EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 January 2018
EMA/86941/2018
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Steglujan

International non-proprietary name: ertugliflozin / sitagliptin

Procedure No. EMEA/H/C/004313/0000

## Note

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

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# Table of contents

# List of abbreviations

| Abbreviation | Definition |
|---|---|
| %AR | Applied radioactivity in percent |
| A1C | glycosylated hemoglobin (hemoglobin A1c) |
| AACE | American Association of Clinical Endocrinologists |
| ABPM | ambulatory blood pressure monitoring |
| ADA | American Diabetes Association |
| AHA | anti-hyperglycemic agent |
| AIBN | 2,2'-Azobis(2-methylpropionitrile) |
| ALT (SGPT) | alanine aminotransferase |
| Alu | aluminium |
| AMP | adenosine monophosphate |
| AST (SGOT) | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| $AUC_{inf}$ | area under the concentration-time curve from time zero to infinity |
| BCS | biopharmaceutical classification system |
| BE | bioequivalence |
| BMI | body mass index |
| CHMP | Committee for Medicinal Products for Human use |
| CFU | colony forming units |
| CI | confidence interval |
| CKD | chronic kidney disease |
| cLDA | constrained longitudinal data analysis |
| $C_{max}$ | maximum observed plasma concentration |
| CPP | critical process parameter |
| CQA | Critical Quality Attribute |
| CS | Control strategy |
| CSR | clinical study report |
| CV | cardiovascular |
| CVOT | cardiovascular outcome trial |
| CYP | cytochrome P450 |
| DBP | diastolic blood pressure |
| DDI | drug-drug interaction |
| DOC | Dissolved Oxygen Concentration |
| DoE | Design of experiments |
| DPP | dipeptidyl peptidase |
| 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 |
| EASD | European Association for the Study of Diabetes |
| ECG | electrocardiogram |
| ECHA | European Chemicals Agency |
| eGFR | estimated glomerular filtration rate |
| EMA | European Medicines Agency |
| ESFA | European Food Safety Authority |
| ESI-MS | electrospray positive ionization mass spectra |
| ESRD | end stage renal disease |
| ER | excluding rescue |
| ERA | Environmental risk assessment |
| EU | European Union |
| FA | Focus area |
| FAS | full analysis set |
| FDA | Food and Drug Administration |
| FDC | fixed-dose combination |
| FeCl3 | Iron (III) chloride |
| Fpen | Market penetration factor |
| FPG | fasting plasma glucose |
| GC | gas chromatography |
| GCP | Good Clinical Practice |

| Abbreviation | Definition |
|---|---|
| GIP | glucose-dependent insulinotropic polypeptide |
| GLP-1 | glucagon-like peptide-1 |
| GMP | good manufacturing practice |
| GMR | geometric mean ratio |
| HCTZ | hydrochlorothiazide |
| HDL-C | high-density lipoprotein-cholesterol |
| HDPE | high density polyethylene |
| hOAT-3 | human organic anion transporter-3 |
| 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 approach |
| IV | intravenous |
| $Kd_{oc}$ | Adsorption distribution coefficient normalized to organic content in matrix |
| KF | Karl Fischer |
| KOH | potassium hydroxide |
| J2R | jump-to-reference multiple-imputation method |
| LDA | longitudinal data analysis |
| 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 |
| MAR | missing at random |
| MNAR | missing-not-at-random assumption |
| MCAR | missing completely at random |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mFAS | modified FAS |
| 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 |
| PD | pharmacodynamic(s) |
| PDLC | pre-defined limit of change |
| $PEC_{SED}$ | Predicted environmental concentration in sediments |
| $PEC_{SW}$ | Predicted environmental concentration in surface waters |
| P-gp | P-glycoprotein |
| Ph. Eur. | European Pharmacopoeia |
| PK | pharmacokinetic(s) |
| PNEC | Predicted no-effect concentration |
| PPG | post-prandial glucose |
| 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 |
| QTc | QT interval corrected |
| QTPP | quality target product profile |
| RA | risk assessment |
| RH | relative humidity |
| RQ | (Environmental) Risk Quotient |
| RTG | renal threshold for glucose |

| Abbreviation | Definition |
|---|---|
| SBP | systolic blood pressure |
| SCE | Summary of Clinical Efficacy |
| SCS | Summary of Clinical Safety |
| SD | standard deviation |
| SGLT1 | sodium-glucose co-transporter 1 |
| SGLT2 | sodium-glucose co-transporter 2 |
| SmPC | summary of product characteristics |
| SMQ | standardized MedDRA query |
| SOC | system organ class |
| TAMC | total aerobic microbial count |
| T2DM | type 2 diabetes mellitus |
| TECOS | Trial Evaluating Cardiovascular Outcomes with Sitagliptin |
| $T_{max}$ | time to $C_{max}$ |
| TYMC | total combined yeasts/moulds count |
| UGE | urinary gluclose excretion |
| UGT | uridine 5'-diphospho-glucuronosyltransferase |
| UK | United Kingdom |
| UKPDS | United Kingdom Prospective Diabetes Study |
| ULN | upper limit of normal |
| US | United States |
| 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 1 February 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Steglujan, 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:

Steglujan, fixed-dose combination of ertugliflozin and sitagliptin, 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

- when metformin and/or a sulphonylurea (SU) do not provide adequate glycaemic control.

- when metformin and/or a sulphonylurea (SU) and one of the monocomponents of Steglujan do not provide adequate glycaemic control.

- in patients already being treated with the combination of ertugliflozin and sitagliptin as separate tablets.

(See sections 4.2, 4.4, 4.5, and 5.1 for available data on combination studied.)

**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/0032/2014 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.

## 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 non-clinical and 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 1 February 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 Steglujan on 25 January 2018.

# 2. Scientific discussion

## *2.1. Problem statement*

### 2.1.1. Disease or condition

The indication as initially proposed for Steglujan is:

“Steglujan, fixed-dose combination of ertugliflozin and sitagliptin, 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

- when metformin and/or a sulphonylurea (SU) do not provide adequate glycaemic control.

- when metformin and/or a sulphonylurea (SU) and one of the monocomponents of Steglujan do not provide adequate glycaemic control.

- in patients already being treated with the combination of ertugliflozin and sitagliptin as separate tablets.

(See sections 4.2, 4.4, 4.5, and 5.1 for available data on combination studied.)

### 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/sitagliptin FDC combines two AHAs with complementary mechanisms of action to improve glycaemic control in patients with T2DM. Because of the complementary mechanisms of actions of ertugliflozin and sitagliptin, it is expected that the combination of ertugliflozin and sitagliptin will provide additional glycaemic improvement without increasing risk of hypoglycaemia, while maintaining the beneficial effects on body weight and SBP from SGLT2 inhibition.

## *About the product*

This is an application for the use of ertugliflozin administered as a fixed-dose combination (FDC) with sitagliptin. Two strengths of film-coated, immediate-release, FDC tablets of ertugliflozin and sitagliptin for qd administration were developed and proposed for commercialization.

- Ertugliflozin 5 mg/sitagliptin 100 mg
- Ertugliflozin 15 mg/sitagliptin 100 mg.

Initially two additional strengths were proposed (ertugliflozin 5 mg/sitagliptin 50 mg and ertugliflozin 15 mg/sitagliptin 50 mg). However, due to changes regarding the use of sitagliptin in patients with renal impairment, these strengths became redundant and were withdrawn.

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.

Sitagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Concentrations of the active intact hormones are increased by sitagliptin, thereby increasing and prolonging the action of these hormones. By increasing and prolonging active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner.

## *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 5 mg or 15 mg ertugliflozin (as ertugliflozin L-pyroglutamic acid) with 100 mg sitagliptin (as sitagliptin phosphate monohydrate) as active substances.

Other ingredients are: tablet core; microcrystalline cellulose (E460), calcium hydrogen phosphate (anhydrous), croscarmellose sodium, sodium stearyl fumarate (E487), magnesium stearate (E470b), tablet coat; hypromellose (E464), hydroxypropyl cellulose (E463), titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172), iron oxide black (E172), carnauba wax (E903).

The product is available in Alu/PVC/PA/Alu blisters in packs of 14, 28, 30, 84, and 90 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 a co-crystal 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) haveve the following structures:

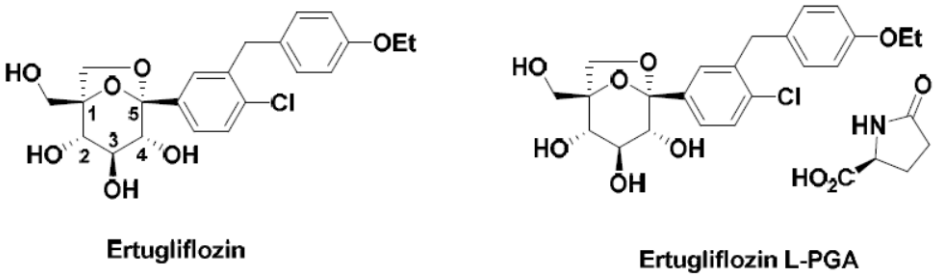



**Figure 1: Ertugliflozin L-PGA active substance structure**

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.

The acceptability of L-PGA as coformer was confirmed.Relevant information in line with requirements stated in the reflection paper on the use of co-crystals and other solid state forms of active substances in medicinal products (CHMP/CVMP/QWP/284008/2015) was provided.The safety of L-PGA was acceptably confirmed by the applicant by reference to toxicological studies, the fact that pyroglutamic acid is generated endogenously and that L-PGA had been previously reviewed by the European Food Safety Authority (EFSA) where its use in supplements up to 3 grams per day was considered to be of no concern. (This amount is significantly higher than the 3.42 mg L-PGA present in the maximum daily dose (15 mg) of ertugliflozin.) CHMP agreed that L-PGA can be considered a reagent and not a starting material in line with ICH Q11 based on the fact that L-PGA is a commonly available commodity chemical used in several industries and it may be obtained from L-glutamic acid upon heating, it is not incorporated into the structure of the active substance via a covalent bond and it exists as an endogenous substance. The synthesis and quality control strategy of L-PGA was described by the applicant. Impurities likely to arise during the manufacture of L-PGA were discussed and have been evaluated according to ICH M7.

***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 specification (Ertugliflozin L-PGA) 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 batches of 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 - sitagliptin

### *General information*

The chemical name of sitagliptin phosphate monohydrate is 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-[3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine phosphate (1:1) monohydrate corresponding to the molecular formula $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$. It has a relative molecular mass of 523.32 g/mol and the following structure:

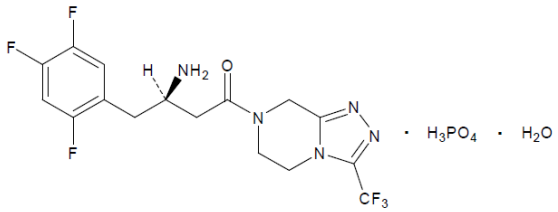



**Figure 2: Sitagliptin active substance structure**

The chemical structure of sitagliptin phosphate was elucidated by a combination of UV, IR, MS, 1H-NMR, 13C- NMR. The solid state properties of the active substance were measured by X-ray crystallography.

Sitagliptin phosphate monohydrate is a white to off-white powder, non-hygroscopic and soluble in water. Sitagliptin phosphate monohydrate is the subject of a Ph. Eur. monograph (2778).

Sitagliptin phosphate exhibits stereoisomerism due to the presence of one chiral centre. Enantiomeric purity is controlled routinely in the active substance specification by a chiral HPLC test. Polymorphism has been investigated. . Sitagliptin phosphate used for commercial manufacture is a crystalline monohydrate.

### *Manufacture, characterisation and process controls*

Sitagliptin phosphate monohydrate is synthesized in four main steps using well defined starting materials with acceptable specifications. The development/optimisation of the commercial manufacturing process for sitagliptin active substance followed a mix of traditional and enhanced approach principles. Quality by Design (QbD) elements were used for the development ofthe manufacturing process. The process development utilized formal risk assessment (RA), multivariate design of experiments (DOEs), first principles modeling and appropriate univariate experiments to establish a design space (DS) and/or Proven Acceptable Ranges (PARs) leading to a holistic control strategy (CS) to produce active substance conforming to the desired critical quality attributes (CQA).

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented and are acceptable. Design Spaces and Proven Acceptable Ranges (PARs) are defined for a number of manufacturing steps. PAT-methods can be used as alternative to conventional methods for some in-process controls.

During the procedure the applicant confirmed that the content of the MAA dossier concerning the manufacture and control of sitagliptin phosphate monohydrate active substance is in line with the latest amendments made during earlier procedures for other sitagliptan-containing medicinal products of the same MAH.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.

***Specification***

The active substance specification includes tests for assay (HPLC), appearance, identity (IR, phosphates), impurities (HPLC), residue on ignition (Ph. Eur.), water (KF), particle size distribution (laser diffraction), residual solvents (GC) and chiral purity (HPLC).

The specification tests and acceptance criteria ensure compliance with the sitagliptin phosphate monohydrate Ph. Eur. monograph (2778).

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 onpilot and commercial batches in support of development, process validation and stability programs 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 manufacturers stored in a container closure system representative of that intended for the market for up to 36 monthsunder 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*:* assay, appearance, impurities, water content. 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 also performed and confirmed photostability.

Stress /forced degradation studies (at extreme thermal, humidity, photolytic, acidic, basic and oxidative stress considtions) to induce the formation of potential degradation products and demonstrate the stability indicating nature of the HPLC analytical procedures has been performed.

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***

Steglujan 5 mg/100 mg film-coated tablet is presented as a beige, almond-shaped, film-coated tablets debossed with “554” on one side and plain on the other side.

Steglujan 15 mg/100 mg film-coated tablet is presented as a brown, almond-shaped, film-coated tablets debossed with “555” on one side and plain on the other side.

The product is available in Alu/PVC/PA/Alu blisters in packs of 14, 28, 30, 84, and 90 film-coated tablets as described in section 6.5 of the SmPC.

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 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).

Excipients were chosen to provide a stable formulation that would be bioequivalent to the individual monotherapy tablets when co-administered. Prior knowledge on sitagliptin monotherapy tablets demonstrated that all selected excipients were compatible with sitagliptin. Excipient compatibility studies for ertugliflozin were conducted and confirmed compatibility.Prior knowledge of sitagliptin monotherapy tablet development was used to design the formulation and process. 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.

Ertugliflozin and sitagliptin monotherapy tablets were used throughout the clinical development programme, including in Phase III studies. A bioequivalence study was performed between the proposed market formulation tablets and the ertugliflozin and sitagliptin monotherapy tablets used in Phase III studies. The proposed market formulation tablets administered in the bioequivalence study are identical to the final market image with the exception that the tablets were not debossed. The study indicates that all strengths of Ertugliflozin/Sitagliptin Tablets are bioequivalent to their respective monotherapy tablet combinations which were used throughout Phase III safety and efficacy studies.

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 are claimed for a number of the manufacturing stepsand were acceptably justified. Both ertugliflozin and sitagliptin meet the requirements of a Biopharmaceutics Classification System (BCS) Class I drug due to high solubility across physiological pH range and high permeability. Ertugliflozin / sitagliptin tablets display rapid *in vitro* dissolution characteristics over the pH range (1.2 – 6.8). 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 (less than 2 min) and highly soluble active substances, and 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 Steglujan 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 five main steps:

1. Blending/Lubrication,
2. Compression,
3. Film coating,
4. Bulk packaging,
5. Blister packaging.

The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. Design spaces are claimed for a number of the manufacturing stepsand were acceptably justified.

A process validation protocol has been provided. The applicants position that the manufacturing process can be considered as standard despite having < 2% drug load for the ertugliflozin L-PGA cocrystal in 5/100 mg tablet, 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 and 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 sitagliptin (HPLC, UV), assay ertugliflozin (HPLC), assay sitagliptin (HPLC), degradation products ertugliflozin (HPLC), degradation products sitagliptin (HPLC), uniformity of dosage units ertugliflozin (Ph. Eur.), uniformity of dosage units sitagliptin (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 sitagliptin are both highly soluble and highly permeable, classified as BCS 1, 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 confirming 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 approachwas 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 Steglujan 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 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/sitagliptin tablets are of human or animal origin. The magnesium stearate and sodium stearyl fumarate used to manufacture ertugliflozin/sitagliptin tablets are of vegetable origin.

## 2.2.5. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substanced (ertugliflozin L-PGA and sitagliptin phosphate) 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

Steglujan, contains an active substance which was previously authorised in a medicinal product (sitagliptin, in JANUVIA), and an active substance which was not previously authorised (ertugliflozin). Steglujan (ertugliflozin/sitagliptin) is formulated as an immediate-release tablet for oral administration in 2 dose strengths (i.e. 5 mg or 15 mg ertugliflozin, each in combination with 100 mg sitagliptin).

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 $\geq$ 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 $\geq$ 5 mg/kg/day. Increased blood urea nitrogen (BUN) was also observed in all SD rat toxicity studies, at $\geq$ 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 $\geq$ 5 and $\geq$ 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 $\geq$ 25 mg/kg/day. Increased incidence of tubular mineralization occurred in males at $\geq$ 5 mg/kg/day in the 6-month study.

Dilatation of the renal pelvis was observed in males at $\geq$ 5 mg/kg/day in the 3- and 6-month studies, with the additional finding of pelvic inflammation at $\geq$ 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 ertuglfilozin 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*

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*

Ertuglfiflozin 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*

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 support 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). Together with a maximum dose of 15mg, both default and prevalence Fpen based surface water predicted environmental concentration PEC ($PEC_{SW}$) were >0.01ug/L and triggered a phase II assessment. The Phase I default Fpen (1%) gave a $PEC_{SW}$ of 0.075µg/L while the prevalence Fpen for type 2 diabetes (8.3%) gave 0.62ug/L.

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).

