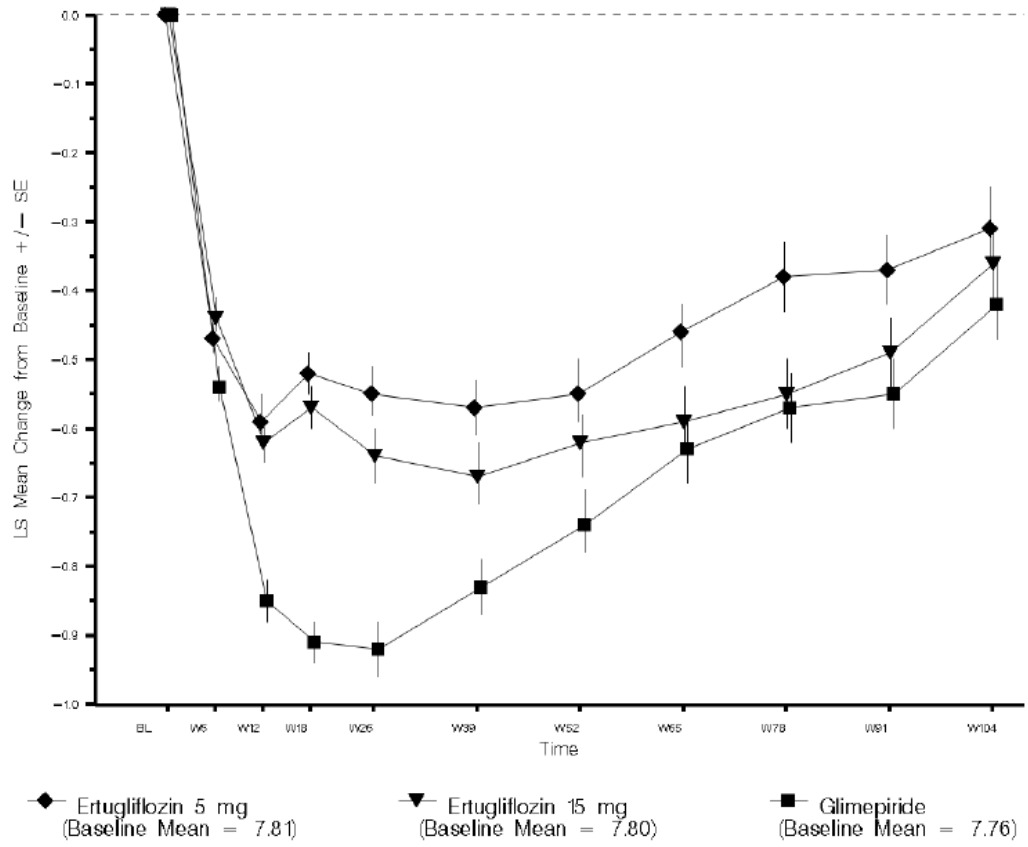
Long-term data, study P002/1013

In the 52-week Phase A period of the SU comparator study (Study P002/1013), the primary efficacy analysis showed a persistent A1C reduction from baseline though 52 weeks for ertugliflozin 15 mg and 5 mg. In contrast to the time-course of A1C reduction from baseline for glimepiride, which returned towards baseline after Week 26, the time-course of A1C reduction from baseline for ertugliflozin 15 mg and 5 mg was flat throughout the 52 weeks, showing no sign of deterioration **(**

Figure 6).

Data from the 52-week Phase B period of the SU comparator study (Study P002/1013) was also presented. LS mean reductions from baseline in A1C at Week 104 were similar in the ertugliflozin groups and glimepiride group, where the mean and median dose was 3.5 mg/day. A1C responses through Week 52 were gradually attenuated through Week 104 in all treatment groups.

Figure 6: A1C (%): LS Mean Change From Baseline Over Time (cLDA; FAS: Excluding Rescue Approach - Study P002/1013)



Date of Reporting Dataset Creation: 13JUN2017 Date of Figure Creation: 15JUN2017 (6:40)

Change From Baseline in A1C: Sensitivity and Supplemental Analyses

Sensitivity analyses were performed in all Phase 3 studies where the primary hypothesis results were significant in order to assess the impact of missing data on the primary analysis results for the change from baseline in A1C. The conclusions of these sensitivity analyses, which include J2R and tipping-point analyses, consistently supported the primary A1C analysis. The J2R analyses, which were applied in all studies with a superiority hypothesis compared to the control group, showed that while the conclusions were supportive of the primary analysis and the statistical significance of the primary analysis was maintained in these J2R sensitivity analysis across all studies, the point estimates of the ertugliflozin changes from baseline were smaller under the J2R approach compared with the primary approach. The tipping-point analyses, applied to all studies with significant primary hypothesis results, demonstrated the robustness of the primary A1C results to missing data.

The IR approach was also applied in all studies as a supplemental analysis. These are not technically sensitivity analyses for the primary estimand, as they address a different estimand. The statistical significance of the primary analysis was maintained under the IR approach in all studies; however, in placebo-controlled studies: (1) the initiation of rescue therapy occurred at a substantially higher rate in the placebo group than in the ertugliflozin groups; (2) the impact of rescue therapy on drug response was mainly seen in the placebo group and produced only small changes in the estimates of mean change from baseline in the ertugliflozin groups; and, (3) as expected when active rescue therapy is added to inactive (placebo) treatment, placebo-adjusted differences were attenuated compared to the primary ER approach, mainly due to the increased size of the estimated placebo response.

In the active-controlled studies, Studies P002/1013 and P005/1019, the initiation of rescue therapy occurred at a lower rate than in the placebo-controlled studies and was comparable among the treatment groups. In these active-controlled studies the differences between the primary ER and supplemental IR estimated mean A1C changes from baseline were small.

Secondary endpoints

Change from baseline in FPG

Change from baseline in FPG was measured in all 4 studies but was included in the statistical testing sequence in 3 of the 4 Phase 3 studies; change in FPG was not included in the statistical testing sequence for Study P002/1013. Results for the change from baseline in FPG are presented in **Table 15**.

Table 15: FPG (mg/dL): Change from Baseline at Primary Timepoint by Study - Full Analysis Set: 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	169.1 ± 41.66	-0.85 ± 2.589		
Ertugliflozin 5 mg	207	168.1 ± 45.49	-27.54 ± 2.453	-26.69 (-32.90,-20.48)	<0.001
Ertugliflozin 15 mg	205	167.9 ± 44.38	-39.10 ± 2.479	-38.25 (-44.50,-31.99)	<0.001
P006/1015 (Week 26) Add-on to Metformin+Sitagliptin					
Placebo	153	169.6 ± 37.82	-1.76 ± 3.022		
Ertugliflozin 5 mg	156	167.7 ± 37.72	-26.91 ± 2.883	-25.15 (-32.76,-17.54)	<0.001
Ertugliflozin 15 mg	153	171.7 ± 39.06	-33.04 ± 2.888	-31.28 (-38.90,-23.66)	<0.001
P002/1013 (Week 52) Ertugliflozin vs. Glimepiride					
Glimepiride	437	157.9 ± 33.79	-16.17 ± 1.718		
Ertugliflozin 5 mg	448	161.8 ± 34.22	-18.74 ± 1.734	-2.57 (-6.98,1.84)	0.254§
Ertugliflozin 15 mg	440	163.2 ± 36.27	-23.86 ± 1.722	-7.70 (-12.09,-3.30)	<0.001§
P005/1019 (Week 26) Ertugliflozin+Sitagliptin factorial					
Sitagliptin 100 mg	247	177.4 ± 46.64	-25.56 ± 2.229		

	N	Baseline Mean ± SD	LS Mean Change ± SE	LS Mean Difference (95% CI)	p-value
Ertugliflozin 5 mg	250	184.1 ± 52.23	-35.73 ± 2.198		
Ertugliflozin 15 mg	248	179.5 ± 45.71	-36.91 ± 2.192		
Ertugliflozin 5 mg + Sitagliptin 100 mg	243	183.8 ± 44.28	-43.96 ± 2.205	-18.40[†] (-24.03,-12.77)	<0.001[†]
				-8.23[‡] (-13.82,-2.65)	0.004[‡]
Ertugliflozin 15 mg + Sitagliptin 100 mg	244	177.2 ± 49.38	-48.70 ± 2.196	-23.14[†] (-28.76,-17.53)	<0.001[†]
				-12.97[‡] (-18.54,-7.40)	<0.001[‡]

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

[†]For the comparison to Sitagliptin alone.

[‡]For the comparison to the Ertugliflozin alone.

§Nominal p-value.

Source: [P002V01: analysis-adeff] [P005V01: analysis-adeff] [P006V01: analysis-adeff] [P007V01: analysis-adeff]

2-hour post-prandial glucose

Change from baseline in 2-hour PPG at Week 26 was measured in the ertugliflozin co-administration with sitagliptin factorial study (Study P005/1019) in the subset of subjects who participated in the mixed meal tolerance test (MMTT). This endpoint was not part of the formal testing sequence. Ertugliflozin 5 mg and 15 mg added to metformin background therapy demonstrated clinically meaningful reductions from baseline in 2-hour PPG.

Proportion of Subjects with A1C<7.0%

The proportion of subjects with A1C<7.0% was measured in all studies as a secondary efficacy endpoint but was not subject to formal hypothesis testing in Study P002/1013 or amongst the single treatment arms on Study P005/1019. Results for the proportion of subjects with A1C <7.0%, in the Phase 3 studies in support of the ertugliflozin/metformin FDC submission are presented in **Table 16**.

Table 16: Analysis of Subjects with A1C<7.0% at Primary Timepoint by Study - Full Analysis Set: 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)
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)
P002/1013 (Week 52) Ertugliflozin vs. Glimepiride				
Glimepiride	437	190 (43.5)		
Ertugliflozin 5 mg	448	154 (34.4)	0.68	(0.50, 0.91)
Ertugliflozin 15 mg	440	167 (38.0)	0.79	(0.59, 1.05)
P005/1019 (Week 26) Ertugliflozin+Sitagliptin factorial				
Sitagliptin 100 mg	247	81 (32.8)		
Ertugliflozin 5 mg	250	66 (26.4)		
Ertugliflozin 15 mg	248	79 (31.9)		
Ertugliflozin 5 mg + Sitagliptin 100 mg	243	127 (52.3)	2.95[‡]	(1.92, 4.54)[‡]
			4.14[§]	(2.68, 6.40)[§]
Ertugliflozin 15 mg + Sitagliptin 100 mg	244	120 (49.2)	2.56[‡]	(1.69, 3.89)[‡]
			2.53[§]	(1.68, 3.83)[§]

[†]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.

Source: [P002V01: analysis-adeff] [P005V01: analysis-adeff] [P006V01: analysis-adeff] [P007V01: analysis-adeff]

Proportion of Subjects Receiving Glycaemic Rescue Therapy and Time to Glycaemic Rescue

Subjects who met progressively more stringent glycaemic rescue criteria during a study were to initiate treatment with glycaemic rescue therapy. The proportion of subjects rescued and time to rescue are presented in **Table 17**.

Table 17: Analysis of Time to Glycaemic Rescue at Primary Timepoint 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.

Source: [P002V01: analysis-adtte] [P005V01: analysis-adtte] [P006V01: analysis-adtte] [P007V01: analysis-adtte]

Change From Baseline in Body Weight

Change from baseline in body weight was measured in all studies as a secondary efficacy endpoint. Results for the change from baseline in body weight are presented in **Table 18**.

Table 18: Body Weight (kg): Change from Baseline at Primary Timepoint by Study - Full Analysis Set: 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
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
P002/1013 (Week 52) Ertugliflozin vs. Glimepiride					
Glimepiride	437	86.8 ± 20.73	0.91 ± 0.176		
Ertugliflozin 5 mg	448	87.9 ± 18.93	-2.96 ± 0.177	-3.87 (-4.36,-3.38)	<0.001[§]
Ertugliflozin 15 mg	440	85.6 ± 19.05	-3.38 ± 0.177	-4.29 (-4.77,-3.80)	<0.001
P005/1019 (Week 26) Ertugliflozin+Sitagliptin factorial					
Sitagliptin 100 mg	247	89.8 ± 23.46	-0.67 ± 0.229		
Ertugliflozin 5 mg	250	88.6 ± 22.19	-2.69 ± 0.225		
Ertugliflozin 15 mg	248	88.0 ± 20.33	-3.74 ± 0.227		
Ertugliflozin 5 mg + Sitagliptin 100 mg	243	89.5 ± 20.85	-2.52 ± 0.228	-1.85[†] (-2.48,-1.22)	<0.001[†]
Ertugliflozin 15 mg + Sitagliptin 100 mg	244	87.5 ± 20.48	-2.94 ± 0.228	-2.27[†] (-2.90,-1.64)	<0.001[†]
LS means and p-value are based on the cLDA model for the primary analysis.					

	N	Baseline Mean ± SD	LS Mean Change ± SE	LS Mean Difference (95% CI)	p-value
[†]For the comparison to Sitagliptin alone. [§]Nominal p-value.					

Source: [P002V01: analysis-adeff] [P005V01: analysis-adeff] [P006V01: analysis-adeff] [P007V01: analysis-adeff]

Change From Baseline in Systolic Blood Pressure

Change from baseline in SBP was measured in all studies as a secondary efficacy endpoint. Results are presented in **Table 19**, excluding data after initiation of glycaemic rescue therapy.

Table 19: Sitting Systolic Blood Pressure (mmHg): Change from Baseline at Primary Timepoint by Study - Full Analysis Set: 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.					

Source: [P002V01: analysis-adeff] [P005V01: analysis-adeff] [P006V01: analysis-adeff] [P007V01: analysis-adeff]

Change From Baseline in Diastolic Blood Pressure

Changes in DBP were in line with results described above in SBP. Decreases in DBP were numerically greater in ertugliflozin treatment groups compared to placebo or glimepiride, and numerically greater in ertugliflozin 15 mg treatment groups compared to 5 mg treatment groups. In Study P007/1017, the LS mean reductions in DBP were significantly greater for both ertugliflozin doses compared to placebo.

Summary of main studies

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

Table 20: Summary of efficacy for trial P007/1017

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 26-Week Multicenter Study with a 78-Week Extension to Evaluate the Efficacy and Safety of Ertugliflozin in Subjects with Type 2 Diabetes Mellitus and Inadequate Glycemic Control on Metformin Monotherapy			
Study identifier	P007/1017		
Design	Multicenter, randomized (1:1:1), double-blind, placebo-controlled Phase A and active-controlled Phase B		
	Duration of placebo run-in phase:		2 weeks
	Duration of placebo-controlled main period (Phase A):		26 weeks
	Duration of active-controlled extension treatment period (Phase B):		78 weeks - ongoing
Hypothesis	Superiority		
Treatments groups	Placebo		placebo once daily, background metformin, 26 weeks, n=209
	Ertugliflozin 5 mg		ertugliflozin 5 mg once daily, background metformin, 26 weeks, n=207
	Ertugliflozin 15 mg		ertugliflozin 15 mg once daily, background metformin, 26 weeks , n=205
Endpoints and definitions	Primary endpoint	A1C	Change from baseline in A1C at Week 26
		FPG	Change from baseline in FPG at Week 26

	Secondary endpoints	Body weight	Change from baseline in body weight at Week 26
		A1C	Proportion of subjects with A1C <7.0% at Week 26
		SBP	Change from baseline in systolic blood pressure at Week 26
		DBP	Change from baseline in diastolic blood pressure at Week 26
Database lock	Completion of the 26 week Phase A portion of this study defined as database lock.		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	cLDA FAS, 26 weeks			
Descriptive statistics and estimate variability	Treatment group	Placebo	Ertugliflozin 5 mg	Ertugliflozin 15 mg
	Change from Baseline in A1C (%)			
	Number of subjects	209	207	205
	LS Mean	-0.03	-0.73	-0.91
	(95% CI)	(-0.15, 0.10)	(-0.85, -0.61)	(-1.03, -0.78)
	Change from Baseline in FPG (mg/dL)			
	Number of subjects	209	207	205
	LS Mean	-0.85	-27.54	-39.10
	(95% CI)	(-5.93, 4.23)	(-32.36, -22.73)	(-43.96, -34.23)
	Change from Baseline in Body Weight (kg)			
	Number of subjects	209	207	205
	LS Mean	-1.33	-3.01	-2.93

	(95% CI)	(-1.74, -0.92)	(-3.40, -2.62)	(-3.33, -2.53)
	Change from Baseline in Sitting Systolic Blood Pressure (mmHg)			
	Number of subjects	209	207	204
	LS Mean	-0.70	-4.38	-5.20
	(95% CI)	(-2.46, 1.06)	(-6.01, -2.75)	(-6.87, -3.54)
	Change from Baseline in Sitting Diastolic Blood Pressure (mmHg)			
	Number of subjects	209	207	204
	LS Mean	0.23	-1.59	-2.19
	(95% CI)	(-0.85, 1.31)	(-2.59, -0.59)	(-3.21, -1.17)
	A1C < 7.0% (logistic regression with multiple imputation based on cLDA model)			
	Number of subjects	209	207	205
	n	33	73	82
	(%)	(15.8)	(35.3)	(40.0)

Effect estimate per comparison		Ertugliflozin 5 mg vs. Placebo	Ertugliflozin 15 mg vs. Placebo
	Primary endpoint:		
	Change from Baseline in A1C (%)		
	Difference in LS Means	-0.70	-0.88
	(95% CI)	(-0.87, -0.53)	(-1.05, -0.71)
	P-value	<0.001	<0.001
	Secondary endpoints:		
	Change from Baseline in FPG (mg/dL)		
	Difference in LS Means	-26.69	-38.25
	(95% CI)	(-32.90, -20.48)	(-44.50, -31.99)
	P-value	<0.001	<0.001
	Change from Baseline in Body Weight (kg)		
	Difference in LS Means	-1.67	-1.60

	(95% CI)	(-2.24, -1.11)	(-2.16, -1.03)
	P-value	<0.001	<0.001
	Change from Baseline in Sitting Systolic Blood Pressure (mmHg)		
	Difference in LS Means	-3.68	-4.50
	(95% CI)	(-5.96, -1.39)	(-6.81, -2.19)
	P-value	0.002	<0.001
	Change from Baseline in Sitting Diastolic Blood Pressure (mmHg)		
	Difference in LS Means	-1.82	-2.42
	(95% CI)	(-3.24, -0.39)	(-3.86, -0.98)
	P-value	0.013	0.001
	A1C < 7.0% (logistic regression with multiple imputation based on cLDA model)		
	Odds Ratio vs. Placebo	3.03	4.48
	(95% CI)	(1.81, 5.06)	(2.64, 7.62)
	P-value	<0.001	<0.001
Notes	Results of other endpoints are not included in this table.		

Table 21: Summary of efficacy for trial P002/1013

Title: A Phase III, Multicenter, Randomized, 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 Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Metformin		
Study identifier	P002/1013	
Design	Multicenter, randomized (1:1:1), double-blind, active-controlled Phase A and active-controlled Phase B	
	Duration of placebo run-in phase:	2 weeks
	Duration main period (phase A):	52 weeks
	Duration of extension period (Phase B):	52 weeks - ongoing
Hypothesis	Non-inferiority	
Treatments groups	Ertugliflozin 5 mg	ertugliflozin 5 mg once daily, background metformin, for up to 104 weeks, n=448

	Ertugliflozin 15 mg		ertugliflozin 15 mg once daily, background metformin, for up to 104 weeks, n=441
	Glimepiride		up to a maximum approved dose (6 or 8 mg q.d. based on the local country label) or maximum tolerated dose, background metformin, for up to 104 weeks , n=437
Endpoints and definitions	Primary endpoint	A1C	Change from baseline in A1C at Week 52
	Secondary endpoints	Body weight	Change from baseline in body weight at Week 52
		SBP	Change from baseline in systolic blood pressure at Week 52
	Other endpoints		Proportion of subjects with A1C <7.0% at Week 52
			Change from baseline in FPG at Week 52
			Change from baseline in diastolic blood pressure at Week 52
Database lock	25-May-2016 for Phase A		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	cLDA FAS, 52 weeks			
Descriptive statistics and estimate variability	Treatment group	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Glimepiride
	Change from Baseline in A1C (%)			
	Number of subjects	448	440	437
	LS Mean	-0.56	-0.64	-0.74
	(95% CI)	(-0.65, -0.47)	(-0.73, -0.55)	(-0.83, -0.65)
	Change from Baseline in Body Weight (kg)			
	Number of subjects	448	440	437

	LS Mean	-2.96	-3.38	0.91
	(95% CI)	(-3.31, -2.61)	(-3.73, -3.03)	(0.56, 1.25)
	Change from Baseline in Sitting Systolic Blood Pressure (mmHg)			
	Number of subjects	448	440	437
	LS Mean	-2.25	-3.81	0.95
	(95% CI)	(-3.36, -1.13)	(-4.91, -2.71)	(-0.15, 2.06)
	A1C < 7.0% (logistic regression using multiple imputation)			
	Number of subjects	448	440	437
	Number of Subjects With A1C <7.0%	154	167	190
	(Raw Proportions) (%)	(34.4)	(38.0)	(43.5)
	Change from Baseline in FPG (mg/dL)			
	Number of subjects	448	440	437
	LS Mean	-18.74	-23.86	-16.17
	(95% CI)	(-22.14, -15.34)	(-27.24, -20.49)	(-19.54, -12.80)
	Change from Baseline in Sitting Diastolic Blood Pressure (mmHg)			
	Number of subjects	448	440	437
	LS Mean	-0.92	-1.22	0.32
	(95% CI)	(-1.64, -0.19)	(-1.94, -0.51)	(-0.39, 1.04)

Effect estimate per comparison		Ertugliflozin 5 mg vs. Glimepiride	Ertugliflozin 15 mg vs. Glimepiride
	Primary endpoint:		
	Change from Baseline in A1C (%)		
	Difference in LS Means	0.18	0.10
	(95% CI)	(0.06, 0.30)	(-0.02, 0.22)
	Secondary endpoints:		

	Change from Baseline in Body Weight (kg)		
	Difference in LS Means	-3.87	-4.29
	(95% CI)	(-4.36, -3.38)	(-4.77, -3.80)
	P-value	<0.001	<0.001
	Change from Baseline in Sitting Systolic Blood Pressure (mmHg)		
	Difference in LS Means	-3.20	-4.77
	(95% CI)	(-4.73, -1.67)	(-6.29, -3.25)
	P-value	<0.001	<0.001
	Other endpoints:		
	A1C < 7.0% (logistic regression using multiple imputation)		
	Adjusted Odds Ratio Relative to Glimepiride	0.68	0.79
	(95% CI)	(0.50, 0.91)	(0.59, 1.05)
	P-value	0.010	0.104
	Change from Baseline in FPG (mg/dL)		
	Difference in LS Means	-2.57	-7.70
	(95% CI)	(-6.98, 1.84)	(-12.09, -3.30)
	P-value	0.254	<0.001
	Change from Baseline in Sitting Diastolic Blood Pressure (mmHg)		
	Difference in LS Means	-1.24	-1.55
	(95% CI)	(-2.24, -0.24)	(-2.54, -0.55)
	P-value	0.015	0.002
Notes	Results for only some of the other endpoints are included in this table.		

Table 22: Summary of efficacy for trial P006/1015

Title: A Phase III, Multicenter, Randomized, 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 Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Metformin and Sitagliptin			
Study identifier	P006/1015		
Design	Multicenter, randomized (1:1:1), double-blind, placebo-controlled Phase A and double-blind, placebo-controlled Phase B		
	Duration of placebo run-in phase:		2 weeks
	Duration of main period (Phase A):		26 weeks
	Duration of extension period (Phase B):		26 weeks - ongoing
Hypothesis	Superiority		
Treatments groups	Placebo		placebo once daily, background metformin and sitagliptin, up to 52 weeks; 153 subjects
	Ertugliflozin 5 mg		ertugliflozin 5 mg once daily, background metformin and sitagliptin, up to 52 weeks; 156 subjects
	Ertugliflozin 15 mg		ertugliflozin 15 mg once daily, background metformin and sitagliptin, up to 52 weeks; 154 subjects
Endpoints and definitions	Primary endpoint	A1C	Change from baseline in A1C at Week 26
	Secondary	FPG	Change from baseline in FPG at Week 26
		Body weight	Change from baseline in body weight at Week 26
		Sitting SBP	Change from baseline in sitting systolic blood pressure at Week 26
		A1C	Proportion of subjects with A1C <7.0% at Week 26
	Other	Sitting DBP	Change from baseline in sitting diastolic blood pressure at Week 26
Database lock	07-Jan-2016 for Phase A		
Results and Analysis			

Analysis description	**Primary Analysis**			
Analysis population and time point description	FAS, 26 weeks			
Descriptive statistics and estimate variability	Treatment group	Placebo	Ertugliflozin 5 mg	Ertugliflozin 15 mg
	Change from Baseline in A1C (%)			
	Number of subjects	153	156	153
	LS Mean	-0.09	-0.78	-0.86
	(95% CI)	(-0.23, 0.04)	(-0.91, -0.65)	(-0.99, -0.72)
	Change from Baseline in FPG (mg/dL)			
	Number of subjects	153	156	153
	LS Mean	-1.76	-26.91	-33.04
	(95% CI)	(-7.70, 4.18)	(-32.58, -21.24)	(-38.71, -27.36)
	Change from Baseline in Body Weight (kg)			
	Number of subjects	153	156	153
	LS Mean	-1.32	-3.35	-3.04
	(95% CI)	(-1.77, -0.87)	(-3.78, -2.91)	(-3.48, -2.60)
	Change from Baseline in Sitting Systolic Blood Pressure (mmHg)			
	Number of subjects	153	156	153
	LS Mean	-0.88	-3.81	-4.82
	(95% CI)	(-2.70, 0.94)	(-5.52, -2.09)	(-6.55, -3.09)
	A1C < 7.0% (logistic regression with multiple imputation based on cLDA model)			
	Number of subjects	153	156	153

	n	26	50	61
	(%)	(17.0)	(32.1)	(39.9)
	Change from Baseline in Diastolic Systolic Blood Pressure (mmHg)			
	Number of subjects	153	156	153
	LS Mean	-0.43	-1.68	-1.81
	(95% CI)	(-1.71, 0.84)	(-2.88, -0.48)	(-3.02, -0.60)

Effect estimate per comparison		Ertugliflozin 5 mg vs. Placebo	Ertugliflozin 15 mg vs. Placebo
	Primary endpoint:		
	Change from Baseline in A1C (%)		
	Difference in LS Means	-0.69	-0.76
	(95% CI)	(-0.87, -0.50)	(-0.95, -0.58)
	P-value	<0.001	<0.001
	Secondary endpoints:		
	Change from Baseline in FPG (mg/dL)		
	Difference in LS Means	-25.15	-31.28
	(95% CI)	(-32.76, -17.54)	(-38.90, -23.66)
	P-value	<0.001	<0.001
	Change from Baseline in Body Weight (kg)		
	Difference in LS Means	-2.03	-1.72
	(95% CI)	(-2.65, -1.40)	(-2.35, -1.09)
	P-value	<0.001	<0.001
	Change from Baseline in Sitting Systolic Blood Pressure (mmHg)		
	Difference in LS Means	-2.93	-3.94
	(95% CI)	(-5.36, -0.49)	(-6.39, -1.50)
	P-value	0.019	0.002
	A1C < 7.0% (logistic regression with multiple imputation based on cLDA model)		
	Odds Ratio	3.16	4.43
	(95% CI)	(1.74, 5.72)	(2.44, 8.02)
	P-value	<0.001	<0.001

	Other endpoint:		
	Change from Baseline in Sitting Diastolic Blood Pressure (mmHg)		
	Difference in LS Means	-1.24	-1.38
	(95% CI)	(-2.97, 0.48)	(-3.11, 0.36)
	P-value	0.157	0.119
Notes	Results for only one of the other endpoints are included in this table.		

