



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Ertugliflozin, Ertugliflozin / Sitagliptin, Ertugliflozin / Metformin

Proprietary Product Names: Steglatio, Steglujan,
Segluromet

Sponsor: Merck Sharpe and Dohme Pty Ltd

February 2019

About the Therapeutic Goods Administration (TGA)

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

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- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Attachment 4. Extract from the Clinical Evaluation Report for Segluromet 124

Common abbreviations

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

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

| Abbreviation | Meaning |
|--------------|--|
| GIP | Glucose-dependent insulinotropic polypeptide |
| GLP-1 | Glucagon-like peptide-1 |
| GMR | Geometric mean ratio |
| h | Hour(s) |
| HbA1c | Glycosylated haemoglobin (haemoglobin (Hb) A1c) |
| HCTZ | Hydrochlorothiazide |
| HDL-C | High-density lipoprotein-cholesterol |
| hOAT-3 | Human organic anion transporter-3 |
| HPLC-MS/MS | High-performance liquid chromatography tandem mass spectrometric |
| HTCZ | Hydrochlorothiazide |
| LDA | Longitudinal data analysis |
| LDL | Low-density lipoprotein |
| LDL-C | Low-density lipoprotein-cholesterol |
| LLOQ | Lower limit of quantitation |
| L-PGA | L-pyroglutamic acid |
| LS | Least-squares |
| MACE | Major adverse cardiovascular event |
| min | Minute(s) |
| MR | Modified-release |
| MRI | Magnetic Resonance Imaging |
| NONMEM | Non-linear mixed effects modelling |
| NTX-1 | N-terminal telopeptide-1 |
| OAD | Oral anti-diabetic |
| OC | Osteocalcin |
| P1NP | Procollagen type 1 amino-terminal propeptide |

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

| Abbreviation | Meaning |
|---------------------|---|
| T2DM | Type 2 diabetes mellitus |
| TEAE | Treatment-emergent adverse event |
| TECOS | Trial Evaluating Cardiovascular Outcomes with Sitagliptin |
| T _{max} | Time for C _{max} |
| UGE | Urinary glucose excretion |
| UGE ₀₋₂₄ | Cumulative urinary glucose excretion over 24 h |
| UGT | Uridine 5'-diphospho-glucuronosyltransferase |
| UK | United Kingdom |
| ULN | Upper limit of normal |
| US | United States |
| Vc/F | Apparent Central Volume Of Distribution |
| Vz/F (oral) | Apparent volume of distribution following oral administration |

I. Introduction to product submission

Submission details

| | |
|------------------------------------|---|
| <i>Type of submission:</i> | New chemical entity/ New drug combinations |
| <i>Decision:</i> | Approved |
| <i>Date of decision:</i> | 14 May 2018/14 May 2018/15 May 2018 |
| <i>Date of entry onto ARTG:</i> | 17 May 2018 |
| <i>ARTG numbers:</i> | <ol style="list-style-type: none"> 287619 and 287622; 287621 and 287634, 287630 and 287626; 287625 and 287637 287636, 287635, 287633 and 287627, 287629, 287623, 287632 and 287631 |
| <i>Active ingredients:</i> | Ertugliflozin; ertugliflozin/sitagliptin; ertugliflozin/metformin |
| <i>Product names:</i> | <ol style="list-style-type: none"> Steglatro, MSD-Ertugliflozin, Steglujan, MSD-Ertugliflozin /Sitagliptin and Segluromet, MSD-Ertugliflozin / Metformin |
| <i>Sponsor's name and address:</i> | <p>Merck Sharpe and Dohme Pty Ltd North Ryde Post Business Centre Locked Bag 2234 North Ryde NSW 1670</p> |
| <i>Dose forms:</i> | Film-coated tablets |
| <i>Strengths:</i> | <p>Steglatro: 5 mg and 15 mg Steglujan: 5/100; 15/100 Segluromet: 2.5/500; 7.5/500; 2.5/1000; 7.5/1000</p> |
| <i>Containers:</i> | Blister pack |
| <i>Pack sizes:</i> | <p>7 and 28 tablets (Steglatro and Steglujan) 14 and 56 tablets (Segluromet)</p> |
| <i>Approved therapeutic use:</i> | <p>1. Steglatro (ertugliflozin) is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus as: monotherapy when metformin is considered inappropriate due to intolerance; or in combination with other anti-hyperglycaemic agents [see 5.1 Pharmacodynamic Properties, Clinical trials and 4.4 Special Warnings and Precautions For Use for available data on different add-on combination therapies].</p> <p>2. Steglujan (ertugliflozin and sitagliptin phosphate monohydrate) is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is</p> |