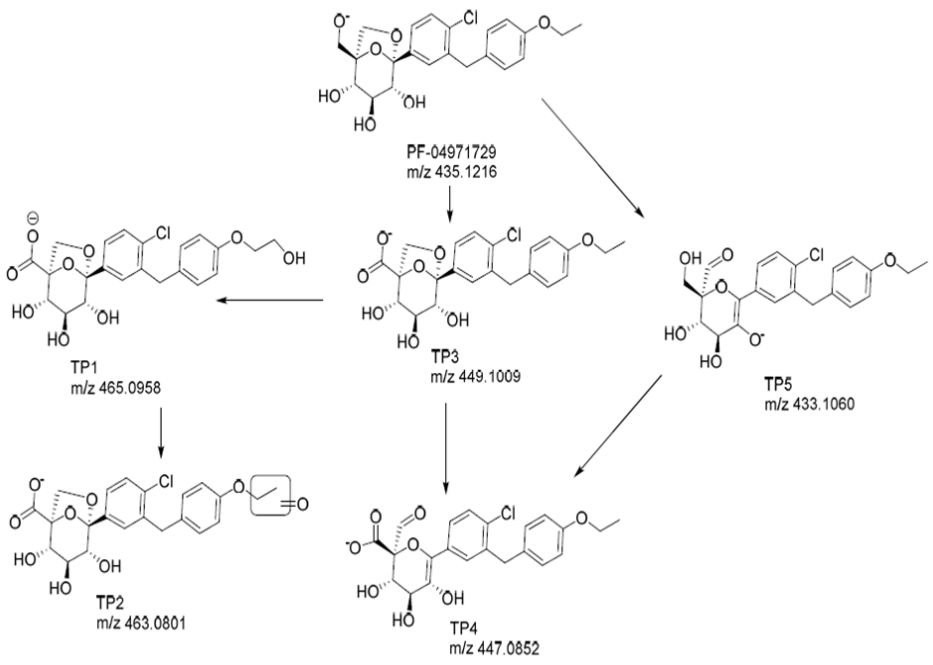



**Figure 3: Overview of proposed transformation product / degradation pathway for ertugliflozin (PF-04971729, m / z 435.1216). Transformation product 5 (TP5, m / z 433.1060) was found in all environmental compartments (sludge, surface water and sediment systems).**

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 | <u>*OECD TG308*</u><br>$DT_{50,\ water}$ = ~24-32d<br>$DT_{50,\ sediment}$ = ~15-56d<br>$DT_{50,\ whole\ system}$ = ~45-57d | Overall, unlikely to be persistent.<br><br>Also considering OECD TG309<br>$DT_{50,\ water}$ = 0.55d |
| Toxicity | NOEC or CMR | NOEC > 0.01mg/L<br>No genotoxicity but the test substance caused hyperplasia in male adrenal medulla and benign pheochromo-cytoma in a 2 year rat study (TT #13-7800). | Not T based on aquatic toxicity results. Possibly CMR. |
| **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) | 0.62 | 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<br>$K_{doc}$ sed. 2 = 927 L/kg<br>$K_{doc}$ sludge 1 = 198 L/kg<br>$K_{doc}$ sludge 2 = 250 L/kg<br>$K_{doc}$ soil 1 = 755 L/kg<br>$K_{doc}$ soil 2 = 490 L/kg | $K_{doc}$ sludge < 10 000 L/kg. |
| Biodegradability Simulation Test | OECD TG314B | <u>*Ertugliflozin*</u><br>$DT_{50}$ = 0.695h<br>Mineralization 28d: 40.8%<br>High primary degradation in sludge<br><br><u>*Transformation products*</u><br>$DT_{50}$ (“TP3.7”) = 24.4h<br>$DT_{50}$ (“TP8”) = 1.59h<br>AR at 1h >10% | Sludge from Easton WWTP, 28d incubation. |
| 28d Surface water biodegradation Test | OECD TG309 | <u>*Ertugliflozin*</u><br>$DT_{50,\ water}$ = 0.55d<br>$DT_{90,\ water}$ = 1.83d<br>$CO_2$-mineralization = 36.7% | Most of ertugliflozin degraded within 24h. |

| | | | | | |
|---|---|---|---|---|---|
| | | *Transformation products*<br>$DT_{50,\ water}$ ("TP5") = 4.66d<br>$DT_{90,\ water}$ ("TP5") = 15.56d | | | |
| Aerobic and Anaerobic Transformation in Aquatic Sediment systems | OECD TG308 | $DT_{50,\ water}$ = ~24 - 32d<br>$DT_{50,\ sediment}$ = ~15 - 56d<br>$DT_{50,\ whole\ system}$ = ~45 - 57d<br>% 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<br>$EC_{50}$ | 50 000<br>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* |

***Sitagliptin***

The ERA is based on sitagliptin which has a molecular weight of 523.32 g/mol and is hydrophilic with a high water solubility of 69.8mg/mL (pH 7.1) and a log $K_{OW}$ = -0.03 (pH 7). Together with a maximum dose of 100mg, both default and market consumption (2016 IMS data) Fpen based surface water predicted environmental concentration PEC ($PEC_{SW}$) were >0.01ug/L, the former triggering a phase II assessment. The default Fpen (1%) based $PEC_{SW}$ was calculated to 0.50µg/L. The market consumption Fpen (1.8%) gave a $PEC_{SW}$ of 0.90µg/L.

Sitagliptin is both hydrolytically stable at pH 7 at 25°C (estimated half-life of 895d) and photolytically stable (no absorbance maxima above 295 nm at pH5, pH 7 or pH 9). The persistence against aerobic degradation in whole fresh water-sediment systems is between $DT_{50}$ 138.6d – 169.0d (20°C) with a strong tendency to sediment accumulation (66.1-86% AR >10% after 14d). A water-sediment $DT_{50}$ recalculation to 12°C (according to ECHA R.11, 2014; page 39) gave a value of $DT_{50}$ 290d - 361d.

An OECD TG302B study did not find any clear biodegradability in sludge (<20% DOC reduction across 28d) while an OECD TG314B study detected a moderate primary (from 93.3% to 52.6% parent compound) and ultimate biodegradation (8.2%) within 24h. The organic content solid adsorption coefficients ($Kd_{oc}$) for sitagliptin were $Kd_{oc}$ > 10 000L/kg for soil (~12023- 39811L/kg) but not sludge (18.6L/kg). Microalgae (*P. subcapitata*) demonstrated the most sensitive aquatic toxicity NOEC and LOEC (72h yield 840µg/L and 2200µg/L respectively). For sediment-dweller organisms, the epi-benthic *L. variegatus* was more sensitive (reproduction NOEC 31 mg/kg and LOEC 63mg/kg) to sitagliptin compared to tube-dwelling chironomid larvae (developmental time NOEC 500mg/kg and LOEC 1000mg/kg). Due to minor corrections from the rapporteur AR80 report, the ERA table is included below **(Table 2)**:

**Table 2: The ERA table**

| **Substance (INN/Invented Name): Sitagliptin** | | | |
|---|---|---|---|
| **CAS-number (if available):** 65467-77-9 | | | |
| ***PBT screening*** | | Result | **Conclusion** |
| *Bioaccumulation potential*- log $K_{ow}$ | OECD TG107 | -0.03 | Potential PBT (N) |
| ***PBT-assessment*** | | | |
| **Parameter** | **Result relevant** | | **Conclusion** |

| | | | |
|---|---|---|---|
| | **for conclusion** | | |
| Bioaccumulation | log $K_{ow}$ | -0.03 | not B |
| | BCF | NA | not B |
| Persistence | DT50 or ready biodegradability | $DT_{50whole\ system}$ (20°C) = 138.6-169d | P |
| Toxicity | NOEC or CMR | NOEC > 0.01 mg/L | not T. |
| **PBT-statement :** | The compound is not considered as PBT nor vPvB | | |

| ***Phase I*** | | | |
|---|---|---|---|
| ***Calculation*** | **Value** | **Unit** | **Conclusion** |
| $PEC_{surfacewater}$ , default or refined (e.g. prevalence, literature) | 0.90 | 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 = 12022.3 L/kg<br>$K_{doc}$ soil 2 = 25118.9 L/kg<br>$K_{doc}$ soil 3 = 25704.0 L/kg<br>$K_{doc}$ soil 4 = 39810.7 L/kg<br>$K_{doc}$ sludge 1 = 18.6 L/kg | $K_{doc}$ sludge < 10 000 L/kg. Likely to be persistent in soils but unlikely to reach them via sludge. |
| Hydrolysis | OECD TG111 | *$t_{1/2,\ water}$: 895 days (pH7, 25°C)*<br>*$t_{1/2,\ water}$: 402 days (pH7, 30°C)*<br>*$t_{1/2,\ water}$: 124 days (pH7, 40°C)*<br>*$t_{1/2,\ water}$: 94.7 days (pH9, 25°C)*<br>*$t_{1/2,\ water}$: 52.3 days (pH9, 30°C)*<br>*$t_{1/2,\ water}$: 20.7 days (pH9, 40°C)* | Very weak chemical degradation in water at environmental settings of pH7 and <25°C. |
| Ready Biodegradability Test | OECD TG302B | DOC degradation, 28d: ~3%. | Denton WWTP sludge. No inherent biodegradability in sludge. |
| Aerobic and Anaerobic Transformation in Aquatic Sediment systems | OECD TG308 | $DT_{50,water}$ = 6.5 – 14.6d<br>$DT_{50,whole\ system}$ = 138.6-169d<br><br>% shifting to sediment = 66.1-86% AR after 12d. | Only $DT_{50}$ (20°C) calculated. Not calculated for 12°C.<br><br>Likely persistent in sediments. %AR(14d) > 10 Triggers an OECD TG218 test. |
| Biodegradability Simulation Test | OECD TG314B | $DT_{50}$: 21.1h<br>Mineralization 24h: 8.2% AR<br>Mineralization 28d: 39.7% AR<br>Parent 24h: 52.6%<br>Parent 28d: 24.6%<br>Transf. prod., 24h: 9.2% AR<br>Transf. prod., 28d: 12.9% AR<br>Water phase, 24h: 10.3% AR<br>Water phase, 28d: 2.6% AR | Cambridge WWTP sludge. |
| Photolysis | OECD TG316 | No potential for photolysis. | |

| ***Phase IIa Effect studies*** | | | | | |
|---|---|---|---|---|---|
| **Study type** | **Test protocol** | **Endpoint** | **value** | **Unit** | **Remarks** |
| Algae, Growth Inhibition Test/*Species* | OECD TG201 | $NOEC_{yield}$<br>$EC_{50,yield}$ | 0.840<br>0.390 | mg/L | *P. subcapitata (yield endpoint after 72h)* |
| *Daphnia* sp. Reproduction | OECD TG211 | NOEC | 9.8 | mg/L | *D. magna* |

| | | | | | |
|---|---|---|---|---|---|
| Test | | | | | |
| Fish, Early Life Stage Toxicity Test/*Species* | OECD TG210 | NOEC | 9.2 | mg/L | *P. promelas* |
| Activated Sludge, Respiration Inhibition Test | OECD TG209 | NOEC | 150 | mg/L | Loxahatchee WWTP sludge |
| ***Phase IIb Studies*** | | | | | |
| Sediment dwelling organism (tube-dweller) | OECD TG218 | NOEC<br>$NOEC_{OC10}$ | 500<br>2777.8 | mg/kg | *C. riparius* |
| Sediment dwelling organism (epi-benthic) | OECD TG225 | NOEC<br>$NOEC_{OC10}$ | 31<br>221.4 | mg/kg | *L. variegatus* |

## 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 ± 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 Cmax 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 are 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 $\geq$ 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. 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. 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 non-clinical 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 erugliflozin is absorbed in male and female rats respectively. It is 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 provided 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.

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*: The applicant has provided updated ERAs with new refined calculations for the PEC values and associated risk quotients/ratios (RQ) calculations. Based on type 2 diabetes prevalence Fpen for ertugliflozin (8.3%) and market consumption Fpen for sitagliptin (1.8%), the surface water PEC ($PEC_{SW}$) for ertugliflozin was 0.62ug/L and the $PEC_{SW}$ for sitagliptin 0.90ug/L. These values helped generate risk quotients/ratios (RQs) which were below 1 for both aquatic and sediment organisms (and RQ<0.1 for sludge microorganisms).

Regarding the environmental fate of ertugliflozin, it seems to be biodegradable in sludge but with a low sludge adsorption potential - indicating that there is little risk for terrestrial effects from agricultural sludge usage and that the main entry into the environment is into surface waters via the effluent. In a similar manner, sitagliptin demonstrated some degree of primary biodegradation in sludge but a low sludge adsorption potential. In contrast to ertugliflozin, sitagliptin is highly persistent in water-sediment systems with a strong tendency to accumulate in sediment ($DT_{50,\ sediment}$ > 120d ($DT_{50}$ at 12°C estimated to 290d-361d). Based on the overall data, neither ertugliflozin nor sitagliptin are classified as a PBT or vPvB candidates.

Overall, the available data based on the provided PEC and RQ values indicate that ertugliflozin and sitagliptin are unlikely to become/constitute risks for the aquatic/sediment environments.

### 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: Phase 3 Studies in Support of the Ertugliflozin / Sitagliptin FDC Clinical Development Program**

| Study | Randomized Population | N | Study Design | Treatment Groups and Number of Subjects Randomized | Treatment Duration |
|---|---|---|---|---|---|
| **Active-controlled study** | | | | | |
| 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)<br>Ertugliflozin 15 mg (n=248)<br>Ertugliflozin 5 mg (n=250)<br>Ertugliflozin 15 mg/ sitagliptin 100 mg (n=245)<br>Ertugliflozin 5 mg/ sitagliptin 100 mg (n=243) | 52 Weeks<br>Phase A: 26 weeks<br>Phase B: 26 weeks<br><br>**Completed** |
| **Placebo-controlled studies** | | | | | |
| 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)<br>Ertugliflozin 15 mg (n=154)<br>Ertugliflozin 5 mg (n=156) | 52 Weeks<br>Phase A: 26 weeks<br>Phase B: 26 weeks<br><br>**Completed** |

| Study | Randomized Population | N | Study Design | Treatment Groups and Number of Subjects Randomized | Treatment Duration |
|---|---|---|---|---|---|
| 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)<br>Ertugliflozin 15 mg/sitagliptin 100 mg (n=96)<br>Ertugliflozin 5 mg/ sitagliptin 100 mg (n=98) | 26 weeks<br><br>**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 Duration | 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)<br>Sitagliptin 100 mg (n=55)<br>Ertugliflozin 1 mg (n=54)<br>Ertugliflozin 5 mg (n=55)<br>Ertugliflozin 10 mg (n=55)<br>Ertugliflozin 25 mg (n=55) | 12 weeks | Primary: change from baseline in A1C<br>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)†<br>HCTZ 12.5 mg (n=39)<br>Ertugliflozin 1 mg (n=39)<br>Ertugliflozin 5 mg (n=38)<br>Ertugliflozin 25 mg (n=39) | 4 weeks | Primary: change from baseline in average, 24-hour SBP<br>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/sitagliptin (Steglujan) comes from the clinical pharmacology program for ertugliflozin as mono-component Steglatro. Five additional clinical studies have been performed to support the FDC ertugliflozin/sitagliptin **(Table 5)**.

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

| Description | Phase | Subject | n | Dose | Reference |
|---|---|---|---|---|---|
| BE - FDC ertu 15 mg/ sita 100 mg vs individual components | 1 | HV | 18 | 15 mg | P025 (B1521038) |
| BE - FDC ertu 15 mg/ sita 50 mg vs individual components | 1 | HV | 18 | 15 mg | P044 (B1521053) |
| BE - FDC ertu 5 mg/ sita 100 mg vs individual components | 1 | HV | 18 | 5 mg | P048 (B1521056) |
| BE - FDC ertu 5 mg/ sita 50 mg vs individual components | 1 | HV | 19 | 5 mg | P049 (B1521057) |
| Food effect, FDC ertu 15 mg/sita 100 mg | 1 | HV | 14 | 15 mg | P026 (B1521050) |

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<br>- 100 mg fed | P036 (B1521001) |
| MAD<br>2 weeks | 1 | Obese HV | 40 | Placebo, 1, 5, 25, 100 mg | P037 (B1521002) |
| Repeated dosing<br>6 days<br><br>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<br>Fraction absorbed | 1 | HV | 8 | - 15 mg oral ertugliflozin<br>- 100 µg iv 14C-ertugliflozin<br>- 100 µg oral 14C-ertugliflozin | P020 (B1521043) |
| Relative F - tablet amorphous vs cocrystal | 1 | HV | 16 | 15 mg | P011 (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<br>- 100 µCi 14C-ertugliflozin | P038 (B1521003) |
| Renal impairment | 1 | HV<br>T2DM pats<br>T2DM RI | 8<br>6<br>22-24 | 15 mg | P009 (B1521023) |
| Hepatic impairment | 1 | HV<br>HI CP7-9 | 8<br>8 | 15 mg | P014 (B1521024) |
| Japanese | 1 | HV | | - 1, 5, 25 mg single | P041 (B1521009) |

| Description | Phase | Subject | n | Dose | Reference |
|---|---|---|---|---|---|
| | | | | - 25 mg qd for 7 days | |
| PD - od *versus* bid dosing | 1 | T2DM | 26 | - 2 mg od *vs* 1 mg bid<br>- 4 mg od *vs* 2 mg bid | P040<br>(B1521007) |
| DDI metformin | 1 | HV | 18 | 15 mg | P019<br>(B1521032) |
| DDI sitagliptin | 1 | HV | 12 | 15 mg | P022<br>(B1521033) |
| DDI glimepiride | 1 | HV | 18 | 15 mg | P032<br>(B1521044) |
| DDI simvastatin | 1 | HV | 18 | 15 mg | P030<br>(B1521036) |
| DDI rifampicin | 1 | HV | 12 | 15 mg | P021<br>(B1521040) |

The basic PK of sitagliptin are based on the Januvia SmPC.

***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.

Pre- and within study validations of the bioanalytical assay for determination of ertugliflozin+sitagliptin in plasma following FDC administration seem adequate for the intended purpose fulfilling acceptance criteria.

**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).

Ertugliflozin accounted for approximately 50% of the circulating radioactivity and M5a and M5c of ca 12 and 25%, respectively.

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* study. 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.

**Sitagliptin**

***Absorption***

Sitagliptin is rapidly absorbed following oral administration. The absolute F is determined to be 87%. Co-administration with food had no effect on the PK of sitagliptin.

***Distribution***

For sitagliptin the $V_{ss}$ was estimated to 198L and the $f_u$ to 38%.

***Elimination***

The $t_{1/2}$ of sitagliptin is calculated to about 12h. Following a 14C-sitagliptin dose, 13% of the radioactivity was eliminated in faeces and 87% in in the urine. Ca 79% of sitagliptin was excreted unchanged in the urine. Renal CL was calculated to 350 ml/min. Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion.

Sitagliptin is a substrate of OAT3 though its clinical relevance is unknown. Sitagliptin is also a substrate of Pgp, however, ciclosporin (a p-glycoprotein inhibitor) did not reduce the renal CL.

Metabolism is a minor pathway, following a 14C-sitagliptin oral dose, ca 16 % of the radioactivity was excreted as metabolites. *In vitro* studies indicated that the primary enzyme responsible was CYP3A4 with contribution from CYP2C8.

***Dose proportionality***

Total systemic exposure of sitagliptin increased in a dose-proportional manner but the increase in $C_{max}$ was greater than dose-proportional.

***Special populations***

No meaningful increase in the plasma concentration of sitagliptin was seen in patients with mild RI. In patients with moderate RI, a ca 2-fold increase in AUC of sitagliptin was observed and approximately a 4-fold increase in patients with severe RI as well as in patients with ESRD on haemodialysis compared to normal healthy control subjects.

No dose adjustment of sitagliptin is necessary for patients with mild or moderate HI. There is no clinical experience in patients with severe HI.

No dose adjustment of sitagliptin is required based on gender, race, weight and age. No data are available of sitagliptin in children.

***Drug-drug-interactions***

Sitagliptin is a substrate of OAT3 and Pgp. Ciclosporin (Pgp inhibitor) did not reduce $CL_R$ of sitagliptin. Sitagliptin is not a substrate for OCT2 or OAT1 or PEPT1/2.

In vitro, sitagliptin did not inhibit OAT3 at therapeutically relevant plasma concentrations. In a clinical study sitagliptin had a small effect on plasma digoxin concentrations, indicating that sitagliptin may be a mild inhibitor of p-glycoprotein.

In clinical studies, sitagliptin did not meaningfully alter the PK of metformin, glyburide, simvastatin, rosiglitazone, warfarin or oral contraceptives, providing evidence of low propensity for causing interactions with CYP3A4, CYP2C8, CYP2C9 and OCT substrates.

**FDC ertugliflozin / sitagliptin**

Bioequivalence (BE) of the FDC ertugliflozin 15 mg/sitagliptin 100 mg compared to co-administration of ertugliflozin 15 mg (10 mg + 5mg) and sitagliptin 100 mg was shown for both compounds.

BE of the FDC ertugliflozin 15 mg/sitagliptin 50 mg compared to co-administration of ertugliflozin 15 mg (10 mg + 5mg) and sitagliptin 50 mg was shown for both compounds.