Table 23: Summary of efficacy for trial P005/1019

Title: A Phase III, Randomized, Double-Blind, Multicenter 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 Glycemic Control on Metformin Monotherapy			
Study identifier	P005/1019		
Design	Multicenter, randomized (1:1:1:1:1), double-blind, factorial		
	Duration of placebo run-in phase:		2 weeks
	Duration of main period:		26 weeks
	Duration of extension period:		26 weeks - ongoing
Hypothesis	Superiority		
Treatments groups	ertugliflozin 5 mg + sitagliptin 100 mg (E5/S100)		ertugliflozin 5 mg q.d. + sitagliptin 100 mg q.d., background metformin, for up to 52 weeks, n=243
	ertugliflozin 15 mg + sitagliptin 100 mg (E15/S100)		ertugliflozin 15 mg q.d. + sitagliptin 100 mg q.d., background metformin, for up to 52 weeks, n=245
	ertugliflozin 5 mg (E5)		ertugliflozin 5 mg q.d., background metformin, for up to 52 weeks, n=250
	ertugliflozin 15 mg (E15)		ertugliflozin 15 mg q.d., background metformin, for up to 52 weeks, n=248
	sitagliptin 100 mg (S100)		sitagliptin 100 mg q.d., background metformin, for up to 52 weeks, n=247
Endpoints and definitions	Primary endpoint	A1C	Change from baseline in A1C at Week 26
	Secondary	Body weight	Change from baseline in body weight at Week 26

		FPG	Change from baseline in FPG at Week 26
		Sitting SBP	Change from baseline in sitting systolic blood pressure at Week 26
		A1C	Proportion of subjects with A1C <7.0% (53 mmol/mol) at Week 26
		β-cell responsivity static component (Φs)	Change from baseline in Φs at Week 26
	Other	Sitting DBP	Change from baseline in sitting diastolic blood pressure
Database lock	22-JAN-2016 for Phase A		

Results and Analysis

Analysis description	**Primary Analysis**					
Analysis population and time point description	cLDA FAS, 26 weeks					
Descriptive statistics and estimate variability	Treatment group	Ertugliflozin 5 mg	Ertugliflozin 15 mg	Sitagliptin 100 mg	Ertugliflozin 5 mg + Sitagliptin 100 mg	Ertugliflozin 15 mg + Sitagliptin 100 mg
	Change from Baseline in A1C (%)					
	Number of subjects	250	248	247	243	244
	LS Mean	-1.02	-1.08	-1.05	-1.49	-1.52
	(95% CI)	(-1.14, -0.90)	(-1.20, -0.96)	(-1.17, -0.93)	(-1.61, -1.36)	(-1.64, -1.40)
	Change from Baseline in FPG (mg/dL)					
	Number of subjects	250	248	247	243	244
	LS Mean	-35.73	-36.91	-25.56	-43.96	-48.70
	(95% CI)	(-40.04, -31.42)	(-41.21, -32.62)	(-29.93, -21.19)	(-48.29, -39.63)	(-53.01, -44.39)

	Change from Baseline in Body Weight (kg)					
	Number of subjects	250	248	247	243	244
	LS Mean	-2.69	-3.74	-0.67	-2.52	-2.94
	(95% CI)	(-3.13, -2.25)	(-4.18, -3.29)	(-1.12, -0.22)	(-2.97, -2.07)	(-3.39, -2.49)
	Change from Baseline in Sitting Systolic Blood Pressure (mmHg)					
	Number of subjects	250	248	247	243	244
	LS Mean	-3.89	-3.69	-0.66	-3.42	-3.67
	(95% CI)	(-5.28, -2.50)	(-5.08, -2.30)	(-2.07, 0.76)	(-4.82, -2.03)	(-5.06, -2.29)
	Change from Baseline in β-cell Responsivity Static Component (φs) (10-9min-1) From the 8-Point Meal Tolerance Test					
	Number of subjects	66	67	63	55	61
	LS Mean	8.62	9.71	21.11	16.24	11.51
	(95% CI)	(1.28, 15.96)	(2.29, 17.13)	(13.55, 28.67)	(8.36, 24.11)	(3.76, 19.26)
	A1C < 7.0% (logistic regression with multiple imputation based on cLDA model)					
	Number of subjects	250	248	247	243	244
	n	66	79	81	127	120
	(%)	(26.4)	(31.9)	(32.8)	(52.3)	(49.2)
	Change from Baseline in Sitting Diastolic Blood Pressure (mmHg)					
	Number of subjects	250	248	247	243	244
	LS Mean	-1.11	-0.97	-0.33	-0.65	-1.30
	(95% CI)	(-1.96, -0.26)	(-1.81, -0.12)	(-1.19, 0.53)	(-1.50, 0.20)	(-2.15, -0.45)
Effect estimate per comparison		E 5 mg + S 100 mg vs. Ertugliflozin	E 15 mg + S 100 mg vs. Ertugliflozin	E 5 mg + S 100 mg vs. Sitagliptin	E 15 mg + S 100 mg vs. Sitagliptin	

	Primary endpoint:				
	Change from Baseline in A1C (%)				
	Difference in LS Means	-0.46	-0.44	0.43	-0.47
	(95% CI)	(-0.63, -0.30)	(-0.61, -0.27)	(-0.60, -0.27)	(-0.63, -0.30)
	P-value	<0.001	<0.001	<0.001	<0.001
	Secondary endpoints:				
	Change from Baseline in FPG (mg/dL)				
	Difference in LS Means	-8.23	-11.79	-18.40	-23.14
	(95% CI)	(-13.82, -2.65)	(-17.35, -6.23)	(-24.03, -12.77)	(-28.76, -17.53)
	P-value	0.004	<0.001	<0.001	<0.001
	Change from Baseline in Body Weight (kg)				
	Difference in LS Means			-1.85	-2.27
	(95% CI)			(-2.48, -1.22)	(-2.90, -1.64)
	P-value			<0.001	<0.001
	Change from Baseline in Sitting Systolic Blood Pressure (mmHg)				
	Difference in LS Means			-2.76	-3.01
	(95% CI)			(-4.69, -0.83)	(-4.94, -1.09)
	P-value			0.005	0.002
	Change from Baseline in β-cell Responsivity Static Component (φs) (10-9min-1) From the 8-Point Meal Tolerance Test				
	Difference in LS Means	7.61	1.81	-4.87	-9.59
	(95% CI)	(-2.90, 18.13)	(-8.66, 12.27)	(-15.54, 5.80)	(-20.17, 0.98)
	P-value	0.155	0.734	0.369	0.075
	A1C < 7.0% (logistic regression with multiple imputation based on cLDA model)				
	Odds Ratio	4.14	2.53	2.95	2.56
	(95% CI)	(2.68, 6.40)	(1.68, 3.83)	(1.92, 4.54)	(1.69, 3.89)
	P-value	<0.001	<0.001	<0.001	<0.001

	Other endpoint:				
	Change from Baseline in Sitting Diastolic Blood Pressure (mmHg)				
	Difference in LS Means			-0.32	-0.97
	(95% CI)			(-1.50, 0.86)	(-2.15, 0.21)
	P-value			0.593	0.106
Notes	Results for only one of the other endpoints are included in this table.				

Clinical studies in special populations

The only study in special populations conducted was study P001/1016 which included patients with renal impairment.

A substantial proportion of patients included in the controlled trials (21.3%) were aged 65 to 74 years, whereas 4.3% were aged 75 to 84 years. Only 8 subjects were older than 85 years, most of which (7) were treated with ertugliflozin.

Controlled Trials	**Age 65-74 (Older subjects number /total number, n/N)**	**Age 75-84 (Older subjects number /total number, n/N)**	**Age 85+ (Older subjects number /total number, n/N)**
Non-ertugliflozin	311/1450	66/1450	1/1450
Ertugliflozin 5 mg	374/1716	70/1716	5/1716
Ertugliflozin 15 mg	350/1693	75/1693	2/1693
All Ertugliflozin	724/3409	145/3409	7/3409
Total population	**1035/4859**	**211/4859**	**8/4859**
N is the total number of subjects in the Broad Pool for the respective row.			

Renal impairment: Study P001/1016

Study P001/1016 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of ertugliflozin in subjects with T2DM and Stage 3 CKD (eGFR ≥30 to <60 mL/min/1.73 m^2) to assess the efficacy and safety of ertugliflozin compared with placebo **(Table 24)**.

Table 24: Study in special populations

Study	Randomized Population	N	Study Design	Treatment Groups and Number of Subjects Randomized	Treatment Duration
P001/1016 Moderate renal impairment	Adult subjects ≥25 years of age with T2DM, Stage 3 chronic kidney disease, and inadequate glycaemic control (A1C 7.0% to 10.5%, inclusive) on treatment with standard diabetes therapy(-ies)	468†	Multicenter, randomized (1:1:1), double-blind, placebo- controlled	Placebo (n=154) Ertugliflozin 15 mg (n=156) Ertugliflozin 5 mg (n=158)	52 Weeks Phase A: 26 weeks Phase B: 26 weeks **Completed**

† Randomization was stratified by eGFR ≥45 to <60 mL/min/1.73 m^2 (Stage 3A chronic kidney disease; 309 subjects) and eGFR ≥30 to <45 mL/min/1.73 m^2 (Stage 3B chronic kidney disease; 159 subjects).

Abbreviations: A1C=glycosylated hemoglobin A1c; eGFR=estimated glomerular filtration rate; n=number of subjects randomly assigned to study medication; N=overall number of subjects randomly assigned to study medication; T2DM=type 2 diabetes mellitus

The primary study analysis concerned the change from baseline at Week 26 in A1C in the Overall Cohort. Change from baseline in A1C was further analysed in the Stage 3A CKD (eGFR ≥45 to <60 mL/min/1.73 m^2) cohort as a secondary endpoint. All additional key secondary endpoints were pre-specified for analysis only in the Stage 3A CKD cohort.

Changes to Planned Analyses

Post-hoc analyses to evaluate the A1C change from baseline in subjects with and without positive metformin assay results were added after review of the pre-specified A1C analysis results identified an unusual placebo response, characterized by notable decreases in A1C between Week 18 and Week 26, in the Overall Cohort and Stage 3A CKD stratum. Metformin was not allowed as a concomitant background medication in this study given the eGFR entry criterion. Retained pharmacokinetic (PK) and future biomedical research (FBR) samples were assayed for metformin concentrations. The assays subsequently identified surreptitious metformin use in some subjects in all treatment groups that was not reported to investigators. Because concomitant metformin use could confound the comparison of ertugliflozin vs placebo, post-hoc analyses were added to evaluate the treatment response in subjects with (1) at least 1 positive metformin assay result at any time point; and (2) no positive metformin assay results.

Demographic and Baseline Characteristics

In total, 468 subjects were randomly assigned to study medication and 467 subjects took at least 1 dose of study medication. Of the treated patients, a total of 159 subjects were stratified to the Stage 3B CKD stratum and 308 subjects to the Stage 3A CKD stratum.

For the Overall Cohort, 49.5% of subjects were males, the mean age was 67.3 years, 81.4% were White, and approximately 50% had a history of CV disease or heart failure. The mean duration of T2DM (approximately 14 years) was not meaningfully different across treatment groups. More than 95% of subjects in each treatment group were on background AHA therapy at screening. The majority of these subjects were receiving insulin and analogues for injection (55.9%), and/or SUs (40.3%). There were no important differences in demographics and baseline characteristics between the 3 treatment groups.

The post-hoc analysis excluded those subjects who had at least 1 assay result positive for metformin (ie, plasma sample with measurable concentration of metformin). Given that metformin was not allowed per the protocol and its use was not reported to the investigators, the presence of metformin at any time point had the potential to confound the glycaemic efficacy analyses. These analyses were conducted for both the Overall Cohort and Stage 3A CKD stratum. Removal of the subjects from these cohorts did not result in any meaningful changes in the subject demographics or baseline characteristics.

Archived blood samples collected for PK from Weeks 6, 12, and 18, and for FBR at Week 26 were analysed for metformin. In all, 78 subjects had at least 1 sample positive for metformin. The percentages of subjects with positive assay results were similar across the 3 treatment groups.

Key Efficacy Endpoint Results

Table 25 shows the key results from both the primary and post-hoc analysis.

In the primary analysis, although the LS mean reduction from baseline in A1C at Week 26 in the ertugliflozin 15 mg group was numerically greater than in the placebo group, the between-group difference was not statistically significant. The LS mean reduction in the ertugliflozin 5 mg group was similar to that of the placebo group. Hypothesis testing within the ordered testing procedure was therefore stopped after the first test, and secondary hypotheses were not tested.

The post-hoc analysis of change from baseline in A1C at Week 26 excluded subjects who had positive metformin assay results. Exclusion of subjects who had positive metformin assay results markedly dampened the A1C response in the placebo group with little impact to the change from baseline in the ertugliflozin groups; in the placebo group, the estimated decrease in A1C from baseline at Week 26 was reduced by nearly half after removal of subjects who had positive metformin assay results (post-hoc analysis: -0.14% vs pre-specified analysis: -0.26%). As a result, in the post-hoc analysis, the LS mean reduction from baseline in A1C at Week 26 was greater in the ertugliflozin 15 mg group and numerically greater in the ertugliflozin 5 mg group compared with the placebo group. For the ertugliflozin 15 mg vs placebo comparison, the 95% CI for the between-group difference excluded 0.

Table 25: (Ertugliflozin Protocol MK-8835-001/B1521016) - Key Efficacy Endpoints - Full Analysis Set: Excluding Rescue Approach

Treatment	N	LS Mean (95% CI)	Pairwise Comparisons	
			Difference in LS Means (95% CI) vs. Placebo[†]	p-Value
Change from Baseline in A1C (%) at Week 26: Overall Cohort				

Treatment	N	LS Mean (95% CI)	Pairwise Comparisons	
			Difference in LS Means (95% CI) vs. Placebo[†]	p-Value
Placebo	154	-0.26 (-0.41, -0.11)		
Ertugliflozin 5 mg	158	-0.29 (-0.44, -0.14)	-0.03 (-0.23, 0.18)	0.807
Ertugliflozin 15 mg	155	-0.41 (-0.56, -0.27)	-0.15 (-0.35, 0.06)	0.155
Change from Baseline in A1C (%) at Week 26: eGFR ≥45 to <60 mL/min/1.73m^2 Stratum				
Placebo	99	-0.28 (-0.47, -0.08)		
Ertugliflozin 5 mg	105	-0.31 (-0.49, -0.13)	-0.03 (-0.28, 0.23)	0.828
Ertugliflozin 15 mg	97	-0.37 (-0.56, -0.18)	-0.09 (-0.35, 0.17)	0.496
Change from Baseline in A1C (%) at Week 26: Overall Cohort Post-hoc Analysis				
Placebo	128	-0.14 (-0.31, 0.02)		
Ertugliflozin 5 mg	134	-0.28 (-0.44, -0.13)	-0.14 (-0.36, 0.08)	
Ertugliflozin 15 mg	127	-0.47 (-0.63, -0.31)	-0.33 (-0.55, -0.11)	
Change from Baseline in A1C (%) at Week 26: eGFR ≥45 to <60 mL/min/1.73m^2 Stratum Post-hoc Analysis				
Placebo	79	-0.09 (-0.30, 0.13)		
Ertugliflozin 5 mg	89	-0.29 (-0.48, -0.10)	-0.20 (-0.48, 0.08)	
Ertugliflozin 15 mg	75	-0.44 (-0.65, -0.22)	-0.35 (-0.64, -0.05)	
Change from Baseline in Body Weight (kg) at Week 26: eGFR ≥45 to <60 mL/min/1.73m^2 Stratum				
Placebo	99	0.46 (-0.13, 1.04)		
Ertugliflozin 5 mg	105	-1.31 (-1.86, -0.76)	-1.77 (-2.57, -0.96)	<0.001
Ertugliflozin 15 mg	97	-1.39 (-1.97, -0.81)	-1.84 (-2.66, -1.02)	<0.001
Change from Baseline in Sitting Systolic Blood Pressure (mmHg) at Week 26: eGFR ≥45 to <60 mL/min/1.73m^2 Stratum				
Placebo	99	-0.90 (-3.73, 1.92)		
Ertugliflozin 5 mg	105	-2.33 (-4.98, 0.33)	-1.42 (-5.13, 2.29)	0.451

Treatment	N	LS Mean (95% CI)	Pairwise Comparisons	
			Difference in LS Means (95% CI) vs. Placebo[†]	p-Value
Ertugliflozin 15 mg	97	-4.36 (-7.11, -1.62)	-3.46 (-7.24, 0.31)	0.072
Change from Baseline in FPG (mg/dL) at Week 26: eGFR ≥45 to <60 mL/min/1.73m^2 Stratum				
Placebo	99	-4.95 (-15.03, 5.13)		
Ertugliflozin 5 mg	105	-11.76 (-21.07, -2.45)	-6.81 (-19.47, 5.85)	0.291
Ertugliflozin 15 mg	97	-20.47 (-30.20, -10.73)	-15.51 (-28.50, -2.53)	0.019
Treatment	N	n (%)	Odds Ratio (95% CI) vs. Placebo	p-Value
A1C < 7.0% at Week 26: eGFR ≥45 to <60 mL/min/1.73m^2 Stratum: (logistic regression)[§]				
Placebo	99	12 (12.1)		
Ertugliflozin 5 mg	105	17 (16.2)	1.16 (0.53, 2.56)	0.713
Ertugliflozin 15 mg	97	11 (11.3)	1.06 (0.44, 2.55)	0.890

N is the number of subjects in the analysis population. For the post-hoc analysis, N is the number of subjects without positive metformin assays in the analysis population.

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

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

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

The overall model based analysis fitted with terms for eGFR stratum (<45 or ≥45 mL/min/1.73m^2), baseline treatment with insulin stratum (yes/no).

All eGFR stratum model based analyses fitted with terms for baseline treatment with insulin stratum (yes/no).

CI=Confidence Interval; LS =Least Squares

Subgroup analysis on background insulin and SU treatment, study P001/1016

Study P001/1016 was the only study which allowed insulin and/or SU as background AHA therapy. In total, 56.7% of patients included used insulin and 43.7% used SU at baseline.

Table 26 and **Table 27** show the change from baseline in HbA1c at week 26 in the subgroups on background insulin and SU treatment respectively.

Table 26: A1C (%): Change from Baseline at Week 26 – cLDA - Subgroup on Background Insulin - Full Analysis Set: Excluding Rescue Approach

	Baseline		Week 26		Change from Baseline at Week 26	
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD) / LS Mean (95% CI)[†]
Placebo	85	8.17 (0.883)	66	7.96 (1.058)	86	-0.14 (0.961) / -0.17 (-0.38, 0.04)
Ertugliflozin 5 mg	91	8.32 (1.038)	68	8.07 (1.195)	92	-0.12 (0.745) / -0.12 (-0.33, 0.09)
Ertugliflozin 15 mg	87	8.22 (0.865)	70	7.79 (0.952)	89	-0.34 (1.074) / -0.36 (-0.57, -0.16)
Estimated Difference						Difference in LS Means (95% CI)[†]
Ertugliflozin 5 mg vs. Placebo						0.05 (-0.24, 0.34)
Ertugliflozin 15 mg vs. Placebo						-0.20 (-0.49, 0.09)
Conditional Pooled SD of Change from Baseline						0.90

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

[†] Based on cLDA model with fixed effects for treatment, time, eGFR stratum (<45 or ≥45 mL/min/1.73m^2), baseline treatment with insulin stratum (yes/no) and the interaction of time by treatment. Time was treated as a categorical variable.

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

Data Source: [ADEFF] Date of Reporting Dataset Creation: 30JUL2016 Date of Table Creation: 30JUL2016 (18:35)

Table 27: A1C (%): Change from Baseline at Week 26 – cLDA - Subgroup on Background Sulfonylurea - Full Analysis Set: Excluding Rescue Approach

	Baseline		Week 26		Change from Baseline at Week 26	
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD) / LS Mean (95% CI)[†]
Placebo	45	8.08 (0.903)	36	7.66 (0.990)	46	-0.51 (1.044) / -0.43 (-0.68, -0.18)
Ertugliflozin 5 mg	53	8.01 (0.936)	48	7.46 (0.808)	55	-0.45 (0.723) / -0.51 (-0.74, -0.28)
Ertugliflozin 15 mg	49	8.13 (0.912)	43	7.58 (0.670)	51	-0.50 (0.928) / -0.45 (-0.69, -0.22)
Estimated Difference						Difference in LS Means (95% CI)[†]
Ertugliflozin 5 mg vs. Placebo						-0.08 (-0.40, 0.24)
Ertugliflozin 15 mg vs. Placebo						-0.02 (-0.35, 0.30)
Conditional Pooled SD of Change from Baseline						0.75

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, eGFR stratum (<45 or ≥45 mL/min/1.73m^2), baseline treatment with insulin stratum (yes/no) and the interaction of time by treatment. Time was treated as a categorical variable.

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

Data Source: [ADEFF] Date of Reporting Dataset Creation: 30JUL2016 Date of Table Creation: 30JUL2016 (18:35)

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

Efficacy data were pooled for the 2 placebo-controlled studies (Studies P007/1017 and P006/1015) to assess efficacy on a background of metformin (hereafter referred to as the Ertu/Met FDC Pool). The primary purpose of pooling these efficacy data was to provide a more robust analysis of efficacy by subgroup. Pooled efficacy endpoints for subgroup analyses included change from baseline in A1C, responders (A1C <7.0%), and change from baseline in body weight. The subgroup analyses are exploratory and no formal hypotheses were tested. Subgroup factors assessed included age, gender, race, ethnicity, region, baseline A1C, baseline body mass index (BMI), baseline eGFR, and duration of T2DM.

Subgroup Analysis: Change from Baseline in A1C

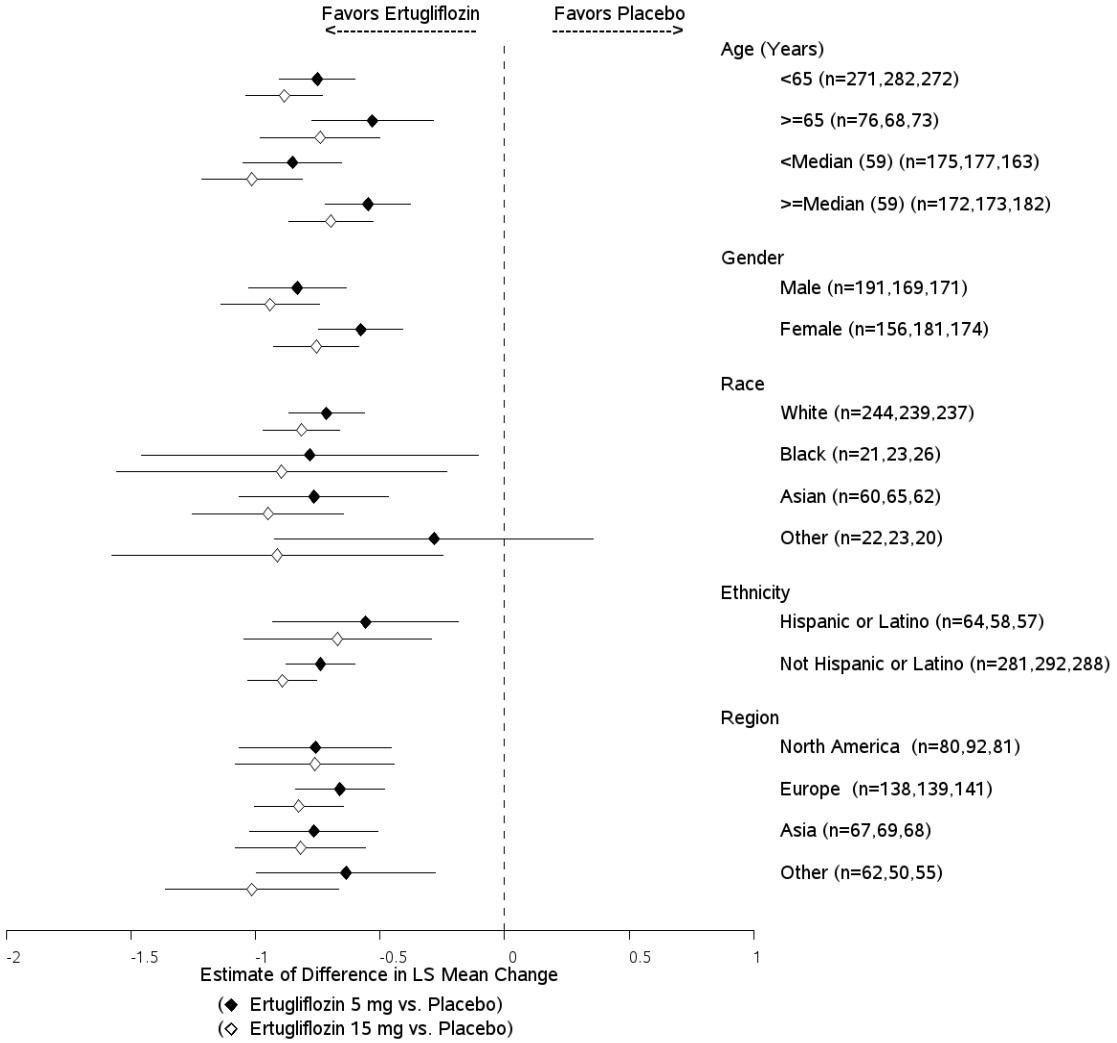
In the Ertu/Met FDC Pool, treatment with ertugliflozin on a background of metformin resulted in reductions in A1C that were superior to the results in the placebo group at Week 26, irrespective of gender, age, sex, race, ethnicity, geographic region, baseline BMI, baseline A1C, and duration of T2DM, **Figure 7** and **Figure 8**.

In general, clinically meaningful reductions from baseline in A1C were observed with ertugliflozin 5 mg and ertugliflozin 15 mg compared with 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 versus a lower baseline A1C.

The placebo-adjusted LS mean reduction from baseline in A1C was greater in subjects with normal renal function compared with subjects with renal impairment. Subjects with mild renal impairment had clinically meaningful reductions in A1C relative to placebo with both doses of ertugliflozin tested. Although the subgroup sample size was small (n =31), meaningful lowering of A1C was also observed with ertugliflozin 15 mg in subjects with eGFR <60 mL/min/1.73 m^2. The results must be interpreted with caution in light of the sample size.

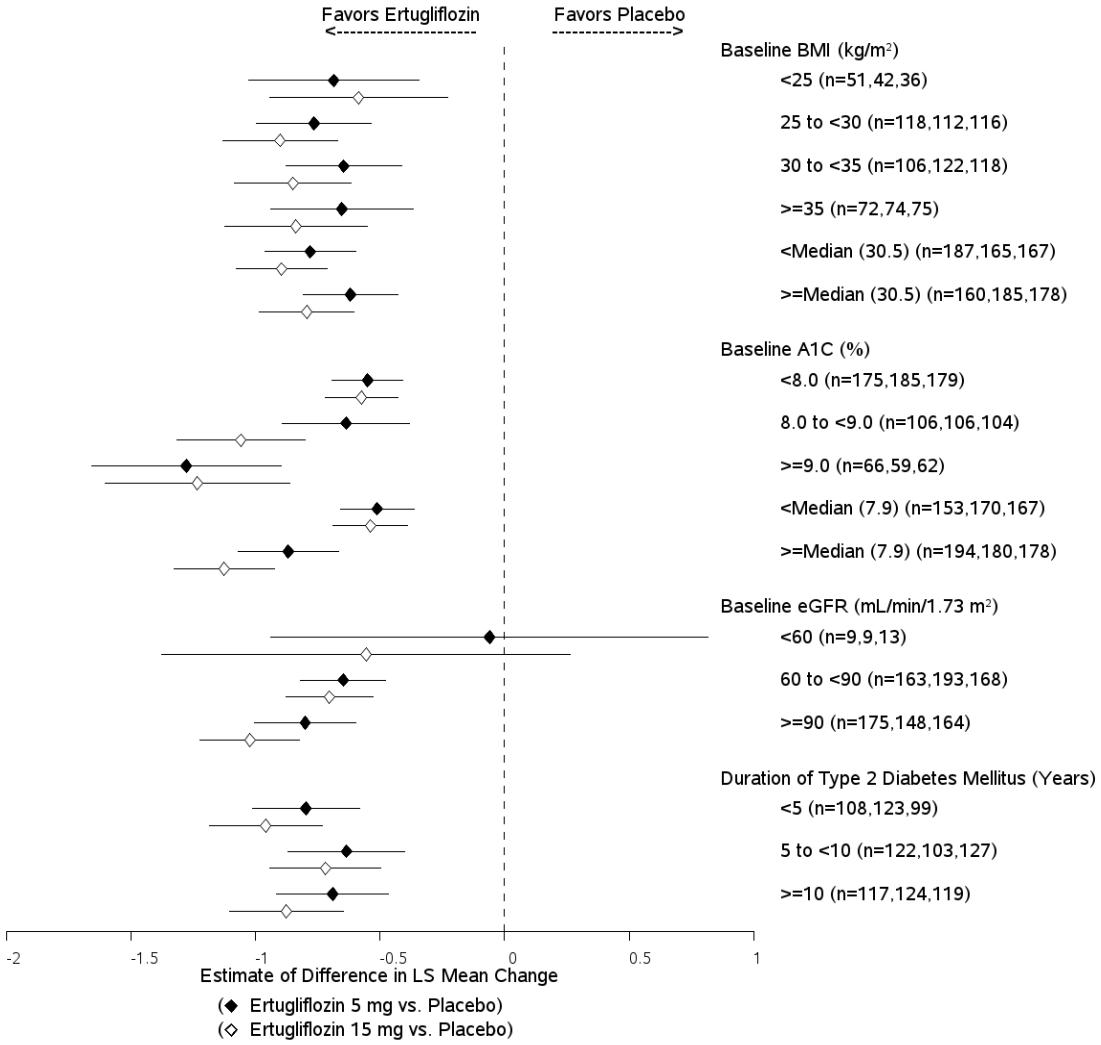
Figure 7: A1C (%): Forest Plot of Change from Baseline at Week 26 for All Subgroups - Point Estimate and 95% Confidence Interval - Full Analysis Set: Excluding Rescue Approach - Ertu/Met FDC Pool



(n = n1,n2,n3): n1 = number of subjects in the placebo group, n2 = number of subjects in the Ertugliflozin 5 mg group, n3 = number of subjects in the Ertugliflozin 15 mg group.