appropriate [see 5.1 Pharmacodynamic Properties, Clinical trials and 4.2 Dose and Method of Administration].

3. Segluromet (ertugliflozin and metformin hydrochloride) is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and metformin is appropriate. [see 5.1 Pharmacodynamic Properties, Clinical trials, and 4.4 Special Warnings and Precautions for Use]

Route of administration:

Oral (PO)

Dosage:

1. The recommended starting dose of Steglatro is 5 mg once daily, taken in the morning, with or without food. In patients tolerating Steglatro 5 mg once daily the dose may be increased to 15 mg once daily if additional glycaemic control is needed.
2. The recommended starting dose of Steglujan is 5 mg ertugliflozin/100 mg sitagliptin once daily, taken in the morning, with or without food. In patients tolerating Steglujan, the dose may be increased to 15 mg ertugliflozin/100 mg sitagliptin once daily if additional glycaemic control is needed.

For patients treated with ertugliflozin who are being switched to Steglujan, the dose of ertugliflozin can be maintained.

3. Take Segluromet twice daily with meals, with gradual dose escalation for those initiating metformin to reduce the gastrointestinal side effects due to metformin.

Individualise the starting dose of Segluromet (ertugliflozin and metformin hydrochloride) based on the patient's current regimen:

-In patients on metformin, switch to Segluromet tablets containing 2.5 mg ertugliflozin, with a similar total daily dose of metformin.

-In patients already treated with ertugliflozin and metformin, switch to Segluromet tablets containing the same total daily dose of ertugliflozin and a similar daily dose of metformin.

Dosing may be adjusted based on effectiveness and tolerability while not exceeding the maximum recommended daily dose of 15 mg ertugliflozin and 2,000 mg metformin HCl.

Product background

This AusPAR describes an application by the sponsor to register a new chemical entity (NCE) ertugliflozin (as L-pyroglutamic acid), under the proposed trade names of Steglatro or MSD-ertugliflozin.

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 HbA1c (HbA1c) in patients with type 2 diabetes mellitus (T2DM). It possesses a high selectivity for SGLT2 versus SGLT1 and other glucose transporters (GLUT1-4). Steglatio is proposed to be used as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM as monotherapy when metformin is considered inappropriate due to intolerance, or in combination with other anti-hyperglycaemic agents. The recommended starting dose is 5 mg PO once daily, and the maximum recommended human dose is 15 mg PO once daily.

The sponsor has also concurrently submitted two applications to register two (2) new fixed dose combination (FDC) drug products indicated for glycaemic control which contain the above mentioned NCE ertugliflozin with either sitagliptin (as phosphate monohydrate under the proposed trade name Steglujan) or metformin hydrochloride (proposed trade name Segluromet). Whilst ertugliflozin is not currently registered in any dosage form on the Australian Register of Therapeutic Goods (ARTG), there are multiple sitagliptin or metformin immediate release and modified release tablet formulations on the ARTG, either as monotherapy or dual active FDC formulations.

Steglujan (ertugliflozin/sitagliptin) is proposed to be used as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate. The proposed dosage regimen, a starting dose of 5/100 mg ertugliflozin/sitagliptin PO once daily and a maximum recommended dose of 15/100 mg ertugliflozin/sitagliptin PO once daily, is consistent with that proposed for ertugliflozin (Steglatio) and approved for sitagliptin (Januvia) as single agents.