BE of the FDC ertugliflozin 5 mg/sitagliptin 100 mg compared to co-administration of ertugliflozin 5 mg and sitagliptin 100 mg was shown for both compounds.

BE of the FDC ertugliflozin 5 mg/sitagliptin 50 mg compared to co-administration of ertugliflozin 5 mg and sitagliptin 50 mg was shown for both compounds.

A decrease in exposure of ertugliflozin was seen when the FDC ertugliflozin/sitagliptin was administered together with food, for AUC and $C_{max}$ *ca* 5 and 30%, respectively. No meaningful change in exposure of sitagliptin was seen administered in fed compared to fasted condition.

## 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.

***Sitagliptin***

Sitagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Concentrations of the active intact hormones are increased by sitagliptin, thereby increasing and prolonging the action of these hormones. Incretin hormones including GLP-1 and GIP are released by the intestine throughout the day, and levels are increased in response to a meal. These hormones are rapidly inactivated by DPP-4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic β-cells by intracellular signaling pathways involving cyclic adenosine monophosphate (cAMP). GLP-1 also lowers glucagon secretion from pancreatic α-cells, leading to reduced hepatic glucose production. By increasing and prolonging active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity in vitro at concentrations approximating those from therapeutic doses.

## *Primary and Secondary pharmacology*

### Primary pharmacology

#### *Ertugliflozin*

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

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.

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.

### 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 FDCs of the NCE ertugliflozin, with the MAA procedure for Steglatro® ongoing in parallel, and the well-known substance sitagliptin. The Applicant has provided a solid clinical pharmacology program for ertugliflozin and very well presented.

The MAA for Steglujan® contains the complete ertugliflozin clinical pharmacology program submitted for Steglatro® and five additional phase 1 studies in support of the FDC tablets. This assessment report focuses on the assessment of ertugliflozin and the additional studies submitted. The presented PK on sitagliptin are based on the Januvia 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. $C_{max}$ and AUC is determined to *ca* 260 ng/ml and 1400 ng/ml.h, respectively, at 15 mg od.

Bioequivalence of the FDCs compared to co-administration of single components for both ertugliflozin and sitagliptin were shown following dosing of all four FDC tablet strengths.

The decrease in exposure of ertugliflozin seen when the FDC ertugliflozin/sitagliptin was administered together with food is not considered clinical relevant. No meaningful change in exposure of sitagliptin was seen administered in fed compared to fasted condition. Thus there is no dose restriction considering concomitant food intake with Steglujan®.

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.

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 Steglujan, a FDC of ertugliflozin/sitagliptin, 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.

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 is more ambiguous, but as no signals were observed in any of the assays this 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. This will not be further pursued as the increase was not considered clinically relevant.

Both single and multiple escalating dose studies with ertugliflozin 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. 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. Notably, the difference between the two dose levels (5 vs 15 mg daily) 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.

The effect of qd and bid dosing was investigated in subjects with T2DM. No meaningful difference in the UGE was observed between the two different dosing regimens. Notably, the difference between the two dose levels (2 vs 4 mg daily) was small.

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 currently 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.

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

### 2.4.5. Conclusions on clinical pharmacology

Overall the clinical pharmacology properties of the FDCs ertugliflozin/sitagliptin have been appropriately described.

## *2.5. Clinical efficacy*

In total, seven of phase 3 studies were included with this submission, all part of the initial regulatory submission for ertugliflozin alone.

Three of the Phase 3 studies were conducted in support of the ertugliflozin/sitagliptin submission, including one active-controlled factorial study (Study P005/1019) and two placebo-controlled studies (Study P006/1015 and Study P017/1047), that evaluated the safety and efficacy of ertugliflozin in combination with sitagliptin in adult subjects with T2DM. Because of differences in study designs, data from the 3 individual studies were not pooled for analysis, and therefore the individual study data are presented.

The following three studies from the ertugliflozin program are considered supportive; P003/1022 (Monotherapy), P007/1017 (Add-on to metformin) and P002/1013 (Ertugliflozin vs glimepiride as add-on to metformin). Study P001/1016 was a special populations study in moderate renal impairment.

### 2.5.1. Dose response studies

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

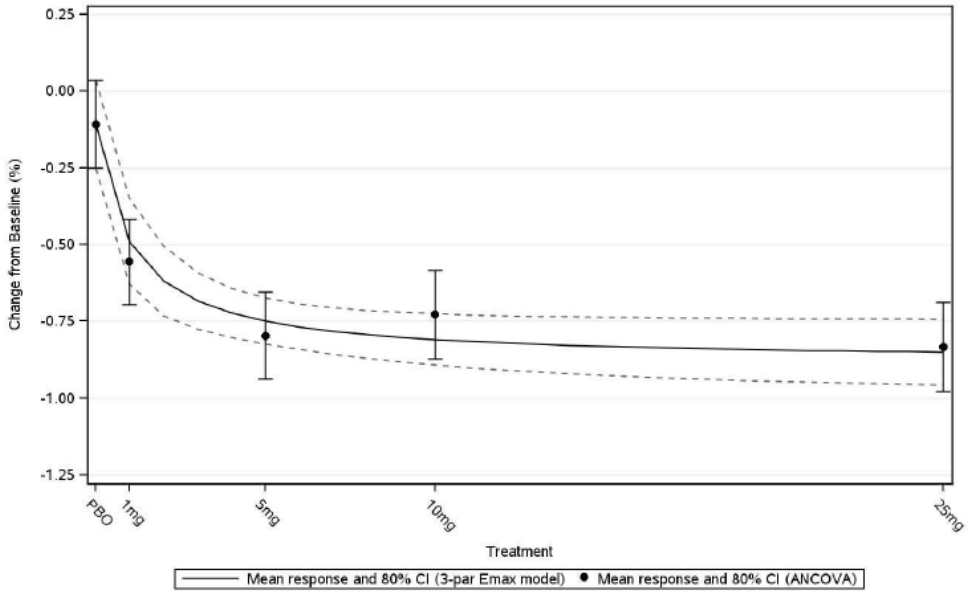
Ertugliflozin doses of 5 mg and 15 mg qd were evaluated in all phase 3 studies (dosed in the morning without regard to food). The primary driver for dose selection was the dose-response modelling for the change from baseline in A1C, FPG, body weight, and the mechanistic biomarker 24 hour UGE in subjects 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

Three of phase 3 studies were conducted in support of the ertugliflozin/sitagliptin submission, including one active-controlled factorial study (Study P005/1019) and two placebo-controlled studies (Study P006/1015 and Study P017/1047), that evaluated the safety and efficacy of ertugliflozin in combination with sitagliptin in adult subjects with T2DM **(Table 3)**. Because of differences in study designs, data from the three individual studies were not pooled for analysis.

The following three studies from the ertugliflozin program are considered supportive; P003/1022 (Monotherapy), P007/1017 (Add-on to metformin) and P002/1013 (Ertugliflozin vs glimepiride as add-on to metformin). Study P001/1016 was a special populations study in moderate renal impairment.

All but one study (P017/1047) have extensions (phase B) and are still ongoing.

A total of 4863 subjects were randomly assigned to treatment in the Phase 3 studies supporting registration of ertugliflozin. A total of 1985 subjects were randomized and received at least 1 dose of study medication in the three Phase 3 studies in support of this submission, including 990 subjects randomized to receive co-administration of ertugliflozin with sitagliptin.

### *Methods*

All Phase 3 studies were randomized, double-blind, parallel-group studies **(Table 3)**. The primary assessment of efficacy was performed after 26 weeks of treatment.

All studies had a 2-week placebo run-in period prior to randomization.

Study P005/1019 was a randomized double-blind, parallel-group, active-controlled factorial study that evaluated the safety and efficacy of the co-administration of ertugliflozin and sitagliptin compared with ertugliflozin alone and sitagliptin alone, in subjects with T2DM on a background of metformin. There were 5 treatment arms in this study: ertugliflozin 5 mg (E5), ertugliflozin 15 mg (E15), sitagliptin 100 mg (S100), ertugliflozin 5 mg co-administered with sitagliptin 100 mg (E5/S100), and ertugliflozin 15 mg co-administered with sitagliptin 100 mg (E15/S100). The objective of this factorial study was to demonstrate greater glycaemic efficacy for the combination of ertugliflozin and sitagliptin vs the individual treatments alone.

Study P006/1015 was a randomized, double-blind, placebo-controlled, parallel-group study that evaluated the safety and efficacy of the addition of ertugliflozin 5 mg (E5) and ertugliflozin 15 mg (E15) compared with the addition of placebo in subjects with T2DM on a background of metformin and sitagliptin 100 mg (S100).

For both studies P005/1019 and P006/105, subjects were required to be receiving a stable dose of metformin ≥1500 mg/day as background therapy (in addition to S100 for study P006/1015).

Study P017/1047 was a randomized, double-blind, placebo-controlled, parallel-group study that evaluated the safety and efficacy of ertugliflozin 5 mg co-administered with sitagliptin 100 mg (E5/S100) and ertugliflozin 15 mg co-administered with and sitagliptin 100 mg (E15/S100) as initial combination therapy compared with placebo in subjects with T2DM on a background therapy of diet and exercise alone. This study has completed.

### *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 studies that included co-administration treatment arms, Studies P005/1019 (7.5%-11.0%, inclusive) and P017/1047(8.0%-10.5%, inclusive) relative to Study P006/1015 (7.0%-10.5%, inclusive) **(Table 3)**.

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.

For the three Phase 3 studies in support of this application, subjects were excluded from the study if the screening estimated glomerular filtration rate (eGFR) was <60 mL/min/1.73 $m^2$. This criterion was selected for two reasons. First, at the time of study conduct, the US label for metformin included a contraindication for the use of metformin in subjects with abnormal creatinine clearance. Metformin ≥1500 mg/day was required background therapy in Studies P005/1019 and P006/1015. Additionally, it is well recognized that there is a transient reduction in eGFR following initiation of SGLT2 inhibitor therapy. A creatinine clearance value of <50 mL/min requires the use of the 50 mg dose of sitagliptin. Therefore, establishing the exclusionary cut-off of an eGFR of <60 mL/min/1.73 $m^2$ permitted the use of the 100 mg dose of sitagliptin while accounting for the initial transient reduction in eGFR and avoiding need for sitagliptin dose reduction.

### *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).

### *Outcomes/endpoints*

The primary assessment of efficacy was performed after 26 weeks. 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) was measured in studies P005/1019 and P017/1047.

### *Sample size*

In all the studies, a conventional type I error (two-sided 0.05) was used and expected dropout rate and/or information loss due to missing data and the correlation among repeated measures was accounted for.

In study P005/1019 the planned total sample size was 1250 subjects where 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%.

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 of 120 per arm (accounting for e.g. information loss due to missing data) was to provide 97% power to detect a true difference in HbA1c of 0.5% between a given ertugliflozin dose and placebo.

In study P017/1047 the planned total sample size was approximately 300 subjects, 100 subjects per arm. The sample size was chosen to provide adequate exposure data to assess safety for 26 weeks An effective sample size of 87 per arm was to provide >99% power to detect a true difference of 1.0% in the mean change from baseline in A1C between a given ertugliflozin plus sitagliptin dose and placebo.

### *Randomisation*

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. In all studies an equal allocation ratio was used (i.e. 1:1:1 or, in study P005/1019 1:1:1:1:1). Randomisation was performed through the use of an interactive voice response system/integrated web response system (IVRS/IWRS).

In study P005/1019 randomisation was stratified by participation in the mixed meal tolerance test (MMTT) (yes/no), in study P006/1015 according to use of sulfonylurea (SU) at screening (yes/no) and in study P017/1047 randomisation was stratified by AHA wash-off status (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, placebo matching sitagliptin in study P005/1019.

Both study P005/1019 and study P006/1015 had 2 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 in study P002/1013 and for analyses of BMD endpoints in study P007/1017.

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 glycemic 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.

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 glycemic rescue therapy were considered as missing data and in supplemental sensitivity analyses, A1C measurements collected after the start of glycemic rescue therapy were included as reported. In addition, summary statistics showing the observed HbA1C change from baseline over time by treatment group and missing data pattern were provided.

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.

*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

### Active-controlled study

**Table 10: 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.

**Placebo-controlled studies**

**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.

**Table 12: Disposition of subjects – study P017/1047 (26 weeks)**

| | Placebo | | Ertugliflozin 5 mg + Sitagliptin 100 mg | | Ertugliflozin 15 mg + Sitagliptin 100 mg | | Total | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Entered Screening | | | | | | | 1201 | |
| Not Randomized | | | | | | | 910 | |
| Subjects Randomized | 97 | | 98 | | 96 | | 291 | |
| **Subject Study Medication Disposition** | | | | | | | | |
| Completed | 76 | (78.4) | 90 | (91.8) | 88 | (91.7) | 254 | (87.3) |
| Discontinued | 21 | (21.6) | 8 | (8.2) | 8 | (8.3) | 37 | (12.7) |
| Adverse Event | 3 | (3.1) | 2 | (2.0) | 2 | (2.1) | 7 | (2.4) |
| Excluded Medication | 0 | (0.0) | 1 | (1.0) | 0 | (0.0) | 1 | (0.3) |
| Hyperglycemia | 2 | (2.1) | 0 | (0.0) | 0 | (0.0) | 2 | (0.7) |
| Lack of Efficacy | 1 | (1.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.3) |
| Lost To Follow-Up | 5 | (5.2) | 2 | (2.0) | 1 | (1.0) | 8 | (2.7) |
| Physician Decision | 1 | (1.0) | 0 | (0.0) | 1 | (1.0) | 2 | (0.7) |
| Subject Moved | 1 | (1.0) | 1 | (1.0) | 3 | (3.1) | 5 | (1.7) |
| Withdrawal By Subject | 8 | (8.2) | 2 | (2.0) | 1 | (1.0) | 11 | (3.8) |
| 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: 14MAR2016 Date of Table Creation: 25MAR2016 (6:28)

The discontinuation rates were balanced between the ertugliflozin groups and highest in the placebo group (22%), the overall discontinuation rate being 13%. This is explained by higher discontinuation due to loss-to-follow-up and withdrawal by subject. Discontinuation due to hyperglycaemia was also only observed in the placebo 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 deviation was 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”. Notably, multiple enrolments were discovered in all studies, mostly in the US. Furthermore, after breaking the blind in phase A of study P001/1016 (renal impairment), it was discovered that 78 subjects (out of 467) had blood samples positive for metformin.

## Baseline data

The mean age of the subjects was similar across the Phase 3 studies, ranging from 55.1 to 59.1 years. With regards to age, 16.2% to 29.9% of subjects were ≥65 years of age and 2.3% to 2.8% of subjects were ≥75 years of age. Males represented 53.9% to 57.4% of the study population. The majority of subjects in each study were White, ranging from 72.9% to 90.4%. Most subjects were in either North America (excluding Central America) or Europe (including Russia).

At baseline, the mean body mass index (BMI) was similar across all studies, ranging from 30.8 to 32.2 $kg/m^2$. The 2 ertugliflozin and sitagliptin co-administration studies (Studies P005/1019 and P017/1047) had higher baseline A1C (8.6% and 8.9%, respectively) and FPG (180.4 mg/dL and 197.8 mg/dL, respectively), compared to the add-on to metformin and sitagliptin study (Study P006/1015) (8.0% and 169.7 mg/dL). The higher mean baseline A1C values in Studies P005/1019 and P017/1047 compared to Study P006/1015 were the result of the study-specific A1C entry criteria which were appropriate given the initiation of 2 agents simultaneously. The mean baseline eGFR was similar across the 3 studies, ranging from 87.9 to 92.4 mL/min/1.73 $m^2$.

The average duration of T2DM was 9.5 years for the subjects in the add-on to metformin and sitagliptin study (Study P006/1015), longer than the 2 ertugliflozin/sitagliptin co-administration studies (Studies P005/1019 and P017/1047), which were 6.9 years and 6.3 years, respectively. The longer duration of T2DM was consistent with the finding that the subjects in Study P006/1015 also had higher rates of diabetic microvascular complications and more prevalent use of anti-hypertensive and lipid-lowering medications at baseline.

## 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 13** and **Figure 5**, excluding data after initiation of glycaemic rescue therapy.

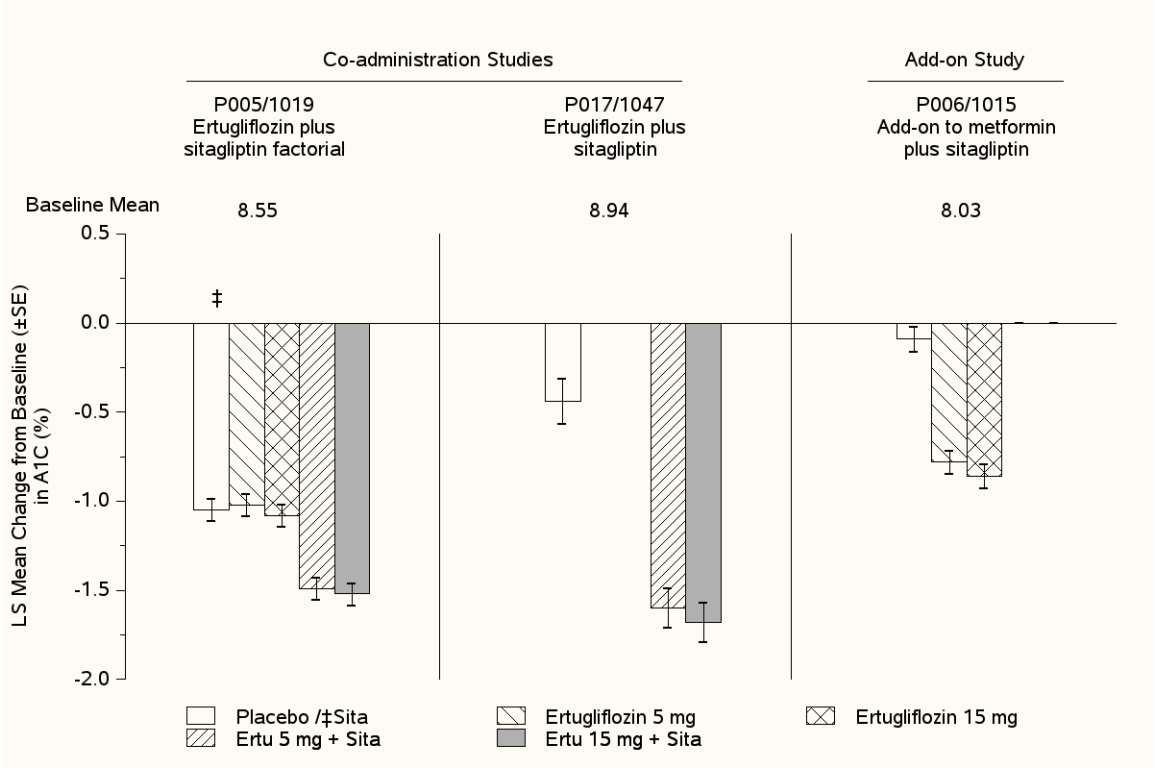
**Table 13: A1C (%): Change from Baseline at Primary Timepoint by Study - Full Analysis Set: Excluding Rescue Approach - Ertugliflozin/Sitagliptin Studies**

| | N | Baseline Mean ± SD | LS Mean Change ± SE | LS Mean Difference (95% CI) | p-value |
|---|---|---|---|---|---|
| **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[‡] |
| **P017/1047 (Week 26) Ertugliflozin+Sitagliptin** | | | | | |
| Placebo | 96 | 8.9 ± 0.86 | -0.44 ± 0.127 | | |
| Ertugliflozin 5 mg + Sitagliptin 100 mg | 98 | 8.9 ± 0.87 | -1.60 ± 0.110 | -1.16 (-1.49,-0.84) | <0.001 |
| Ertugliflozin 15 mg + Sitagliptin 100 mg | 96 | 9.0 ± 0.87 | -1.68 ± 0.112 | -1.24 (-1.57,-0.91) | <0.001 |
| **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 |

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: [P005V01: analysis-adeff] [P006V01: analysis-adeff] [P017: analysis-adeff]

**Figure 5: A1C (%): Change from Baseline at Week 26 by Study - Full Analysis Set: Excluding Rescue Approach - Ertugliflozin/Sitagliptin Studies**




For Studies P005/1019 and P017/1047, co-administration includes co-initiation of therapy with ertugliflozin and sitagliptin.