LS = Least Squares

Figure 8: A1C (%): Forest Plot of Change from Baseline at Week 26 for All Subgroups - Point Estimate and 95% Confidence Interval - Full Analysis Set: Excluding Rescue Approach - Ertu/Met FDC Pool



(n = n1,n2,n3): n1 = number of subjects in the placebo group, n2 = number of subjects in the Ertugliflozin 5 mg group, n3 = number of subjects in the Ertugliflozin 15 mg group.

LS = Least Squares

Subgroup Analysis: Change From Baseline in Body Weight

Treatment with ertugliflozin 5 mg and 15 mg on a background therapy of metformin resulted in reductions in body weight that were superior to the placebo group at Week 26 for the Ertu/Met FDC Pool.

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.

Supportive studies

Two studies are considered supportive.

Table 28: Supportive studies

Study	Randomized Population	N	Study Design	Treatment Groups and Number of Subjects Randomized	Treatment Duration
Monotherapy					
P003/1022 Monotherapy	Adult subjects ≥18 years of age with T2DM and inadequate glycaemic control (A1C 7.0% to 10.5%, inclusive) on diet and exercise	461	Multicenter, randomized (1:1:1), double-blind, placebo-controlled	Placebo (n=153) Ertugliflozin 15 mg (n=152) Ertugliflozin 5 mg (n=156) Subjects receiving placebo who did not receive glycaemic rescue therapy in Phase A were switched to metformin in Phase B	52 weeks Phase A: 26 weeks Phase B: 26 weeks **Completed**
Co-administration with sitagliptin in subjects on diet and exercise alone					
P017/1047 Ertugliflozin plus sitagliptin initial combination	Adult subjects ≥18 years with T2DM and inadequate glycaemic control (A1C 8.0% to 10.5%, inclusive) on diet and exercise	291	Multicenter, randomized (1:1:1), double-blind, placebo-controlled	Placebo (n=97) Ertugliflozin 15 mg/sitagliptin 100 mg (n=96) Ertugliflozin 5 mg/ sitagliptin 100 mg (n=98)	26 weeks **Completed**
Abbreviations: A1C=glycosylated haemoglobin A1c; n=number of subjects randomly assigned to study medication; N=overall number of subjects randomly assigned to study medication; T2DM=type 2 diabetes mellitus					

Study P003/1022: Monotherapy Study

Study Design

Study P003/1022 was a multicenter, randomized, parallel-group study with a 26-week, double-blind, placebo-controlled treatment period (Phase A) followed by a 26-week active-controlled treatment period (Phase B) in subjects with T2DM and inadequate glycaemic control on diet and exercise to assess the A1C-lowering efficacy of ertugliflozin compared with placebo and to provide pivotal Phase 3 data on the efficacy and safety of ertugliflozin as monotherapy (no treatment with other AHAs) **(Table 28)**.

The primary efficacy analysis was carried out excluding post-rescue efficacy data.

Demographic and Baseline Characteristics

In total, 461 subjects were randomly assigned to study medication. The mean age of the subjects was 56.4 years, 56.6% were male, 83.7% of subjects were White, 8.5% were Asian, and 6.3% were Black or African American. The mean duration of T2DM was 4.99 years. Baseline demographic and anthropometric characteristics were similar between treatment groups.

Key Efficacy Endpoint Results

Table 29 show the results of the primary analysis of change from baseline in A1C at Week 26 using the cLDA model in the FAS population ER approach. The LS mean reductions from baseline in A1C at Week 26 were significantly greater in the 15 mg and 5 mg ertugliflozin groups compared to the placebo group (p<0.001 for both comparisons).

The results for the key efficacy endpoints are also presented in **Table 29**.

Table 29: Key Efficacy Endpoints: Full Analysis Set: Excluding Rescue Approach - Study P003/1022

Treatment	N	LS Mean (95% CI)	Pairwise Comparisons	
			Difference in LS Means (95% CI) vs. Placebo[†]	p-Value
Change from Baseline in A1C (%) at Week 26: cLDA				
Placebo	153	0.20 (0.02, 0.37)		
Ertugliflozin 5 mg	156	-0.79 (-0.95, -0.63)	-0.99 (-1.22, -0.76)	<0.001
Ertugliflozin 15 mg	151	-0.96 (-1.12, -0.80)	-1.16 (-1.39, -0.93)	<0.001
Change from Baseline in FPG (mg/dL) at Week 26: cLDA				
Placebo	153	0.57 (-6.02, 7.16)		
Ertugliflozin 5 mg	155	-33.96 (-39.85, -28.06)	-34.53 (-42.76, -26.29)	<0.001
Ertugliflozin 15 mg	152	-43.44 (-49.39, -37.49)	-44.01 (-52.28, -35.74)	<0.001
Change from Baseline in Body Weight (kg) at Week 26: cLDA				

Placebo	153	-1.42 (-2.02, -0.81)		
Ertugliflozin 5 mg	156	-3.18 (-3.72, -2.63)	-1.76 (-2.57, -0.95)	<0.001
Ertugliflozin 15 mg	152	-3.58 (-4.13, -3.02)	-2.16 (-2.98, -1.34)	<0.001
Change from Baseline in Sitting Systolic Blood Pressure (mmHg) at Week 26: cLDA				
Placebo	152	-2.22 (-4.30, -0.14)		
Ertugliflozin 5 mg	156	-5.54 (-7.32, -3.76)	-3.31 (-5.98, -0.65)	0.015
Ertugliflozin 15 mg	152	-3.93 (-5.74, -2.12)	-1.71 (-4.40, 0.98)	0.213
Change from Baseline in Sitting Diastolic Blood Pressure (mmHg) at Week 26: cLDA				
Placebo	152	-0.72 (-2.05, 0.60)		
Ertugliflozin 5 mg	156	-2.52 (-3.65, -1.40)	-1.80 (-3.51, -0.09)	0.039
Ertugliflozin 15 mg	152	-1.10 (-2.24, 0.05)	-0.37 (-2.09, 1.35)	0.669
Change from Baseline in 2-hr PPG (mg/dL): at Week 26: cLDA				
Placebo	151	4.88 (-6.15, 15.92)		
Ertugliflozin 5 mg	153	-64.15 (-74.34, -53.96)	-69.03 (-83.24, -54.83)	<0.001
Ertugliflozin 15 mg	148	-62.45 (-72.91, -51.98)	-67.33 (-81.73, -52.93)	<0.001
Treatment	N	n (%)	Odds Ratio (95% CI) vs. Placebo	p-Value
A1C < 7.0% at Week 26 (logistic regression with multiple imputation based on cLDA model)[§]				
Placebo	153	20 (13.1)		
Ertugliflozin 5 mg	156	44 (28.2)	3.59 (1.85, 6.95)	<0.001
Ertugliflozin 15 mg	151	54 (35.8)	6.77 (3.46, 13.24)	<0.001

N is the number of subjects in the analysis population.

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

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

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

data imputed using the cLDA model fitted.

All model based analyses fitted with terms for prior antihyperglycaemic medication (yes, no), baseline eGFR (continuous).

CI=Confidence Interval; LS =Least Squares

Data cut date: 11FEB2016

PFIZER CONFIDENTIAL Source Data: [Ref. 5.3.5.1: P003V01: Table 14.2.11.1.1] Date of Reporting Dataset Creation: 28MAR2016 Date of Table Creation: 06APR2016 (11:51)

Study P017/1047: Ertugliflozin Plus Sitagliptin Initial Combination Study

Study Design

Study P017/1047 was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of initial combination therapy with ertugliflozin and sitagliptin in subjects with T2DM with inadequate glycaemic control on diet and exercise alone **(Table 28)**.

The primary efficacy analysis was carried out excluding post-rescue efficacy data.

Demographic and Baseline Characteristics

In total, 291 subjects were randomly assigned to study medication. The mean age of the subjects was 55.6 years, 57.4% were male, 90.4% of subjects were White and 4.5% were Black or African American. The mean duration of T2DM was 6.30 years. Baseline demographic and anthropometric characteristics and the distribution of subjects by AHA use at screening were generally similar between treatment groups, with the exception that more subjects in the placebo group were in North America (excluding Central America) compared to the E15/S100 and E5/S100 groups.

Key Efficacy Endpoint Results

Table 30 show the results of the primary analysis of change from baseline in A1C at Week 26, excluding data after initiation of glycaemic rescue therapy. The LS mean reductions from baseline in A1C at Week 26 were significantly greater in the E15/S100 and E5/S100 groups than in the placebo group ($p<0.001$ for both comparisons).

Large reductions in A1C in the co-administration groups at Week 6 (first scheduled post-randomization assessment) were followed by smaller subsequent reductions through Week 26. The reduction in A1C was numerically greater in the E15/S100 group than in the E5/S100 group at each time point. In the placebo group, there was essentially no change from baseline in A1C through Week 12; thereafter, a reduction in A1C was observed at Week 26.

The results for the key efficacy endpoints are also presented in **Table 30**.

Table 30 Key Efficacy Endpoints: Full Analysis Set: Excluding Rescue Approach - Study P017/1047

Treatment	N	LS Mean (95% CI)	Pairwise Comparisons	
			Difference in LS Means (95% CI) vs. Placebo[†]	p-Value
Change from Baseline in A1C (%) at Week 26: cLDA				
Placebo	96	-0.44 (-0.69, -0.19)		
Ertugliflozin 5 mg + Sitagliptin 100 mg	98	-1.60 (-1.82, -1.39)	-1.16 (-1.49, -0.84)	<0.001

Treatment	N	LS Mean (95% CI)	Pairwise Comparisons	
			Difference in LS Means (95% CI) vs. Placebo[†]	p-Value
Ertugliflozin 15 mg + Sitagliptin 100 mg	96	-1.68 (-1.90, -1.46)	-1.24 (-1.57, -0.91)	<0.001
Change from Baseline in FPG (mg/dL) at Week 26: cLDA				
Placebo	96	-9.30 (-18.58, -0.02)		
Ertugliflozin 5 mg + Sitagliptin 100 mg	98	-48.25 (-56.12, -40.38)	-38.94 (-49.93, -27.96)	<0.001
Ertugliflozin 15 mg + Sitagliptin 100 mg	96	-55.36 (-63.29, -47.42)	-46.05 (-57.09, -35.02)	<0.001
Change from Baseline in Body Weight (kg) at Week 26: cLDA				
Placebo	97	-0.94 (-1.70, -0.18)		
Ertugliflozin 5 mg + Sitagliptin 100 mg	98	-2.94 (-3.60, -2.28)	-2.00 (-2.99, -1.01)	<0.001
Ertugliflozin 15 mg + Sitagliptin 100 mg	96	-3.04 (-3.71, -2.38)	-2.10 (-3.10, -1.11)	<0.001
Change from Baseline in Sitting Systolic Blood Pressure (mmHg) at Week 26: cLDA				
Placebo	97	2.41 (-0.34, 5.15)		
Ertugliflozin 5 mg + Sitagliptin 100 mg	98	-2.04 (-4.23, 0.16)	-4.44 (-7.87, -1.01)	0.011
Ertugliflozin 15 mg + Sitagliptin 100 mg	96	-3.98 (-6.19, -1.78)	-6.39 (-9.83, -2.95)	<0.001
Change from Baseline in Sitting Diastolic Blood Pressure (mmHg) at Week 26: cLDA				
Placebo	97	1.21 (-0.73, 3.15)		
Ertugliflozin 5 mg + Sitagliptin 100 mg	98	-0.44 (-1.99, 1.11)	-1.65 (-4.09, 0.79)	0.184
Ertugliflozin 15 mg + Sitagliptin 100 mg	96	-0.97 (-2.52, 0.59)	-2.18 (-4.62, 0.26)	0.080
Change from Baseline in 2-hr PMG (mg/dL): at Week 26: cLDA				
Placebo	91	-20.38 (-35.62, -5.14)		
Ertugliflozin 5 mg + Sitagliptin 100 mg	97	-82.80 (-95.96, -69.64)	-62.42 (-80.47, -44.37)	<0.001
Ertugliflozin 15 mg + Sitagliptin	95	-90.03 (-103.34, -	-69.65 (-87.83, -	<0.001

Treatment	N	LS Mean (95% CI)	Pairwise Comparisons	
			Difference in LS Means (95% CI) vs. Placebo[†]	p-Value
100 mg		76.71)	51.46)	
Treatment	N	n (%)	Odds Ratio (95% CI) vs. Placebo	p-Value
A1C < 7.0% at Week 26 (logistic regression with multiple imputation based on cLDA model)[§]				
Placebo	96	8 (8.3)		
Ertugliflozin 5 mg + Sitagliptin 100 mg	98	35 (35.7)	6.88 (2.81, 16.83)	<0.001
Ertugliflozin 15 mg + Sitagliptin 100 mg	96	30 (31.3)	7.39 (2.98, 18.31)	<0.001

N is the number of subjects in the analysis population.

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

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

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

All model based analyses fitted with terms for prior antihyperglycaemic medication (yes, no), baseline eGFR (continuous).

The term post-meal glucose (PMG) used in this study is equivalent to the term post-prandial glucose (PPG) used in other parts of this document.

CI=Confidence Interval; LS =Least Squares.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Seven studies are submitted in support of the current application. All studies have reached the primary endpoint at either 26 or 52 weeks. All but one study (P017/1047) have extensions (phase B) and were still ongoing at the time of the submission of the application. The final CSRs for 5 of the 6 studies with Phase B periods have been submitted during the procedure. Four of the studies are considered pivotal for the current application for the fixed dose combination of ertugliflozin and metformin, whereas three studies are included to further support the efficacy and safety of ertugliflozin as monocomponent. One of these three studies was performed in patients with renal impairment (P001/1016) whereas the other two studies are considered supportive (P003/1022 and P017/1047).

A total of 4864 subjects were randomly assigned to treatment in the Phase 3 studies supporting registration of ertugliflozin, with 2597 of these subjects randomly assigned to treatment with ertugliflozin on a background of metformin. In the studies, ertugliflozin and metformin were administered as free combination and metformin was given according to label.

The decision of which doses to investigate in the phase 3 program was based on data from the phase 1 program and from two dose finding studies. Study P016/1006 was a 12-week study investigating the effect of ertugliflozin at doses ranging from 1 mg qd up to 25 mg qd. Placebo and sitagliptin were included as control. A dose-response effect with regards to HbA1c was observed, but the additional effect observed at doses above 5 mg qd was very modest as the efficacy observed with the 5 mg qd dose was >80% of the maximal response for HbA1c. At doses ranging from 5 mg to 25 mg qd, the magnitude of the effect on HbA1c was comparable to that observed with sitagliptin 100 mg. A decrease in body weight and blood pressure was also observed.

Study P042/1004 was a 4-week study designed to primarily investigate the effect of ertugliflozin on blood pressure compared to HCTZ and placebo. An increased effect on systolic BP was observed at 5 mg qd compared to 1 mg qd, whereas no additional effect was observed at the highest dose of 25 mg qd. The magnitude of the effect was comparable to that observed with a low dose of HCTZ 12.5 mg. The effects observed on UGE were in line with the effects observed in the Phase 1 studies.

The 5 mg qd and 15 mg qd dose were further investigated in the phase 3 studies.

The clinical development program is in line with the EMA guideline "Clinical investigation of medicinal product in the treatment or prevention of diabetes mellitus" (CPMP/EWP/1080/00 Rev.1) and the EMA guideline "Clinical development of fixed combination medicinal products" (CHMP/EWP/240/95 Rev. 1).

Two of the pivotal studies investigated ertugliflozin as add-on to ongoing metformin treatment. In study P007/1017, ertugliflozin 5 mg and 15 mg respectively was compared to placebo. The overall study duration was 104 weeks with the primary endpoint measured at 26 weeks. In study P002/1013, ertugliflozin 5 mg and 15 mg respectively was compared to glimepiride and the primary objective was to show that ertugliflozin 15 mg and 5 mg was non-inferior to glimepiride. The overall study duration was 104 weeks with the primary endpoint measured at 52 weeks.

In the other two studies, triple combination with ertugliflozin, metformin and sitagliptin was investigated. Study P006/1015 included patients on stable background therapy with metformin ≥1500 mg/day and sitagliptin 100 mg/day. Ertugliflozin 5 mg and 15 mg respectively (as add-on to metformin + sitagliptin) was compared to placebo. The overall study duration was 52 weeks with the primary endpoint measured at 26 weeks. Study P005/1019 was a factorial study comparing ertugliflozin 5 mg and 15 mg with the combined treatment of both ertugliflozin doses with sitagliptin 100 mg as add-on to metformin treatment. A treatment arm with sitagliptin 100 mg was also included. The overall study duration was 52 weeks with the primary endpoint measured at 26 weeks.

In addition to these studies, three studies from the ertugliflozin clinical development program were included. The supportive studies were study P003/1022 (26 weeks + 26 weeks), which was a monotherapy study comparing ertugliflozin 5 mg and 15 mg with placebo, and study P017/1047 (26 weeks), in which the concomitant use of ertugliflozin (5 mg and 15 mg) and sitagliptin 100 mg, was compared to placebo. The third study was conducted in patients with moderate renal impairment (study P001/1016). Patients were to be on stable AHA therapy (including insulin) and all AHAs except metformin, rosiglitazone and other SGLT2-inhibitors were allowed. Ertugliflozin 5 mg and 15 mg were compared to placebo. The overall study duration was 52 weeks with the primary endpoint measured at 26 weeks.

The studies were of adequate designed and duration. One study (study P002/1013) provides one-year data. All studies applied run-in phases where background medication was stabilised.

The inclusion criteria were in most part aligned between studies. The inclusion criteria regarding HbA1c varied somewhat between studies, as did the inclusion criteria with regards to renal function. The inclusion and exclusion criteria were adequate.

The same primary endpoint, change from baseline HbA1c, was applied in all studies. Apart from "2-hour postprandial glucose" and "change from baseline in β cell responsivity static component" which were only measured in one study, all secondary endpoints were the same in all studies although not always included in the statistical testing. All key endpoints were relevant.

Sample size calculations were overall adequate and randomisation procedures performed as planned. Masking was achieved and maintained in each study through the use of a double-dummy approach and was appropriate. All the studies had two post-randomisation treatment periods, Phase A and Phase B; when phase A had been completed data from this phase was unblinded. This is acceptable since phase A was the primary time period for evaluation of hypotheses; those associated with the conduct of a study as well as trial site personnel and subjects were to remain blinded until after the Phase B portion had been completed.

Statistical methods were generally similar across the individual phase 3 studies. The estimand for all of the primary hypotheses was the difference in mean A1C improvement at the primary timepoint, in the target population defined by the inclusion / exclusion criteria, if all subjects adhered to therapy without use of rescue medication.

The analysis population for all efficacy analyses was the Full Analysis Set (FAS), which was to consist of all randomised subjects who received at least one dose of study medication and had at least one measurement for the analysis endpoint (baseline or post-randomisation). Data obtained after the initiation of rescue therapy or after bariatric surgery were to be treated as missing to avoid the confounding influence of rescue therapy. However, in a superiority study versus placebo, in theory, if the experimental treatment works, the IR (including rescue) approach should result in a more conservative estimate. In study P002/1013 with the primary objective being to show non-inferiority, the ER (excluding rescue) is agreed with.

For analyses of continuous endpoints (including the primary endpoint) a constrained longitudinal data analysis (cLDA) model framework was used in which no explicit imputation of missing assessments is performed. Of importance for the credibility of any estimated primary outcome will then be to what extent subjects stayed in a study and contributed with data considering that missing at random (MAR) seldom is a plausible assumption. To assess the robustness of the primary analyses to departures from the MAR assumption, sensitivity analyses using the tipping-point approach and a jump-to-reference (J2R) multiple-imputation method were performed. The sensitivity approach using the J2R approach is considered a reasonably conservative method for treatment of missing data that is not considered missing at random. Patients in the active treatment group are assigned a placebo-like value and the placebo treated patients are assigned a value that does not punish the placebo treatment. In study P006/1015 and P007/1017, data from any subject incorrectly stratified at randomization were analysed according to the intended stratum rather than the actual stratum. An accounting of all incorrectly stratified subjects was provided. The primary analysis should reflect the restriction on the randomisation implied by the stratification.

With regards to the conduct of the studies, major protocol deviation was reported for between 24 and 33% of subjects across the phase III studies except for the renal impairment study (P001/1016) where major protocol deviations were reported for 48% of subjects. Across the studies, the most common

deviations were "failure to conduct major/significant evaluations" and "subjects who did not give appropriate Informed Consent". Notably, multiple enrolments were discovered in all studies, mostly in the US. When this issue was detected, adequate preventive measures were taken. With regard to those who were randomised multiple times across sites within a study and/or across studies the Applicant's conclusion is agreed with, i.e. that the significant misconduct of these particular subjects compromised the integrity of their study data, and therefore results from these subjects were excluded from all analyses. It is concluded that the protocol deviations did not influence the outcome and interpretation of results in the studies.

Furthermore, after breaking the blind in part A of study P001/1016 (renal impairment), it was discovered that 78 subjects (out of 467) had blood samples positive for metformin. Post-hoc analyses were performed, since concomitant metformin use confounds the comparison of ertugliflozin versus placebo. The high use of prohibited medication raises concerns with regards to the conduct of the study, also taking into consideration the high rate of major protocol deviations in this study. The Applicant has discussed potential reasons for the use of prohibited medication and claims that the use appears to have been patient-initiated. Internal audits were conducted which showed no indication that study P001/1016 was not generally performed according to GCP.

Efficacy data and additional analyses

The demographics and baseline characteristics of the subjects in the phase 3 program were comparable across the studies. The demographics and baseline characteristics of the phase 3 population are considered representative for the target population. About 40% (36-45%) of patients were recruited in Europe (including Russia).

Across the phase 3 studies, i.e. including the supportive studies, discontinuation rates were generally low (6-13%) and balanced between groups. There were two exceptions. In study P002/1013 the overall discontinuation rate was 21%, however this study was of 52 weeks duration and discontinuations were balanced between groups. In the supportive monotherapy study (P003/1022) the discontinuation rate was slightly higher in the placebo group (22%), the overall discontinuation rate being 17%. The difference is explained by higher discontinuation due to hyperglycaemia and lack of efficacy in the placebo group. No efficacy analyses were planned or have been performed including all randomised subjects. Overall, across the studies, very few subjects if any were however excluded from the primary analysis set (FAS). Depending on how data collected after rescue was handled, the proportion of subjects with missing endpoint data week 26/52 varied where the primary ER approach (treating data obtained after initiation of rescue therapy as missing) implied higher proportions of patients with missing week 26/52 data. In the non-inferiority study P002/1013, supportive analyses were performed based also on a PP population. The proportion of patients excluded from the PP analyses was highest in the ertugliflozin 5 mg group, approximately 26%, with a slightly lower but similar proportions in the ertugliflozin 15 mg and glimepiride arm, respectively (approximately 22%).

In two of the studies, ertugliflozin was given as add-on to metformin alone. In study P007/1017 (where ertugliflozin was compared to placebo), the treatment difference versus placebo was -0.70% (-0.87,-0.53) for the 5 mg dose and -0.88% (-1.05,-0.71) for the 15 mg dose. In the non-inferiority study P002/1013, ertugliflozin 5 mg and 15 mg was compared to glimepiride. The treatment target for glimepiride is stated to have been 6 to 8 mg daily; however the actual dose was 3 mg daily. According to European label, the maximum dose is 6 mg but increases above 4 mg seldom results in added effect (Amaryl, NL/H/0101). The achieved glimepiride dose is therefore considered relevant. The treatment difference vs glimepiride was 0.18% (0.06, 0.30) for the 5 mg dose and 0.10 (-0.02, 0.22) for the 15 mg dose. Thus non-inferiority was shown for the 15 mg dose as the non-inferiority margin chosen was

0.3% whereas the outcome for the 5 mg was of borderline character since the chosen delta of 0.3% was included in the upper limit of the 95% CI. The change from baseline in HbA1c was clinically relevant for both doses (-0.56 ± 0.045 for the 5 mg dose and -0.64 ± 0.045 for the 15 mg dose). For assessment of robustness of primary outcomes, PP analyses and analyses based on modified FAS (using both the ER and IR approach) were performed; the outcomes, irrespective of analysis and comparison, were very similar and supported the primary outcome.

In study P006/1015, ertugliflozin was given as add-on to metformin and sitagliptin with placebo as control. In this study, the treatment difference versus placebo was -0.69% (-0.87,-0.50) for the 5 mg dose and -0.76% (-0.95,-0.58) for the 15 mg dose. In the factorial study P005/1019, where ertugliflozin was either given as single therapy or co-administered with sitagliptin on background metformin therapy, single therapy with ertugliflozin 5 mg and 15 mg resulted in very similar HbA1c reductions of -1.02% and -1.08%, respectively. The HbA1c reduction with single therapy sitagliptin 100 mg was -1.05%. Both combinations (ertugliflozin 5mg + sitagliptin 100 mg and ertugliflozin 15 mg + sitagliptin 100 mg) resulted in very similar differences in treatment effect compared to the respective single component of -0.43% to -0.49%.

In the placebo-controlled studies, statistically significant and clinically relevant treatment differences in the change from baseline in HbA1c were observed for both doses compared to placebo. The magnitude of effect of about 0.7-0.9% was consistent in studies P007/1017 (metformin only) and P006/1015 (metformin + sitagliptin). In studies P002/1013 and P005/1019, no placebo-adjustment was made. In these studies, the change from baseline in HbA1c ranged from -0.6% to -1.1%. It may therefore be concluded that ertugliflozin provides a relevant contribution to the effect of the FDC.

In study P002/1013, the duration of phase A of the study was 52 weeks, thus this study provides some long-term data on the effect of ertugliflozin. The data show that the maximum effect was observed after 12 weeks and the remained stable in contrast with the effect of glimepiride which reached its maximum effect after 18 weeks thereafter the effect slowly decreased. Data was also provided from the 52-week Phase B of study P002/1013 showing that, although the HbA1c response was gradually attenuated through week 104, a relevant HbA1c reduction was still observed (-0.31% for ertugliflozin 5 mg, -0.36 for ertugliflozin 15 mg and -0.42 for glimepiride).

Additional long-term data was provided from the four studies (P003/1022, P005/1019, P006/1015, and P001/1016) that have finalised the extension phase and thus provide 52 week data. Across the studies, the treatment effect was maintained over the 52 week duration of treatment, both with regards to metabolic control, as reflected by HbA1c and responder rates (HbA1c <7%), and body weight.