Segluromet (ertugliflozin/metformin) is proposed to be used as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM when treatment with both ertugliflozin and metformin is appropriate. The proposed dosage regimen, twice daily PO administration of 2.5 or 7.5 mg ertugliflozin with 500 or 1000 mg metformin hydrochloride, is consistent with the proposed daily dose for single-agent ertugliflozin (Steglatio) and the dosing regimen for metformin as a single agent and in various existing combination products (for example, Glucophage; Janumet).

The following table summarises the 3 products that the sponsor has applied to include on the ARTG.

Table 1: Summary of the 3 concurrent applications submitted to the TGA

| PM-2017-01328-1-5 | | PM-2017-01329-1-5 | | PM-2017-01330-1-5 | |
|----------------------|--|--|--|---|-------------------------|
| Trade name(s) | Steglatio X mg MSD-ertugliflozin X mg | Steglujan X /Y MSD-ertugliflozin-sitagliptin X /Y | | Segluromet X /Y MSD-ertugliflozin-metformin X /Y | |
| Active(s) | Ertugliflozin (as L-pyroglutamic acid) | Ertugliflozin (as L-pyroglutamic acid) | | Ertugliflozin (as L-pyroglutamic acid) | |
| | | | Sitagliptin (as phosphate monohydrate) | | Metformin hydrochloride |
| Dosage form | Tablet, film-coated | | | | |
| Strengths | 5 mg and 15 mg | Ertugliflozin/Sitagliptin | | Ertugliflozin/ | |

| PM-2017-01328-1-5 | | PM-2017-01329-1-5 | PM-2017-01330-1-5 |
|--------------------------------|--|---|--|
| | | 5 mg/100 mg 15 mg/100 mg | Metformin HCl 2.5 mg/500 mg 2.5 mg/1000 mg 7.5 mg/500 mg 7.5 mg/1000 mg |
| Route of administration | Oral | | |
| Posology | 1 tablet per day | 1 tablet per day | 1 tablet twice a day |
| Maximum daily dose | 15 mg ertugliflozin | 15 mg ertugliflozin 100 mg sitagliptin | 15 mg ertugliflozin 2000 mg metformin HCl |
| Pack type | Al/Al blisters | | |
| Pack size(s) | 7 and 28 tablets | 7 and 28 tablets | 14 and 56 tablets |
| Proposed indications | Steglatro (ertugliflozin) is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus as monotherapy when metformin is considered inappropriate due to intolerance or in combination with other anti-hyperglycaemic agents. | Steglujan (ertugliflozin and sitagliptin phosphate monohydrate) is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate. | Segluromet (ertugliflozin and metformin hydrochloride) is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM when treatment with both ertugliflozin and metformin is appropriate. |
| Storage conditions | Store below 30°C | | |
| Shelf life | 24 months | | |

SGLT-2 inhibitors

There are three other ARTG registered SGLT-2 inhibitors: empagliflozin, dapagliflozin and canagliflozin and these are summarised in the table below.