*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, the placebo-controlled study (Studies P017/1047 and P006/1015) data show that: (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 ertugliflozin plus sitagliptin factorial

Study P005/1019, the initiation of rescue therapy occurred at a lower rate than in the placebo-controlled studies and was comparable among the 5 treatment groups. In this active-controlled study 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 studies as a secondary efficacy endpoint. Results are presented in **Table 14**, excluding data after initiation of glycaemic rescue therapy.

**Table 14: FPG (mg/dL): Change from Baseline at Primary Timepoint by Study - Full Analysis Set: Excluding Rescue Approach - Ertugliflozin/Sitagliptin Studies**

| | N | Baseline Mean ± SD | LS Mean Change ± SE | LS Mean Difference (95% CI) | p-value |
|---|---|---|---|---|---|
| **P005/1019 (Week 26) Ertugliflozin+Sitagliptin factorial** | | | | | |
| Sitagliptin 100 mg | 247 | 177.4 ± 46.64 | -25.56 ± 2.229 | | |
| Ertugliflozin 5 mg | 250 | 184.1 ± 52.23 | -35.73 ± 2.198 | | |
| Ertugliflozin 15 mg | 248 | 179.5 ± 45.71 | -36.91 ± 2.192 | | |
| Ertugliflozin 5 mg + Sitagliptin 100 mg | 243 | 183.8 ± 44.28 | -43.96 ± 2.205 | -18.40[†] (-24.03,-12.77) | <0.001[†] |
| | | | | -8.23[‡] (-13.82,-2.65) | 0.004[‡] |
| Ertugliflozin 15 mg + Sitagliptin 100 mg | 244 | 177.2 ± 49.38 | -48.70 ± 2.196 | -23.14[†] (-28.76,-17.53) | <0.001[†] |
| | | | | -12.97[‡] (-18.54,-7.40) | <0.001[‡] |
| **P017/1047 (Week 26) Ertugliflozin+Sitagliptin** | | | | | |
| Placebo | 96 | 207.5 ± 44.94 | -9.30 ± 4.714 | | |
| Ertugliflozin 5 mg + Sitagliptin 100 mg | 98 | 198.0 ± 47.73 | -48.25 ± 3.997 | -38.94 (-49.93,-27.96) | <0.001 |
| Ertugliflozin 15 mg + Sitagliptin 100 mg | 96 | 187.7 ± 46.67 | -55.36 ± 4.031 | -46.05 (-57.09,-35.02) | <0.001 |
| **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 |

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: [P005V01: analysis-adeff] [P006V01: analysis-adeff] [P017: analysis-adeff]

*2-hour post-prandial glucose*

Change from baseline in 2-hour PPG was measured in studies P005/1019 and P017/1047. Reductions from baseline in 2-hour PPG at Week 26 were observed with ertugliflozin 15 mg and 5 mg in combination with sitagliptin (with and without metformin background therapy).

In the ertugliflozin plus sitagliptin factorial study (study P005/1019), 2-hour PPG was assessed in the subset of subjects who participated in the MMTT and this endpoint was not part of the formal testing

sequence. E15/S100 resulted in reduction in 2-hour PPG of 95.19 mg/dL and E5/S100 of 75.81 mg/dL which was numerically greater than the individual agents alone at corresponding doses.

In the ertugliflozin plus sitagliptin initial combination study (study P017/1047), the reductions in 2-hour PPG from baseline were significantly greater ($p<0.001$) in the E15/S100 (69.65 mg/dL) and E5/S100 (62.42 mg/dL) groups compared to the placebo group on diet and exercise alone.

*Proportion of Subjects With A1C <7.0%*

The proportion of subjects with A1C <7.0% at Week 26 was analysed in all studies as a secondary efficacy endpoint. Results are presented in **Table 15**, excluding data after initiation of glycaemic rescue therapy.

**Table 15: Analysis of Subjects with A1C<7.0% at Primary Timepoint by Study - Full Analysis Set: Excluding Rescue Approach - Ertugliflozin/Sitagliptin Studies**

| | N | Number (%) of Subjects With A1C<7.0% (Raw Proportion) | Adjusted Odds Ratio[†] | |
|---|---|---|---|---|
| | | | Point Estimate | 95% CI |
| **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)[§] |
| **P017/1047 (Week 26) Ertugliflozin+Sitagliptin** | | | | |
| Placebo | 96 | 8 ( 8.3) | | |
| Ertugliflozin 5 mg + Sitagliptin 100 mg | 98 | 35 ( 35.7) | 6.88 | (2.81, 16.83) |
| Ertugliflozin 15 mg + Sitagliptin 100 mg | 96 | 30 ( 31.3) | 7.39 | (2.98, 18.31) |
| **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) |

[†]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: [P005V01: analysis-adeff] [P006V01: analysis-adeff] [P017: 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 16**.

**Table 16: Analysis of Time to Glycaemic Rescue at Primary Timepoint by Study - All Subjects Treated - Ertugliflozin/Sitagliptin Studies**

| | N | Number (%) of Subjects Rescued | Time to Rescue (days) | | p-value |
|---|---|---|---|---|---|
| | | | Minimum | Maximum | |
| **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[†]<br>0.042[‡] |
| Ertugliflozin 15 mg + Sitagliptin 100 mg | 244 | 0 (0.0) | N/A | N/A | <0.001[†]<br>0.009[‡] |
| **P017/1047 (Week 26) Ertugliflozin+Sitagliptin** | | | | | |
| Placebo | 97 | 31 (32.0) | 9 | 166 | |
| Ertugliflozin 5 mg + Sitagliptin 100 mg | 98 | 6 (6.1) | 79 | 148 | <0.001 |
| Ertugliflozin 15 mg + Sitagliptin 100 mg | 96 | 0 (0.0) | N/A | N/A | <0.001 |
| **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 |

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: [P005V01: analysis-adtte] [P006V01: analysis-adtte] [P017: 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 are presented in **Table 17**, excluding data after initiation of glycaemic rescue therapy.

**Table 17: Body Weight (kg): Change from Baseline at Primary Timepoint by Study - Full Analysis Set: Excluding Rescue Approach - Ertugliflozin/Sitagliptin Studies**

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

| | N | Baseline Mean ± SD | LS Mean Change ± SE | LS Mean Difference (95% CI) | p-value |
|---|---|---|---|---|---|
| **P017/1047 (Week 26) Ertugliflozin+Sitagliptin** | | | | | |
| Placebo | 97 | 95.0 ± 20.53 | -0.94 ± 0.386 | | |
| Ertugliflozin 5 mg + Sitagliptin 100 mg | 98 | 90.8 ± 20.72 | -2.94 ± 0.334 | -2.00 (-2.99,-1.01) | <0.001 |
| Ertugliflozin 15 mg + Sitagliptin 100 mg | 96 | 91.2 ± 22.47 | -3.04 ± 0.338 | -2.10 (-3.10,-1.11) | <0.001 |
| **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 |
| LS means and p-value are based on the cLDA model for the primary analysis.<br>[†]For the comparison to Sitagliptin alone. | | | | | |

Source: [P005V01: analysis-adeff] [P006V01: analysis-adeff] [P017: analysis-adeff]

*Change from baseline in SBP*

Change from baseline in SBP was measured in all studies as a secondary efficacy endpoint. Results are presented in **Table 18**, excluding data after initiation of glycaemic rescue therapy.

**Table 18: Sitting Systolic Blood Pressure (mmHg): Change from Baseline at Primary Timepoint by Study - Full Analysis Set: Excluding Rescue Approach - Ertugliflozin/Sitagliptin Studies**

| | N | Baseline Mean ± SD | LS Mean Change ± SE | LS Mean Difference (95% CI) | p-value |
|---|---|---|---|---|---|
| **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[†] |
| **P017/1047 (Week 26) Ertugliflozin+Sitagliptin** | | | | | |
| Placebo | 97 | 127.4 ± 14.05 | 2.41 ± 1.392 | | |
| Ertugliflozin 5 mg + Sitagliptin 100 mg | 98 | 130.7 ± 12.74 | -2.04 ± 1.115 | -4.44 (-7.87,-1.01) | 0.011 |
| Ertugliflozin 15 mg + Sitagliptin 100 mg | 96 | 129.2 ± 12.17 | -3.98 ± 1.119 | -6.39 (-9.83,-2.95) | <0.001 |
| **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 |
| LS means and p-value are based on the cLDA model for the primary analysis.<br>[†]For the comparison to Sitagliptin alone. | | | | | |

Source: [P005V01: analysis-adeff] [P006V01: analysis-adeff] [P017: analysis-adeff]

## 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 19: 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. | | | | |

**Table 20: 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 21: Summary of efficacy for trial P017/1047**

| | | | |
|---|---|---|---|
| **Title:** A Phase III, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Clinical Trial to Evaluate the Efficacy and Safety of the Initial Combination of Ertugliflozin (MK-8835/PF-04971729) with Sitagliptin in the Treatment of Subjects with T2DM with Inadequate Glycemic Control on Diet and Exercise | | | |
| Study identifier | P017/1047 | | |
| Design | Multicenter, randomized (1:1:1), double-blind, placebo-controlled | | |
| | Duration of placebo run-in phase: | | 2 weeks |
| | Duration of placebo-controlled main period: | | 26 weeks |
| Hypothesis | Superiority | | |
| Treatments groups | Placebo | | placebo 26 weeks, n=97 |
| | Ertugliflozin 5 mg | | ertugliflozin 5 mg q.d. and sitagliptin 100 mg q.d., 26 weeks , n=98 |
| | Ertugliflozin 15 mg | | ertugliflozin 15 mg q.d. and sitagliptin 100 mg q.d., 26 weeks , n=96 |
| Endpoints and definitions | Primary endpoint | A1C | Change from baseline in A1C at Week 26 |
| | Secondary | FPG | Change from baseline in FPG at Week 26 |
| | | 2-hour PMG | Change from baseline in 2-hour PMG at Week 26 |
| | | Target A1C control | Proportion of subjects at target A1C control <7.0% (53 mmol/mol) 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 |
| | | Sitting DBP | Change from baseline in sitting diastolic blood pressure at Week 26 |
| | Other | | Time to rescue |
| | | | Proportion of patients requiring rescue |
| | | | Change from baseline in HOMA-%β |
| | | | Change from baseline in insulinogenic index |
| | | | Change from baseline in fasting C-peptide |
| | | | Proportion of subjects at target A1C control <6.5% |
| Database lock | 11-Mar-2016 | | |

| **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 | 96 | 98 | 96 |
| | LS Mean | -0.44 | -1.60 | -1.68 |
| | (95% CI) | (-0.69, -0.19) | (-1.82, -1.39) | (-1.90, -1.46) |
| | **Change from Baseline in FPG (mg/dL)** | | | |
| | Number of subjects | 96 | 98 | 96 |
| | LS Mean | -9.30 | -48.25 | -55.36 |
| | (95% CI) | (-18.58, -0.02) | (-56.12, -40.38) | (-63.29, -47.42) |
| | **Change from Baseline in Body Weight (kg)** | | | |
| | Number of subjects | 97 | 98 | 96 |
| | LS Mean | -0.94 | -2.94 | -3.04 |
| | (95% CI) | (-1.70, -0.18) | (-3.60, -2.28) | (-3.71, -2.38) |
| | **Change from Baseline in Sitting Systolic Blood Pressure (mmHg)** | | | |
| | Number of subjects | 97 | 98 | 96 |
| | LS Mean | 2.41 | -2.04 | -3.98 |
| | (95% CI) | (-0.34, 5.15) | (-4.23, 0.16) | (-6.19, -1.78) |
| | **Change from Baseline in Sitting Diastolic Blood Pressure (mmHg)** | | | |
| | Number of subjects | 97 | 98 | 96 |
| | LS Mean | 1.21 | -0.44 | -0.97 |
| | (95% CI) | (-0.73, 3.15) | (-1.99, 1.11) | (-2.52, 0.59) |
| | **Change from Baseline in 2-hr PMG (mg/dL): at Week 26: cLDA** | | | |
| | Number of subjects | 91 | 97 | 95 |
| | LS Mean | -20.38 | -82.80 | -90.03 |
| | (95% CI) | (-35.62, -5.14) | (-95.96, -69.64) | (-103.34, -76.71) |

| | | | | |
|---|---|---|---|---|
| | **A1C < 7.0% (logistic regression with multiple imputation based on cLDA model)** | | | |
| | Number of subjects | 96 | 98 | 96 |
| | n | 8 | 35 | 30 |
| | (%) | (8.3) | (35.7) | (31.3) |
| Effect estimate per comparison | | Ertugliflozin 5 mg + Sitagliptin 100 mg vs. Placebo | Ertugliflozin 15 mg+ Sitagliptin 100 mg vs. Placebo | |
| | **Primary endpoint:** | | | |
| | **Change from Baseline in A1C (%)** | | | |
| | Difference in LS Means | -1.16 | -1.24 | |
| | (95% CI) | (-1.49, -0.84) | (-1.57, -0.91) | |
| | P-value | <0.001 | <0.001 | |
| | **Secondary endpoints:** | | | |
| | **Change from Baseline in FPG (mg/dL)** | | | |
| | Difference in LS Means | -38.94 | -46.05 | |
| | (95% CI) | (-49.93, -27.96) | (-57.09, -35.02) | |
| | P-value | <0.001 | <0.001 | |
| | **Change from Baseline in Body Weight (kg)** | | | |
| | Difference in LS Means | -2.00 | -2.10 | |
| | (95% CI) | (-2.99, -1.01) | (-3.10, -1.11) | |
| | P-value | <0.001 | <0.001 | |
| | **Change from Baseline in Sitting Systolic Blood Pressure (mmHg)** | | | |
| | Difference in LS Means | -4.44 | -6.39 | |
| | (95% CI) | (-7.87, -1.01) | (-9.83, -2.95) | |
| | P-value | 0.011 | <0.001 | |
| | **Change from Baseline in Sitting Diastolic Blood Pressure (mmHg)** | | | |
| | Difference in LS Means | -1.65 | -2.18 | |
| | (95% CI) | (-4.09, 0.79) | (-4.62, 0.26) | |
| | P-value | 0.184 | 0.080 | |
| | **Change from Baseline in 2-hr PMG (mg/dL): at Week 26: cLDA** | | | |
| | Difference in LS Means | -62.42 | -69.65 | |
| | (95% CI) | (-80.47, -44.37) | (-87.83, -51.46) | |
| | P-value | <0.001 | <0.001 | |
| | **A1C < 7.0% (logistic regression with multiple imputation based on cLDA model)** | | | |
| | Odds Ratio vs. Placebo | 6.88 | 7.39 | |
| | (95% CI) | (2.81, 16.83) | (2.98, 18.31) | |
| | P-value | <0.001 | <0.001 | |
| Notes | Results of other endpoints are not included in this table. | | | |

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

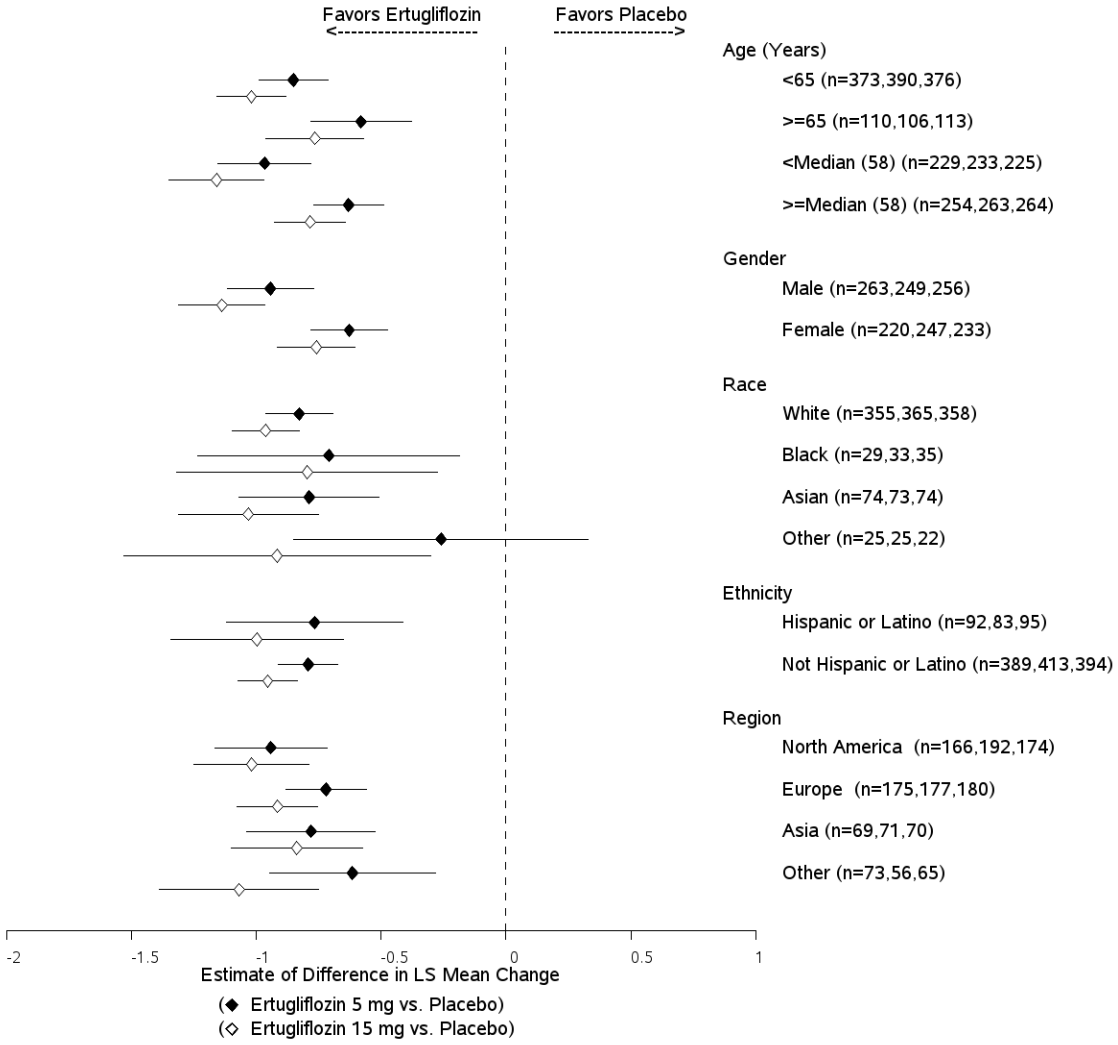
No pooled analysis was performed due to the diversity of study designs and populations. In study-specific subgroup analyses for Studies P005/1019 and P017/1047, the A1C reduction with ertugliflozin in combination with sitagliptin was consistent across age, gender, race, ethnicity, and baseline A1C subgroups.