The primary scientific question of interest was defined by the Applicant as "the intervention effect in the setting where all subjects tolerate and adhere to treatment". This was not fully agreed with since this would reflect efficacy in a hypothetical setting where patients are compliant which may not obviously apply in normal clinical practice. The analyses using the IR approach addresses efficacy in a treatment policy setting, which is a different question of scientific interest. The results based on the IR approach and the missing data handling using J2R is considered a more reasonable and conservative estimate of the treatment effect in a treatment policy setting, hence, a greater focus will be on the results using the IR approach and with J2R handling of missing data. All the sensitivity and supportive analyses performed had been provided although have only been found for each study separately. The Applicant was therefore requested to provide a summary table for the primary endpoint for the placebo-controlled studies, P007/1017 and P006/1015 and the active-controlled study P005/1019 using the IR approach and J2R handling of missing data. By now, the requested table has been provided. The IR (J2R) analysis provides conservative estimate of the treatment effect, especially in

the placebo-controlled studies, due to the fact that the patients in the placebo arms received rescue treatment controlling their A1C-levels. As further discussed below the treatment effect remains, however the point estimates indicate a smaller treatment effect. In their response, the applicant argued that the inclusion of post-glycaemic rescue measurements leads to uninterpretable results. This is not agreed, but rather that it addresses a different question and can be of great relevance in the understanding of the treatment effect compared to other treatments. The results based on the two different approaches are however not comparable due to the differences in analysis approach. Within the above request, the applicant was made aware that the product documentation such as SmPC may need to be updated as based on these outcomes in case considered the most relevant. History and consistency across labels for other members of the SGLT2 inhibitor class is however essential and this application follows after several other products in the same class. The labelling for the already approved products includes data on control of A1C-levels, excluding post-rescue medication efficacy data. Hence, considering that this product has predecessors in the same class it is concluded that for consistency, it is the pre-specified primary analysis excluding data post-rescue treatment that should be presented in the product labelling.

Comparing the primary (ER) and supportive (IR) analyses, statistical significance of the primary analysis was maintained under the IR approach. Estimated treatment differences between ertugliflozin doses and placebo in both study P006/1015 and P007/1017 were however smaller based on differences in rescue therapy use that occurred at a higher rate in the placebo group than in the ertugliflozin groups in both studies. The differences in the use of rescue are considered to support the treatment efficacy of ertugliflozin in each setting, respectively. In study P005/1019 use of rescue occurred at a lower rate and hence, analysis approach had a smaller impact on estimated differences.

The outcome of the secondary endpoints was consistent with the primary endpoint across the studies. Reductions from baseline in FPG were in line with the reductions observed for HbA1c. In the studies where ertugliflozin was coadministered with sitagliptin, a greater effect was observed with the combination compared to the single components. Treatment with ertugliflozin resulted in significant reductions in 2-hour PPG in study P005/1019.

In all studies, 26 to 40% of subjects achieved the treatment goal of HbA1c <7.0% when ertugliflozin was given in combination with metformin only. Higher responder rates were observed when ertugliflozin was given in triple combination with sitagliptin. The proportion of subjects receiving glycaemic rescue therapy in all ertugliflozin groups was low, ranging from 0% to 6.4%. The proportion of subjects rescued was higher in the placebo groups, ranging from 16.3% to 17.7%.

Across the studies, consistent reductions from baseline in body weight were observed with ertugliflozin 5 mg and 15 mg. The placebo or active control adjusted weight reduction ranged from 1.6 to 4.3 kg. The largest treatment difference was observed in the ertugliflozin vs glimepiride study (study P002/1013) due to the weight increase observed in the glimepiride treated group. There was no clear dose response relationship with regards to body weight.

Reductions from baseline in sitting SBP were observed with ertugliflozin 15 mg and 5 mg across the phase 3 studies regardless of between-study differences in background medication and study designs. The reduction in SBP ranged from -2.8 mmHg to -4.8 mmHg with slightly larger reductions in the higher ertugliflozin dose groups. Reductions in DBP were observed in line with the data for SBP.

Study P001/1016 included with patients renal impairment and is part of the clinical study program supporting the MAA for ertugliflozin. All AHAs (including insulin) except metformin, rosiglitazone and other SGLT2-inhibitors were allowed. Due to different entry criteria than in the other studies in the phase 3 program, subjects who were older, had a lower baseline eGFR, and a longer duration of T2DM

were included. In the primary analysis, no relevant effect on HbA1c was observed for any of the doses compared to placebo. In the post-hoc analysis in the overall cohort (which excluded patients who had blood samples positive for metformin), a statistically significant reduction in HbA1c was observed in the high dose group (-0.33%, 95%CI: -0.55, -0.11). The post-hoc analysis was also conducted in the subgroup of patients with eGFR 45-60. The change from baseline in HbA1c was comparable to that of the overall cohort, thus of questionable clinical relevance. The outcome of the secondary glycaemic endpoints was also lower than in studies including patients with eGFR >60. The effect on body weight and SBP was also attenuated. No difference in the proportion of responders was observed in any of the dose groups compared to placebo.

In the "grade 3B renal impairment" stratum, removal of data of metformin-users had negligible impact on HbA1C results. Ertugliflozin seemed ineffective in subjects with eGFR lower than 45 mL/min/1.73m^2. This was not influenced by removing or including corrupted data. This fact, which should be interpreted with caution due to the post-hoc nature and small sample size, can further support that ertugliflozin may not have benefit in these patients.

Study P001/1016 was the only study where patients were allowed to use insulin and/or SU as background medication. Subgroup analyses of the primary endpoint in patients on background insulin showed no difference in outcome versus placebo for the ertugliflozin 5 mg group and a very modest and statistically non-significant improvement of -0.2% for the ertugliflozin 15 mg group. The corresponding analysis for patients on background SU treatment showed no treatment difference compared to placebo. The subgroup of subjects using insulin at baseline (N= 263/467) showed a HbA1c change from baseline both in the ertugliflozin 15 mg group (-0.36% [-0.57, -0.16]) and in the ertugliflozin 5 mg group (-0.12% [-0.33, 0.09]). In the subgroup of subjects on a sulfonylurea at baseline (N=147/467), the HbA1c change from baseline was -0.45% (-0.69, -0.22) and -0.51% (-0.74, -0.28) for the ertugliflozin 15 mg and 5 mg groups, respectively. It can be hypothesised that a more pronounced effect would be observed in patients with normal renal function.

Subgroup analyses were performed on pooled data from the two placebo-controlled studies (studies P007/1017, and P006/1015) which is considered adequate. Demographic and baseline characteristics were comparable across the two studies included in the analysis. Across the subgroup analysis a greater effect was observed with the higher dose, but there is a considerable overlap of the confidence intervals. There was a greater effect of ertugliflozin in younger subjects compared to older subjects, which may be explained by the decrease in renal function by age. A greater effect was also observed in males than in females. Both groups experienced relevant effects but there is currently no data that can explain the gender difference. A relevant treatment effect was observed in patients with mild renal impairment, whereas the effect in patients with eGFR < 60 is questionable. Although the point estimates are in favour of ertugliflozin, the confidence intervals are wide and include 0. In contrast to the data on change from baseline in HbA1c, the effect on body weight was observed across all subgroups studies. Again the least convincing effect was observed in the group with eGFR < 60.

Two supportive studies which are part of the clinical study program supporting the MAA for ertugliflozin were also included in the submission.

Study P003/1022 investigated the effect of ertugliflozin as monotherapy versus placebo. Statistically significant and clinically relevant treatment differences in the change from baseline in HbA1c were observed for both the 5 mg and the 15 mg dose compared to placebo (-0.99% (-1.22,-0.76) for ertugliflozin 5 mg and -1.16% (-1.39, -0.93) for ertugliflozin 15 mg, respectively). The numerical difference in HbA1c reduction was small (-0.14%). Secondary glycaemic endpoints all supported the primary endpoint. Only a modest increase in the proportion of patients with HbA1c<7.0% was observed with the higher dose of ertugliflozin (28% vs 36%). A significant decrease in body weight of

about 2 kg was observed with both doses. Decreases in SBP and DBP were also observed, being more pronounced in the lower dose.

In study P017/1047, combination therapy with ertugliflozin and sitagliptin was initiated without other AHA background treatment. The treatment effect was comparable to that observed in study P005/1019 (-1.16% (95%CI:-1.49, -0.84) for the 5 mg dose and -1.24% (95%CI:-1.57, -0.91) for the 15 mg dose). Notably, the treatment effect in the placebo group was larger than in any of the other studies (-0.44%) and especially when compared to the monotherapy study where patients also did not receive any active treatment. This difference is most likely due to differences in baseline HbA1c between studies. The combination treatments resulted in clinically relevant and statistically significant HbA1c reductions compared to placebo. Secondary glycaemic endpoints all supported the primary endpoint. The proportion of patients with HbA1c<7.0% was higher in the low dose of ertugliflozin compared to the high dose (36% vs 31%). A significant decrease in body weight of about 2 kg was observed with both doses. Decreases in SBP and DBP were also observed.

No formal comparisons were made between the two doses of ertugliflozin. The treatment difference between the doses ranged from 0.06% to 0.18%. The difference in responder rates (HbA1c <7.0%) between the two ertugliflozin doses was generally small (about 4-6%). However, numerically larger HbA1c reductions were consistently observed with the higher dose. The treatment difference was most pronounced in the population with median HbA1c > 7.9%. Thus the higher dose may provide additional benefit for patients with a greater need for better metabolic control.

2.5.4. Conclusions on the clinical efficacy

The clinical data provided show that ertugliflozin has clinically relevant effects on both glycaemic control, in terms of HbA1c reduction, and reductions in body weight and SBP, when given in combination with metformin thus supporting the FDC. The data submitted also show that the effect is maintained up to one year.

The effect of ertugliflozin is dependent on renal function. Taking into account the modest effect also with the highest dose in patients with eGFR 45-60, it is recommended not to initiate treatment in patients with eGFR < 60 although treatment may be continued until eGFR falls below 45.

The proposed indication states that Segluromet can be used in combination with other AHA including insulin. Patients were allowed to use insulin and/or SU as background medication only in study (P001/1016) in which the primary endpoint was not met. As the effect of ertugliflozin decreases with declining renal function, it can be hypothesised that the effect will be more pronounced in a population with normal renal function. Since the MOA for SGLT2 inhibitors is independent on the background antihyperglycaemic therapy a clinically relevant effect is expected when ertugliflozin is used together with insulin or SU in patients with normal renal function.

Study P001/1016 provides sufficient data to support a pharmacological effect of ertugliflozin in combination with insulin or SU.

2.6. Clinical safety

The safety assessment is focused on safety data from 7 phase III studies, including 3,409 subjects exposed to ertugliflozin. Overall, 1,716 subjects were treated with ertugliflozin 5 mg, 1,693 with ertugliflozin 15 mg, and 1,450 with comparator (placebo or active control).

The primary safety evaluation is derived from the phase III development program which contributed to two safety pools; the placebo-controlled (PBO) Pool and the Broad Pool **(Table 31)**.
The PBO Pool includes pooled safety data for 3 placebo-controlled phase III studies (P003/1022, P006/1015, P007/1017) with similar study design, duration of treatment, and baseline characteristics. This pool includes data from the 26 week placebo-controlled phase (Phase A) for each study.
The Broad Pool includes pooled safety data from the 7 phase III studies. This pool includes data through completion of study P017/1047 and includes Phase A data and Phase B data up to the LDA (last data analysed) date for the other 6 studies. The Phase B periods were ongoing at the time of the data cut for pooled analyses. The final results from the ongoing Phase B studies should be submitted when data is available.

Table 31: Phase III Clinical Studies Included In the Pooled Analyses

Study	Description	Design	Number of subjects exposed to ERTU/ non-ERTU	PBO Pool	Broad Pool
P001/1016	Moderate renal impairment	Randomized, double-blind, **placebo-controlled**, parallel-group (Phase A: 26 weeks Phase B: 26 weeks)	ERTU (n=313) Non-ERTU (n=154)		X‡
P002/1013	Add-on to MET, ERTU vs GLIM	Randomized, double-blind, **active comparator**, parallel-group (Phase A: 52 weeks Phase B: 52 weeks)	ERTU (n=888) Non-ERTU (n=437)		X‡
P003/1022	Monotherapy	Randomized, double-blind, **placebo-controlled**, parallel-group (Phase A: 26-weeks Phase B: 26 weeks)	ERTU (n=308) Non-ERTU (n=153)	X†	X‡
P005/1019	ERTU + SITA factorial	Randomized double-blind, parallel-group, **factorial** (Phase A: 26-weeks Phase B: 26 weeks)	ERTU (n=985) Non-ERTU (n=247)		X‡
P006/1015	Add-on to MET and SITA	Randomized, double-blind, **placebo-controlled**, parallel- group (Phase A: 26 weeks Phase B: 26 weeks)	ERTU (n=309) Non-ERTU (n=153)	X†	X‡
P007/1017	Add-on to MET	Randomized, double-blind, **placebo-controlled**, parallel-group (Phase A: 26 weeks Phase B: 78 weeks)	ERTU (n=412) Non-ERTU (n=209)	X†	X‡

P017/1047	Initial combination ERTU + SITA	Randomized, double-blind, **placebo-controlled**, parallel-group (Single phase: 26 weeks)	ERTU (n=194) Non-ERTU (n=97)		X[§]
[†] Includes Phase A only, [‡] Includes Phase A and Phase B to last data available date, [§] Includes complete study data					

In addition, two Phase III studies, study P004/1021 (a cardiovascular (CV) outcome trial) and study P012/1045 (a 26-week Phase III Asia Pacific regional study), are still recruiting at the time of this submission. No results from study P004/1021 or meta-analysis have been included in the MAA. Results from the CV outcome study should be provided upon study completion.

Safety of metformin

The safety profile of metformin is well-characterized. As reflected in the United States Prescribing Information (USPI), in a double-blind clinical study of patients with T2DM receiving metformin (up to 2550 mg daily), the adverse reactions reported for ≥5% of subjects on metformin and greater than placebo were diarrhoea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache. Diarrhoea led to discontinuation of study medication in 6% of patients treated with metformin.

The European Union SmPC labels gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite as very common (>10%) and occurring most frequently during initiation of therapy and resolving spontaneously in most cases. Metallic taste was common (3%).

In both the USPI and EU SmPC, there are a number of warnings and precautions associated with metformin use.

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment; when it occurs, it is fatal in approximately 50% of cases. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years).

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. This information is included in the SmPC for 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 characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotaemia. This is included in the SmPC for Metformin.

The use of concomitant medication that may affect renal function, such as cationic drugs that are eliminated by renal tubular secretion, is a precaution with the use of metformin. Metformin is known to be substantially excreted by the kidney. Renal function should be monitored before initiation of metformin therapy and at least annually, as stated in the SmPC of Metformin.

A decrease to subnormal levels of previously normal serum vitamin B12 levels has been seen in patients taking metformin; 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. This is covered in the SmPC of Metformin.

Safety data for ertugliflozin/metformin combination will be presented and discussed in comparison with the safety data of monocomponent ertugliflozin

Ertugliflozin add-on to Metformin Phase III program

No Phase III studies have been performed with the ertugliflozin/metformin fixed-dose combination (FDC) tablet. The Applicant's Summary of Clinical Safety (SCS) for ertugliflozin/metformin summarizes the safety data from four Phase III clinical studies that assessed the safety and efficacy of ertugliflozin when administered in combination with metformin (≥1500 mg/day) to improve glycaemic control in adults with T2DM. This SCS presents the results from analyses of a pooled dataset (Ertugliflozin/Metformin [Ertu/Met] Pool) derived from the 2 placebo-controlled Phase III studies, P006/1015 and P007/1017. In one of the studies, P006/1015, all patients were also co-treated with sitagliptin. Additionally, data from 2 active-comparator studies of ertugliflozin in combination with metformin, that were not included in the Ertu/Met Pool, are summarized individually in the SCS. Study P002/1013 compared treatment with ertugliflozin (5 mg and 15 mg) to the sulphonyl urea glimepiride and Study P005/1019 compared co-administration treatment with ertugliflozin (5 mg and 15 mg) and sitagliptin (100 mg) to ertugliflozin alone (5 mg and 15 mg) and sitagliptin alone (100 mg) on background metformin. It should be kept in mind that the expression "placebo" means that the subjects in this group did not take ertugliflozin, but had a background metformin treatment.

Table 32: Phase III Clinical Studies Supporting the Ertugliflozin/Metformin FDC

Protocol Number (Short Title)	Study Design	Treatments (Sample Size)	Background AHA Therapy	Key Elements of Subject Population
Studies included in the pooled dataset (Ertu/Met pool)				
P006/1015 (Add-on to Met and Sita Study)	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†) Pbo (N=153)	Metformin and Sitagliptin	≥18 years T2DM A1C 7.0%−10.5%, inclusive eGFR ≥60 mL/min/1.73 m^2
P007/1017 (Pbo-controlled Add-on to Met study)	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 T2DM 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 (Ertu/Met pool)				
P002/1013 (Ertu vs Glim as Add-on to Met Study)	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†) Glim (up to 6 or 8 mg)‡ (N=437)	Metformin	≥18 years T2DM A1C 7.0% -9.0%, inclusive eGFR ≥55 mL/min/1.73 m^2
P005/1019 (Ertu+Sita Factorial Study)	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†) Ertu 5 mg (N=250) Ertu 15 mg (N=248) Sita 100 mg (N=247)	Metformin	≥18 years T2DM A1C 7.5% - 11%, inclusive eGFR ≥60 mL/min/1.73 m^2

Patient exposure

In total, 3,409 subjects in the phase III studies (Broad Pool) received at least one dose ertugliflozin (5 mg or 15 mg) of which 2,575 subjects were exposed for at least 50 weeks.

A total of 1,083 subjects were randomized and received at least 1 dose of study medication in the two studies comprising the Ertu/Met Pool; 721 subjects in the ertugliflozin groups and 362 in the placebo groups. 888 and 985 subjects were exposed to ertugliflozin on a background of metformin in Study P002/1013 and Study P005/1019, respectively, giving a total of 2,594 ertugliflozin/metformin exposed subjects. Total exposure is summarized in **Table 33**. The Ertugliflozin add-on to Metformin Phase III program includes approximately 75% of the subjects in the Broad pool. Of note, all subjects, both ertugliflozin and non-ertugliflozin treated, were on metformin.

Table 33: Subjects by Trial and Treatment Group All Subjects as Treated Ertu/Met

	Non-Ertugliflozin	Ertugliflozin 5 mg n (%)	Ertugliflozin 15 mg n (%)	All Ertugliflozin n (%)	Total n (%)
Broad Pool	1,450	1,716	1,693	3,409	4,859
Ertu/Met pool n (% of Broad pool)					
P006/1015	153 (10.6)	156 (9.1)	153 (9.0)	309 (9.1)	462 (9.5)
P007/1017	209 (14.4)	207 (12.1)	205 (12.1)	412 (12.1)	621 (12.8)
Not pooled add-on metformin studies n (% of Broad pool)					
P002/1013	437 (30.1)	448 (26.1)	440 (26.0)	888 (26.0)	1,325 (27.3)
P005/1019	247 (17.0)	493 (28.7)	492 (29.1)	985 (28.9)	1,232 (25.4)

In the Ertugliflozin add-on to Metformin Phase III program, the mean durations of exposure were similar across the treatment groups ranging from 174 to 178 days in the Ertu/Met pool, from 318 to 324 days Study P002/1013 and from 167 to 171 days in Study P005/1019.
Long-term safety data (52 weeks) has been submitted from the phase B of study P005/1019 and P006/1015. Submitted follow-up data demonstrated that the overall (phase A and B), mean durations of exposure (to any dose) in study P005/1019 were ranged from 325 days in the E15/S100 group to 335 days in the E5/S100 group. Similar, in study P006/1015 the mean duration of exposure (to any dose) ranged from 336 to 337days among the three treatment groups.

Adverse events

General overview of AEs

Ertugliflozin Phase III development program

The overall incidence of subjects with one or more adverse events was not notably different across the ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo/comparator groups in the PBO Pool and Broad Pool, respectively. In the PBO Pool, about 50% of the patients reported AEs, and in the Broad Pool about 60% of the patients. Investigator-assessed drug-related AEs were reported more frequently in the 5 and 15 mg ertugliflozin groups (14.3% and 14.7%, respectively) than in the comparator group (9.3%) in the PBO Pool and in the Broad Pool (18.4%, 19.2% and 16.5%, respectively). The frequency of SAEs was low in both PBO and Broad Pool (about 3% and 6%, respectively). The discontinuation rates due to AEs and SAEs, respectively, were similar across the treatment groups in both the PBO Pool and the Broad Pool.

Ertugliflozin add-on to Metformin Phase III program

In the Ertu/Met pool and Study P005/1019, about 50% of the subjects reported an AE, whereas in Study P002/1013, in which Phase A was 52 weeks as opposed to 26 weeks in the other studies, the corresponding number was about 60%.

The incidence of drug-related adverse events in the Ertu/Met pool was numerically higher in the ertugliflozin 5 mg group (11.6%) and higher in ertugliflozin 15 mg (13.1%) relative to the placebo group (7.5%). This was primarily due to a numerically increased incidence of adverse events related to genital mycotic infections, osmotic diuresis and hypoglycaemia in ertugliflozin-treated subjects. This is discussed below under Special Safety Topics. There was an overall low, and not notably different incidence, of serious adverse events (2.8-3.6% in all treatment groups) and adverse events resulting in discontinuation (1.1-2.2%). There were no deaths in the Ertu/Met Pool during Phase A.

In study P002/1013, the incidence of drug-related AEs was similar in the ertugliflozin 5 mg group (18.3%) relative to the glimepiride group (17.8%) but numerically higher in the ertugliflozin 15 mg group (21.6%). The incidence of SAEs was higher in the ertugliflozin 5 mg group (6.3%) and numerically higher in the ertugliflozin 15 mg group (3.9%), relative to the glimepiride group (2.7%).

In study P005/1019, the incidence of drug-related AEs was higher in the E5/S100 (11.1%) and E15/S100 (16.0%) groups than in the S100 group (4.9%), but was not notably different from those in the E5 (16.8%) and E15 (12.1%) groups. Serious adverse events also occurred at a low incidence across groups (<4%) and small numeric differences in the incidence of serious adverse events were not due to an increased incidence of any particular serious adverse event term. No deaths were reported during Phase A.

Most frequently reported adverse events

Ertugliflozin Phase III development program

In the PBO Pool, the most frequently reported events for ertugliflozin were *upper respiratory infection* (higher frequency in the placebo group), *hypoglycaemia* (similar frequencies for all groups), *headache* (higher frequencies in the ertugliflozin groups), *vulvovaginal mycotic infection* (higher frequencies in the ertugliflozin groups) and *urinary tract infections* (higher frequency in the placebo group).

Of note is the higher incidence of adverse events for ertugliflozin in the SOC Renal and urinary disorders and SOC Reproductive system disorders. Events of renal failure/ renal impairment and osmotic diuresis-related events and genital infections are further discussed below.

Ertugliflozin add-on to Metformin Phase III program

In the Ertu/Met pool, adverse events (AE) in the Infection and infestations SOC were the most frequently reported in all groups (E5 17.1%, E15 20.1%, placebo 21.0%). The incidence of AE by SOC in the Ertu/Met pool was higher in ertugliflozin-treated subjects relative to subjects in the placebo group in two SOC categories: the *Renal and urinary disorders SOC* and *Reproductive system and breast disorders SOC*. Within the *Renal and urinary disorders SOC*, the most frequently reported adverse events in the ertugliflozin 5 mg and 15 mg groups were pollakiuria, polyuria and dysuria. Within the *Reproductive and breast disorders* SOC, the most frequently reported adverse events in the ertugliflozin 5 mg and 15 mg groups were balanoposthitis and vulvovaginal pruritus. Among AEs occurring in ≥ 2% of subjects in any group, the only event that occurred at a higher incidence in either of the ertugliflozin dose groups or the all ertugliflozin group relative to the placebo group was the vulvovaginal mycotic infection (E5 1.9%, E15 2.2%, placebo 0.3%). **(Table 34)**

Among adverse events that occurred in ≤2% of subjects in all groups, those that occurred at a higher incidence in either of the ertugliflozin dose groups or in the all ertugliflozin group relative to the placebo group included several terms related to Special Safety Topics (balanoposthitis, dysuria, polyuria, and dry mouth) and 1 term unrelated to any Special Safety Topic (dyspepsia).