Table 2: Comparison to 3 other SGLT-2 inhibitors on the ARTG

| | Ertugliflozin | Canagliflozin | Empagliflozin | Dapagliflozin |
|--------------------------|---|---|---|---|
| Year registered | | 2013 | 2014 | 2016 |
| Indication (abbreviated) | <p>Steglatro is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes as monotherapy when metformin is considered inappropriate in combination with other anti-hyperglycaemic agents</p> | <p>Invokana is indicated in T2DM as an adjunct to diet and exercise as -monotherapy when metformin is contraindicated -as add on combination therapy with other anti-hyperglycaemic agents</p> | <p>Jardiance is indicated for improvement of glycaemic control as - monotherapy when metformin is considered inappropriate -in combination with other glucose lowering medications</p> <p>To reduce the risk of cardiovascular events in those at high risk</p> | <p>-as monotherapy when metformin is not tolerated or contraindicated -initial combination with metformin -Add on combination with other anti-hyperglycemic agents.</p> |
| Other differences | <p>contraindication with eGFR < 30 mL/min/1.73 m² or persistently 45 mL/min/1.73 m²</p> <p>-risk of volume depletion of 1% and 1.7% with 5 and 15 mg</p> | <p>contraindication with eGFR < 30mL/min or persistently 45</p> <p>-in the pooled analysis of 26 week studies, the risk of reduced intravascular volume was 1.2% for 100 mg dose, 1.3% for 300 mg dose and 1.1% for placebo. In patients at higher risk, the rates were 2.8% and 4.6% and 1.9%.</p> <p>- increased risk of fracture</p> <p>-increased risk of amputation in long term cardiovascular studies</p> | <p>Contraindication with eGFR< 45</p> <p>-risk of volume depletion 0.6% 10 mg and 0.4% 25 mg and 0.3% placebo</p> | <p>Contraindication with eGFR < 60</p> <p>-risk of volume depletion 1.1% 10 mg and 0.7% placebo</p> |
| Pregnancy category | Nonclinical evaluator recommended D | C | D | D |

As a class, these are potent agents in reducing blood glucose levels in an insulin independent mechanism. In addition, long term cardiovascular studies have demonstrated benefits in cardiovascular (CV) deaths and heart failure with empagliflozin;¹ and canagliflozin.² The CV real study demonstrated supportive evidence for dapagliflozin in a real-life setting; however the long term CV study will not be available until 2019.

Secondary effects include diuresis with a risk of volume depletion, transient decrease in estimated glomerular filtration rate (eGFR), increase lipids, increased risk of genital infections, decrease weight and decrease blood pressure (BP).

Information on the condition being treated

The increasing worldwide prevalence of T2DM, along with its microvascular and macrovascular complications, is a major health issue and poses an increasing burden to health care systems around the world. The worldwide prevalence of diabetes in adults is expected to increase from 8.8% in 2015 (approximately 415 million people) to an estimated 10.4% (642 million people) by 2040; this represents a 55% increase in the number of people with diabetes relative to 2015³. There are 1.7 million Australians with diabetes (85% of these have T2DM)⁴. T2DM is associated with reduced life expectancy, significant morbidity due to the specific diabetes related microvascular complications (retinopathy, nephropathy and neuropathy), and the increased risk of macrovascular complications (ischemic heart disease, stroke and peripheral vascular disease). The development of these complications impacts on quality of life.

Multiple pathophysiologic deficits contribute to hyperglycaemia in patients with T2DM. Insulin resistance in muscle and liver as well as beta-cell failure represent the core pathophysiologic defects in T2DM. Approximately 85% of patients with T2DM are obese or overweight, a key factor underlying the development and maintenance of insulin resistance. In addition to muscle and liver, the kidney also plays a key role in glucose homeostasis. Under normal physiologic conditions, the kidney reabsorbs all of the glucose from the glomerular filtrate, and returns it to the blood. The SGLT2 protein, which is primarily expressed in the renal proximal tubules, is responsible for approximately 90% of the reabsorption of glucose filtered through the glomerulus. Filtered glucose is completely reabsorbed until the transporters reach their maximum capacity, which is called the transport maximum for glucose. The plasma glucose concentration at which this occurs is referred to as the renal threshold for glucose (RTG). Above this threshold, UGE increases in proportion to plasma glucose concentrations. In healthy subjects, the RTG is approximately 10 mmol/L. Patients with diabetes have an increase in the RTG compared with healthy subjects such that glucosuria generally does not occur until plasma glucose values reach approximately 13.5 mmol/L. Studies have shown that SGLT2 inhibitors lower the RTG, resulting in increased UGE, which is responsible for many of the pharmacodynamic (PD) effects seen with this class of agents. While SGLT2 inhibitors lower the RTG, the new RTG set point is above the usual threshold for hypoglycaemia suggesting that hypoglycaemia is unlikely with this mechanism.

¹Wanner C Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes, *N Engl J Med* 375:323-334

² Neal B. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes *N Engl J Med* 377:644-657

³ IDF Diabetes Atlas Group. Update of mortality attributable to diabetes for the IDF Diabetes Atlas: Estimates for the year 2013. *Diabetes Res Clin Pract*. 2015;109:461-465.