***Ertugliflozin - Subgroup analyses***

A pooled population of the 3 placebo-controlled studies (Studies P003/1022, P007/1017, and P006/1015, all included in the development program supporting the MAA for ertugliflozin) was formed to explore whether the treatment effects were consistent across subjects with different baseline characteristics. Further information on these studies is provided in the section on supportive studies.

Subgroup analysis results for change from baseline in A1C for the placebo-controlled pool by baseline categories of age, gender, race, ethnicity, region, BMI, A1C, eGFR, and duration of T2DM are presented in **Figure 6** and **Figure 7**.

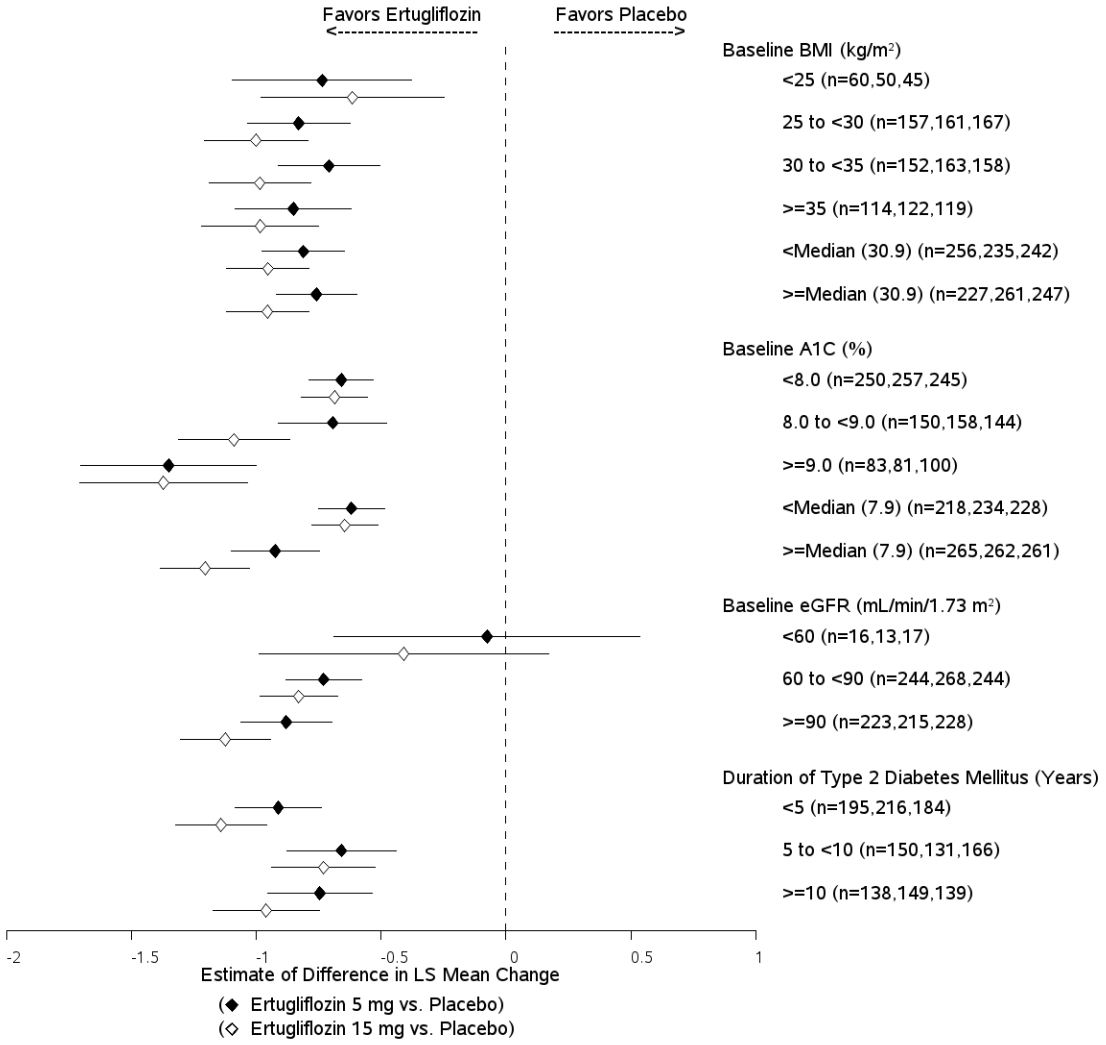
**Figure 6: A1C (%): Forest Plot of Change from Baseline at Week 26 for All Subgroups, Point Estimate and 95% Confidence Interval - Full Analysis Set: Excluding Rescue Approach - Placebo-Controlled Pool**




(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 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 - Placebo-Controlled 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

## 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 22)**.

**Table 22**: **Study in special populations**

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

| Study | Randomized Population | N | Study Design | Treatment Groups and Number of Subjects Randomized | Treatment Duration |
|---|---|---|---|---|---|
| † 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).<br><br>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 23** 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 23**: **(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** | | | | |
| 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** | | | | |

| Treatment | N | LS Mean (95% CI) | Pairwise Comparisons<br>Difference in LS Means (95% CI) vs. Placebo† | p-Value |
|---|---|---|---|---|
| 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/1.73m² 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/1.73m² 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/1.73m² 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 |
| 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/1.73m² 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. | p-Value |

| Treatment | N | LS Mean (95% CI) | Pairwise Comparisons | |
|---|---|---|---|---|
| | | | Difference in LS Means (95% CI) vs. Placebo[†] | p-Value |
| | | | Placebo | |
| **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 24** and **Table 25** show the change from baseline in HbA1c at week 26 in the subgroups on background insulin and SU treatment respectively.

**Table 24: 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 25: 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)

### *Supportive studies*

## 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 are still ongoing. The final CSRs for 5 of the 6 studies with Phase B periods have been submitted during the procedure. Three of these studies are considered pivotal for the current application for the fixed dose combination of ertugliflozin and sitagliptin, whereas four studies are included to further support the efficacy and safety of ertugliflozin as monocomponent. One of these four studies was performed in patients with renal impairment (P001/1016) whereas the other three studies are considered supportive (P003/1022, P007/1017 and P002/1013).

A total of 4864 subjects were randomly assigned to treatment in the Phase 3 studies supporting registration of ertugliflozin. A total of 1985 subjects were randomized and received at least 1 dose of study medication in the three Phase 3 studies in support of this submission, including 990 subjects randomized to receive co-administration of ertugliflozin with sitagliptin. In the studies, ertugliflozin and sitagliptin were administered as free combination and sitagliptin was given according to label.

The decision of which doses of ertugliflozin 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 ertugliflozin 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 and sitagliptin in triple combination with metformin treatment. 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. In addition a treatment arm with sitagliptin 100 mg was included. The overall study duration was 52 weeks with the primary endpoint measured at 26 weeks. Study P006/1015 included patients on stable background therapy with metformin in combination with sitagliptin. Ertugliflozin 5 mg and 15 mg respectively was compared to placebo. The overall study duration was 52 weeks with the primary endpoint measured at 26 weeks.

Study P017/1047 included patients on no other AHA. Ertugliflozin 5 mg and 15 mg, both doses in combination with sitagliptin 100 mg, was compared to placebo. The overall study duration was 26 weeks.

In addition to these studies, four studies from the ertugliflozin clinical development program were included. The following studies are considered supportive. Study P003/1022 was a monotherapy study comparing ertugliflozin 5 mg and 15 mg with placebo. Study P007/1017 included patients on stable background metformin treatment. 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. Study P002/1013 also included patients on stable background metformin treatment. This study had a non-inferiority design and ertugliflozin 5 mg and 15 mg respectively was compared to glimepiride. The overall study duration was 104 weeks with the primary endpoint measured at 52 weeks. The fourth 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. Notably, patients with eGFR <60 were not included in the studies pivotal to this application, since metformin (given as background therapy) at that time was not accepted in these patients. Furthermore, the sitagliptin dose was fixed at 100 mg and would have been reduced to 50 mg if patients with eGFR <50 were to be included. 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 two and one study, respectively, all secondary endpoints were the same in all studies although not always included in the statistical testing.

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 seems appropriate. Study P017/1047 had a single post-randomisation treatment period. Study P005/1019 and study P006/1015 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 time-point, 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 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). 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. 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.

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 (as is generally the case), 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 P001/1016, P006/1015, P007/1017 and P017/1047, 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 deviations 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 subjects compromised the integrity of their study data, and therefore results from these particular 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.

However, 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 45% (42-51%) of patients in the pivotal studies 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 the supportive 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 analyses were planned or have performed including all randomised subjects. Overall, across the studies very few subjects were however excluded from the primary analysis set (FAS). In each of study P005/1019, P006/1015 and P017/1047 respectively, it was only one subject that was excluded from the primary endpoint analysis. Depending on how data collected after rescue was handled, the proportion of subjects with missing endpoint data week 26 (obviously) 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 data.

In studies P005/1019 and P017/1047, ertugliflozin was co-administered with sitagliptin either with background metformin (P005/1019) or with no AHA (P017/1047). In the factorial study P005/1019, 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 sitagliptin 100 mg was -1.05%. The contribution of the ertugliflozin component was -0.43% and -0.47% for ertugliflozin 5 mg and 15 mg respectively, compared to sitagliptin alone. The corresponding contribution of the sitagliptin component was -0.46% compared to ertugliflozin 5 mg and -0.49% compared to ertugliflozin 15 mg. Thus it appears that both components (ertugliflozin and sitagliptin) equally contribute to the effect of the FDC.

In study P017/1047, where combination therapy was initiated without other AHA background treatment, the treatment effect was comparable to that observed for the combination in the factorial

study P005/1019 (treatment difference -1.16% (-1.49,-0.84) for the 5 mg dose and -1.24% (-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 (see section on supportive studies) 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.

In study P006/1015, ertugliflozin was given as add-on to metformin and sitagliptin and compared to 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 (treatment difference -0.69% (-0.87,-0.50) for the 5 mg dose and -0.76% (-0.95,-0.58) for the 15 mg dose).

Thus the added effect, in terms of change from baseline in HbA1c, when ertugliflozin was given in triple combination with sitagliptin and metformin, either in initial combination with sitagliptin (study P005/1019, factorial study) or as add-on (study P006/1015) varied from -0.43% to -0.76%. It may therefore be concluded that ertugliflozin provides a relevant contribution to the effect of the FDC.

In the supportive 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, these results were considered of importance in assessing the treatment effect of ertugliflozin. All the sensitivity and supportive analyses performed had been provided although had 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 P006/1015 and P017/1047 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 P017/1047 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.

The outcome of the secondary endpoints was consistent with the primary endpoint across the studies. Reductions from baseline in FPG were consistent with the reductions observed for HbA1c. In the studies where ertugliflozin was co-administered with sitagliptin, a greater effect was observed with the combination compared to the single components. In both studies where change from baseline in 2-hour PPG was included as key secondary or as other secondary endpoints (P005/1019 and P017/1047), the treatment with ertugliflozin resulted in significant reductions in 2-hour PPG.

In all studies, 26 to 40% of subjects achieved the treatment goal ofHbA1c <7.0% when ertugliflozin was given as monotherapy. Higher responder rates were observed when ertugliflozin was given in combination with sitagliptin (50%). The difference between the two ertugliflozin doses was generally small (about 4-6%). The proportion of subjects receiving glycaemic rescue therapy in all ertugliflozin groups (either alone or co-administered with sitagliptin 100 mg) was low, ranging from 0% to 6.4%. The proportion of subjects rescued was higher in the placebo groups, ranging from 16.3% to 32.0%.

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 1.7 to 2.3 kg. 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 -6.4 mmHg with slightly larger reductions in the higher ertugliflozin dose groups.

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. Among 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.

No pooled analysis was performed due to the diversity of study designs and populations. In study-specific subgroup analyses for studies P005/1019 and P017/1047, the HbA1C reduction with ertugliflozin in combination with sitagliptin was consistent across age, gender, race, ethnicity, and baseline A1C subgroups.

Subgroup analyses were performed on pooled data from all placebo-controlled studies included in the clinical study programme supporting the MAA for ertugliflozin. 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.

Three 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 (-0.17%). 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 P007/1017, the effect of ertugliflozin was investigated as add-on to metformin and compared to 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 (treatment difference -0.70% (-0.87, -0.53) for ertugliflozin 5 mg and -0.88% (-1.05, -0.71) for ertugliflozin 15 mg, respectively). 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 (35% vs 40%). A significant decrease in body weight of about 1.6 kg was observed with both doses. Decreases in SBP and DBP were also observed, being more pronounced in the higher dose.

Study P002/1013 was a non-inferiority study comparing the effect of ertugliflozin 5 mg and 15 mg 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 primary objective was to test non-inferiority between ertugliflozin 15 mg and glimepiride against background metformin treatment. Non-inferiority between ertugliflozin 5 mg and glimepiride was also included as a secondary endpoint. 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. The proportion of patients with HbA1c<7.0% was lower in the ertugliflozin treated groups (34% vs 38%) than in the glimepiride group (44%). A significant treatment difference in decrease in body weight of 3.9 and 4.3 kg was observed with the respective doses vs glimepiride. The larger effect in this study was due to the weight increase observed in the glimepiride group. Decreases in SBP were also observed, being more pronounced in the higher dose.

Across the clinical study programme, 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 sitagliptin. 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 Steglujan can be used “when metformin and/or a sulphonylurea (SU) do not provide adequate glycaemic control”. In the only study (P001/1016) where patients were allowed to SU as background medication, subgroup analyses of the primary endpoint in patients on background SU showed only modest improvement in HbA1c when ertugliflozin was added to SU treatment. As the effect of ertugliflozin decreases with declining renal function, it is expected 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 SU in patients with normal renal function. Since the combination of ertugliflozin with SU has been sufficiently supported by data, the triple combination with ertugliflozin, sitagliptin and SU is considered justified alongside with the triple combination with metformin.

## *2.6. Clinical safety*

## *Patient exposure*

**Extent and duration of exposure**

*Sitagliptin*

Overall, approximately 2,325 healthy volunteers and 40,367 patients have been randomized and treated in the sitagliptin clinical program, of which approximately 25,361 subjects have received sitagliptin (information from sitagliptin PSUR with reporting interval 04-AUG-2011 to 03-AUG-2014).

*Ertugliflozin Phase 3 program*

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. The Broad Pool includes 1716 randomized to the ertugliflozin 5 mg group; 1693 to the ertugliflozin 15 mg group; and 1450 to the non-ertugliflozin group. The mean observation period on study medication was 356.3 days in the ertugliflozin 5 mg, 355.1 days in the 15 mg groups and 354.9 days in the non-ertugliflozin group. Furthermore, the study P002/1013 and P007/1017, respectively, will generate 2-years data from phase A + B when finalised.

*Ertugliflozin/sitagliptin FDC Phase 3 programme*

In total, 990 subjects were randomized to co-administration treatment with ertugliflozin and sitagliptin in the three phase 3 ertugliflozin/sitagliptin combination studies (studies P005/1019 and P017/1047) or to ertugliflozin on a background of metformin and sitagliptin therapy (study P006/1015). The remaining 995 subjects received treatment with ertugliflozin alone (5 mg or 15 mg; n = 498), sitagliptin 100 mg alone (n = 247), or placebo (n = 250) **(Table 26)**.

The mean duration of exposure in each treatment group with co-administration with ertugliflozin and sitagliptin across the 3 studies varied between 171 days to 174 days **(Table 26)**. Thus a sufficient amount of patients were exposed to co-administration treatment with ertugliflozin and sitagliptin. 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 325.2 days in the E15/S100 group to 334.7 days in the E5/S100 group. Similar, in study P006/1015 the mean duration of exposure (to any dose) ranged from 336.3 to 337.1 days among the three treatment groups.

In the three phase 3 ertugliflozin/sitagliptin combination studies the proportion of subjects who discontinued study medication was not higher in the ertugliflozin/sitagliptin combination groups (7%-9%) compared to the monotherapy treatments or placebo.

**Table 26**: **Exposure to Study Medication by Study, in all subjects as treated population (phase A)**

| | Duration of Exposure | | |
|---|---|---|---|
| | N | Mean Duration (Days) | Min-Max (Days) |
| **Study P005/1019 Ertugliflozin + Sitagliptin Factorial Study** | | | |
| Ertugliflozin 5 mg + Sitagliptin 100 mg | 243 | 172.5 | 1-203 |
| Ertugliflozin 15 mg + Sitagliptin 100 mg | 244 | 170.9 | 1-241 |
| Ertugliflozin 5 mg | 250 | 173.7 | 1-199 |
| Ertugliflozin 15 mg | 248 | 172.1 | 1-217 |
| Sitagliptin 100 mg | 247 | 171.8 | 1-220 |
| **Study P006/1015 Add-on to Metformin and Sitagliptin Study** | | | |
| Ertugliflozin 5 mg | 156 | 172.7 | 2-196 |
| Ertugliflozin 15 mg | 153 | 174.0 | 1-210 |
| Placebo | 153 | 172.9 | 7-215 |
| **Study P017/1047 Ertugliflozin + Sitagliptin Initial Combination Study** | | | |
| Ertugliflozin 5 mg + Sitagliptin 100 mg | 98 | 173.1 | 1-204 |
| Ertugliflozin 15 mg + Sitagliptin 100 mg | 96 | 172.7 | 5-201 |
| Placebo | 97 | 157.8 | 1-210 |

**Demographic and Other Characteristics of the Study Population**

*Ertugliflozin/sitagliptin FDC Phase 3 programme*

Age

The mean age in the three study populations varied between 55 years and 59 years. In total, among the three studies, 212 subjects ≥65 years and 23 subjects ≥75 years were exposed to the combination of ertugliflozin and sitagliptin. Thus, the exposure in subject above 75 years is limited. This is reflected in the SmPC.

Renal function

Most of the subjects (approx. 98%) had normal renal function or mild renal impairment (≥60 < 90 mL/min/1.73 $m^2$) at baseline. Even though an eGFR of ≥60 mL/min/1.73 $m^2$ was an inclusion criteria in all three studies, a total of 39 subjects (18 in the ertugliflozin/sitagliptin combination groups) presented an eGFR < 60 mL/min/1.73 $m^2$. The exposure of the ertugliflozin/sitagliptin combination should not be initiated in the population with an eGFR below 60 mL/min/1.73 $m^2$. Treatment with the ertugliflozin/sitagliptin combination should be discontinued when eGFR persistently is less than 45ml/min. This is reflected in the SmPC.

## *Adverse events*

*Ertugliflozin Phase 3 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 subjects reported AEs and in the Broad Pool about 60%.

*Ertugliflozin/sitagliptin FDC Phase 3 programme*

In the three Phase 3 studies, 43-46% of the subjects on ertugliflozin/sitagliptin combination therapy experienced at least one AE during Phase A (26 weeks). Study P005/1019 demonstrated that frequencies of subjects with one or more adverse events were in general similar in the ertugliflozin/sitagliptin combination groups (46% in E5/S100 group and 47% in E15/S100 group) as in the monotherapy groups with sitagliptin (42%) and ertugliflozin (52% inE5 mg group and 44% in E15 mg group), respectively.

**Most frequently reported adverse events**

*Ertugliflozin Phase 3 program*

In the PBO Pool, the most frequently reported events for ertugliflozin were *upper respiratory infection* (higher in the placebo group [5.2%] vs the all ertugliflozin treatment group [3.6%]), *hypoglycaemia* (3.3% in all treatment groups), *headache* (higher in the all ertugliflozin treatment group [3.2%] compared to the placebo group [2.3%]), *vulvovaginal mycotic infection* (higher frequencies in the ertugliflozin groups [2.7%] compared to the placebo group [0.6%]) and *urinary tract infections* (higher frequency in the placebo group [3.3%] compared to the all ertugliflozin treatment group [2.5%]).