Table 34: Subjects With Adverse Events (Incidence ≥ 2% in One or More Treatment Groups) All Subjects as Treated Ertu/Met 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

The incidences of AEs by SOC in study P002/1013 were generally similar in the ertugliflozin 5 mg and 15 mg groups relative to the glimepiride group, except in the *Metabolism and nutrition disorders, Renal and urinary disorders*, and *Reproductive system and breast disorders SOC*s. **(Table 35)**

Table 35: Subjects With Adverse Events (Incidence ≥ 1% in One or More Treatment Groups) All Subjects as Treated Phase A: Excluding Rescue Approach (study P002/1013)

	E5		E15		Glim	
	n	(%)	n	(%)	n	(%)
Subjects in population	448		440		437	
with one or more adverse events	263	(58.7)	262	(59.5)	269	(61.6)
with no adverse events	185	(41.3)	178	(40.5)	168	(38.4)
Blood and lymphatic system disorders	**5**	**(1.1)**	**7**	**(1.6)**	**5**	**(1.1)**
Anaemia	2	(0.4)	5	(1.1)	3	(0.7)
Cardiac disorders	**10**	**(2.2)**	**6**	**(1.4)**	**12**	**(2.7)**
Ear and labyrinth disorders	**8**	**(1.8)**	**8**	**(1.8)**	**3**	**(0.7)**
Eye disorders	**9**	**(2.0)**	**7**	**(1.6)**	**7**	**(1.6)**
Gastrointestinal disorders	**60**	**(13.4)**	**53**	**(12.0)**	**48**	**(11.0)**
Constipation	7	(1.6)	10	(2.3)	7	(1.6)
Diarrhoea	11	(2.5)	10	(2.3)	17	(3.9)
Dyspepsia	8	(1.8)	3	(0.7)	4	(0.9)
Gastritis	4	(0.9)	5	(1.1)	2	(0.5)
Gastro-Oesophageal Reflux	2	(0.4)	1	(0.2)	5	(1.1)
Nausea	8	(1.8)	13	(3.0)	5	(1.1)
Toothache	5	(1.1)	0	(0.0)	3	(0.7)
General disorders and administration site conditions	**13**	**(2.9)**	**14**	**(3.2)**	**14**	**(3.2)**
Asthenia	1	(0.2)	1	(0.2)	5	(1.1)
Fatigue	7	(1.6)	3	(0.7)	2	(0.5)
Hepatobiliary disorders	**8**	**(1.8)**	**5**	**(1.1)**	**3**	**(0.7)**
Hepatic steatosis	5	(1.1)	1	(0.2)	1	(0.2)
Infections and infestations	**142**	**(31.7)**	**119**	**(27.0)**	**129**	**(29.5)**
Bronchitis	8	(1.8)	10	(2.3)	10	(2.3)
Gastroenteritis	7	(1.6)	1	(0.2)	5	(1.1)
Influenza	14	(3.1)	12	(2.7)	16	(3.7)
Nasopharyngitis	23	(5.1)	15	(3.4)	27	(6.2)
Pharyngitis	7	(1.6)	10	(2.3)	3	(0.7)
Respiratory tract infection viral	7	(1.6)	8	(1.8)	7	(1.6)
Sinusitis	3	(0.7)	5	(1.1)	4	(0.9)
Upper respiratory tract infection	20	(4.5)	11	(2.5)	15	(3.4)
Urinary tract infection	23	(5.1)	20	(4.5)	24	(5.5)
Vaginal infection	4	(0.9)	5	(1.1)	0	(0.0)

	E5		E15		Glim	
	n	(%)	n	(%)	n	(%)
Viral infection	6	(1.3)	4	(0.9)	9	(2.1)
Vulvovaginal candidiasis	6	(1.3)	8	(1.8)	3	(0.5)
Injury, poisoning and procedural complications	**14**	**(3.1)**	**16**	**(3.6)**	**13**	**(3.0)**
Investigations	**21**	**(4.7)**	**37**	**(8.4)**	**27**	**(6.2)**
Alanine aminotransferase increased	5	(1.1)	5	(1.1)	0	(0.0)
Blood pressure increased	0	(0.0)	2	(0.5)	7	(1.6)
Glomerular filtration rate decreased	0	(0.0)	6	(1.4)	2	(0.5)
Weight decreased	1	(0.2)	9	(2.0)	3	(0.7)
Metabolism and nutrition disorders	**41**	**(9.2)**	**56**	**(12.7)**	**116**	**(26.5)**
Dyslipidaemia	3	(0.7)	6	(1.4)	3	(0.7)
Hyperglycaemia	13	(2.9)	13	(3.0)	13	(3.0)
Hyperuricaemia	2	(0.4)	0	(0.0)	8	(1.8)
Hypoglycaemia	17	(3.8)	25	(5.7)	96	(22.0)
Musculoskeletal and connective tissue disorders	**44**	**(9.8)**	**43**	**(9.8)**	**38**	**(8.7)**
Arthralgia	5	(1.1)	10	(2.3)	7	(1.6)
Back pain	13	(2.9)	11	(2.5)	10	(2.3)
Osteoarthritis	5	(1.1)	3	(0.7)	1	(0.2)
Pain in extremity	5	(1.1)	4	(0.9)	3	(0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**7**	**(1.6)**	**7**	**(1.6)**	**4**	(0.9)
Nervous system disorders	**35**	**(7.8)**	**30**	**(6.8)**	**44**	**(10.1)**
Dizziness	7	(1.6)	5	(1.1)	9	(2.1)
Headache	16	(3.6)	14	(3.2)	13	(3.0)
Psychiatric disorders	**13**	**(2.9)**	**9**	**(2.0)**	**9**	**(2.1)**
Insomnia	5	1.1	4	(0.9)	2	(0.5)
Renal and urinary disorders	**24**	**(5.4)**	**33**	**(7.5)**	**15**	**(3.4)**
Dysuria	5	(1.1)	9	(2.0)	4	(0.9)
Nocturia	5	(1.1)	3	(0.7)	0	(0.0)
Pollakiuria	5	(1.1)	9	(2.0)	3	(0.7)
Polyuria	3	(0.7)	5	(1.1)	1	(0.2)
Reproductive system and breast disorders	**24**	**(5.4)**	**22**	**(5.0)**	**8**	**(1.8)**
Balanoposthitis	7	(1.6)	3	(0.7)	0	(0.0)
Pruritus genital	1	(0.2)	5	(1.1)	0	(0.0)
Vulvovaginal pruritus	4	(0.9)	5	(1.1)	2	(0.5)
Respiratory, thoracic and mediastinal disorders	**15**	**(3.3)**	**22**	**(5.0)**	**21**	**(4.8)**
Cough	4	(0.9)	11	(2.5)	7	(1.6)
Skin and subcutaneous tissue disorders	**18**	**(4.0)**	**21**	**(4.8)**	**15**	**(3.4)**
Vascular disorders	**18**	**(4.0)**	**12**	**(2.7)**	**11**	**(2.5)**
Hypertension	8	(1.8)	6	(1.4)	7	(1.6)

In study P005/1019, only comparisons between the ertugliflozin/sitagliptin/metformin groups, and ertugliflozin and sitagliptin respectively in combination with metformin were performed. No comparisons are provided between the ertugliflozin/metformin and sitagliptin/metformin groups. The overall most common adverse reactions in the ertugliflozin/sitagliptin combination groups were *hypoglycaemia*, *urinary tract infections*, *nasopharyngitis* and *bronchitis*. **(Table 36)**

Table 36: Study 005/1019 Subjects with Adverse Events (incidence ≥ 1% in one or more treatment groups

	E5		E15		S100		E5/S100		E15/S100	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	250		248		247		243		244	
with one or more adverse events	130	(52.0)	108	(43.5)	104	(42.1)	111	(45.7)	114	(46.7)
with no adverse events	120	(48.0)	140	(56.5)	143	(57.9)	132	(54.3)	130	(53.3)
Blood and lymphatic system disorders	**2**	**(0.8)**	**1**	**(0.4)**	**1**	**(0.4)**	**3**	**(1.2)**	**2**	**(0.8)**
Cardiac disorders	**8**	**(3.2)**	**3**	**(1.2)**	**3**	**(1.2)**	**2**	**(0.8)**	**2**	**(0.8)**
Ear and labyrinth disorders	**3**	**(1.2)**	**1**	**(0.4)**	**1**	**(0.4)**	**2**	**(0.8)**	**2**	**(0.8)**
Eye disorders	**2**	**(0.8)**	**0**	**(0.0)**	**2**	**(0.8)**	**3**	**(1.2)**	**2**	**(0.8)**
Gastrointestinal disorders	**29**	**(11.6)**	**16**	**(6.5)**	**12**	**(4.9)**	**23**	**(9.5)**	**18**	**(7.4)**
Abdominal pain upper	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	3	(1.2)
Constipation	6	(2.4)	6	(2.4)	1	(0.4)	4	(1.6)	1	(0.4)
Diarrhoea	9	(3.6)	4	(1.6)	2	(0.8)	2	(0.8)	2	(0.8)
Dry mouth	1	(0.4)	3	(1.2)	0	(0.0)	1	(0.4)	2	(0.8)
Dyspepsia	0	(0.0)	1	(0.4)	0	(0.0)	2	(0.8)	3	(1.2)
Gastritis	2	(0.8)	1	(0.4)	2	(0.8)	4	(1.6)	1	(0.4)
Nausea	3	(1.2)	2	(0.8)	5	(2.0)	5	(2.1)	0	(0.0)
Toothache	1	(0.4)	0	(0.0)	0	(0.0)	3	(1.2)	1	(0.4)
General disorders and administration site conditions	**3**	**(1.2)**	**5**	**(2.0)**	**5**	**(2.0)**	**3**	**(1.2)**	**9**	**(3.7)**
Asthenia	1	(0.4)	1	(0.4)	2	(0.8)	0	(0.0)	3	(1.2)
Hepatobiliary disorders	**3**	**(1.2)**	**1**	**(0.4)**	**1**	**(0.4)**	**0**	**(0.0)**	**1**	**(0.4)**
Infections and infestations	**51**	**(20.4)**	**54**	**(21.8)**	**45**	**(18.2)**	**50**	**(20.6)**	**43**	**(17.6)**
Bronchitis	2	(0.8)	5	(2.0)	2	(0.8)	6	(2.5)	4	(1.6)
Gastroenteritis	0	(0.0)	2	(0.8)	3	(1.2)	4	(1.6)	3	(1.2)
Influenza	4	(1.6)	4	(1.6)	5	(2.0)	3	(1.2)	3	(1.2)

	E5		E15		S100		E5/S100		E15/S100	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Nasopharyngitis	2	(0.8)	6	(2.4)	3	(1.2)	6	(2.5)	5	(2.0)
Pharyngitis	1	(0.4)	1	(0.4)	3	(1.2)	0	(0.0)	1	(0.4)
Respiratory tract infection	3	(1.2)	0	(0.0)	3	(1.2)	1	(0.4)	0	(0.0)
Respiratory tract infection viral	3	(1.2)	0	(0.0)	1	(0.4)	2	(0.8)	2	(0.8)
Sinusitis	1	(0.4)	0	(0.0)	1	(0.4)	4	(1.6)	1	(0.4)
Upper respiratory tract infection	5	(2.0)	4	(1.6)	9	(3.6)	5	(2.1)	2	(0.8)
Urinary tract infection	13	(5.2)	11	(4.4)	8	(3.2)	7	(2.9)	7	(2.9)
Viral infection	3	(1.2)	1	(0.4)	1	(0.4)	1	(0.4)	1	(0.4)
Vulvovaginal mycotic infection	2	(0.8)	5	(2.0)	0	(0.0)	4	(1.6)	3	(1.2)
Injury, poisoning and procedural complications	**10**	**(4.0)**	**6**	**(2.4)**	**7**	**(2.8)**	**7**	**(2.9)**	**4**	**(1.6)**
Investigations	**14**	**(5.6)**	**18**	**(7.3)**	**12**	**(4.9)**	**11**	**(4.5)**	**11**	**(4.5)**
Alanine aminotransferase increased	3	(1.2)	3	(1.2)	2	(0.8)	0	(0.0)	0	(0.0)
Aspartate aminotransferase increased	3	(1.2)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Blood creatinine increased	0	(0.0)	3	(1.2)	0	(0.0)	1	(0.4)	1	(0.4)
Blood glucose increased	3	(1.2)	2	(0.8)	4	(1.6)	1	(0.4)	2	(0.8)
Glomerular filtration rate decreased	3	(1.2)	4	(1.6)	1	(0.4)	4	(1.6)	2	(0.8)
Investigations	**14**	**(5.6)**	**18**	**(7.3)**	**12**	**(4.9)**	**11**	**(4.5)**	**11**	**(4.5)**
Weight decreased	3	(1.2)	3	(1.2)	1	(0.4)	0	(0.0)	3	(1.2)
Metabolism and nutrition disorders	**19**	**(7.6)**	**23**	**(9.3)**	**18**	**(7.3)**	**21**	**(8.6)**	**22**	**(9.0)**
Dyslipidaemia	1	(0.4)	2	(0.8)	1	(0.4)	3	(1.2)	1	(0.4)
Hypercholesterolaemia	1	(0.4)	3	(1.2)	0	(0.0)	0	(0.0)	2	(0.8)
Hyperglycaemia	4	(1.6)	3	(1.2)	3	(1.2)	4	(1.6)	0	(0.0)
Hyperuricaemia	0	(0.0)	1	(0.4)	3	(1.2)	4	(1.6)	0	(0.0)
Hypoglycaemia	8	(3.2)	9	(3.6)	6	(2.4)	8	(3.3)	17	(7.0)
Musculoskeletal and connective tissue disorders	**21**	**(8.4)**	**8**	**(3.2)**	**17**	**(6.9)**	**20**	**(8.2)**	**7**	**(2.9)**
Arthralgia	1	(0.4)	1	(0.4)	4	(1.6)	4	(1.6)	1	(0.4)
Back pain	5	(2.0)	0	(0.0)	6	(2.4)	5	(2.1)	2	(0.8)
Muscle spasms	4	(1.6)	0	(0.0)	2	(0.8)	2	(0.8)	1	(0.4)
Musculoskeletal pain	0	(0.0)	0	(0.0)	0	(0.0)	3	(1.2)	0	(0.0)
Pain in extremity	2	(0.8)	2	(0.8)	3	(1.2)	4	(1.6)	0	(0.0)
Nervous system disorders	**10**	**(4.0)**	**12**	**(4.8)**	**13**	**(5.3)**	**11**	**(4.5)**	**11**	**(4.5)**

	E5		E15		S100		E5/S100		E15/S100	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Dizziness	3	(1.2)	5	(2.0)	0	(0.0)	2	(0.8)	1	(0.4)
Headache	1	(0.4)	6	(2.4)	9	(3.6)	4	(1.6)	5	(2.0)
Hypoaesthesia	3	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)
Psychiatric disorders	**3**	**(1.2)**	**1**	**(0.4)**	**4**	**(1.6)**	**6**	**(2.5)**	**4**	**(1.6)**
Renal and urinary disorders	**9**	**(3.6)**	**6**	**(2.4)**	**6**	**(2.4)**	**13**	**(5.3)**	**12**	**(4.9)**
Pollakiuria	2	(0.8)	0	(0.0)	1	(0.4)	3	(1.2)	3	(1.2)
Reproductive system and breast disorders	**8**	**(3.2)**	**6**	**(2.4)**	**1**	**(0.4)**	**4**	**(1.6)**	**5**	**(2.0)**
Balanoposthitis	5	(2.0)	2	(0.8)	0	(0.0)	3	(1.2)	2	(0.8)
Pruritus genital	2	(0.8)	3	(1.2)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**2**	**(0.8)**	**11**	**(4.4)**	**7**	**(2.8)**	**8**	**(3.3)**	**7**	**(2.9)**
Cough	1	(0.4)	4	(1.6)	3	(1.2)	1	(0.4)	3	(1.2)
Skin and subcutaneous tissue disorders	**8**	**(3.2)**	**2**	**(0.8)**	**4**	**(1.6)**	**4**	**(1.6)**	**12**	**(4.9)**
Rash	2	(0.8)	0	(0.0)	3	(1.2)	0	(0.0)	2	(0.8)
Vascular disorders	**8**	**(3.2)**	**3**	**(1.2)**	**3**	**(1.2)**	**5**	**(2.1)**	**8**	**(3.3)**
Hypertension	4	(1.6)	2	(0.8)	2	(0.8)	3	(1.2)	4	(1.6)

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 18.1

The AEs osmotic diuresis/volume depletion, renal-related events, genital mycotic infections and hypoglycaemia are discussed further under Special Safety Topics below.

In general, long-term safety data from phase A+ B (52 weeks) of study P005/1019 and P006/1015, demonstrated the same pattern regarding most frequently reported SOCs (*Infections and infestations, Metabolism nutrition disorders and Gastro-intestinal disorders)* as the 26 weeks data. However, the Applicant has been asked to provide pooled 2 years safety data from study P007/1017 and P002/1013 that further will evaluate long-term safety for ertugliflozin.

Special Safety Topics

Osmotic diuresis/volume depletion

Ertugliflozin Phase III development program

The incidence of osmotic diuresis-related adverse events was increased in ertugliflozin 5 mg (4.6%) and 15 mg (3.3%) groups relative to placebo (1.6%). The most commonly reported symptoms were pollakiuria, polyuria, thirst and dry mouth. Most events were mild or moderate in severity and only one event led to discontinuation. No serious case was reported.

In the placebo-controlled Pool, the incidence of volume depletion events was low (<2%) and not notably different across the ertugliflozin and placebo groups. In the subgroup analyses in the Broad Pool, patients with eGFR <60 mL/min/1.73 m^2, patients ≥65 years of age and patients on diuretics had a higher incidence of volume depletion in the ertugliflozin groups relative the comparator group.

In patients with eGFR <60 mL/min/1.73 m^2, the incidence of volume depletion events was 5.1%, 2.6% and 0.5% for ertugliflozin 5 mg, ertugliflozin 15 mg and the comparator group. For patients with eGFR 45 to <60 mL/min/1.73 m^2, the incidence was 6.4%, 3.7% and 0% respectively.
In patients ≥65 years of age, the incidence of volume depletion was 2.2%, 2.6% and 1.1% for ertugliflozin 5 mg, ertugliflozin 15 mg and the comparator group. For patients using diuretics, the incidence was 3.3%, 2.3% and 1.3% for ertugliflozin 5 mg, ertugliflozin 15 mg and the comparator group, respectively. The incidence was even more increased in patients using loop-diuretics; however, the total number of subjects on a loop diuretic was too small (n=197) to draw any firm conclusions.

Ertugliflozin add-on to Metformin Phase III program

The was a trend towards an increased incidence of *osmotic diuresis*-related adverse events in the ertugliflozin 5 mg and 15 mg groups (2.2% and 2.0%, respectively) relative to the placebo group (0.6%) in the Ertu/Met pool. However, the only statistically significant difference was an increased incidence of polyuria in the ertugliflozin 15 mg (1.1%) group compared to placebo and ertugliflozin 5 mg (both 0.0%). 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%). The incidence of *volume depletion* events was similar across the ertugliflozin 5 mg and 15 mg groups (both 0.6%) and the placebo group (0.9%).

In study P002/1013, the incidence of *osmotic diuresis*-related adverse events of *nocturia, pollakiuria,* and *polyuria* occurred more frequently in one or both ertugliflozin groups relative to the glimepiride group, and for all except *nocturia* the incidence was numerically higher in the ertugliflozin 15 mg group compared with the 5 mg group **(Table 35)**. Two subjects discontinued the study drug due to *pollakiuria*. The incidence of *hypovolaemia* AEs was numerically higher in the ertugliflozin 5 mg group (1.3%) than in the ertugliflozin 15 mg and glimepiride groups (0.7% in both). All hypovolaemia AEs were non-serious, and were mild or moderate in intensity, except one event in the ertugliflozin 5 mg group, which was severe (syncope).

In study P005/1019, the incidence of adverse events related to *osmotic diuresis* was low across groups (≤2.1%), without any notable pattern of occurrence in the co-administration groups relative to the ertugliflozin alone and sitagliptin alone groups **(Table 36)**. The incidence of *dry mouth* was numerically higher in the ertugliflozin treated subjects than in the sitagliptin group. All events were non-serious and mild or moderate in intensity. There were no adverse events related to hypovolemia (referred to as volume depletion in the ertugliflozin registration dossier) in the E5/S100 or E15/S100 groups, or in the S100 group. Four subjects (1.6%) in the ertugliflozin 5 mg group and 2 subjects (0.8%) in the ertugliflozin 15 mg group had adverse events related to *hypovolaemia*. All the events but one (syncope) was reported as non-serious and mild or moderate in intensity.

Genital infections

Ertugliflozin Phase III development program

The incidence of genital infections in female subjects was highly increased in the ertugliflozin 5 mg and 15 mg group (9.1% and 12.2%, respectively) as compared to placebo (3.0%) with a notable dose-dependent relation. *Vulvovaginal candidiasis* and *vulvovaginal mycotic infection* were the most commonly reported events. Most of the events were mild or moderate and no serious case was

reported. Recurrent events were reported in 26% (14/53) of the female patients experiencing a genital infection.
The incidence of genital infections was highly increased also in males. However, the absolute numbers lower than in females; ertugliflozin 5 mg (3.7%), ertugliflozin 15 mg (4.2%) and placebo (0.4%) and no dose-response relation. *Balanoposthitis* was the most commonly reported event. All events were mild or moderate in intensity and no event was serious.
Two (10%) of the male patients experienced a recurrent event of genital infection. In ertugliflozin-treated subjects, events of genital mycotic infections were more frequent in men who were not circumcised at baseline (5.2%) relative to those who were circumcised (1.9%).

An expanded CMQ search, including additional less specific terms for genital mycotic infection, was performed in both the PBO and Broad Pool. Using the expanded CMQ in the PBO Pool, 2 events were serious (cellulitis of the male genital organ in the ertugliflozin 5 mg group and phimosis in the ertugliflozin 15 mg group). In the Broad Pool, the most commonly reported event in the extended search was phimosis, reported in 8 (0.5%) subjects in the all ertugliflozin group and in one subject (0.1%) in the comparator group. Among the 8 phimosis events in ertugliflozin-treated subjects, 2 were serious and in 4 cases were the subjects treated with circumcision. One more serious case (balanoposthitis) was reported in the Broad Pool.

Ertugliflozin add-on to Metformin Phase III program

In all Ertugliflozin add-on to Metformin Phase III program, there was a significantly greater incidence of genital mycotic infections in male and female ertugliflozin-treated subjects. In males, the incidence ranged from 2.1-4.7% in ertugliflozin treated subjects relative to 0% in the non-ertugliflozin group. In females, the incidence ranged from 4.9-10.0% in ertugliflozin treated subjects relative to 1.1-1.4% in the non-ertugliflozin group.

Among males, but not females, complicated infections were more common in the ertugliflozin 15 mg group (1.1/0% in males/females) than in the ertugliflozin 5 mg (0.2/0.3% in males/ females) and the non-ertugliflozin groups (0/0.2% in males/ females) in the Ertugliflozin add-on to Metformin program.

Urinary tract infections

Ertugliflozin Phase III development program

The incidence of UTI was not notably different in the ertugliflozin 5 mg and 15 mg groups (4.0% and 4.1%) and placebo group (3.9%). Most of the events were mild or moderate and no serious case was reported.

In the Broad Pool, the incidence of UTI in the comparator group (7.9%) was slightly higher compared to the ertugliflozin 5 mg (6.9%) and 15 mg (7.0%) groups. The incidence of serious events was low in all groups (≤0.4%).

Ertugliflozin add-on to Metformin Phase III program

In the Ertu/Met pool, the incidence of urinary tract infections was significantly higher in the ertugliflozin 15 mg group (4.2%) and numerically higher in the ertugliflozin 5 mg group (2.8%) compared to the placebo group (1.7%), as opposed to the Ertugliflozin Phase III development program**.** This is considered as random variability.
Also in study P005/1019, there was a numerically higher incidence of UTI in the E5 and E15 groups (6.0% and 5.6%, respectively) relative to the E5/S100 and E15/S100 groups (3.3% and 3.7%, respectively) and the S100 group (3.2%). The incidence of UTI in study P002/1013 was similar across

the ertugliflozin 5 mg and 15 mg treatment groups (6.7% and 6.4%, respectively) and the glimepiride group (6.9%).

Hypoglycaemia

Ertugliflozin Phase III development program

In the placebo-controlled Pool, the incidence of hypoglycaemia was relatively low, although increased for ertugliflozin 5 mg and 15 mg (5.0% and 4.5%) compared to placebo (2.9%). When ertugliflozin was used as monotherapy, there was a small, not dose-dependent, increase in hypoglycaemic events in the ertugliflozin groups (2.6% in both groups) as compared to placebo (0.7%). The increased risk of hypoglycaemia compared to placebo should be reflected in the SmPC.

In study P001/1016 in patients with moderate renal impairment, there was a higher incidence of hypoglycaemia relative to the other phase III studies. This was expected given the high rate (90%) of insulin and/or insulin secretagogues as background therapy in this study. The incidence of documented hypoglycaemia AEs was higher for E5 group (34.2%) compared to E15 group (25.2%) in study P001/1016. Furthermore, the incidence of documented hypoglycaemia was higher for E5 group (compared to E15) in CKD-3A stratum (eGFR ≥45 to <60 mL/min/1.73m^2) in subjects taking background medication of insulin and/ or insulin secretagogue.

Ertugliflozin add-on to Metformin Phase III program

An increased risk of hypoglycaemic events was noted for ertugliflozin 5 mg (7.2%) and ertugliflozin 15 mg (7.8%) relative to placebo (4.3%) when ertugliflozin was used as add-on to metformin (study P007/1017). About half of the events across the groups were events of symptomatic hypoglycaemia.

When used as add-on to metformin and sitagliptin (P006/1015), the incidence of hypoglycaemic events was higher in the ertugliflozin 5 mg group (4.5%) but lower in the ertugliflozin 15 mg (2.0%) compared to placebo (3.3%). In the factorial study (P005/1019) where ertugliflozin and sitagliptin were co-initiated, the incidence of hypoglycaemia was higher in both ertugliflozin groups (5.6% and 5.2% for 5 mg and 15 mg, respectively) and the ertugliflozin + sitagliptin groups (5.3% and 9.0% for E5/S100 and E15/S100, respectively) relative to the sitagliptin group (3.6%).

When ertugliflozin was used add-on to metformin and compared to the sulphonyl urea product glimepiride (Study P002/1013), the incidence of hypoglycaemia was markedly lower in the ertugliflozin groups (6-8%) relative to the glimepiride group (27%).

Changes in renal function

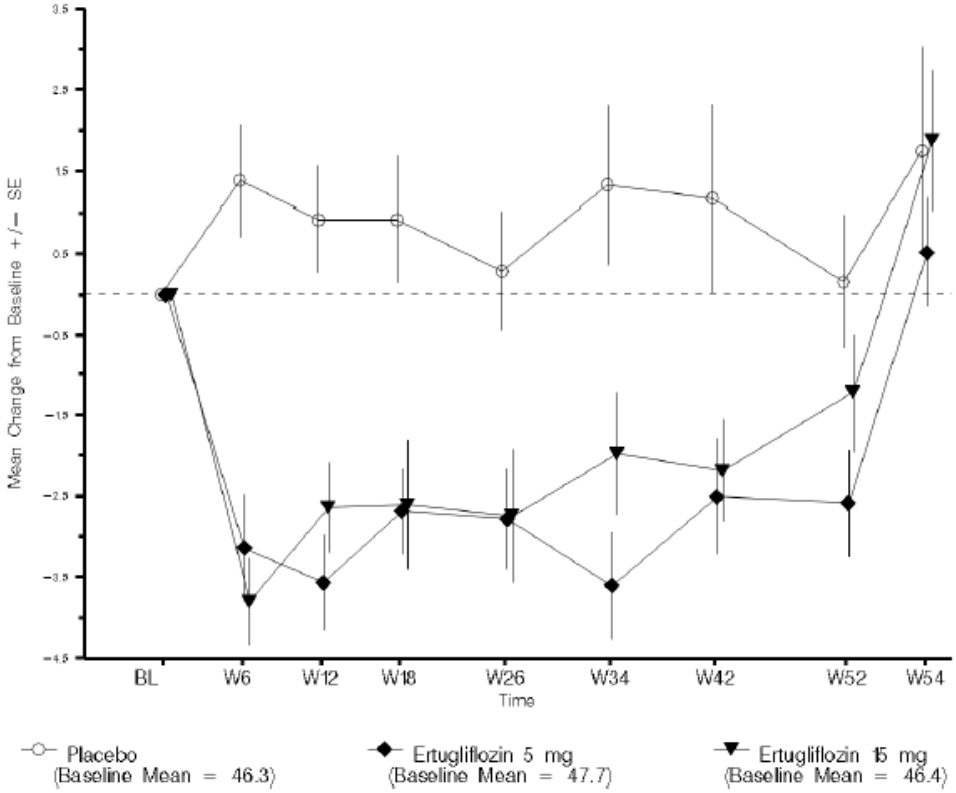
Ertugliflozin Phase III development program

In the placebo-controlled pool, treatment with ertugliflozin was associated with small decreases in eGFR that returned to or towards baseline at week 26. Also in a longer-term study (P002/1013), eGFR in both ertugliflozin dose groups was above baseline between week 26 and 52. Mean changes from baseline in BUN was higher in the ertugliflozin groups relative to the placebo group at week 26. However, this is not considered to reflect impairment in renal function. The same phenomenon has been seen with other medicinal products in the class, but the explanation has so far been elusive.

The incidence of renal-related events (renal impairment/renal failure) was low and similar across the ertugliflozin groups and placebo. In the PBO Pool, there were two cases of non-serious renal failure in the ertugliflozin group and no case of renal failure in the placebo group. In the Broad Pool, there was a slight imbalance between ertugliflozin and comparator in renal-related events (0.6% in ertugliflozin 5 mg, 0.8% in ertugliflozin 15 mg and 0.4% in the comparator group).

In ertugliflozin treated subjects with moderate renal impairment, the decrease in eGFR was slightly larger than in the PBO Pool (about 1 mL/min/1.73 m^2 more) and did not return to baseline at week 26; however, reversed after treatment discontinuation **(Figure 9)**. In Study P001/1016, the incidence of renal-related events was higher for ertugliflozin (2.5% and 1.3% for 5 mg and 15 mg ertugliflozin, respectively) relative to placebo (0.6%).

Figure 9: eGFR (mL/min/1.73m^2): Mean Change from Baseline Over Time (Mean ± SE) All Subjects as Treated study P001/1016: Including Rescue Approach



Ertugliflozin add-on to Metformin Phase III program

As in the ertugliflozin phase III development program, a small decrease in eGFR that returned to or towards baseline at week 26 was seen in the Ertugliflozin add-on to Metformin Phase III program. A small additive effect of sitagliptin was seen when combined with ertugliflozin on renal function was noted in study P005/1019. Results from phase B (week 52) of study P005/1019 demonstrated generally similar eGFR results to those observed at Week 26, except for the E15/S100 group which demonstrated a further decrease in eGFR at week 52 compared to week 26. However, an analysis was performed in subjects who had eGFR measurements at baseline, on-treatment, and at least 7 days after the last dose of study medication. Even if the number of patients in each group are few (below 20), these data demonstrates a reversibility in eGFR values post treatment in both E5/S100 and E15/S100 groups.

In the Ertu/Met pool, the proportion of subjects who had any occurrence of a decrease in eGFR of >30% from baseline was not notably different in the ertugliflozin 5 mg and 15 mg groups (3.1% and 3.7%, respectively) relative to the placebo group (3.4%).

The incidence of renal-related events not including adverse events related to decreased eGFR or increased creatinine 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. Adverse events related to decreased eGFR and increased creatinine were infrequent, each being reported in ≤1 subject per group.

In study P002/1013, the incidences of renal-related AEs were not meaningfully different across the 3 groups. However, renal-related SAEs and renal-related AEs leading to study medication discontinuation were only observed in the ertugliflozin 15 mg group. The proportions of subjects who had at least 1 decrease in eGFR >30% from baseline were similar across the 3 treatment groups (3.7%, 4.7%, and 4.9% in the ertugliflozin 5 mg, ertugliflozin 15 mg, and glimepiride groups, respectively). The number of subjects with one or more AEs of eGFR decreased or blood creatinine increased was 3 (0.7%), 7 (1.6%), and 2 (0.5%) in the ertugliflozin 5 mg, ertugliflozin 15 mg, and glimepiride groups, respectively. The eGFR/serum creatinine values for 3 subjects, all in the ertugliflozin 15 mg group, did not return to baseline levels as of the last available measurement or after discontinuing study medication. Adverse events suggestive of acute or chronic renal dysfunction, including *acute kidney injury, chronic kidney disease, renal impairment, nephropathy,* or *diabetic nephropathy* were reported for 1 (0.2%), 4 (0.9%), and 3 (0.7%) subjects in the ertugliflozin 5 mg, ertugliflozin 15 mg, and glimepiride groups, respectively.
The proportion of subjects with at least 1 decrease in eGFR >30% from baseline in study P005/1019 was 5.9% in the E5/S100 group, 3.8% in the E15/S100, 2.8% in the E5 group, 4.1% in the E15 group and 2.9% in the subjects in the S100 group. An adverse event of *eGFR decreased* or blood creatinine increased was reported for: 5 (2.1%) and 4 (1.6%) subjects in the E5/S100 and E15/S100 groups, respectively; 4 (1.6%) and 7 (2.8%) subjects in the E5 and E15 groups, respectively; and 4 subjects (1.6%) in the S100 group during phase A + B. None of these events was severe or serious.
An adverse event of *acute kidney injury, chronic kidney disease, renal impairment,* or *nephropathy* was reported for 1.6% and 1.2% of the subjects in the E5/S100 and E15/S100 groups, respectively vs 0.8% in both the E5 and E15 group. One subject in the S100 group reported a renal-related event. All of these AEs were considered to be mild in intensity by the investigator except for one SAE of acute kidney injury (in S100 group) and a non-serious AE of acute kidney injury (E5 group) during the phase A+ phase B. In total, in study P005/1019 (phase A and B), eight renal related AEs led to discontinuation (three in group E15/S100, two in E5, one in E15 and two in S100 group).

The Applicant has provided data showing that the renal function did not deteriorate further over time in the subset of subjects with baseline eGFR <60 mL/min/1.73 m^2 in the four studies with ertugliflozin in combination with metformin.

In the Ertu/met pool, no subjects with eGFR <60 mL/min/1.73 m^2 reported any volume depletion- or renal-related adverse events. In both Studies P002/1013 and P005/1019, volume depletion- and/or renal-related adverse events were reported in subjects with eGFR <60 mL/min/1.73 m^2. However, there were too few renal-related or volume depletion adverse events in this category (0-1 subjects per group) to be able to draw any meaningful conclusions.

Hepatic events

Ertugliflozin Phase III development program

In the placebo-controlled Pool, there were decreases in ALT and AST in the both ertugliflozin groups relative placebo, persistent to week 26.

In the Broad Pool, the percentages of subjects with increases in ALT or AST that met a PDLC ≥3XULN were similar (0.8-1.3% across all groups for ALT; 0.3-0.6% across the groups for AST). The proportion of subjects with increases in ALT or AST that met a PDLC >5X ULN was low (0.1-0.2% across all groups). No ertugliflozin-treated subject met the definition for Hy's law case.

Of the 6 ertugliflozin-treated subjects with an event adjudicated as possibly related to study medication, 2 subjects were using paracetamol, 1 subject was hepatitis C positive and 2 subjects' events resolved on treatment; the last case resolved following interruption of study medication. No cases were adjudicated as very likely or probable.

Ertugliflozin add-on to Metformin Phase III program

Like in the Ertugliflozin Phase III development program, there were decreases in ALT and AST in the both ertugliflozin groups relative placebo persistent to week 26. There were no significant differences in the proportion of subjects meeting PDLC criteria between treatment groups in the studies.

Out of the total of 11 subjects in the Broad Pool meeting the criteria for hepatic adjudication, 6 of were in the Ertugliflozin add-on to Metformin Phase III program (2 in the non-ertugliflozin group, 1 in the ertugliflozin 5 mg group and 3 in the ertugliflozin 15 mg group). One of the events was adjudicated "doubtful", the others "possible".

Hypersensitivity reactions

Ertugliflozin Phase III development program
In the Broad Pool, ertugliflozin treatment did not result in a higher incidence of hypersensitivity reactions relative to the comparator group. The incidence of potential hypersensitivity events from the hypersensitivity SMQ was low and similar in the ertugliflozin 5 mg and 15 mg groups (3.3% and 2.4%, respectively) and the comparator group (2.5%). There have been no serious events of hypersensitivity reactions, anaphylactic reactions or serious skin reactions reported for ertugliflozin. One case in the comparator group, an event of angioedema, was serious.

In the PBO Pool, ertugliflozin did not result in a higher incidence of hypersensitivity reactions relative placebo. The incidence of hypersensitivity events from the hypersensitivity SMQ was low and similar in the ertugliflozin 5 mg (2.1%) and 15 mg (1.4%) and the placebo (1.9%) group. No serious adverse events were reported in any group.

Ertugliflozin add-on to Metformin Phase III program

Hypersensitivity reactions were not evaluated in the Ertugliflozin add-on to Metformin Phase III program.
One subject in study P005/1019 (in the E15/S100 group) reported a non-serious, moderate adverse event of dermatitis allergic on Day 105, reported as not related to study medication by the investigator. Hypersensitivity reactions, including anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome, are included in labelling of sitagliptin based upon post-marketing reports.

Bone safety/ fractures

Ertugliflozin Phase III development program

Long-term data regarding fractures was received from the Broad Pool. The cumulative incidence of adjudicated confirmed fractures at week 104 was similar across the groups; 0.9% (n=15) for ertugliflozin 5 mg, 0.6% (n=11) for ertugliflozin 15 mg and 0.8% (n=12) for the comparator group.

In one placebo-controlled study (P007/1017; included in Ertu/Met pool), ertugliflozin had no impact on bone mineral density during the 26-week treatment period. Interim 52-week BMD data in study P007/1017 was provided for the overall study population and the subgroup of post-menopausal women (approximately 38% of the overall). At week 52, there were small changes in BMD in all treatment groups across the anatomical sites in both populations. The decrease in BMD was in general slightly greater in the subgroup of post-menopausal women relative to the overall study population. However, the BMD change from baseline was not consistent regarding magnitude and dose relationship and, moreover, was nominally statistically significant only for the 'total hip' data in the ertugliflozin 15 mg group in the overall study population of study P007/1017. The 104 week data was also statistically significant only for the 'total hip' data in the ertugliflozin 15 mg group.

Changes in serum phosphate (6.8% and 8.5% vs. 1.9%) and magnesium (7.8% and 9.9% vs. -0.9%) but no change in serum calcium were seen with ertugliflozin treatment (5 mg and 15 mg) in the placebo-controlled Pool. In study P007/1017, there was a dose-dependent increase from baseline to week 26 in the bone resorption marker CTX for ertugliflozin 5 mg and 15 mg (29% and 38%, respectively) relative to placebo (10%), and a non-dose-dependent increase in PTH (6.8% and 6.9% vs. 1.1% for ertugliflozin 5 mg and 15 mg vs. placebo). The proportion of subjects meeting the PDLC (pre-defined limits of change) criterion PTH increase ≥30% (regardless of whether above the ULN) was higher in the ertugliflozin 5 mg group (21%) and 15 mg group (21%) relative to the placebo group (13%). The bone formation marker P1NP increased two times more in the ertugliflozin 15 mg group (15%) compared to ertugliflozin 5 mg group (7.5%) but increased even more in the placebo group (19%).

In study P007/1017, a subgroup analysis at week 26 in pre- versus postmenopausal women did not indicate any difference regarding ertugliflozin effect on CTX. The mean percent change from baseline in CTX was greater in both ertugliflozin groups relative placebo in all 4 subgroups: males, pre-, peri- and postmenopausal women, with a dose-dependent increase in all groups except the male group. A subgroup analysis in subjects with and without osteopenia at baseline did not demonstrate any clinically significant differences in mean percent changes at week 26 in BMD, CTX, P1NP and PTH between the groups. In moderately renal impaired patients, the event rate of fractures was too low for meaningful conclusions.

Changes in serum phosphate (9.7 and 7.8% vs. 0.8%) and magnesium (11% and 11% vs. 0.4%) for ertugliflozin 5 mg and 15 mg vs. placebo, but no meaningful change in calcium, were noted in this patient group. PTH increased 27% in the ertugliflozin 5 mg group and increased similarly in the ertugliflozin 15 mg group (12%) and the placebo group (11%). CTX increased in the ertugliflozin groups (33% and 34%) relative placebo (9.6%); although not dose-dependent. P1NP increase was higher in the ertugliflozin 5 mg group (41%) and numerically higher in the placebo group (33%) relative to the ertugliflozin 15 mg group (19%).

Data on bone markers was provided at week 52 in study P001/1016 and P007/1017 and at week 104 in study P007/1017. The bone resorption marker CTX was more increased in the ertugliflozin groups than in the placebo/comparator group at week 26, 52 and 104; although the difference to the comparator group was less pronounced at week 104. The bone formation marker P1NP was increased

in both the ertugliflozin and the comparator groups. The clinical implication of the observed changes in the bone markers is not clear.

Ertugliflozin add-on to Metformin Phase III program

In all studies, small increases were seen in phosphate and magnesium in ertugliflozin treated subjects relative to placebo. There was no meaningful change in calcium in the ertugliflozin or the placebo groups in the Ertu/Met pool, neither in study P002/1013. In study P005/1019, there was a higher proportion of subjects who had a last on-treatment increase in calcium ≥1.0 mg/dL and value >ULN in the E15/S100 group than in the S100 group. Adverse events of hypercalcaemia were reported for 1 subject in the E5 group and 1 subject in the E15 group. Both AEs were mild in intensity, one was considered to be related to study medication, and neither resulted in discontinuation.

Overall, 13 (0.4%) subjects in the Ertugliflozin add-on to Metformin Phase III program had an event of fracture that was sent for adjudication: 3 subjects in the ertugliflozin 5 mg group, 6 in the ertugliflozin 15 mg group and 4 in the non-ertugliflozin group.

Lower limb amputations

Ertugliflozin Phase III development program

In the Broad Pool, there were 10 subjects with non-traumatic limb amputations (all post-randomization treatment analysis): 1 of 1,450 (0.1%) in the non-ertugliflozin group, 1 of 1,716 (0.1%) in the ertugliflozin 5 mg group and 8 of 1,693 (0.5%) in the ertugliflozin 15 mg group (resulting in 9 of 3,409 (0.3%) in the all ertugliflozin group). Among these cases, the most frequently reported amputation was toe amputation. One subject in the ertugliflozin 15 mg group underwent 2 amputation procedures (left second toe and left third toe amputations).

The absolute numbers of toe amputation was low, wherefore it is difficult to draw any firm conclusions from the data. Moreover, baseline history revealed risk factors such as peripheral neuropathy, peripheral artery disease (including one subject with a pre-existing peripheral artery aneurysm), diabetic foot, or former/current smoking to be present in all subjects. Associated adverse events included those related to limb infection, peripheral artery disease, and gangrene.

Ertugliflozin add-on to Metformin Phase III program

6 of the 10 subjects with non-traumatic limb amputations were from the Ertugliflozin add-on to Metformin Phase III program: 1 of 1,046 (0.1%) in the non-ertugliflozin group, 1 of 1,304 (<0.1%) in the ertugliflozin 5 mg group and 4 of 1,290 (0.8%) in the ertugliflozin 15 mg group (resulting in 5 of 2,594 (0.2%) in the all ertugliflozin group).

Ketoacidosis

Ertugliflozin Phase III development program

In the Broad Pool, three (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 comparator group. The rest of the cases were either determined unlikely to represent ketoacidosis (20 cases) or were unclassifiable (2 cases). All events of ketoacidosis resolved, two after discontinuation of study medication and one resolved on treatment.

Ertugliflozin add-on to Metformin Phase III program

All three cases in the Ertugliflozin Phase III development program which were assessed to have met the case definition of ketoacidosis with either certain or possible likelihood were ertugliflozin add-on to

metformin treated subjects. The Ertugliflozin add-on to Metformin Phase III program includes approximately 75% of the subjects in the Broad pool.

Serum lipids

A small increase in LDL-C, HDL-C and total cholesterol was noted in week 26, similar as what has been seen with other SGLT-2 inhibitors. Mean percent changes from baseline at week 26 for ertugliflozin 5 mg and 15 mg versus placebo, respectively, were: LDL-cholesterol 5.8% and 8.4% versus 3.2%; HDL-cholesterol 6.2% and 7.6% versus 1.2%; total cholesterol 2.8% and 5.7% versus 1.1 % and triglycerides -3.9 % and -1.7% versus 4.5%.
LDL-C/HDL-C-ratio was evaluated in study P003/1022 and study P007/1017. In study P003/1022, there were small changes in LDL-C/HDL-C-ratio over time and no relevant differences between the groups. LDL-C/HDL-C ratio will be assessed in the ongoing study P007/1017 at completion.

The results in the Ertugliflozin add-on to Metformin Phase III program were not notably different from the Ertugliflozin Phase III development program.

Malignancy

There was an imbalance in the SOC Neoplasms for ertugliflozin (0.6% and 1.2% for ertugliflozin 5 mg and 15 mg respectively) relative comparator (0.3%).
Further analysis, to identify subjects reporting a malignancy with onset greater than 6 months after the first dose of study medication, did show an increased incidence in the ertugliflozin group 15 mg (0.9%) in comparison to ertugliflozin 5 mg (0.3%) and comparator (0.4%). Malignancies reported in more than one subject in the ertugliflozin groups were 2 cases of breast cancer/ invasive ductal breast cancer, 2 cases of malignant melanoma and 2 cases of basal cell carcinoma. The 2 events of pancreatic neoplasm and pancreatic carcinoma were erroneously reported by the investigator for the same malignancy in one subject.

Malignancies in ertugliflozin treated subjects on metformin have not been evaluated specifically.

Serious adverse event/deaths/other significant events

Deaths

Ertugliflozin Phase III development program

A total of 26 deaths occurred in the phase III studies, of which 6 (0.4%) in the comparator group and in total 20 (0.6%) deaths in the ertugliflozin groups.

The most frequently reported AEs with fatal outcome (15/26) were in the SOC Cardiac disorders (n=7) and in the SOC General disorders (n=8), including sudden death, sudden cardiac death and multiple organ dysfunction syndrome. The remaining deaths (n=11) were distributed among different SOCs. None of the fatal cases were considered related to the treatment by the investigator; however one case had no information on causality assessment from the investigator.

Ertugliflozin add-on to Metformin Phase III program

No deaths occurred in the phase A treatment period of studies P005/1019, P006/1015 and P007/1017. There were four fatal events in phase B: one in study P006/1015 (meningitis tuberculous) in non-ertugliflozin group, one in study P007/1017 (plasma cell myeloma) in the ertugliflozin 15 mg group and two in study P005/1019 (pancreatic carcinoma; ischaemic stroke) in the ertugliflozin 15 mg group.

In study P002/1013, there were five (1.1%) fatal events in the ertugliflozin 5 mg group, one (0.2%) in the ertugliflozin 15 mg group, and none in the glimepiride group. One subject in the glimepiride group experienced a fatal event in the post-treatment period. Moreover, there were three fatal events in Phase B. The causes of death in Phase A in ertugliflozin treated subjects were sudden cardiac death (two subjects), multiple organ failure after car accident, suicide (depression after stroke) and exacerbation of COPD.

In summary, Of the 26 fatal events in the ertugliflozin phase III studies, 6 events were reported from the add-on to metformin studies, all from ertugliflozin treated patients in study P002/1013, giving an incidence of deaths of 0.2% in the Ertugliflozin add-on to Metformin program in whole and 0.5% in study P002/1013. Phase A of study P002/1013 was 52 weeks, as opposed to 26 weeks in the other studies of the Ertugliflozin add-on to Metformin program.

Non-fatal serious adverse events

Ertugliflozin Phase III development program

Non-fatal SAEs were most frequently reported in the SOC *Infections and infestations* (no imbalance between ertugliflozin and comparator group) and the SOC *Cardiac disorders* (slightly higher incidences in the ertugliflozin groups [1.3%] vs. comparator [0.9%]), of which angina pectoris was the most commonly reported event. Data supporting an assessment of CV safety profile is very limited with only few cases in each treatment group. There is a numerical imbalance between ertugliflozin and placebo, but no conclusion can be drawn. However, considering the known mechanism of action and experience from other products in the class, it is acceptable to provide data from the CV outcome study after a potential approval.

Ertugliflozin add-on to Metformin Phase III program

The incidence of non-fatal serious adverse events in the Ertu/Met Pool was low and similar in the ertugliflozin 5 mg and 15 mg (both 2.8%) and placebo groups (3.6%).

Non-fatal serious adverse events occurred across multiple SOCs with no obvious event pattern. Only 1 specific adverse event preferred term (*acute myocardial infarction*) occurred in more than 1 subject in any group (2 subjects in the placebo group). The PTs *acute myocardial infarction* and *angina pectoris* both occurred in 1 subject in the E5 group, and the PT *myocardial ischaemia* occurred once in the E15 group.

The incidence of SAEs in study P002/1013 was higher in the ertugliflozin 5 mg group (6.3%) and numerically higher in the ertugliflozin 15 mg group (3.9%), relative to the glimepiride group (2.7%).

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 incidence of SAEs in the *Cardiac disorders* SOC was numerically higher in the ertugliflozin groups (3 subjects in each group) than in the glimepiride group (1 subject). The incidence of SAEs in the *Neoplasms benign, malignant and unspecified* SOC was numerically higher in the ertugliflozin groups (five subjects in each group; 1.1%) than in the glimepiride group (1 subject; 0.2%). Of the 10 SAEs in the ertugliflozin groups, 3 were benign (1 AE of ovarian adenoma and 2 AEs of uterine leiomyoma). For the malignant neoplasms, there was no pattern of specific tumour types.

In study P005/1019, the incidence of SAEs was numerically higher in the ertugliflozin 5 mg (3.2%) and E5/S100 (2.5%) groups compared to the other treatment groups (1.2-1.6%). The incidence of SAEs in SOC *Cardiac disorders* was similar in ertugliflozin treated (0.6%) relative to non-ertugliflozin treated (0.4%) subjects. There was one SAE in the E5/S100 group in the SOC *Neoplasms.* In the SOC *Gastrointestinal disorders*, there were 3 events (1.2%) in the ertugliflozin 5 mg group relative to 0 in the remaining treatment groups. The only serious adverse event that occurred in >1 subject in a treatment group was *acute myocardial infarction*, which occurred in 2 subjects (0.8%) in the E15/S100 group.

Laboratory findings

Haematology

Ertugliflozin Phase III development program

In the placebo-controlled Pool, slight increases from baseline to week 26 in haemoglobin concentration was observed in the 5 mg and 15 mg ertugliflozin groups (3.5% in both groups) compared to a decrease in the placebo group (-1.4%). The observed increases in haemoglobin/haematocrit are considered related to volume depletion associated with the diuretic effect of ertugliflozin, as for other SGLT-2 inhibitors.

The results in the Ertugliflozin add-on to Metformin Phase III program do not differ in a meaningful way from the Ertugliflozin Phase III development program.

Potassium

Ertugliflozin Phase III development program

In the Broad Pool, the proportion of subjects having any occurrence of an increase in potassium meeting PDLC increase criterion ≥1.0 mEq/L and value >ULN, were similar for ertugliflozin and comparator group (8-9%). Subjects meeting PDLC criteria of >5.4 mEq/L and 15% above baseline, were 7.7% for ertugliflozin 5 mg, 8.9% for ertugliflozin 15 mg and 7.1% for comparator.

In patients with moderate renal impairment, subjects meeting the PDLC criteria ≥1.0 mEq/L and value >ULN, were seen slightly more often in subjects treated with ertugliflozin (11% for both groups) than with placebo 8.6%. Incidences of elevated serum potassium meeting the PDLC criteria >5.4 mEq/L and 15% above baseline, were seen in 12% subjects treated with ertugliflozin 5 mg, 10% subjects treated with ertugliflozin 15 mg, and 7.9% subjects treated with placebo in a none dose-dependent manner.

Ertugliflozin add-on to Metformin Phase III program

The mean change in potassium levels from baseline was not different in ertugliflozin treated subjects (-0.03 and -0.04 mEq/L respectively) compared to placebo (-0.05 mEq/L) in the Ertu/Met pool, and the proportion of subjects meeting a PDLC criterion was similar in all groups.

Similarly, there were no notable changes from baseline potassium in any treatment group in the 2 active-comparator studies (P002/1013: all ertugliflozin -0.01-0.0 mEq/L vs glimepiride 0.00 mEq/L and P005/1019: all ertugliflozin 0.00-0.005 mEq/L vs sitagliptin 0.00 mEq/L), neither any meaningful difference between treatment groups in the proportion of patients meeting PDLC criteria for potassium. In study P005/1019, there was one SAE with decreased potassium.

Uric acid

Ertugliflozin Phase III development program

In the placebo-controlled studies, modest decreases (-7.7% and -6.3%) from baseline in serum uric acid was observed at week 26 in the 5 mg and 15 mg ertugliflozin groups compared to an increase in the placebo group (3.2%). Decreases in uric acid levels could be secondary to increased secretion of uric acid in the urine, with an increased risk for nephrolithiasis as a possible consequence. However, the incidence of urolithiasis and nephrolithiasis was similar across the groups in the Broad Pool. Urinary uric acid was not measured in the clinical program.

Ertugliflozin add-on to Metformin Phase III program

As in the ertugliflozin phase III development program, there were modest decreases from baseline in uric acid was observed at week 26 in the 5 mg and 15 mg ertugliflozin groups compared to an increase in the placebo group in the Ertugliflozin add-on to Metformin Phase III program. No confidence interval or P-values were provided.

Blood pressure/pulse rate

Ertugliflozin Phase III development program

A clear, but not dose-dependent, decrease in blood pressure was observed with ertugliflozin (mean changes of -4.8 mmHg in SBP with ertugliflozin). This is consistent with the known osmotic diuretic effect of ertugliflozin. No clinically relevant mean change from baseline in pulse rate was observed.

Ertugliflozin add-on to Metformin Phase III program

A statistically and clinically relevant reduction from baseline in sitting SBP was observed with ertugliflozin 15 mg and 5 mg across the phase III studies regardless of between-study differences in background medication and study designs. This is further discussed in section 2.5.2 under Results, as sitting systolic and diastolic blood pressure were secondary efficacy endpoints in the Ertugliflozin add-on to Metformin Phase III program.

There was no statistically significant increase in orthostatic blood pressure change between groups.

Safety in special populations

Ertugliflozin Phase III development program

Elderly

Age-delineated data was provided for age groups: <65 y (n=3,605), 65-74 y (n=1,035), 75-85 y (n=211) and 85+y (n=8). There is rather limited data for subjects 75-85 years and too limited data for subjects ≥85 years of age, wherefore no meaningful conclusions could be drawn in this age group (n=8).

Subjects ≥ 75 of age are in general likely more prone to adverse events, such as volume depletion and renal impairment, due to frequent use of concomitant medication and baseline impaired renal function. In the Broad Pool, in the *age group <65'*, *65-74'* and *75-84'*, the mean eGFR was 90, 73-75 and 60-66 mL/min/1.73 m^2, respectively. Within each age groups the mean eGFR was similar across the treatment groups, except in the *age group 75-84'* in which the mean eGFR was slightly higher (66 mL/min/1.73 m^2) in the ertugliflozin 5 mg group compared to the ertugliflozin 15 mg group (61 mL/min/1.73 m^2) and the comparator group (60 mL/min/1.73 m^2). Also the median eGFR was higher in the ertugliflozin 5 mg group compared to the other treatment groups in the *age group 75-84'*. Among subjects ≥ 65 years of age, but not in younger subjects, the incidence of volume depletion events was numerically higher in both ertugliflozin 5 mg and 15 mg (2.2% and 2.6% respectively)

relative to the comparator group (1.1%). The incidence of volume depletion was 1.6%, 3.1% and 1.0% in the *age group 65-74'* and 5.7%, 0% and 1.5% in the *age group 75-85'* for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, respectively.
In subjects ≥ 65 years of age, renal-related events were more common in ertugliflozin groups (1.3% and 1.4%; for 5 mg and 15 mg ertugliflozin, respectively) than in the comparator group (0.5%) in subjects ≥ 65 years of age. The incidence of renal-related events was 1.6%, 0.9% and 0% in the *age group 65-74'* and 0%, 4% and 0% in the *age group 75-85'* for ertugliflozin 5 mg, ertugliflozin 15 mg and comparator group, respectively.
A similar increase in genital mycotic infections (both male and female) in ertugliflozin-treated subjects, as seen in the overall population, was seen in both subjects <65 years and ≥ 65 years. The incidence of female genital infections was 3.7%, 2.9% and 1.0% in the *age group 65-74'* and 2.9%, 4.0% and 0% in the *age group 75-85'* for ertugliflozin 5 mg, ertugliflozin 15 mg and the comparator group, respectively. The incidence of male genital infections was 1.9%, 1.1% and 0% in the *age group 65-74'* and 1.4%, 1.3% and 0% in the *age group 75-85'* for ertugliflozin 5 mg, ertugliflozin 15 mg and comparator group, respectively.
Use of ACE/ARB was similar across the treatment groups and between the *age group 65-74'* (69-75%) and the *age group 75-84'* (70-76%) and as expected less in the *age group <65'* (53-57%). Use of diuretics was similar across the treatment groups in the *age group 65-74'* (38-39%). However, in the *age group 75-84'*, the use of diuretics was less common in the ertugliflozin 5 mg group (29%) compared to ertugliflozin 15 mg group (47%) and the comparator group (45%). The total number of subjects on a loop diuretic was overall too small (n=197) to draw any firm conclusions.

Gender
Adverse events were in general more common in females (66-69%) than males (57-62%) across the groups. The proportion of patients who had a genital infection was higher (about 2-fold or more) for women than for men, irrespective of the treatment group. UTI was also more common in females compared to men.