Of note is the higher incidence of adverse events for ertugliflozin compared to the placebo group in the SOC Renal and urinary disorders (4.6% vs 2.1%) and SOC Reproductive system disorders (3.5% vs 1.4%). Events of renal failure/ renal impairment and osmotic diuresis-related events and genital infections are further discussed below.

*Ertugliflozin/sitagliptin FDC Phase 3 programme*

Data for the three ertugliflozin/sitagliptin combination studies was presented separately study by study. Consequently, no pooled ADR data for treatment with ertugliflozin/sitagliptin combination is available. There was no new or unexpected reactions identified with the ertugliflozin/sitagliptin combination treatment compared to ertugliflozin as monotherapy. The overall most frequently reported adverse reactions in the ertugliflozin/sitagliptin combination groups in the three studies were *hypoglycaemia* (5%) in study P005/1019, *vulvovaginal mycotic infections* (6% among the females) in study P006/1015 and *urinary tract infections* (4%) in study P017/1047. An additive effect of ertugliflozin/sitagliptin combination on reactions was noted compared to sitagliptin as monotherapy with regards to both *vulvovaginal mycotic infection* (2.9% among females in E5/S100 and E15/S100 groups *vs* 0% in S100 group in study P005/1019) and *hypoglycaemia* events (7% in E15/S100 *vs* 2.4% in S100 group in study P005/1019). Otherwise, the frequencies did not differ compared to the monotherapies. In general, no difference in AE frequencies were noted with regards to the different ertugliflozin doses and the AE pattern was in accordance with the findings in the *Ertugliflozin Phase 3 program.*

Since the three ertugliflozin/sitagliptin combination studies were presented separately study by study, no pooled ADR data for treatment with ertugliflozin/sitagliptin combination is available. Therefore, ADR

data from the largest study, P005/1019 Ertugliflozin + Sitagliptin Factorial Study is presented in **Table 27** below.

In study P005/1019 a notable high frequency of subjects reporting *hypoglycaemia* (7%) was seen in the E15/S100 treatment arm compared to all other treatment groups (2.4-3.6%). The Applicant has suggested that this observation most likely is due to random variability and that increased frequency of reporting was not noted in the two other studies. It is agreed with the Applicant that overall, study P005/1019 and P017/1047 demonstrates that co-initiation of ertugliflozin and sitagliptin do not demonstrate a higher incidence of documented hypoglycaemia compared to initiating treatment with ertugliflozin alone (regardless of dose). Hypoglycaemia is further discussed below.

**Table 27**: **Study 005/B1521019 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) |

| | E5 n (%) | | E15 n (%) | | S100 n (%) | | E5/S100 n (%) | | E15/S100 n (%) | |
|---|---|---|---|---|---|---|---|---|---|---|
| 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) |
| 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 | 2 | (0.8) | 5 | (2.0) | 0 | (0.0) | 4 | (1.6)* | 3 | (1.2)** |

| | E5 n (%) | | E15 n (%) | | S100 n (%) | | E5/S100 n (%) | | E15/S100 n (%) | |
|---|---|---|---|---|---|---|---|---|---|---|
| mycotic infection | | | | | | | | | | |
| **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) |

| | E5 n (%) | | E15 n (%) | | S100 n (%) | | E5/S100 n (%) | | E15/S100 n (%) | |
|---|---|---|---|---|---|---|---|---|---|---|
| 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)** |
| 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

| | E5<br>n<br>(%) | E15<br>n (%) | S100<br>n<br>(%) | E5/S100<br>n (%) | E15/S100<br>n (%) |
|---|---|---|---|---|---|
| columns meets the incidence criterion in the report title, after rounding.<br>MedDRA Version 18.1 | | | | | |

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 studies P007/1017 and P002/1013 that further will evaluate long-term safety for ertugliflozin.

**Drug-related adverse events**

*Ertugliflozin Phase 3 program*

In the placebo pool, the incidence of drug related adverse events (determined by the investigator to be related to the drug) were higher in the all ertugliflozin group (14.5%) compared to the placebo group (9.3%).

*Ertugliflozin/sitagliptin FDC Phase 3 programme*

Overall, in the three studies the frequencies of drug related AEs were within the same range in the ertugliflozin/sitagliptin combination groups (11%-13%) as in the groups with ertugliflozin as monotherapy (17% in E5 and 12% in E15, study P005/1019) but higher compared to the groups only with sitagliptin (5% in S100 group in study P005/1019) and placebo (8.5% in P006/1015 and 9% in study P017/1047 respectively). The most common drug-related adverse events in the ertugliflozin/sitagliptin combination groups were *genital mycotic infections* (study P005/1019 and P006/1015) and *hypoglycaemia* in study P017/1047.

**Adverse events of special interest**

***Osmotic diuresis/volume depletion***

*Ertugliflozin Phase 3 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, 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 volume depletion events was 5.1%, 2.6% and 0.5% for ertugliflozin 5mg, 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.

In subjects ≥65 years of age, the incidence of events related to volume depletion was 2.2%, 2.6% and 1.1% for ertugliflozin 5mg, ertugliflozin 15 mg and the comparator group and for subjects using

diuretics, the incidence was 3.3%, 2.3% and 1.3% for ertugliflozin 5mg, ertugliflozin 15 mg and the comparator group. The incidence was even more increased in subjects using loop-diuretics; however, the total number of subjects on a loop diuretic was too small (n=197) to draw any firm conclusions.

*Ertugliflozin/sitagliptin FDC Phase 3 programme*

As noted in the Ertugliflozin Phase 3 program, adverse events related to *osmotic diuresis* were reported in all treatment arms including ertugliflozin. In study P005/1019, the incidences were slightly higher in the ertugliflozin/sitagliptin combination arms (1.6% in total among subjects in the E5/S100 and E15/S100 groups) compared to the monotherapy with ertugliflozin (0.8% in total among subjects in the E5 and E15 groups).

In total, five adverse events related to *hypovolemia* (referred to as volume depletion in the ertugliflozin registration dossier) were reported within the ertugliflozin/sitagliptin combination treatment arms in the combination studies ( four in study P017/1047, one in study P006/1016 and none in study P005/1019), with no notable increased incidence compared to the monotherapies.

***Genital infections***

Adverse reactions related to genital infections are known for DPP-4 inhibitors but not for sitagliptin.

*Ertugliflozin Phase 3 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 subjects 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 subjects 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/sitagliptin FDC Phase 3 programme*

In the presented phase 3 studies with combination treatment with ertugliflozin/sitagliptin, genital mycotic infections occurred more frequently in men and in women treated with ertugliflozin both as monotherapy and in combination with sitagliptin compared to sitagliptin as monotherapy **(Table 28** and **Table 29)**. The pattern was the same in study P017/1047 and P006/1015.

In summary the presented data did not demonstrate further increased risk for genital infections with ertugliflozin and sitagliptin combination therapy compared to use of ertugliflozin as monotherapy.

**Table 28**: **Subjects with adverse events related to genital mycotic infections in males - by SOC and PT**

| | **E5 (n=127) n (%)** | **E15 (n=134) n (%)** | **S100 (n=154) n (%)** | **E5/S100 (n=123) n (%)** | **E15/S100 (n=126) n (%)** |
|---|---|---|---|---|---|
| Male subjects with at least one adverse event related to genital infection | 6 (4.7) | 5 (3.7) | 0 (0) | 5 (4.1) | 3 (2.4) |

**Table 29**: **Subjects with adverse events related to genital mycotic infection in females - by SOC and PT**

| | **E5 (n=123) n (%)** | **E15 (n=114) n (%)** | **S100 (n=93) n (%)** | **E5/S100 (n=120) n (%)** | **E15/S100 (n=118) n (%)** |
|---|---|---|---|---|---|
| Female subjects with at least one adverse event related to genital infection | **6 (4.9)** | **8 (7.0)** | **1 (1.1)** | **6 (5.0)** | **9 (7.6)** |

***Urinary Tract Infection***

*Ertugliflozin Phase 3 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 5mg (6.9%) and 15 mg (7.0%) groups and the incidence of serious events was low in all groups (≤0.4%).

*Ertugliflozin/sitagliptin FDC Phase 3 programme*

The incidence of urinary tract infections in the *P005/1019 Ertugliflozin + Sitagliptin Factorial* study was similar in the E5/S100 and E15/S100 groups (3.3% and 3.7%, respectively) relative to the S100 group (3.2%), but was numerically lower than the incidence in the E5 and E15 groups (6.0% and 5.6%, respectively)

Overall, the results from the three phase 3 studies with ertugliflozin/sitagliptin combination treatment did not identify any additional safety or tolerability concerns with regard to urinary tract infection with

ertugliflozin and sitagliptin combination therapy compare to treatment with the respective monotherapies.

***Hypoglycaemia***

*Ertugliflozin Phase 3 program*

In the placebo-controlled pool, the incidence of documented hypoglycaemia was relatively low, although, increased for ertugliflozin 5 mg and 15mg (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 to placebo (4.3%). 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.

When used as add-on to metformin and sitagliptin, 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%). Also in the ertugliflozin + sitagliptin study (P017/1047), hypoglycaemia was increased in both the E5/S100 (6.1%) and E15/S100 group (3.1%) vs. placebo (1.0%), although, more increased in the lower dose of ertugliflozin.

When add-on to metformin and compared to SU (glimepiride), the incidence of hypoglycaemia was as expected lower in the ertugliflozin groups (6-8%) relative to the glimepiride group (27%).

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 secretagogue as background therapy in this study. The incidence of documented hypoglycaemia AEs was higher for E5 group (34%) compared to E15 group (25%) 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/sitagliptin FDC Phase 3 programme*

Overall the incidence of *documented hypoglycaemia* was not considered higher in the ertugliflozin and sitagliptin combination group compared to the group on ertugliflozin as monotherapy. However, in accordance with the results in the *Ertugliflozin Phase 3 program* a higher incidence of *documented hypoglycaemia* was noted in subjects treated with ertugliflozin (both as monotherapy and in combination with sitagliptin) compared to subjects treated with sitagliptin as monotherapy (study P005/1019) or placebo (study P017/1047)**(Table 30)**.

There was a markedly increase in frequency of hypoglycaemic events in the E15/S100 group (9%) compared to the other groups in study P005/1019. This observation is most likely due to random variability since the observation in this one group in study P005/1019 is not consistent with corresponding group results in study (P006/1015 and P017/1047). The population in study P006/1015 already tolerated sitagliptin when ertugliflozin was added, and could therefore not fully be compared with the population with co-initiation of both ertugliflozin and sitagliptin (study P005/1019 and P017/1047).

Very few episodes of severe hypoglycaemia were reported in the three studies (n=5 in total and 3 of these in combination with sitagliptin and ertugliflozin 15mg).

All three studies demonstrated that the risk of documented hypoglycaemia was not dependent on the of ertugliflozin dose.

Since it is known that the mechanisms of action of both sitagliptin and ertugliflozin are glucose dependent and thereby posing a risk of hypoglycaemia, this seems not to be an issue in clinical practice.

**Table 30**: **Documented (Symptomatic and Asymptomatic) and Severe Hypoglycaemia by Study (Ertugliflozin/Sitagliptin)**

| **P005/1019 (26 weeks)**<br>**Ertugliflozin + Sitagliptin Factorial** | **Sita**<br>**(N=247)** | **Ertu 5 mg**<br>**(N=250)** | **Ertu 15 mg**<br>**(N=248)** | **Ertu 5 mg + Sita 100 mg**<br>**(N=243)** | **Ertu 15 mg + Sita 100 mg**<br>**(N=244)** |
|---|---|---|---|---|---|
| Documented, n (%) | 9 (3.6) | 14 (5.6) | 13 (5.2) | 13 (5.3) | 22 (9.0) |
| Severe, n (%) | 0 (0) | 0 (0) | 1 (0.4) | 0 (0) | 1 (0.4) |
| **P006/1015 (26 weeks)**<br>**Add-on to Metformin and Sitagliptin** | **Placebo**<br>**(N=153)** | **Ertu 5 mg**<br>**(N=156)** | **Ertu 15 mg**<br>**(N=153)** | | |
| Documented, n (%) | 5 (3.3) | 7 (4.5) | 3 (2.0) | | |
| Severe, n (%) | 1 (0.7) | 1 (0.6) | 0 (0) | | |
| **P017/1047 (26 weeks)**<br>**Ertugliflozin + Sitagliptin Initial Combination** | **Placebo**<br>**(N=97)** | | | **Ertu 5 mg + Sita 100 mg**<br>**(N=98)** | **Ertu 15 mg + Sita 100 mg**<br>**(N=96)** |
| Documented, n (%) | 1 (1.0) | | | 6 (6.1) | 3 (3.1) |
| Severe, n (%) | 0 (0) | | | 0 (0) | 2 (2.1) |
| N = number of subjects in the ASaT population, n = number of subjects with one or more events | | | | | |

***Changes in Renal Function***

*Sitagliptin*

There have been post-marketing reports of worsening renal function in subjects taking sitagliptin, including acute renal failure, sometimes requiring dialysis, with a subset of these reports involving subjects with renal insufficiency.

*Ertugliflozin Phase 3 program*

eGFR

In the placebo-controlled pooled, treatment with ertugliflozin was associated with small transient decreases in eGFR at Week 6 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 Week 52. There were small mean increases in serum creatinine in the ertugliflozin groups that decreased to or towards baseline values at week 26. However, mean changes from baseline in BUN was higher in the ertugliflozin groups relative to the placebo group at week 26. T

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 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 5mg, 0.8% in ertugliflozin 15 mg and 0.4% in 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 **(Figure 8)**; however, reversed after treatment discontinuation. 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%).

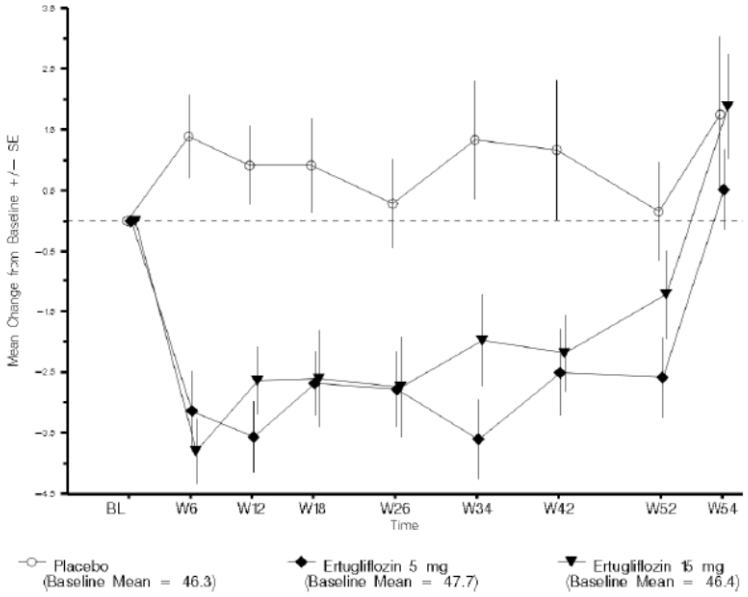



**Figure 8: eGFR (mL/min/1.73m$^2$): Mean Change from Baseline Over Time (Mean ± SE) All Subjects as Treated study P001/1016: Including Rescue Approach**

*Ertugliflozin/sitagliptin FDC Phase 3 programme*

eGFR *(P005/1019 Ertugliflozin + Sitagliptin Factorial Study)*

There were reductions from baseline in eGFR at Week 6 in all four ertugliflozin-treated groups in study P005/1019. The magnitude of the reductions were greater in the E5/S100 and E15/S100 groups (-3.5 mL/min/1.73 m$^2$ and -5.1 mL/min/1.73 m$^2$, respectively) relative to the E5 and E15 groups (-2.4 mL/min/1.73 m$^2$ and -3.4 mL/min/1.73 m$^2$, respectively). There was a subsequent return of eGFR to baseline in the E5/S100 and E5 groups, or toward baseline in the E15/S100 group (-2.1 mL/min/1.73 m$^2$) and E15 group (-1.0 mL/min/1.73 m$^2$) at Week 26. In the S100 group, a small decrease in eGFR through Week 12 (-1.4 mL/min/1.73 m$^2$) was followed by a slight increase toward baseline at Week 26 **(Figure 9)**. The proportion of subjects with at least 1 decrease in eGFR >30% from baseline was numerically greater in the E5/S100 group (5.9%) than in the E5 group (2.8%), but was similar in the E15/S100 (3.8%) and E15 (4.1%) groups, with 2.9% of subjects in the S100 group meeting this criterion.

Results from phase B (week 52) of study P005/1019 demonstrated generally similar eGFR results to those observed at Week 26 **(Figure 9)**, 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.

After phase A+B the proportion of subjects with at least 1 decrease in eGFR >30% from baseline varied from 4.5% in the E5 and S100 group to 7.6% in the E15/S100 group.

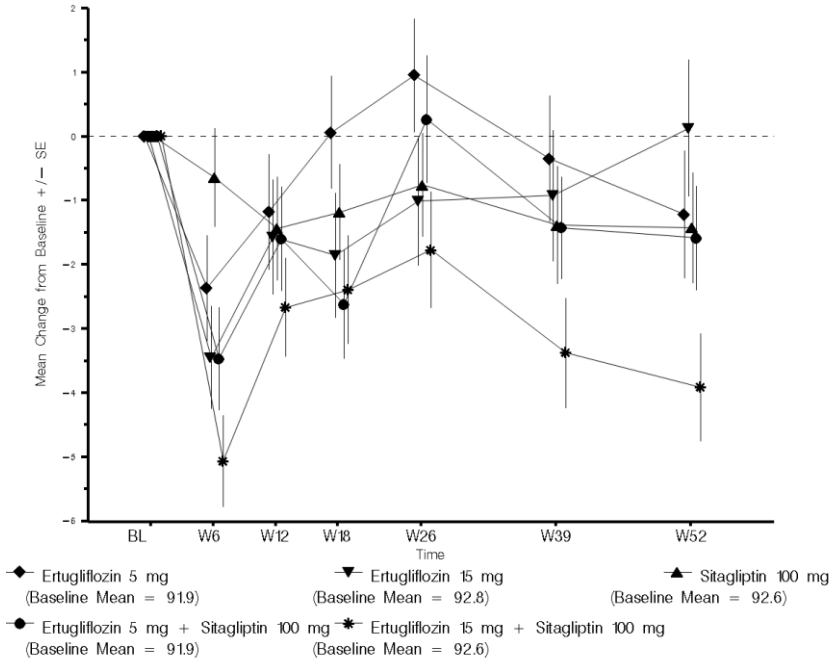



**Figure 9: Mean change in eGFR from baseline over time (Mean ± SE) study P005/1019**

Serum creatinine *(P005/1019 Ertugliflozin + Sitagliptin Factorial Study)*

A subsequent but mainly transient reduced renal function was reflected in increased serum creatinine. The increases of serum creatinine were numerically larger in the E5/S100 and E15/S100 groups (0.032 mg/dL and 0.041 mg/dL, respectively) relative to the E5 and E15 groups (0.018 mg/dL and 0.029 mg/dL). There was a subsequent return of serum creatinine to or near baseline in the E5/S100, E5, and E15 groups at Week 26. In the E15/S100 group, serum creatinine decreased toward baseline after Week 6, but remained slightly elevated at Week 26. There was a small increase in serum creatinine (≤0.012 mg/dL) from Week 6 to Week 26 in the S100 group.

AEs related to decrease in renal function *(P005/1019 Ertugliflozin + Sitagliptin Factorial Study)*

In study P005/1019, adverse event of *eGFR decreased* or *blood creatinine increased* was not reported in higher frequencies for the combination groups compared to subjects in the E5 and E15 groups, respectively after 52 weeks (Phase A+B): 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 subject (1.6%) in the S100 group.

Adverse event of *acute kidney injury, chronic kidney disease, renal impairment,* or *nephropathy* was also reported in similar frequencies after 52 weeks (Phase A+B) for subjects in the combination groups compared to ertugliflozin as monotherapy (1.6% and 1.2% in the E5/S100 and E15/S100 groups, respectively vs 0.8% in both the E5 and the E15 groups). One subject (0.4%) in the S100 group reported one of these events. 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, eight renal related AEs led to discontinuation (three in group E15/S100, two in E5, one in E15 and two in S100 group) after 52 weeks.

Acute renal failure and impaired renal function is labelled in the SmPC for sitagliptin. Blood creatinine increased/eGFR decreased is reflected in the SmPC for ertugliflozin/sitagliptin FDC. In addition, renal impairment is characterised as an important potential risk in the proposed RMP for the ertugliflozin/sitagliptin FDC.

***Hepatic events***

*Ertugliflozin Phase 3 program*

In the placebo-controlled Pool, there were decreases in ALT and AST in the both ertugliflozin groups relative placebo, which were 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 other subjects' events resolved on treatment; the last case resolved following interruption of study medication. No cases were adjudicated as very likely or probable.

In conclusion, there was no increased incidence of hepatic events with ertugliflozin treatment.

*Ertugliflozin/sitagliptin FDC Phase 3 programme*

Results from the three Phase 3 studies with ertugliflozin/sitagliptin combination treatment did not identify any additional safety or tolerability concerns with regard to change in ALT and AST with ertugliflozin and sitagliptin combination therapy compared to the respective monotherapies.

***Hypersensitivity reactions***

*Ertugliflozin Phase 3*

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 5mg (2.1%) and 15mg (1.4%) and the placebo (1.9%) group. No serious adverse events were reported in any group.

*Ertugliflozin/sitagliptin FDC Phase 3 programme*

In total, one event classified as related to hypersensitivity was reported in combination with ertugliflozin and sitagliptin (in the E15/S100 group; study P005/1019) and concerned a non-serious, moderate adverse event of dermatitis allergic on Day 105, reported as not related to study medication by the investigator.

Based on the results from the combination studies, treatment with the combination of ertugliflozin and sitagliptin did not increase the risk for hypersensitivity reactions.

Hypersensitivity reaction including anaphylactic responses is labelled in the SmPC for sitagliptin.

***Bone safety / fractures***

The safety topic "*Bone fractures*" were assessed in the Ertugliflozin Phase 3 program but not separately for the studies in the Ertugliflozin/sitagliptin combination Phase 3 program.

*Ertugliflozin Phase 3 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. The final 104-week CSR for study P007/1017 will be provided in 3Q 2018. The Applicant has confirmed to provide final summarized data of all adjudicated confirmed fractures, including the incidence of low trauma fractures, at the time for submission of the final CSR for the study P007/1017.

In one placebo-controlled study (P007/1017), ertugliflozin had no impact on bone mineral density (BMD) during the 26-week treatment period.

Interim 52-week BMD data 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 and 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 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, 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 5mg and 15 mg(about 29-38%) relative to placebo (10%) and a non-dose-dependent increase in PTH (6.8% and 6.9% vs. 1.1% for ertugliflozin 5mg 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 numerically higher in the 15 mg group (21% relative to the placebo group (13%). The bone formation marker P1NP increased two times more in the ertugliflozin 15 mg (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 moderate 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 5mg and 15 mg vs. placebo but no meaningful change in calcium were noted. 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 two ertugliflozin groups, 5mg and 15

mg (33% and 34%), relative to 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 at and 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***

The safety topic "*Lower limb amputations*" were assessed in the Ertugliflozin Phase 3 program but not separately for the studies in the Ertugliflozin/sitagliptin combination Phase 3 program.

*Ertugliflozin Phase 3 program*

In the Broad Pool, there were 10 subjects with non-traumatic limb amputations (all post-randomization treatment analysis): 1 of 1450 (0.1%) in the non-ertugliflozin group, 1 of 1716 (0.1%) in the ertugliflozin 5 mg group and 8 of 1693 (0.5%) in the ertugliflozin 15 mg group (resulting in 9 of 3,409 (0.3%) in the all ertugliflozin group). Among these cases, the most frequently reported amputation was toe amputation. 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.

***Ketoacidosis***

The safety topic "*Ketoacidosis*" were assessed in the Ertugliflozin Phase 3 program but not separately for the studies in the Ertugliflozin/sitagliptin combination Phase 3 program.

*Ertugliflozin Phase 3 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.

***Serum lipids***

*Ertugliflozin Phase 3 program*

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. 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.

*Ertugliflozin/sitagliptin FDC Phase 3 programme*

The changes in lipid parameters observed with ertugliflozin treatment in the *Ertugliflozin Phase 3 program (i.e* increase in LDL-C, HDL-C and total cholesterol) were also noted in the three Phase 3 ertugliflozin/sitagliptin combination studies. The increase of LDL-C and a decrease in triglycerides tended to be larger in the ertugliflozin/sitagliptin combination groups compared to the ertugliflozin (study P005/1019) and sitagliptin (study P005/1019 and P006/1015) monotherapy.

***Malignancies***

Malignancies were assessed separately in the *Ertugliflozin Phase 3 program* but not specific for the in the ertugliflozin/sitagliptin combination in the *Phase 3 ertugliflozin/sitagliptin combination program*.

*Ertugliflozin Phase 3 program*

There was an imbalance in the SOC Neoplasms for ertugliflozin (0.6% and 1.2% for ertugliflozin 5mg 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 15mg (0.9%) in comparison to ertugliflozin 5mg (0.3%) and comparator (0.4%). Malignancies reported in more than one subject in the ertugliflozin groups were 2 breast cancer/ invasive ductal breast cancer, 2 malignant melanoma and 2 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.

***Pancreatitis***

*Sitagliptin*

Pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, is included in the labelling of sitagliptin.

*Ertugliflozin/sitagliptin FDC Phase 3 programme*

There were no cases of confirmed pancreatitis in subjects treated with ertugliflozin, with or without combination treatment with sitagliptin in any of the three combination studies.

## *Serious adverse event / deaths / other significant events*

**Deaths**

*Ertugliflozin Phase 3 program*

A total of 26 deaths occurred in the *Ertugliflozin* 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), in the Ertugliflozin phase III studies, 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/sitagliptin combination phase 3 studies*

No fatal events occurred in any of the ertugliflozin/sitagliptin combination groups or studies.

**Serious adverse events**

*Ertugliflozin Phase 3 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/sitagliptin FDC Phase 3 programme*

Overall, the frequency and pattern of SAEs with the ertugliflozin/sitagliptin combination did not differ compared with the respective monotherapies.

In total, approximately 2-3% of the subjects in the combination groups (E5/S100 and E15/S100 groups calculated together) in the three phase 3 studies had one or more SAE. Most of the SAEs were presented with single events per PT without any higher incidence in the ertugliflozin/sitagliptin combination group compared to the ertugliflozin in monotherapy. Two serious events (pyelonephritis and transient ischemic attack) with the combination treatment were considered as related to study drug by the investigator.

## *Laboratory findings*

### *Haematology*

*Ertugliflozin Phase 3 program*

In the placebo-controlled Pool, slight increases from baseline to week 26 in hemoglobin 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 hemoglobin and hematocrit are considered related to volume depletion associated with the diuretic effect of ertugliflozin, as for other SGLT-2 inhibitors.

*Ertugliflozin/sitagliptin FDC Phase 3 programme*

In all three phase 3 ertugliflozin/sitagliptin studies, a small increase in haemoglobin with ertugliflozin and sitagliptin combination therapy was noted, both with regard to change over time and individual subject variations. The results are consistent with those seen in the individual ertugliflozin groups in Study P005/1019, and with ertugliflozin treatment in the Phase 3 development program. Thus, results from the three Phase 3 studies with ertugliflozin/sitagliptin combination treatment did not identify any additional safety or tolerability concerns with regard to increase in hemoglobin with ertugliflozin and sitagliptin combination therapy.

**Potassium**

*Ertugliflozin Phase 3 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 5mg, 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 5mg and 15 mg, respectively) 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, 10.0% subjects treated with ertugliflozin 15 mg, and 8% subjects treated with placebo. No dose-dependent manner was noted.

*Ertugliflozin/sitagliptin FDC Phase 3 programme*

Results from the three Phase 3 studies with ertugliflozin/sitagliptin combination treatment did not identify any additional safety or tolerability concerns with regard to change potassium with ertugliflozin and sitagliptin combination therapy compared to the respective monotherapies.

**Uric acid**

*Ertugliflozin Phase 3 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/sitagliptin combination phase 3 studies*

Results from the three Phase 3 studies with ertugliflozin/sitagliptin combination treatment did not identify any additional safety or tolerability concerns with regard to change in uric acid with ertugliflozin and sitagliptin combination therapy compared to the respective monotherapies.

**Blood pressure / pulse rate**

*Ertugliflozin Phase 3 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/sitagliptin FDC Phase 3 programme*

Blood Pressure

As in the ertugliflozin Phase 3 program a reduction in systolic and diastolic BP was demonstrated both in the ertugliflozin and ertugliflozin/sitagliptin treatment groups. The reductions were similar with ertugliflozin as monotherapy (Week 26 changes: -4.48 mmHg [E5 group] and -3.73 mmHg [E15 group]) and ertugliflozin/sitagliptin combination (Week 26 changes: -3.52 mmHg [E5/S100 group] and -3.86 mmHg [E15/S100 group]) but lower compared to sitagliptin as monotherapy (-0.37 mmHg).

Pulse

As in the phase 3 program for ertugliflozin a decrease in sitting pulse rate was noted in the ertugliflozin monotherapy arms with no additional decrease when combining ertugliflozin with sitagliptin, instead, in study P005/1019 the combination therapy tended to even out the pulse decreasing effect caused by ertugliflozin.

## *Safety in special populations*

No specific analyses to assess intrinsic factors were performed for subjects taking the combination of ertugliflozin and sitagliptin in the ertugliflozin/sitagliptin combination phase 3 studies.
In the *ertugliflozin Phase 3 program* subgroup analyses for age, gender, race, ethnicity, and renal function were performed in the 7-study ertugliflozin Broad Pool. Across genders, race and ethnicity, there were no notable differences in the incidence of adverse event summary measures when comparing ertugliflozin and non-ertugliflozin treated subjects, suggesting that these subgroups did not modulate between-treatment effects.

**Results from the Ertugliflozin Phase 3 program**

***Elderly***
Age-delineated data was provided for age groups: <65 y (n=3605), 65-74 y (n=1035), 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 years 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 5mg 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 5mg, ertugliflozin 15 mg and placebo, respectively.

In subjects ≥ 65 years of age, renal-related events were more frequently common for ertugliflozin (1.3% and 1.4%; for 5mg and 15 mg ertugliflozin respectively) than for 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 5mg, 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 5mg, ertugliflozin 15 mg and comparator , 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 5mg, 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 5mg 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 subjects 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 subjects of Hispanic/Latino ethnicity (59-60%) than for subjects 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 $m^2$; however, the imbalance was numerically smaller.

Renal-related events

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. 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), events of renal-related events were more frequent in the ertugliflozin groups relative 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 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 than (11% both for 5mg and 15 mg, respectively) 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.

## *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 modeling, 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 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 of the SmPC.

*Sitagliptin*

Sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19, or 2B6, and is not an inducer of CYP3A4. Sitagliptin is a p-glycoprotein substrate but does not inhibit p-glycoprotein mediated transport of digoxin. Based on these results, sitagliptin is considered unlikely to cause interactions with other drugs that utilize these pathways. Sitagliptin is not extensively bound to plasma proteins. Therefore, the propensity of sitagliptin to be involved in clinically meaningful drug-drug interactions mediated by plasma protein binding displacement is very low.

*Ertugliflozin and Sitagliptin Combination Treatment*

Study P022/1033 was a drug-drug interaction study to estimate the pharmacokinetic interaction between ertugliflozin and sitagliptin. There were no meaningful differences in the PK of either sitagliptin or ertugliflozin when co-administered compared to the PK of each drug administered alone.

## *Discontinuation due to adverse events*

*Ertugliflozin Phase 3 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/sitagliptin FDC Phase 3 programme*

In total, 2% of the subjects on ertugliflozin/sitagliptin combination treatment had an AE leading to discontinuation to study drug without any apparent pattern in the events resulting in discontinuation from study medication. There were no withdrawals due to any SAEs judged as related to study medication.

### *Post marketing experience*

Not applicable

## 2.6.1. Discussion on clinical safety

The database for the E*rtugliflozin Phase 3* program 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 2,575 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.

In three *Ertugliflozin/sitagliptin FDC Phase 3 programme,* 990 subjects were randomized to co-administration treatment with ertugliflozin and sitagliptin (studies P005/1019 and P017/1047), or to ertugliflozin on a background of metformin and sitagliptin therapy (Study P006/1015). All three studies included in the safety data set for the FDC of ertugliflozin/sitagliptin were conducted with combination of ertugliflozin and sitagliptin separately and not as a FDC formulation. Treatment duration was up to 26 weeks. The safety data set for the ertugliflozin/sitagliptin combination therapy is considered sufficient.

In the E*rtugliflozin Phase 3 program,* 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).

In the *Ertugliflozin Phase 3 program,* 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).

*In the Ertugliflozin/sitagliptin combination phase 3 studies,* there were no new or unexpected reactions identified with the ertugliflozin/sitagliptin combination treatment compared to ertugliflozin as monotherapy. The overall most frequently reported adverse reactions among all subjects in the ertugliflozin/sitagliptin combination groups in the three studies were *hypoglycaemia* (5%) in study P005/1019, *vulvovaginal mycotic infections* (6.1% among the females) in study P006/1015 and *urinary tract infections* (4.1%) in study P017/1047. There were no statistical differences in frequencies of the reactions with the ertugliflozin/sitagliptin combination treatment compared to ertugliflozin as monotherapy. However, compared to sitagliptin as monotherapy both *vulvovaginal mycotic infection* and *hypoglycaemia* events were reported in higher frequencies with the ertugliflozin/sitagliptin combination treatment.

Overall, in the *Ertugliflozin/sitagliptin combination phase 3 studies,* the frequencies of drug related AEs were within the same range for the ertugliflozin/sitagliptin combination groups (11-13%) as ertugliflozin as monotherapy (12-17%) but higher compared to the groups only with sitagliptin (5 %) or placebo (8-9%) respectively. The most common drug-related adverse events were *genital mycotic infections.*

*Volume depletion/osmotic diuresis*

In the *Ertugliflozin Phase 3 program* (placebo-controlled Pool), the incidence of volume depletion events was low (<2%) and not notably different across the ertugliflozin and placebo groups. The pattern was similar in the *phase 3 ertugliflozin and sitagliptin combination studies* with in total five events of hypovolemia with no notable increased incidence compared to the monotherapies including sitagliptin.

In the subgroup analyses in the Broad Pool in the Ertugliflozin Phase 3 program, 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 5mg, 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.

As noted in the ertugliflozin Phase 3 program events related to *osmotic diuresis* was reported in all treatment arms including ertugliflozin. The incidences were slightly higher in the ertugliflozin/sitagliptin combination arms compared to the monotherapy with ertugliflozin (1.6% vs 0.8% respectively in study P005/1019). Reactions related to osmotic diuresis is reflected in the SmPC section 4.8.

*Genital infections/ urinary tract infections*

Urinary tract infections and genital infections were classified as adverse events of special interest for ertugliflozin due to its mechanism of action. In the *Ertugliflozin Phase 3 program,* there was an increased risk in ertugliflozin-treated subjects 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 phase 3 studies with *ertugliflozin/sitagliptin combination* treatment the same pattern was noted. There were no differences between ertugliflozin as monotherapy compared to the ertugliflozin and sitagliptin combination groups. However, the frequencies of genital infections were lower in the group with sitagliptin as monotherapy compared to all ertugliflozin containing treatment groups.

In the placebo-controlled pool , in the Ertugliflozin Phase 3 program, no event was serious among the female genital infections and 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 and 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 in the comparator group with phimosis 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 both subjects <65 years and ≥ 65 years.

*Hypoglycaemia*

In the placebo-controlled pool in the *Ertugliflozin Phase 3 program*, the incidence of documented hypoglycaemia was relatively low, although, increased for ertugliflozin 5 mg and 15mg (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 is reflected in the SmPC.

In the moderate renal impairment 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, 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.

In the ertugliflozin/sitagliptin combination studies a similar pattern was noted with higher frequencies of *documented hypoglycaemia* both with ertugliflozin as monotherapy (approx. 5% in both groups) and in combination with sitagliptin (5% [E5/S100] and 9% [E15/S100]) compared to sitagliptin as monotherapy (3.6%) in the Ertugliflozin + Sitagliptin Factorial Study. The marked increase in frequency of hypoglycemic events in the E15/S100 group (9%) compared to the other groups in study P005/1019. This observation is most likely due to random variability since the observation in this one group in study P005/1019 is not consistent with corresponding group results in study (P006/1015 and P017/1047). Since it is known that the mechanisms of action of both sitagliptin and ertugliflozin are glucose dependent and thereby posing a risk of hypoglycaemia, this seems not to be an issue in clinical practice.

*Renal Function*

In the ertugliflozin Phase 3 program, treatment with ertugliflozin was associated with a transient and small decrease 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. Mean changes from baseline in BUN was higher in the ertugliflozin groups relative to the placebo group at week 26. 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 common for ertugliflozin (1.3% and 1.4%; for 5mg and 15 mg ertugliflozin, respectively) than for the comparator (0.5%).

In the phase 3 ertugliflozin/sitagliptin combination studies, a transient decreases in eGFR was also reflected in all ertugliflozin containing treatment groups  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 and increase of serum creatinine in the two combination groups (E5/S100 and E15/S100)  compared to the respective monotherapy group (ertugliflozin 5mg, ertugliflozin 15 mg and sitagliptin 100mg).  Results from phase B (week 52) of study P005/1019 demonstrates that the initial eGFR decreases were followed by a return to or towards baseline in both ertugliflozin /sitagliptin combination groups (E15/S100 and E15/S100), which was least evident in the E15/S100 group, where a modest decrease from baseline remained through Week 52. However, additional data demonstrated reversed eGFR values after treatment discontinuation.  The decrease in eGFR is not considered a significant problem in clinical practice since combination treatment with ertugliflozin and sitagliptin not should be initiated in patients with an eGFR below 60 mL/min/1.73 $m^2$.

In addition, eGFR reversed after treatment discontinuation, which is recommended in patients with eGFR values persistently <45 mL/min/1.73m$^2$ treatment.

The frequencies of AEs related to decrease renal function in the ertugliflozin/sitagliptin combination groups were low (<2%) without any imbalance compared to the ertugliflozin monotherapy groups. However, these events were reported with slightly lower frequencies in the sitagliptin groups compared to all ertugliflozin containing groups.

Acute renal failure and impaired renal function is labelled in the SmPC for sitagliptin. Blood creatinine increased/eGFR decreased is reflected in the SmPC for ertugliflozin/sitagliptin FDC.