Race/ Ethnicity
The overall frequency of adverse events across the treatment groups was comparable for White, Black and Asian (58-66%); however slightly higher in the group 'Other' (73-80%). The overall frequency of adverse events across the groups was slightly lower for patients of Hispanic/Latino ethnicity (59-60%) than for patients who were not of Hispanic/Latino ethnicity (63-66%)

Renal impairment
Volume depletion
The incidence of volume depletion was highly increased in ertugliflozin treated subjects with an eGFR 45-<60 mL/min/1.73 m^2 (6.4% ertugliflozin 5 mg and 3.7% ertugliflozin vs. 0% non-ertugliflozin). In the moderate renal impairment study, which made up a large portion of the subjects with eGFR 45-<60 mL/min/1.73 m^2 subgroup (159 of 173), the incidence of volume depletion was significantly higher in the ertugliflozin groups (4.4% and 1.9% in ertugliflozin 5 mg and 15 mg, respectively) compared to placebo (0%)
Genital infections
Among ertugliflozin-treated subjects, a similar increase in genital infections (male and female) as seen in the overall population was seen in subjects with eGFR >60 mL/min/1.73 m^2. In subjects with eGFR <60 mL/min/1.73 m^2, the imbalance was numerically smaller.
Renal-related events
In ertugliflozin treated subjects with moderate renal impairment, the decrease in eGFR was about 1

mL/min/1.73 m^2 larger than in the PBO Pool, and did not return to baseline at week 26; however, reversed after treatment discontinuation.
The incidence of renal-related events in moderate renal impaired subjects was higher for ertugliflozin (2.5% and 1.3% for 5 mg and 15 mg ertugliflozin, respectively) than for placebo (0.6%).
In subjects with eGFR <60 mL/min/1.73 m^2 in the broader pool, containing all phase III studies (including subjects from the moderate renal impairment study), renal-related events were more frequent in the ertugliflozin groups relative to the comparator and markedly more frequent in subjects with an eGFR <45mL/min/1.73 m^2 (n=173). However, there was no notable differences across the groups in the incidence of renal-related events in subjects with eGFR 45-<60 mL/min/1.73 m^2 (n=402).
Fractures
In moderate renal impaired patients, the event rate of fractures was too low for meaningful conclusions. Similar changes were noted in serum phosphate and magnesium as in the pool with placebo-controlled studies. No meaningful change in calcium was seen.
PTH increased 27% in the ertugliflozin 5 mg group and increased similarly in the ertugliflozin 15 mg (12%) group and the placebo group (11%). A similar change in CTX as for study P007/1017 was seen in the ertugliflozin group 5 mg and 15 mg (33% and 34%) relative to placebo (9.6%). P1NP increase was higher in the ertugliflozin 5 mg group (41%) and numerically higher in the placebo group (33%) relative to the ertugliflozin 15 mg group (19%). At week 52, CTX increased from baseline more in the ertugliflozin groups (30% and 40% for ertugliflozin 5mg and 15mg) than in the placebo/comparator group (15%). P1NP for ertugliflozin 5mg, ertugliflozin 15 mg and placebo/comparator group was 18%, 27% and 30% and PTH 23%, 12% and 7.2%.
Hypoglycaemia
In study P001/1016, there was a higher incidence of hypoglycaemia relative to the other phase III studies. This was expected given the high rate (90%) of insulin and/ or insulin secretagogue as background therapy in this study. The incidence of hypoglycaemia was similar across the groups.
Potassium
In patients with moderate renal impairment, subjects meeting the PDLC criteria ≥1.0 mEq/L and value >ULN, were seen slightly more often in subjects treated with ertugliflozin (11% in both groups) than with placebo 8.6%. Incidences of elevated serum potassium meeting the PDLC criteria >5.4 mEq/L and 15% above baseline, were seen in 12% subjects treated with ertugliflozin 5 mg, 10% subjects treated with ertugliflozin 15 mg, and 7.9% subjects treated with placebo.

Ertugliflozin add-on to Metformin Phase III program
No specific subgroup analyses were performed for subjects taking the combination of ertugliflozin and metformin. Of note, only 1.6%-3.8% of the subjects were ≥75 years old.

Pregnancy and lactation
Ertugliflozin Phase III development program
There were 2 pregnancies in the Broad Pool. One pregnancy, in the ertugliflozin 5 mg group, ended in an elective abortion and the other, in the non-ertugliflozin group, resulted in a spontaneous abortion.
Based on results from animal studies, ertugliflozin may affect renal development and maturation, therefore ertugliflozin is not recommended during the second and third trimesters of pregnancy.
There is no information regarding the presence of ertugliflozin in human milk, the effects on the breastfed infant, or the effects on milk production. Ertugliflozin is present in the milk of lactating rats. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.
Ertugliflozin add-on to Metformin Phase III program

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.
There are no adequate and well-controlled studies in pregnant women with the ertugliflozin/metformin FDC or its individual components.

Safety related to drug-drug interactions and other interactions

Ertugliflozin

Single-dose drug interaction studies of ertugliflozin with metformin, simvastatin, sitagliptin, and glimepiride demonstrated no clinically meaningful interactions, either as a perpetrator or victim. Additionally, based on predictions from physiologically-based PK modelling, administration of ertugliflozin with a urinary glucose transport inhibitor would increase ertugliflozin exposure by ≤1.51-fold. Multiple dose rifampin, an inducer of urinary glucose transporters and cytochromes P450, is associated with a 39% decrease in ertugliflozin exposure. This decrease in exposure with rifampin is not considered clinically relevant. Subgroup analyses were performed in the Broad Pool to evaluate whether selected baseline medications (ACE/ARBs, diuretics, loop diuretics) were associated with an increased risk of volume depletion events or renal-related events.

Concomitant use of ertugliflozin and diuretics increased the incidence of volume depletion AEs in ertugliflozin groups.

For acute kidney injury/failure AEs, no such trend was found for diuretics and ACE-I/ARB concomitant medication subgroups. However, there was a numeric increased incidence for renal-related adverse events overall in ertugliflozin groups (0.9%) compared to comparator group (0.5%) in ACE-I/ARB concomitant medication subgroup. No similar increase could be seen in diuretics subgroup. It is worth noting, however, that the number of renal-related events was low in both the ertugliflozin and comparator groups.

The SmPC already correctly warns that special caution is needed with diuretics. Concomitant use of SGLT-2 inhibitors and ACE-I/ARB medicinal products may increase the risk of acute kidney injury due to the specific mechanism of action of ACE-I/ARB, especially in patients with volume depletion. However, hypotension caused by other anti-hypertensive agents may also increase the risk. This is reflected in section 4.4 in the SmPC.

Metformin

Effects of other medicinal products on metformin:

Glyburide: In a single-dose interaction study in type 2 diabetes patients, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and Cmax were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects make the clinical significance of this interaction uncertain.

Furosemide: A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood Cmax and AUC without any significant change in metformin renal clearance. When administered with metformin, the Cmax and AUC of furosemide were smaller than when administered alone, and the terminal half-life was

decreased, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

Nifedipine: A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin Cmax and AUC and increased the amount excreted in the urine. Tmax and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic drugs: Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of metformin and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Other: Certain drugs tend to produce hyperglycaemia and may lead to loss of glycaemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, oestrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving, sitagliptin and metformin FDC, the patient should be closely observed to maintain adequate glycaemic control.

In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when co-administered in single-dose interaction studies.

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

Ertugliflozin and Metformin Combination Treatment

A clinical drug-drug interaction study to estimate the effect of ertugliflozin on the PK of metformin and vice-versa following single oral dose administration of 15 mg ertugliflozin and 1000 mg metformin was conducted in healthy subjects. Study results indicated that co-administration of ertugliflozin and metformin did not alter ertugliflozin or metformin exposure when compared to ertugliflozin and metformin administered alone (Study P019).

Discontinuation due to adverse events

Ertugliflozin Phase III development program

Overall, the discontinuation rates due to AEs were similar across the treatment groups in both the PBO Pool (about 2%) and the Broad Pool (about 4%). In both Pools, there was a numerical imbalance of more frequent discontinuations due to genital infections in the ertugliflozin groups compared to placebo and the comparator group, respectively. In the Broad Pool, the frequency of events in the SOC Renal and urinary disorders leading to premature discontinuation was numerically higher for the ertugliflozin 15 mg (0.7%) than for the ertugliflozin 5 mg (0.3%) and the comparator (0.3%).

Ertugliflozin add-on to Metformin Phase III program

The incidence of adverse events resulting in discontinuation from study medication in the Ertu/Met Pool was low overall and not notably different in the ertugliflozin 5 mg (2.2%) and 15 mg (1.1%) groups relative to the placebo group (1.1%). The only discernible pattern was a low incidence of discontinuations in ertugliflozin-treated subjects due to adverse events related to *genital mycotic infections*. Two subjects, both in the placebo group, discontinued the study due to a SAE (subcutaneous abscess and ischaemic stroke).

The incidence of adverse events resulting in discontinuation from study medication was somewhat higher in study P002/1013 than in the other studies in the Ertugliflozin add-on to Metformin Phase III program (ertugliflozin 5 and 15 mg groups 4.0% and 5.7% respectively, glimepiride group 3.9%).

In the infection and infestation SOC, a numerically higher occurrence of events leading to discontinuation of study medication in the ertugliflozin groups was due to *genital mycotic infection*-related AEs. In the Investigations SOC, a higher occurrence of events leading to discontinuation of study medication in the ertugliflozin 15 mg group was due to 3 subjects with AEs of *eGFR decreased*. In the Renal and urinary disorders SOC, the numerically higher occurrence of AEs leading to discontinuation of study medication in the ertugliflozin 15 mg group was related to AEs of a*cute kidney injury* (2 subjects) and *pollakiuria* (2 subjects).

In the ertugliflozin 5 mg group, 1 subject each discontinued due to SAEs of *face injury* and *gastric cancer*, and in the ertugliflozin 15 mg group, 1 subject each discontinued due to SAEs of *cholelithiasis*, *decreased eGFR, colon cancer, acute kidney injury*, and *balanoposthitis.* The SAEs of *eGFR decreased, acute kidney injury*, and *balanoposthitis* were considered to be related to study medication. One subject in the glimepiride group discontinued due to a drug-related SAE of cerebrovascular accident.

In the P005/1019 study, adverse events resulting in discontinuation from study medication occurred at a higher incidence in the E15/S100 group (2.9%) relative to the S100 group (0.4%). Incidences in the 3 other groups were 2.4% in the E5 group and 1.2% each in the E15 and E5/S100 groups. The only adverse events that resulted in discontinuation from study medication in >1 subject across the 5 groups were *dizziness* and *balanoposthitis* (each resulted in discontinuation of 2 subjects in the E5 group).

Two subjects, both in the E5/S100 group, discontinued study medication due to a serious adverse event; 1 due to an event of *myocardial infarction* and 1 due to an event of *nodal marginal zone B-cell lymphoma stage III*.

Post marketing experience

Not applicable

2.6.1. Discussion on clinical safety

The ertugliflozin phase III safety database is in general considered sufficient. Overall, 3,409 subjects received at least one dose 5 or 15 mg ertugliflozin in the phase III studies of which 2,204 subjects were exposed for at least 50 weeks. In the placebo-controlled studies, 1,029 subjects received at least one dose of ertugliflozin of which 921 subjects received treatment for at least 25 weeks.

A total of 721 subjects were randomized and received at least 1 dose of ertugliflozin in the two studies comprising the Ertu/Met Pool. 888 and 985 subjects were exposed to ertugliflozin on a background of metformin in Study P002/1013 and Study P005/1019, respectively. The Ertugliflozin add-on to Metformin Phase III program includes approximately 75% of the subjects in the Broad pool and

comprises of 2,594 ertugliflozin/metformin exposed subjects and 1,046 non-ertugliflozin treated subjects.

Discontinuation rates for trial medication were similar in the ertugliflozin groups and slightly higher in the placebo/comparator group in the placebo-controlled studies and phase III studies, respectively. However, discontinuation rates were relatively high (about 20%) in the pool of phase III studies, which should be seen in the light of the longer mean duration of the studies. In the shorter placebo-controlled studies, discontinuation rates were about 10 %. The most common reason for discontinuation from study drug was withdrawal by subject, discontinuation due to adverse events, lost to follow-up and hyperglycaemia (a common reason only in the pool of phase III studies).

The most common adverse events for ertugliflozin were upper respiratory infection (higher frequency in the placebo group), hypoglycaemia (similar frequencies for all groups), headache (higher frequencies in the ertugliflozin groups), vulvovaginal mycotic infection (higher frequencies in the ertugliflozin groups) and urinary tract infections (similar frequencies for all groups).

For most frequent AEs, similar results were observed in Ertu/Met Pool, as vulvovaginal mycotic infections, weight decreased and urinary tract infections were the most frequent AEs occurring with higher frequencies in ertugliflozin groups.

Incidence of most frequent adverse events in Ertu/Met Pool share some other characteristics with the Broad Pool: most frequent diarrhoea (and nausea as well) in placebo group, dose dependency of weight decrease AE and Renal and Urinary Disorder SOC. Hypoglycaemia was observed with higher frequency for non-ertugliflozin group.

Incidences of drug-related adverse events were of the same tendency for the ertugliflozin groups of Broad Pool and Ertu/Met Pool (i.e. slightly increased AE incidence for E15 groups relative to non-ertugliflozin groups). Absolute values of incidence are lower in Ertu/Met Pool.

No new or unexpected adverse reactions or serious adverse reactions were reported in the Ertugliflozin add-on to Metformin Phase III program compared to the Ertugliflozin Phase III development program currently assessed in procedure EMEA/H/C/4315 or to the well-known safety profile for metformin.

Volume depletion

In the ertugliflozin phase III placebo-controlled Pool (PBO pool), the incidence of volume depletion events was low (<2%) and not notably different across the ertugliflozin and placebo groups. In the subgroup analyses in the Broad Pool, subjects with eGFR <60 mL/min/1.73 m^2, subjects ≥65 years of age and subjects on diuretics had a higher incidence of volume depletion in the ertugliflozin groups relative the comparator group. In subjects with eGFR <60 mL/min/1.73 m^2, the incidence of events of volume depletion was 5.1, 2.6% and 0.5% for ertugliflozin 5 mg, ertugliflozin 15 mg and the comparator group and for subjects with eGFR 45 to <60 mL/min/1.73 m^2, the incidence was 6.4%, 3.7% and 0% respectively.

With regard to volume depletion and osmotic diuresis, the data in the Ertugliflozin add-on to Metformin Phase III program identified no additional safety or tolerability concerns for the combination relative to the two individual agents. Incidences of volume depletion AEs in Ertu/met Pool were of about the half of incidences in the Broad Pool.

Genital infections/ urinary tract infections

Urinary tract infections and genital infections were classified as adverse events of special interest due to its mechanism of action. In ertugliflozin-treated subjects, there was an increased risk of genital infections but no increased risk of urinary tract infections in the placebo-controlled pool. Both female

and male genital infections were highly increased compared to placebo. Most of the events were mild or moderate in intensity.

In the placebo-controlled pool, no event was serious among the female genital infections but two events (cellulitis of the male genital organ and phimosis) were serious among the male genital infections; both in the ertugliflozin group.

In the Broad Pool, no event was serious among the female genital infections.Three events (cellulitis of the male genital organ, phimosis and balanoposthitis) were serious among the male genital infections. Phimosis was reported in 8 (0.5%) subjects in the all ertugliflozin group and 1 subject (0.1%) in the comparator group in the male population. Four of 8 phimosis events in ertugliflozin-treated subjects were treated with circumcision. The subject with phimosis, in the comparator group, also underwent a circumcision.

A similar increase in genital mycotic infections (both male and female) in ertugliflozin-treated subjects, as seen in the overall population, was seen in subjects both <65 years and ≥ 65 years.

In the Ertugliflozin add-on to Metformin Phase III program , among males, but not females, complicated infections were more common in the ertugliflozin 15 mg group (1.1/0% in males/females) than in the ertugliflozin 5 mg (0.2/0.3% in males/ females) and the non-ertugliflozin groups (0/0.2% in males/ females) in the Ertugliflozin add-on to Metformin program.

Hypoglycaemia

In the placebo-controlled Pool, the incidence of hypoglycaemia was relatively low, although, increased for ertugliflozin 5 mg and 15 mg (5.0% and 4.5%) compared to placebo (2.9%). When ertugliflozin was used as monotherapy, there was a small, not dose-dependent, increase in hypoglycaemic events in the ertugliflozin groups (2.6% in both groups) as compared to placebo (0.7%). Also when used as add-on to metformin, an increased risk of hypoglycaemic events was noted for ertugliflozin 5 mg (7.2%) and ertugliflozin 15 mg (7.8%) relative placebo (4.3%) of which about half of the events across the groups were events of symptomatic hypoglycaemia. The increased risk of hypoglycaemia compared to placebo is reflected in the SmPC.

In the study in moderate renal impairment (P001/1016), there was a higher incidence of hypoglycaemia relative to the other phase III studies. This was expected given the high rate (90%) of insulin, SU and meglitinides as background therapy in this study. The incidence rates seem generally in line with data with other agents in the class when combined with insulin. It should however be noted that the hypoglycaemia rate was not consistently higher in the ertugliflozin groups compared to placebo, and there was no clear relation to the dose as the highest rates were often observed with the 5 mg dose.

The incidence of hypoglycaemia was similar across the groups.

There was an increase in frequency of hypoglycaemic events in the E15/S100 group compared to the other groups in study P005/1019. This observation is most likely due to random variability since the observation in this is not consistent with corresponding results in study P006/1015 and P017/1047.

Renal function

There were transient and small decreases in eGFR in the ertugliflozin groups that returned to or towards baseline at week 26 but no imbalance between ertugliflozin and placebo in renal-related events. This is consistent with the findings in ertugliflozin/metformin treated subjects. Mean changes from baseline in BUN was higher in the ertugliflozin groups relative to the placebo group at week 26.

However, this is not considered to reflect impairment in renal function. The same phenomenon has been seen with other medicinal products in the class, but the explanation has so far been elusive.

In subjects in the moderate renal impairment study, the decrease in eGFR was slightly larger (and did not return to baseline at week 26); however, reversed after treatment discontinuation. The incidence of renal-related events was higher in the ertugliflozin 5 mg and 15 mg groups (2.5% and 1.3%, respectively) relative to placebo (0.6%).

In subjects ≥65 of age, renal-related events were more frequently occurring in ertugliflozin groups (1.3% and 1.4% for 5 mg and 15 mg ertugliflozin, respectively) than for the comparator group (0.5%).

In the Ertugliflozin add-on to Metformin Phase III program, the inclusion criteria included eGFR ≥ 55-60 mL/min/1.73 m^2. Thus, safety in subjects with moderate and severe renal impairment of the combination has not been sufficiently studied with ertugliflozin on background metformin. Despite the inclusion criteria, there are several subjects included with a baseline eGFR <55 ml/min/1.73 m^2 in the studies. The Applicant has provided data showing that the renal function did not deteriorate further over time in the subset of subjects with baseline eGFR <60 mL/min/1.73 m^2 in the four studies with ertugliflozin in combination with metformin. In the Ertu/met pool, no subjects with eGFR <60 mL/min/1.73 m^2 reported any volume depletion- or renal-related adverse events. In Studies P002/1013 and P005/1019 there were too few renal-related or volume depletion adverse events in this category (0-1 subjects per group) to be able to draw any meaningful conclusions.

In the Ertu/Met 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. Across the Phase 3 one event in the ertugliflozin 5 mg group was adjudicated as "very likely" related, two events in the ertugliflozin 15 mg group and one event in the non-ertugliflozin group were adjudicated as "possibly" related to study medication. Among the four studies with subjects taking background metformin, 2 events, both in the ertugliflozin 15 mg group, were adjudicated as "possibly" related to study medication.
Given these findings, 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.

An enhanced effect of sitagliptin when combined with ertugliflozin on impaired renal function was noted in study P005/1019 reflected by a larger initial decrease in eGFR in the two combination groups (E5/S100 and E15/S100) compared to the respective monotherapy group (ertugliflozin 5mg, ertugliflozin 15 mg and sitagliptin 100mg)

Bone fractures

In the ertugliflozin Phase 3 development program, long-term data regarding fractures was received from the Broad Pool. The cumulative incidence of adjudicated confirmed fractures at week 104 was similar across the groups; 0.9% (n=15) for ertugliflozin 5 mg, 0.6% (n=11) for ertugliflozin 15 mg and 0.8% (n=12) for the comparator group. In the Ertugliflozin add-on to Metformin Phase III program, 0.3% of the ertugliflozin/metformin treated patients had an event of fracture that was sent for adjudication. Interim 52 weeks BMD data in study P007/1017 showed small changes in BMD which was nominally statistically significant only for the 'total hip' data in the ertugliflozin 15 mg group. The 104 week BMD data was also statistically significant only for the 'total hip' data in the ertugliflozin 15 mg group.

Changes in serum phosphate (6.8 and 8.5% vs. 1.9%) and magnesium (7.8% and 9.9% vs. -0.9%) but no change in serum calcium was seen with ertugliflozin treatment (5 mg and 15 mg) in the placebo-controlled Pool. In study P007/1017, there was a dose-dependent increase from baseline to week 26 in the bone resorption marker CTX for ertugliflozin 5 mg and 15 mg (29% and 38%) relative to placebo (10%). The bone formation marker P1NP increased two times more in the ertugliflozin 15 mg group (15%) compared to ertugliflozin 5 mg (7.5%); however, increased even more in the placebo group (19%).

In study P007/1017, subgroup analysis at week 26 in pre- versus postmenopausal women did not indicate any difference regarding ertugliflozin effect on CTX. Another subgroup analysis in subjects with and without osteopenia at baseline did not demonstrate any clinically significant differences in mean percent changes in BMD, CTX, P1NP and PTH between the groups.

In moderate renal impaired patients, the event rate of fractures was too low for meaningful conclusions. Similar changes were noted in serum phosphate and magnesium as in the pool with placebo-controlled studies. No meaningful change in calcium was seen. CTX increased in the ertugliflozin groups 5 mg and 15 mg (33% and 34%) compared to placebo (9.6%) although not in a dose-dependent manner.

Data on bone markers was provided at week 52 in study P001/1016 and P007/1017 and at week 104 in study P007/1017. The bone resorption marker CTX was more increased in the ertugliflozin groups than in the placebo/comparator group at week 26, 52 and 104; although the difference to the comparator group was less pronounced at week 104. The bone formation marker P1NP was increased in both the ertugliflozin and the comparator groups. The clinical implication of the observed changes in the bone markers is not clear.

Lower limb amputations

In the Broad Pool, there were 10 subjects with non-traumatic limb amputations (all post-randomization treatment analysis): 1 of 1,450 (0.1%) in the non-ertugliflozin group, 1 of 1,716 (0.1%) in the ertugliflozin 5 mg group and 8 of 1,693 (0.5%) in the ertugliflozin 15 mg group (resulting in 9 of 3,409 (0.3%) in the all ertugliflozin group). Among these cases, the most frequently reported amputation was toe amputation. One subject in the ertugliflozin 15 mg group underwent 2 amputation procedures (left second toe and left third toe amputations).
Six of the 10 subjects with non-traumatic limb amputations were on background metformin. The studies in the Ertugliflozin add-on to Metformin phase III program comprises of approximately 75% of the subjects in the Broad pool.

The absolute numbers of toe amputation was low wherefore it is difficult to draw any firm conclusions from the data. Moreover, baseline history revealed risk factors such as peripheral neuropathy, peripheral artery disease (including one subject with a pre-existing peripheral artery aneurysm), diabetic foot, or former/current smoking to be present in all subjects. Associated adverse events included those related to limb infection, peripheral artery disease, and gangrene

Ketoacidosis

In the Broad Pool, 3 (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 comparator group. The rest of the cases were either determined unlikely to represent ketoacidosis (20 cases) or were unclassifiable (2 cases). All events of ketoacidosis resolved, 2 after discontinuation of study medication and 1 resolved on treatment.
All three cases of ketoacidosis were ertugliflozin add-on to metformin treated subjects.

Cardiovascular risk

A small increase in LDL-C, HDL-C and total cholesterol was noted at week 26, similar as what has been seen with other SGLT-2 inhibitors. LDL-C/HDL-C-ratio was evaluated in study P003/1022 and study P007/1017. In study P003/1022, there were small changes in LDL-C/HDL-C-ratio over time and no relevant differences between the groups. LDL-C/HDL-C ratio will be assessed in the ongoing study P007/1017 at completion.

Data supporting an assessment of CV safety profile is very limited with only few cases in each treatment group. There is a numerical imbalance between ertugliflozin and placebo, but no conclusion can be drawn. However, considering the known mechanism of action and experience from other products in the class, it is acceptable to provide data from the CV outcome study after a potential approval.

Results from the phase III studies with ertugliflozin/metformin combination treatment did not identify any additional safety or tolerability concerns with regard to lipids and cardiovascular risk relative to ertugliflozin and metformin in monotherapy.

Malignancies

There was a slight imbalance in the SOC Neoplasms for ertugliflozin compared to the comparator groups in the broader pool of phase III studies. No trend could be observed, although, the risk for developing malignancies cannot be fully explored from controlled data in the clinical program covering rather short observation periods (mean duration less than a year).

Laboratory findings

Haemoglobin increased in the ertugliflozin groups and decreased in the placebo group, which is reflected in the SmPC.

Subgroups

In subjects ≥65 years of age, there was an increased risk for events related to volume depletion and events of renal impairment. Further analysis of the data indicate that age per se does not increase the risk of renal-related events but that this risk is related to renal function which is commonly decreased in the elderly.. The risks are reflected in the SmPC.

In subjects with moderate renal impairment treated with ertugliflozin, the decrease in eGFR was slightly larger than in the placebo-controlled Pool, and did not return to baseline at week 26, and the incidence of renal-related events was higher for ertugliflozin than for placebo. In the same subgroup, at week 26 and 52, CTX increased from baseline more in the ertugliflozin groups than in the placebo/comparator group. P1NP was increased for ertugliflozin and the comparator. In subjects with baseline eGFR >45 to <60 mL/min/1.73 m^2, events of volume depletion were more common than for the comparator group.

Lactic acidosis

While metformin is not associated with a decrease in eGFR, it is cleared renally, and in the presence of severe renal impairment metformin has been reported to be associated with lactic acidosis. Osmotic diuresis and volume depletion, with the risk for secondary renal impairment, are known risks with SGLT-2 inhibitors. Treatment with ertugliflozin also induced a transient decrease in eGFR. In subjects with moderate renal impairment, the decrease in eGFR was slightly larger and did not return to baseline at week 26. Thus, there are reasons for being observant to the risk of lactic acidosis with the combination of ertugliflozin and metformin.

However, no events of lactic acidosis or related events (blood lactic acid abnormal, increased blood lactic acid, urine lactic acid, urine lactic acid increased, and hyperlactacidaemia) were reported so far in the Phase III development program for ertugliflozin including subjects on background metformin.

Drug-drug interactions A clinical drug-drug interaction study to estimate the effect of ertugliflozin on the PK of metformin and vice-versa following single oral dose administration of 15 mg ertugliflozin and 1000 mg metformin was conducted in healthy subjects. Study results indicated that co-administration of ertugliflozin and metformin did not alter ertugliflozin or metformin exposure when compared to ertugliflozin and metformin administered alone.

Concomitant use of ertugliflozin and diuretics seemed to increase the incidence of *volume depletion* AEs in ertugliflozin groups. Moreover, concomitant use of SGLT-2 inhibitors and ACE-I/ARB medicinal products increases the risk of acute kidney injury, due to the specific mechanism of action of ACE-I/ARB, especially in patients with volume depletion. However, hypotension caused by other anti-hypertensive agents may also increase the risk. This is reflected in the SmPC, section 4.4.

2.6.2. Conclusions on the clinical safety

The safety profile for ertugliflozin is consistent with other SGLT2 inhibitors. In general, the safety results on ertugliflozin from the ertugliflozin Phase 3 studies could be extrapolated to the ertugliflozin/metformin combination treatment.

In the ertugliflozin phase III studies, the rate of hypoglycaemia was relatively low although increased for ertugliflozin (5.0% and 4.5% for ertugliflozin 5 mg and 15 mg) compared to placebo (2.9%). This is reflected in the SmPC.

There was an increased risk of genital infections in ertugliflozin-treated subjects compared to placebo. In female subjects the incidence of genital infections was 9.1%, 12.2% and 3.0% for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, and in male subjects the incidence was 3.7%, 4.2% and 0.4% respectively. The incidence of UTI was not notably different in the ertugliflozin groups (4.0% and 4.1%) and the placebo group (3.9%).

The incidence of volume depletion events was low (<2%) and not notably different across the ertugliflozin and placebo groups. Subjects with eGFR <60 mL/min/1.73 m^2, subjects ≥65 years of age and subjects on diuretics had a higher incidence of volume depletion in the ertugliflozin groups relative to the comparator group.

The bone resorption marker CTX was more increased in the ertugliflozin groups than in the placebo/comparator group at week 26, 52 and 104; although the difference to the comparator group was less pronounced at week 104. The bone formation marker P1NP was increased in both the ertugliflozin and the comparator groups. Subgroup analysis at week 26 in pre- versus postmenopausal women did not indicate any difference regarding ertugliflozin effect on CTX. Another subgroup analysis in subjects, with and without osteopenia at baseline, did not demonstrate any significant differences in mean percent changes in BMD, CTX, P1NP and PTH between the groups. The clinical implication of the observed changes in the bone markers is not clear. However, interim 52 week and final 104 week BMD data showed small changes in BMD which was statistically significant only for the 'total hip' data in the ertugliflozin 15 mg group, which provides reassurance. Moreover, the cumulative incidence of adjudicated confirmed fractures at week 104 was similar across the groups; 0.9% (n=15) for ertugliflozin 5 mg, 0.6% (n=11) for ertugliflozin 15 mg and 0.8% (n=12) for the comparator group. For completeness, the Applicant agreed to provide final summarized data of all adjudicated confirmed fractures, including the incidence of low trauma fractures, at the time of submission of the final CSR

for the study P007/1017. "Bone fracture" is included in the RMP as an important potential risk, which is considered appropriate.