*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. The final 104-week CSR for study P007/1017 will be provided in 3Q 2018. The Applicant has confirmed to provide final summarized data of all adjudicated confirmed fractures, including the incidence of low trauma fractures, at the time for submission of the final CSR for the study P007/1017. 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 serum magnesium (7.8% and 9.9% vs. -0.9%) but no change in serum calcium was seen with ertugliflozin treatment (5mg 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 5mg and 15 mg (29-38%) relative to placebo (about 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 5mg and 15 mg (33% and 34%) compared to placebo (9.6%); although not dose-dependent.

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.

*Bone fractures* were not separately assessed for the studies in the ertugliflozin/sitagliptin combination Phase 3 program.

*Lower limb amputations*

In the Broad Pool, there were 10 subjects with non-traumatic limb amputations (all post-randomization treatment analysis): 1 of 1450 (0.1%) in the non-ertugliflozin group, 1 of 1716 (0.1%) in the ertugliflozin 5 mg group and 8 of 1693 (0.5%) in the ertugliflozin 15 mg group (resulting in 9 of 3,409 (0.3%) in the all ertugliflozin group). Among these cases, the most frequently reported amputation was toe amputation. 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.

*Ketoacidosis*

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.

Ketoacidosis was not separately assessed for the studies in the ertugliflozin/sitagliptin combination Phase 3 program.

*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.

Overall, the changes in lipid parameters observed with ertugliflozin treatment in the *Ertugliflozin Phase 3 program* were also noted in the three P*hase 3 ertugliflozin/sitagliptin combination* studies.

*Malignancies*

In the ertugliflozin Phase 3 development program, there was a slight imbalance in the SOC Neoplasms for ertugliflozin 5 mg and 15 mg (0.6% and 1.2%) compared to the comparator groups (0.3% 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).

This safety issue was not assessed separately in the ertugliflozin and sitagliptin combination studies.

*Laboratory findings*

*Hemoglobin* was increased in the ertugliflozin groups (3.5% in both groups) and decreased in the placebo group (-1.4%), which is reflected in the SmPC.

*Subgroups*

In subjects ≥65 years of age studied in the ertugliflozin Phase 3 development program, 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 risk is reflected in the SmPC.

Renal impairment

In subjects with moderate renal impairment treated with ertugliflozin in the ertugliflozin Phase 3 studies, the decrease in eGFR was slightly larger than in the placebo Pool, and did not return to baseline at week 26, however reversed after treatment discontinuation. 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. 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.

In the three Phase 3 ertugliflozin/sitagliptin combinations, most of the subjects had normal or mild impaired renal function. In total, 18 subjects had an eGFR 30 to <60 mL/min/1.73 $m^2$ at baseline.

Initiating of ertugliflozin in combination with sitagliptin is not recommended in subjects with an eGFR below 60 ml/min/1.73$m^2$. This is reflected in the SmPC.

## 2.6.2. Conclusions on the clinical safety

The safety profile for ertugliflozin is consistent with other SGLT-2 inhibitors and overall there was no new or unexpected reactions reported with the ertugliflozin/sitagliptin combination treatment compared to ertugliflozin and sitagliptin as monotherapies. In general, the safety results on ertugliflozin from the ertugliflozin Phase 3 studies could be extrapolated to the ertugliflozin/sitagliptin combination treatment.

In the ertugliflozin Phase 3 studies (placebo-pool), the rate of hypoglycaemia was relatively low, although increased for ertugliflozin (5.0% and 4.5% for ertugliflozin 5mg 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 5mg, ertugliflozin 15mg 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 and the placebo group.

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. 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 slightly larger than in the placebo Pool (about 1 mL/min/1.73 $m^2$ more), 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. In the E*rtugliflozin/sitagliptin combination phase 3 studies* events of *hypoglycaemia* and *genital mycotic infections* were reported in higher frequencies with the ertugliflozin/sitagliptin combination treatment compared to sitagliptin as monotherapy but in a similar proportion of subjects compared to ertugliflozin as monotherapy.

A transient decrease in renal function, reflected by decreased eGFR and increased creatinine, is noted with ertugliflozin as monotherapy in the ertugliflozin Phase 3 studies. This decrease was more pronounced in the ertugliflozin/sitagliptin combined treatment groups compared to groups with ertugliflozin as monotherapy and sustained over 52 weeks in the group of subjects treated with ertugliflozin 15mg in combination with sitagliptin 100 mg (E15/S100 group). However, the eGFR returned to baseline after discontinuation and there was no imbalance in frequencies of AEs related to decreased renal function in the ertugliflozin/sitagliptin combination groups compared to the ertugliflozin monotherapy groups.

During treatment with sitagliptin as monotherapy, serious adverse reactions including pancreatitis and hypersensitivity reactions have been reported. Also hypoglycaemia has been reported with sitagliptin in combination with sulphonylurea and insulin. However, in the studies presented in the application no cases of confirmed pancreatitis in subjects treated with ertugliflozin, with or without combination treatment with sitagliptin was reported. Treatment with the combination of ertugliflozin and sitagliptin did not increase the risk for hypersensitivity reactions compared to treatment with ertugliflozin (one non-serious case of hypersensitivity was reported in combination with ertugliflozin and sitagliptin). Overall the incidence of *documented hypoglycaemia* was not considered higher in the ertugliflozin and sitagliptin combination group compared to the group on ertugliflozin as monotherapy however increased compared to sitagliptin as monotherapy.

## 2.7. Risk Management Plan

### Safety concerns

| | |
|---|---|
| Important identified risks | • Volume depletion<br>• DKA with atypical presentation<br>• Hypersensitivity reactions, including anaphylactic reaction, angioedema, rash, urticaria, cutaneous vasculitis, skin exfoliation, and Stevens-Johnson syndrome<br>• Gastrointestinal disorders: nausea, vomiting, constipation, diarrhea, abdominal pain, flatulence, abdominal pain upper, and related terms (dyspepsia and gastritis)<br>• Musculoskeletal disorders: osteoarthritis, pain in extremity, and related terms (eg, arthralgia, myalgia, myopathy)<br>• Pancreatitis |
| Important potential risks | • Impaired renal function, including acute renal failure (sometimes requiring dialysis)<br>• Lower limb amputations<br>• Bone fracture<br>• Infections: URTI, nasopharyngitis, and related terms (bronchitis, acute bronchitis, pharyngitis, sinusitis, and rhinitis)<br>• Neurotoxicity: tremor, ataxia, and balance disorders<br>• Suicidal ideation, suicide and depression<br>• Skin reactions: contact dermatitis<br>• Pancreatic cancer<br>• Rhabdomyolysis |
| Missing information | • Use in elderly patients (≥75 years)<br>• Use in pregnancy and breastfeeding<br>• Use in patients with CHF Class II-IV<br>• 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 | To continue monitoring and gain further information on 1) the characteristics of ertugliflozin use in patients with CHF Class II-III 2) the long-term CV safety profile in patients treated with ertugliflozin 3) the frequency and characteristics of | 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, | Started | Final report: 2020 |

| | | | | |
|---|---|---|---|---|
| Category 3 | volume depletion events in patients treated with ertugliflozin<br>4) the frequency and characteristics of events of DKA in patients treated with ertugliflozin<br>5) the frequency and characteristics of events of renal impairment in patients treated with ertugliflozin<br>6) the frequency and characteristics of events of lower limb amputation in patients treated with ertugliflozin<br>7) the frequency and characteristics of events of bone fracture in patients treated with ertugliflozin,<br>8) the frequency and characteristics of events of pancreatitis in patients treated with ertugliflozin<br>9) the characteristics of ertugliflozin use in elderly patients (≥75 years) | pancreatitis and use in elderly patients (≥75 years) | | |
| 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 antihyperglycemic agents<br><br>Category 3 | To assess the risk of DKA in new users of ertugliflozin, compared with new users of other antihyperglycemic 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.<br><br>Feasibility assessment report: Q4 2020<br><br>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 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 antihyperglycemic agents, 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:<br>Posology and Method of Administration<br>Special Warnings and Precautions for Use<br>Undesirable Effects | None |
| DKA with atypical presentation | Text in product circular including:<br>Special Warnings and Precautions for Use<br>Undesirable Effects | None |
| Hypersensitivity reactions: anaphylactic reaction, angioedema, rash, urticaria, skin exfoliation, and Stevens-Johnson syndrome | Text in product circular including:<br>Contraindications<br>Special Warnings and Precautions for Use<br>Undesirable Effects | None |

| Safety Concern | Routine Risk Minimization Measures | Additional Risk Minimization Measures |
|---|---|---|
| Gastrointestinal disorders: nausea, vomiting, constipation, diarrhea, abdominal pain, flatulence, abdominal pain upper, and related terms (dyspepsia and gastritis) | Text in product circular including: Undesirable Effects | None |
| Musculoskeletal disorders: osteoarthritis, pain in extremity, and related terms (eg, arthralgia, myalgia, myopathy) | Text in product circular including: Undesirable Effects | None |
| Pancreatitis | Text in product circular including: Special Warnings and Precautions for Use<br>Undesirable Effects | None |
| **Important Potential Risks** | | |
| Impaired renal function, including acute renal failure (sometimes requiring dialysis) | Text in product circular including: Posology and Method of Administration<br>Special Warnings and Precautions for Use<br>Undesirable Effects | None |
| Lower limb amputations | Text in product circulars including: Special Warnings and Precautions for Use | None |
| Bone Fracture | None | None |
| Infections: URTI, nasopharyngitis, and related terms (bronchitis, acute bronchitis, pharyngitis, sinusitis, and rhinitis | Text in product circular including: Undesirable Effects | None |
| Neurotoxicity: tremor; ataxia; and balance disorders | None | None |
| Suicidal ideation, suicide, and depression | None | None |
| Skin reactions: contact dermatitis | None | None |
| Pancreatic cancer | None | None |
| Rhabdomyolysis | None | None |
| **Missing Information** | | |
| Use in elderly patients (≥75 years) | Text in product circular including: Posology and Method of Administration<br>Special Warnings and Precautions for Use<br>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 | 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 19.12.2017. 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, Steglujan (ertugliflozin / sitagliptin) 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 Steglujan is:

"Steglujan 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

- when metformin and/or a sulphonylurea (SU) and one of the monocomponents of Steglujan do not provide adequate glycaemic control.
- in patients already being treated with the combination of ertugliflozin and sitagliptin 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

Three 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 weeks of treatment.

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 in patients on background metformin treatment. In addition a treatment arm with sitagliptin 100 mg was included. The overall study duration was 52 weeks with the primary endpoint measured at 26 weeks.

Study P006/1015 included patients on stable background therapy with metformin in combination with sitagliptin. Ertugliflozin 5 mg and 15 mg respectively was compared to placebo. The overall study duration was 52 weeks with the primary endpoint measured at 26 weeks.

Study P017/1047 included patients on no other AHA. Ertugliflozin 5 mg and 15 mg, both doses in combination with sitagliptin 100 mg, was compared to placebo. The overall study duration was 26 weeks.

A total of 1985 subjects were randomized and received at least 1 dose of study medication in the three Phase 3 studies in support of this application, including 990 subjects randomized to receive co-administration of ertugliflozin with sitagliptin. In the studies, ertugliflozin and sitagliptin were administered as free combination and sitagliptin was given according to label.

## *3.2. Favourable effects*

The same primary endpoint, change from baseline HbA1c, was applied in all studies. In the factorial study P005/1019, 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 sitagliptin 100 mg was -1.05%. The contribution of the ertugliflozin component was -0.43% and -0.47% for ertugliflozin 5 mg and 15 mg respectively, compared to sitagliptin alone. The corresponding contribution of the sitagliptin component was -0.46% compared to ertugliflozin 5 mg and -0.49% compared to ertugliflozin 15 mg. Thus it appears that both components (ertugliflozin and sitagliptin) equally contribute to the effect of the FDC.

In study P006/1015, ertugliflozin was given as add-on to metformin and sitagliptin and compared to placebo. The treatment differences in the change from baseline in HbA1c compared to 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 study P017/1047, where combination therapy was initiated without other AHA background treatment, the treatment difference was -1.16% (-1.49,-0.84) for the 5 mg dose and -1.24% (-1.57,-0.91) for the 15 mg dose. The treatment effect was comparable to that observed for the combination in the factorial study P005/1019.

In the supportive 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 as monotherapy. Higher responder rates were observed when ertugliflozin was given in combination with sitagliptin (50%). The difference between the two ertugliflozin doses was generally small (about 4-6%).

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 1.7 to 2.3 kg. 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 -6.4 mmHg with slightly larger reductions in the higher ertugliflozin dose groups.

Four 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. Statistically significant treatment differences in the change from baseline in HbA1c were observed for both the 5 mg (-0.99% (-1.22,-0.76) and the 15 mg dose (-1.16% (-1.39, -0.93) 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. 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 P007/1017, the effect of ertugliflozin was investigated as add-on to metformin and compared to placebo. The treatment differences in the change from baseline in HbA1c was -0.70% (-0.87, -0.53) for the 5 mg dose and -0.88% (-1.05, -0.71) for the 15 mg dose. Secondary glycaemic endpoints all supported the primary endpoint. The proportion of patients with HbA1c<7.0% was 35% for the 5 mg dose and 40% for the 15 mg dose of ertugliflozin compared to 16% in the placebo group. A significant decrease in body weight of about 1.6 kg was observed with both doses. Decreases in SBP and DBP were also observed, being more pronounced in the higher dose.

Study P002/1013 was a non-inferiority study comparing the effect of ertugliflozin 5 mg and 15 mg to glimepiride. The actual mean dose of glimepiride was 3 mg daily. The achieved glimepiride dose is considered relevant. The primary objective was to test non-inferiority between ertugliflozin 15 mg and glimepiride against background metformin treatment. Non-inferiority between ertugliflozin 5 mg and glimepiride was also included as a secondary endpoint. 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 -0.56 ± 0.045 for the 5 mg dose and -0.64 ± 0.045 for the 15 mg dose. The proportion of patients with HbA1c<7.0% was lower in the ertugliflozin treated groups (34% vs 38%) than in the glimepiride group (44%). A significant treatment difference in decrease in body weight of 3.9 and 4.3 kg was observed with the respective doses vs glimepiride. The larger effect in this study was due to the weight increase observed in the glimepiride group. Decreases in SBP were also observed, being more pronounced in the higher dose.

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 5mg 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 5mg, ertugliflozin 15mg 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, 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.

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; however reversed after treatment discontinuation. In the same subgroup, CTX was increased at week 26 and 52. 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.

*Ertugliflozin/sitagliptin SDC phase 3 programme*

The data in the Ertugliflozin add-on to sitagliptin Phase III program identified no additional safety or tolerability concerns for the combination of the medicinal products relative to the two agents given alone. The decrease in eGFR noticed with ertugliflozin in the Ertugliflozin Phase 3 program was more pronounced in the ertugliflozin/sitagliptin combined treatment groups compared to groups with ertugliflozin as monotherapy. In the group of subjects treated with ertugliflozin 15mg in combination with sitagliptin 100 mg (E15/S100 group) the eGFR decrease sustained over 52 weeks. However, the eGFR returned to baseline after discontinuation of treatment and there was no imbalance in frequencies of AEs related to decrease in renal function in the ertugliflozin/sitagliptin combination groups compared to the ertugliflozin monotherapy groups.

During treatment with sitagliptin as monotherapy, serious adverse reactions including pancreatitis and hypersensitivity reactions have been reported. Also hypoglycaemia has been reported with sitagliptin in combination with sulphonylurea and insulin. However, no events of pancreatitis or serious hypersensitivity reactions were reported in the studies submitted in the application in the *Ertugliflozin/sitagliptin SDC phase 3 programme.* In the ertugliflozin/sitagliptin combination studies higher frequencies of *documented hypoglycaemia* was noted with ertugliflozin in combination with sitagliptin compared to sitagliptin alone. However, the frequencies were similar between ertugliflozin as monotherapy and in combination with sitagliptin.

## *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.

## 3.6. Effects Table

**Table 31: Effects Table for Steglujan in the treatment of T2DM.**

| Effect | Short Description | Unit | Treatment | Control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| Change in HbA1c | Ertugliflozin 5 mg + sitagliptin 100 mg vs sitagliptin | % | -1.49 ± 0.062 | -1.05 ± 0.062 | -0.43 (-0.60,-0.27) p<0.001 | Factorial study P005/1019 |
| Change in HbA1c | Ertugliflozin 15 mg + sitagliptin 100 mg vs sitagliptin | % | -1.52 ± 0.062 | -1.05 ± 0.062 | -0.47 (-0.63,-0.30) p<0.001 | Factorial study P005/1019 |
| Change in HbA1c | Ertugliflozin 5 mg vs placebo | % | -0.78 ± 0.067 | -0.09 ± 0.070 | -0.69 (-0.87,-0.50) p<0.001 | Add-on to metformin + sitagliptin P006/1015 |
| Change in HbA1c | Ertugliflozin 15 mg vs placebo | % | -0.86 ± 0.068 | -0.09 ± 0.070 | -0.76 (-0.95,-0.58) p<0.001 | Add-on to metformin + sitagliptin P006/1015 |
| 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 + sitagliptin 100 mg vs sitagliptin | kg | -2.52 ± 0.228 | -0.67 ± 0.229 | -1.85 (-2.48, -1.22) p<0.001 | Factorial study P005/1019 |
| Change in body weight | Ertugliflozin 15 mg + sitagliptin 100 mg vs sitagliptin | kg | -2.94 ± 0.228 | -0.67 ± 0.229 | -2.27 (-2.90, -1.64) p<0.001 | Factorial study P005/1019 |
| Change in body weight | Ertugliflozin 5 mg vs placebo | kg | -3.35 ± 0.221 | -1.32 ± 0.229 | -2.03 (-2.65, -1.40) p<0.001 | Add-on to metformin + sitagliptin P006/1015 |
| Change in body weight | Ertugliflozin 15 mg vs placebo | kg | -3.04 ± 0.223 | -1.32 ± 0.229 | -1.72 (-2.35, -1.09) p<0.001 | Add-on to metformin + sitagliptin P006/1015 |
| **Unfavourable Effects** | | | | | | |

| Effect | Short Description | Unit | Treatment | Control | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| 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 5mg and 15 mg (33% and 34%) | Placebo (9.6%) | Imbalance in bone resorption marker for ERTU vs placebo | Study P001/1016 |
| 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 |

## *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 sitagliptin. 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 factorial study, the added effect of either of the mono-components was in the range of -0.43% to -0.49% which of somewhat borderline clinical relevance. However, when ertugliflozin was given as add-on to combined metformin and sitagliptin treatment, a clinically relevant additional HbA1c reduction of about 0.7% was observed. Thus the data support the use of ertugliflozin and sitagliptin as FDC.

The proposed indication states that Steglujan can be used “when metformin and/or a sulphonylurea (SU) do not provide adequate glycaemic control”. The clinical study program supporting the application however mainly focused on the use of ertugliflozin in combination with metformin and/or sitagliptin, which is acceptable. The data on use of ertugliflozin in combination with SU is limited since patients were allowed to use 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 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

is expected in patients with normal renal function. The safety data provided with study P001/1016 show an increased risk of hypoglycaemia with this combination. This risk is deemed to be adequately mitigated by the warnings included in the SmPC. The triple combination with ertugliflozin, sitagliptin and SU is considered justified alongside with the triple combination with metformin.

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 with ertugliflozin 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 consistent with other SGLT-2 inhibitors. The most important risk for ertugliflozin is associated with the mechanism of action (glucosuria 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 sitagliptin 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 Steglujan 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 Steglujan is favourable in the following indication:

“Steglujan 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:

- when metformin and/or a sulphonylurea (SU) and one of the monocomponents of Steglujan do not provide adequate glycaemic control.
- in patients already being treated with the combination of ertugliflozin and sitagliptin 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.