A slight increase in LDL-C, HDL-C and total cholesterol with ertugliflozin was noted. Data supporting an assessment of CV safety profile is very limited with only few cases in each treatment group. There is a numerical imbalance between ertugliflozin and placebo, but no conclusion can be drawn. However, considering the known mechanism of action and experience from other products in the class, it is acceptable to provide data from the CV outcome study after a potential approval.

Subjects with moderate renal impairment seem to be at a higher risk for events of volume depletion and renal-related events. The decrease in eGFR was about 1 mL/min/1.73 m^2 larger than in the placebo Pool, and was not transient at Week 26; however, reversed after treatment discontinuation. In the study with moderate renal impairment at week 26 and 52, CTX increased from baseline more in the ertugliflozin groups than in the placebo/comparator group. P1NP was increased for ertugliflozin and the comparator. .

The data in the *Ertugliflozin add-on to Metformin Phase III program* identified no additional safety or tolerability concerns for the combination of the medicinal products relative to the two agents given alone. Due to risk of volume depletion and decreased renal function of ertugliflozin, there are reasons for being observant to the risk of lactic acidosis with the combination of ertugliflozin and metformin. No events of lactic acidosis have been reported so far. The Applicant has provided data showing that the renal function did not deteriorate further over time in the subset of subjects with baseline eGFR <60 mL/min/1.73 m^2 in the four studies with ertugliflozin in combination with metformin. In the Ertu/met pool, no subjects with eGFR <60 mL/min/1.73 m^2 reported any volume depletion- or renal-related adverse events.

2.7. Risk Management Plan

Safety concerns

Important identified risks	Volume depletion DKA with atypical presentation Lactic acidosis
Important potential risks	Renal impairment Lower limb amputations Bone fracture Pancreatitis
Missing information	Use in elderly patients (≥75 years) Use in pregnancy and breastfeeding Use in patients with CHF Class II-IV Long-term CV safety

Pharmacovigilance plan

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned/Started)	Date for Submission of Final Study Report (Planned or Actual)
Study 8835-004/B1521021/ Randomized, Double-blind, Placebo-Controlled, Parallel-Group Study To Assess Cardiovascular Outcomes Following Treatment with Ertugliflozin (MK 8835/PF-04971729) in Subjects with T2DM and Established Vascular Disease Category 3	To continue monitoring and gain further information on 1) the characteristics of ertugliflozin/metformin use in patients with CHF Class II-III 2) the long-term CV safety profile in patients treated with ertugliflozin/metformin 3) the frequency and characteristics of volume depletion events in patients treated with ertugliflozin/metformin 4) the frequency and characteristics of events of DKA in patients treated with ertugliflozin/metformin 5) the frequency and characteristics of events of renal impairment in patients treated with ertugliflozin/metformin 6) the frequency and characteristics of events of lower limb amputation in patients treated with ertugliflozin 7) the frequency and characteristics of events of bone fracture in patients treated with ertugliflozin/metformin 8) the frequency and characteristics of events of pancreatitis in patients treated with ertugliflozin/metformin 9) the characteristics of ertugliflozin/metformin use in elderly patients (≥75 years)	Use in patients with CHF Class II-IV, long term CV safety, volume depletion, DKA with atypical presentation, renal impairment, lower limb amputations, bone fracture, pancreatitis and use in elderly patients (≥75 years).	Started	Final report: 2020

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned/Started)	Date for Submission of Final Study Report (Planned or Actual)
Post-authorization safety study (PASS) to assess the risk of diabetic ketoacidosis (DKA) among type 2 diabetes mellitus patients treated with ertugliflozin compared to patients treated with other antihyperglycaemic agents Category 3	To assess the risk of DKA in new users of ertugliflozin, compared with new users of other antihyperglycaemic agents	DKA with atypical presentation	Planned	Study protocol submission to the EMA for review and approval: December 2018. The timeline for start of study, end of study and final study report submission will be included in the full protocol. Feasibility assessment report: Q4 2020 Final study report: The final report will be submitted once the required amount of person-years of exposure to ertugliflozin has been accumulated in a database in order to conduct the study. The timeline for this report will depend on sample size required to

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned/Started)	Date for Submission of Final Study Report (Planned or Actual)
				adequately power the study and the rate of market uptake of ertugliflozin, for which limited information is available at this time. The final report is estimated to be submitted no later than December 2023

In the clinical trial programme of ertugliflozin, the applicant has committed to provide standard queries to investigators when subjects develop preceding events, but have not (yet) progressed to amputations.

For the PASS to assess the risk of diabetic ketoacidosis (DKA) among type 2 diabetes mellitus patients treated with ertugliflozin compared to patients treated with other antihyperglycaemic, the applicant has committed to submit an assessment of the characteristics of the database(s) used for feasibility assessment, including the type of data, availability of relevant data and comparability of the database population to the general T2DM population, at the time of submission of the study protocol for review by PRAC.

Risk minimisation measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important Identified Risks		
Volume depletion	Text in Product Circular including: Posology and Method of Administration Special Warnings and Precautions for Use Undesirable Effect	None
DKA with atypical presentation	Text in Product Circular including: Contraindications Special Warnings and Precautions for Use Undesirable Effect	None
Lactic acidosis	Text in Product Circular including: Contraindications	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	Special Warnings and Precautions for Use Overdosage	
Important Potential Risks		
Renal impairment	Text in Product Circular including: Posology and Method of Administration Contraindications (severe renal impairment) Special Warnings and Precautions for Use Undesirable Effect	None
Lower Limb Amputations	Text in Product Circular including: Special Warnings and Precautions for Use	None
Bone fracture	None	None
Pancreatitis	None	None
Missing Information		
Use in elderly patients (≥75 years)	Text in Product Circular including: Posology and Method of Administration Special Warnings and Precautions for Use Undesirable Effects	None
Use in pregnancy and breastfeeding	Text in Product Circular including: Fertility, Pregnancy and Lactation	None
Use in patients with CHF Class II-IV	Text in Product Circular including: Special Warnings and Precautions for Use Also, text pertaining to the identified risk of lactic acidosis	None
Long-term CV safety	None	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 1.12.2017. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of ertugliflozin with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers ertugliflozin to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Segluromet (ertugliflozin / metformin hydrochloride) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The indication for Segluromet is:

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

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

(For study results with respect to combinations and effects on glycaemic control, see sections 4.4, 4.5 and 5.1.)"

The aim of therapy is to improve metabolic control in terms of blood glucose, thereby decreasing the risk of microvascular and expected to decrease macrovascular long-term complications.

3.1.2. Available therapies and unmet medical need

Despite the availability of a broad array of AHAs, only approximately half of patients with T2DM achieve glycaemic control per treatment guidelines. There are several factors contributing to the low attainment of A1C goals. First, patients with T2DM exhibit declining β-cell function, which influences disease progression and leads to elevated A1C levels over time. Second, increased body weight leads to worsening insulin resistance. Finally, several classes of anti-hyperglycaemic medications are associated with adverse reactions, including weight gain (which may further worsen underlying insulin resistance), hypoglycaemia, oedema, or gastrointestinal effects, which often limit their use.

The management of chronic diseases like T2DM is often limited by clinical inertia: the delay or failure to escalate or alter therapy when the therapeutic effect is not attained. Use of a combination of two different classes of agents may improve the efficacy of the treatment. Use of a FDC has previously been shown to improve adherence with the treatment regimen.

3.1.3. Main clinical studies

Four phase 3 studies are included in this registration dossier. All were randomized, double-blind, parallel-group studies. The primary assessment of efficacy was performed after 26 or 52 weeks of treatment.

Two of the pivotal studies investigated ertugliflozin as add-on to ongoing metformin treatment.

In study P007/1017, ertugliflozin 5 mg and 15 mg respectively was compared to placebo. The overall study duration was 104 weeks with the primary endpoint measured at 26 weeks.

In study P002/1013, ertugliflozin 5 mg and 15 mg respectively was compared to glimepiride and the primary objective was to show that ertugliflozin 15 mg and 5 mg was non-inferior to glimepiride. The overall study duration was 104 weeks with the primary endpoint measured at 52 weeks.

In the other two studies, triple combination with ertugliflozin, metformin and sitagliptin was investigated.

Study P006/1015 included patients on stable background therapy with metformin ≥1500 mg/day and sitagliptin 100 mg/day. Ertugliflozin 5 mg and 15 mg respectively (as add-on to metformin + sitagliptin) was compared to placebo. The overall study duration was 52 weeks with the primary endpoint measured at 26 weeks.

Study P005/1019 was a factorial study comparing ertugliflozin 5 mg and 15 mg with the combined treatment of both ertugliflozin doses with sitagliptin 100 mg as add-on to metformin treatment. A treatment arm with sitagliptin 100 mg was also included. The overall study duration was 52 weeks with the primary endpoint measured at 26 weeks.

A total of 4863 subjects were randomly assigned to treatment in the Phase 3 studies supporting registration of ertugliflozin, with 2597 of these subjects randomly assigned to treatment with

ertugliflozin on a background of metformin. In the studies, ertugliflozin and metformin were administered as free combination and metformin was given according to label.

3.2. Favourable effects

The same primary endpoint, change from baseline HbA1c, was applied in all studies.

In study P007/1017 ertugliflozin was given as add-on to metformin and compared to placebo. The treatment difference versus placebo was -0.70% (-0.87,-0.53) for the 5 mg dose and -0.88% (-1.05,-0.71) for the 15 mg dose.

In the non-inferiority study P002/1013, ertugliflozin 5 mg and 15 mg was compared to glimepiride in patients on background metformin treatment. The treatment difference vs glimepiride was 0.18% (0.06, 0.30) for the 5 mg dose and 0.10 (-0.02, 0.22) for the 15 mg dose. Thus non-inferiority was shown for the 15 mg dose as the non-inferiority margin chosen was 0.3% whereas the outcome for the 5 mg was of borderline character since the chosen delta of 0.3% was included in the upper limit of the 95% CI. Regarding assessment of robustness, in addition to the PP analyses, analyses based on the modified FAS were performed (using both the ER and IR approach). The outcomes, irrespective of analysis and comparison, were very similar and supported the primary outcomes. The change from baseline in HbA1c was -0.56 ± 0.045 for the 5 mg dose and -0.64 ± 0.045 for the 15 mg dose.

In study P006/1015, ertugliflozin was given as add-on to metformin and sitagliptin with placebo as control. In this study, the treatment difference versus placebo was -0.69% (-0.87,-0.50) for the 5 mg dose and -0.76% (-0.95,-0.58) for the 15 mg dose.

In the factorial study P005/1019, where ertugliflozin was either given as single therapy or co-administered with sitagliptin on background metformin therapy, single therapy with ertugliflozin 5 mg and 15 mg resulted in very similar HbA1c reductions of -1.02% and -1.08%, respectively. The HbA1c reduction with single therapy sitagliptin 100 mg was -1.05%. Both combinations (ertugliflozin 5mg + sitagliptin 100 mg and ertugliflozin 15 mg + sitagliptin 100 mg) resulted in very similar differences in treatment effect compared to the respective single component of -0.43% to -0.49%.

In the placebo-controlled studies, the magnitude of effect of about 0.7-0.9% and was consistent in studies P007/1017 (metformin only) and P006/1015 (metformin + sitagliptin). In studies P002/1013 and P005/1019, no placebo-adjustment was made. In these studies, the change from baseline in HbA1c ranged from -0.6% to -1.1%. It may therefore be concluded that ertugliflozin provides a relevant contribution to the effect of the FDC.

In study P002/1013, the duration of phase A of the study was 52 weeks, thus this study provides some long-term data on the effect of ertugliflozin. The data show that the maximum effect was observed after 12 weeks and the remained stable in contrast with the effect of glimepiride which reached its maximum effect after 18 weeks thereafter the effect slowly decreased. The duration of the effect was further supported by data from the four extension studies that were finalised during the procedure.

The outcome of the secondary endpoints was consistent with the primary endpoint across the studies.

In all studies, 26 to 40% of subjects achieved the treatment goal of HbA1c <7.0% when ertugliflozin was given in combination with metformin only. Higher responder rates were observed when ertugliflozin was given in triple combination with sitagliptin (32 to 52%).

Across the studies, consistent reductions from baseline in body weight were observed with ertugliflozin 5 mg and 15 mg. The placebo or active control adjusted weight reduction ranged from 1.6 to 4.3 kg. The largest treatment difference was observed in the ertugliflozin vs glimepiride study (study

P002/1013) due to the weight increase observed in the glimepiride treated group. There was no clear dose response relationship with regards to body weight.

Reductions from baseline in sitting SBP were observed with ertugliflozin 15 mg and 5 mg across the phase 3 studies regardless of between-study differences in background medication and study designs. The reduction in SBP ranged from -2.8 mmHg to -4.8 mmHg with slightly larger reductions in the higher ertugliflozin dose groups. Reductions in DBP were observed in line with the data for SBP.

Three additional phase 3 studies were included in the submission in order to support the efficacy of ertugliflozin. Study P003/1022 investigated the effect of ertugliflozin as monotherapy versus placebo. The treatment differences in the change from baseline in HbA1c was -0.99% (-1.22,-0.76) for the 5 mg and -1.16% (-1.39, -0.93) for the 15 mg dose of ertugliflozin compared to placebo. Secondary glycaemic endpoints all supported the primary endpoint. The proportion of patients with HbA1c<7.0% was 28% for the 5 mg dose and 36% for the 15 mg dose of ertugliflozin compared to 13% in the placebo group.

In study P017/1047, combination therapy with ertugliflozin and sitagliptin was initiated without other AHA background treatment. The treatment effect was -1.16% (95%CI:-1.49, -0.84) for the 5 mg dose and -1.24% (95%CI:-1.57, -0.91) for the 15 mg dose. This effect was comparable to that observed in study P005/1019. Secondary glycaemic endpoints all supported the primary endpoint. The proportion of patients with HbA1c<7.0% was higher in the low dose of ertugliflozin compared to the high dose (36% vs 31%).

In both these studies, a significant decrease in body weight of about 2 kg was observed with both ertugliflozin doses. Decreases in SBP and DBP were also observed.

Study P001/1016 included patients with renal impairment (eGFR of ≥30 to <60 mL/min/1.73 m^2) and on stable AHA treatment. All AHAs (including insulin) except metformin, rosiglitazone and other SGLT2-inhibitors were allowed. In the primary analysis, no relevant effect on HbA1c was observed for any of the doses compared to placebo. In a post-hoc analysis in the overall cohort excluding patients who had blood samples positive for metformin (see below), a statistically significant reduction in HbA1c was observed in the high dose group (-0.33%, 95%CI: -0.55, -0.11). A post-hoc analysis was also conducted in the subgroup of patients with eGFR 45-60. The change from baseline in HbA1c was comparable to that of the overall cohort.

This was the only study where patients were allowed to use insulin and/or SU as background medication. The subgroup of subjects using insulin at baseline showed a change in HbA1c from baseline both in the ertugliflozin 15 mg group (-0.36% [-0.57, -0.16]) and in the ertugliflozin 5 mg group (-0.12% [-0.33, 0.09]). There was no difference in outcome versus placebo for the ertugliflozin 5 mg group and a statistically non-significant improvement of -0.2% for the ertugliflozin 15 mg group. In the subgroup of subjects on a sulfonylurea at baseline, the HbA1c change from baseline was -0.45% (-0.69, -0.22) and -0.51% (-0.74, -0.28) for the ertugliflozin 15 mg and 5 mg groups, respectively. No treatment difference compared to placebo was observed.

Across the studies, no formal comparisons were made between the two doses of ertugliflozin. The treatment difference between the doses ranged from 0.06% to 0.18%. The difference in responder rates (HbA1c < 7.0%) between the two ertugliflozin doses was generally small (about 4-6%). Across the study program, numerically larger HbA1c reductions were observed with the higher dose. The treatment difference was most pronounced in the population with median HbA1c > 7.9%.

3.3. Uncertainties and limitations about favourable effects

Study P001/1016 included patients with moderate renal impairment. After breaking the blind in part A of the study, it was discovered that 78 subjects (out of 467) had blood samples positive for metformin. The reasons for the use of metformin in contrary to protocol could not be clarified. Audits have not identified any systematic GCP issues and the study data was accepted.

Study P001/1016 was also the only study where patients were allowed to use insulin and/or SU as background medication. Although clinically relevant reductions in HbA1c from baseline was observed with at least the higher ertugliflozin dose when used in combination with either insulin or SU, no statistically significant differences were observed compared to placebo. It can, however, be hypothesised that a more pronounced effect is expected in patients with normal renal function.

3.4. Unfavourable effects

The rate of hypoglycaemia was relatively low, although increased for ertugliflozin (5.0% and 4.5% for ertugliflozin 5 mg and 15 mg) compared to placebo (2.9%).

There was an increased risk in ertugliflozin-treated subjects of genital infections. In female subjects the incidence of genital infections was 9.1%, 12.2% and 3.0% for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo and in male subjects the incidence was 3.7%, 4.2% and 0.4% respectively. Most of the events were mild or moderate in intensity.

The incidence of volume depletion events was low (<2%) and not notably different across the ertugliflozin and placebo groups. Subjects with eGFR <60 mL/min/1.73 m^2, subjects ≥65 years of age and subjects on diuretics had a higher incidence of volume depletion in the ertugliflozin groups relative to the comparator group.

The bone resorption marker CTX was more increased in the ertugliflozin groups than in the placebo/comparator group at week 26, 52 and 104; although the difference to the comparator group was less pronounced at week 104. The bone formation marker P1NP was increased in both the ertugliflozin and the comparator groups. In moderate renal impaired patients, there was an imbalance in CTX of the same magnitude as in study P007/1017. The clinical implication of the observed changes in the bone markers is not clear. However, interim 52 week and final 104 week BMD data showed small changes in BMD which was statistically significant only for the 'total hip' data in the ertugliflozin 15 mg group, which provides reassurance. Moreover, the cumulative incidence of adjudicated confirmed fractures at week 104 was similar across the groups; 0.9% (n=15) for ertugliflozin 5 mg, 0.6% (n=11) for ertugliflozin 15 mg group and 0.8% (n=12) for the comparator group. The Applicant has confirmed to provide final summarized data of all adjudicated confirmed fractures, including the incidence of low trauma fractures, at the time of submission of the final CSR for the study P007/1017.

There were transient and small decreases in eGFR and small increases in creatinine in the ertugliflozin groups that returned to or towards baseline at week 26 but no imbalance between ertugliflozin and placebo in renal-related events. In moderate renal impaired patients (P001/1016), the decrease in eGFR was slightly larger and did not return to baseline at week 26; however, reversed after treatment discontinuation. The incidence of renal-related events was higher in the ertugliflozin groups relative to placebo in study P001/1016.

Small increase in LDL-C, HDL-C and total cholesterol was noted at week 26 in the placebo-controlled pool. Data supporting an assessment of CV safety profile is very limited with only few cases in each

treatment group. There is a numerical imbalance between ertugliflozin and placebo in the SOC Cardiac disorder, but no conclusion can be drawn. The CV outcome study is ongoing.

Subgroups

In subjects ≥65 years of age, there was an increased risk for events related to volume depletion and events of renal impairment. Further analysis of the data indicate that age per se does not increase the risk of renal-related events but that this risk is related to renal function which is commonly decreased in the elderly.

In subjects with moderate renal impairment treated with ertugliflozin, the decrease in eGFR was slightly larger than in the placebo-controlled Pool, and did not return to baseline at week 26 at week 26 and 52. In the same subgroup at week 26 and 52, CTX increased from baseline more in the ertugliflozin groups than in the placebo/comparator group. In subjects with baseline eGFR 45 to <60 mL/min/1.73 m^2, events of volume depletion were more common than for the comparator group.

The data in the Ertugliflozin add-on to Metformin Phase III program identified no additional safety or tolerability concerns for the combination of the medicinal products relative to the two agents given alone. No event of lactic acidosis has been reported so far in ertugliflozin/metformin treated subjects.

3.5. Uncertainties and limitations about unfavourable effects

Data supporting an assessment of CV safety profile is very limited with only few cases in each treatment group. There is a numerical imbalance between ertugliflozin and placebo, but no conclusion can be drawn. However, considering the known mechanism of action and experience from other products in the class, it is acceptable to provide data from the CV outcome study after a potential approval.

While metformin is not associated with a decrease in eGFR, it is cleared renally, and in the presence of severe renal impairment, metformin has been reported to be associated with lactic acidosis. Due to risk of volume depletion and decreased renal failure of ertugliflozin, the risk of lactic acidosis is relevant for the combination of ertugliflozin and metformin. Patients with moderate renal impairment may be vulnerable to ertugliflozin - metformin combination therapy as their renal function may further be impaired, questioning the safety, therefore the acceptability, of this combination in this patient group. However, so far no events of lactic acidosis have been reported with the combination.

3.6. Effects Table

Table 37: Effects Table for Segluromet in the treatment of T2DM.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Change in HbA1c	Ertugliflozin 5 mg vs placebo	%	-0.73 ± 0.062	-0.03 ± 0.065	-0.70 (-0.87,-0.53)	Add-on to metformin P007/1017
Change in HbA1c	Ertugliflozin 15 mg vs placebo	%	-0.91 ± 0.063	-0.03 ± 0.065	-0.88 (-1.05,-0.71)	Add-on to metformin P007/1017

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Change in HbA1c	Ertugliflozin 5 mg vs placebo	%	-0.79 ± 0.081	0.20 ± 0.089	-0.99 (-1.22, -0.76) p<0.001	Monotherapy P003/1022
Change in HbA1c	Ertugliflozin 15 mg vs placebo	%	-0.96 ± 0.082	0.20 ± 0.089	-1.16 (-1.39, -0.93) p<0.001	Monotherapy P003/1022
Change in HbA1c	Ertugliflozin 5 mg vs glimepiride	%	-0.56 ± 0.045	-0.74 ± 0.045	Non-inferiority not shown 0.18 (0.06, 0.30)	P002/1013
Change in HbA1c	Ertugliflozin 15 mg vs glimepiride	%	-0.64 ± 0.045	-0.74 ± 0.045	Non-inferiority shown 0.10 (-0.02, 0.22)	P002/1013
Change in HbA1c	Renal impairment Ertugliflozin 5 mg vs placebo	%	-0.28 ± 0.079	-0.14 ± 0.082	-0.14 (-0.36, 0.08)	Post-hoc analysis P001/1016
Change in HbA1c	Renal impairment Ertugliflozin 15 mg vs placebo	%	-0.47 ± 0.082	-0.14 ± 0.082	-0.33 (-0.55, -0.11)	Post-hoc analysis P001/1016
Change in body weight	Ertugliflozin 5 mg vs placebo	kg	-3.01 ± 0.199	-1.33 ± 0.208	-1.67 (-2.24, -1.11) p<0.001	Add-on to metformin P007/1017
Change in body weight	Ertugliflozin 15 mg vs placebo	kg	-2.93 ± 0.202	-1.33 ± 0.208	-1.60 (-2.16, -1.03) p<0.001	Add-on to metformin P007/1017
Change in body weight	Ertugliflozin 5 mg vs glimepiride	kg	-2.96 ± 0.177	0.91 ± 0.176	-3.87 (-4.36, -3.38) p<0.001	P002/1013
Change in body weight	Ertugliflozin 15 mg vs glimepiride	kg	-3.38 ± 0.177	0.91 ± 0.176	-4.29 (-4.77, -3.80) p<0.001	P002/1013
Unfavourable Effects						
Hypo-glycaemia	Ertugliflozin vs placebo	Docum-ented hypo-glycaemia (≤70 mg/dL [3.9 mmol/L])	Ertugliflozin 5 mg and 15 mg (5.0% and 4.5%)	Placebo (2.9%)	The incidence of hypoglycaemia was relatively low, although, increased for ertugliflozin compared to placebo	PBO Pool
Change from baseline to week 26 in CTX	Ertugliflozin vs placebo	% change from baseline	Ertugliflozin 5 mg and 15 mg (29% and 38%)	Placebo (10%)	Imbalance in bone resorption marker for ERTU vs placebo	Study P007/1017
Change from baseline to week 26 in CTX	Ertugliflozin vs placebo	% change from baseline	Ertugliflozin 5 mg and 15 mg (33% and 34%)	Placebo (9.6%)	Imbalance in bone resorption marker for ERTU vs placebo	Study P001/1016
Lactic acidosis	Total incidence	%	Ertugliflozin 0.0%	Comparator 0.0%		Broad pool

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The current application concerns a FDC with the new medicinal product ertugliflozin and metformin. The clinical data provided show that ertugliflozin per se has clinically relevant effects on both glycaemic control, in terms of HbA1c reduction, and reductions in body weight, both when given as monotherapy

and in combination with metformin and/or sitagliptin. The size of the glucose-lowering effect is comparable to that observed with glimepiride although non-inferiority has not been formally shown for the lower dose. The magnitude of effect is comparable to that observed with already approved SGLT2-inhibitors. Beneficial effects were also observed on SBP but although the effect was consistent across the study program, statistical significance was not always reached.

Since not only hyperglycaemia but also hypertension and overweight are substantial treatment challenges in T2DM, these effects are beneficial.

The data submitted also show that the effect is maintained up to one year.

In the studies where ertugliflozin was given as add-on to metformin the added effect was clinically relevant, thus the data support the use of ertugliflozin and metformin as FDC.

The proposed indication states that ertugliflozin can be used in combination with other medicinal products for the treatment of diabetes. The clinical study program supporting the application mainly focused on the use of ertugliflozin in combination with metformin and/or sitagliptin which is acceptable. The data in combination with SU and/or insulin is limited since patients were allowed to use insulin and/or SU as background medication only in study P001/1016. Study P001/1016 provides some data to support a pharmacological effect of ertugliflozin in combination with insulin or SU even though the glucose lowering effect was limited in this setting. However, based on the knowledge about the mechanism of action for ertugliflozin, a more pronounced effect of ertugliflozin when combined with SU and/or insulin is expected in patients with normal renal function. The safety data provided with study P001/1016 show an increased risk of hypoglycaemia with these combinations. This risk is deemed to be adequately mitigated by the warnings included in the SmPC. Therefore the benefit risk is considered positive for the combined use of ertugliflozin and insulin and/or SU.

The effect of ertugliflozin is dependent on renal function. Data in patients with moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73 m^2) only showed a modest treatment effect with the highest dose. Taking into account the modest effect also with the highest dose in patients with eGFR 45-60, it is recommended not to initiate treatment in patients with eGFR < 60 although treatment may be continued until eGFR falls below 45.

Across the studies, no formal comparisons were made between the two doses of ertugliflozin. The treatment difference between the doses ranged from 0.06% to 0.18%. The difference in responder rates (HbA1c < 7.0%) between the two ertugliflozin doses was generally small (about 4-6%). These data are in line with the data from the phase 1 and phase 2 studies. However, numerically larger HbA1c reductions were consistently observed with the higher dose. The treatment difference was most pronounced in the population with median HbA1c > 7.9%. Thus the higher dose may provide additional benefit for patients with a greater need for better metabolic control.

The safety profile for ertugliflozin is mostly consistent with other SGLT-2 inhibitors. The most important risk for ertugliflozin is associated with the mechanism of action (glycosuria and diuretic effect) such as volume depletion, genital infections and hypoglycaemia. The majority of these events were mild or moderate and manageable.

3.7.2. Balance of benefits and risks

The effect of the FDC with ertugliflozin and metformin on glycaemic control in patients with normal renal function or mild renal impairment has been adequately shown as well as beneficial effects on body weight and SBP. The effects observed in this population are considered to outweigh the observed risks with treatment.

The benefits in patients with moderate renal impairment are less pronounced than in patients with better renal function. Therefore initiation of treatment is restricted to patients with eGFR > 60.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Segluromet is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Segluromet is favourable in the following indication:

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

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

(For study results with respect to combinations and effects on glycaemic control, see sections 4.4, 4.5 and 5.1.)"

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that ertugliflozin is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.