⁴ www.diabetesaustralia.com.au

Current treatment options

Current guidelines from the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD) and Diabetes Australia recommend a stepwise and individualised treatment approach to T2DM. These guidelines recommend metformin as the optimal first line anti-hyperglycaemic agent (AHA), unless the patient has contraindications to metformin. Subsequently, if the HbA1C 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 HbA1C goal is not achieved.

A number of systematic reviews have examined the relationship between blood glucose control and long term complications in people with T2DM. These studies concluded that improved glycaemic control can reduce retinopathy, renal disease and neuropathy in T2DM. Long term data from the United Kingdom Prospective Diabetes Study (UKPDS);⁵ 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 HbA1c levels, and glycaemic control deteriorates over time. The SGLT2 inhibitors are a new class of agents for T2DM therapy that have been shown to improve glycaemic control, reduce body weight and lower blood pressure.

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

Related submissions

Registration of ertugliflozin (Steglatro), ertugliflozin/sitagliptin FDC (Steglujan) and ertugliflozin/metformin FDC (Segluromet) for the treatment of T2DM are being pursued concurrently.

Regulatory status

This AusPAR includes the submission of an application to register a NCE ertugliflozin (Steglatro) on its own as well as in two separate FDCs is also proposed: with sitagliptin as Steglujan and with metformin as Segluromet. Metformin has been approved for many decades in Australia and sitagliptin was first registered in Australia in 2007.

International regulatory history

Ertugliflozin, ertugliflozin/metformin and ertugliflozin/sitagliptin were approved by the FDA in December 2017.

Ertugliflozin, ertugliflozin/metformin and ertugliflozin/sitagliptin were given a positive recommendation by the Committee for Medicinal Products for Human Use (CHMP) in January 2018.

⁵ Stratton IM, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. *BMJ* 2000; 321: 405-412.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1a Steglatro; Attachment 1b Steglujan; Attachment 1c Segluromet. For the most recent PIs, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration time line

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR and Attachment 2.

Table 3: Timeline for submissions PM 2017-01328-1-5, PM 2017-01329-1-5 and PM 2017-01330-1-5

| Milestone | Date |
|--|--------------------------------------|
| Submission dossier accepted and first round evaluation commenced | 31 May 2017 |
| First round evaluation completed | 15 December 2017 |
| Sponsor provides responses on questions raised in first round evaluation | 19 December 2017 |
| Second round evaluation completed | 2 February 2018 |
| Delegate's Overall benefit-risk assessment and request for Advisory Committee advice | 16 February 2018 |
| Sponsor's pre-Advisory Committee response | 13 March 2018 |
| Advisory Committee meeting | 5-6 April 2018 |
| Registration decision (Outcome) | 14 May 2018/14 May 2018/ 15 May 2018 |
| Completion of administrative activities and registration on ARTG | 17 May 2018 |
| Number of working days from submission dossier acceptance to registration decision* | 235 to 236 |

*The statutory timeframe for a standard applications is 255 working days

Evaluations included under Quality findings and Nonclinical findings incorporate both the first and second round evaluations.

III. Quality findings

Introduction

This quality summary document summarises the pharmaceutical chemistry and quality control aspects of all three submissions listed in Table 2.

There is no British Pharmacopeia (BP)/European Pharmacopeia (Ph.Eur.) or US Pharmacopeia (USP) monographs for either the drug substance, ertugliflozin pyroglutamic acid or for any of the finished products.

There is BP/Ph.Eur. and USP monographs for the drug substance, sitagliptin phosphate and BP and USP monographs for sitagliptin tablets.

There are BP/Ph.Eur. and USP monographs for the drug substance, metformin hydrochloride and a BP. monograph for metformin tablets. The USP also has a monograph for metformin hydrochloride tablets as well as dual active tablets for glyburide and metformin tablets, glipizide and metformin tablets and pioglitazone and metformin tablets.

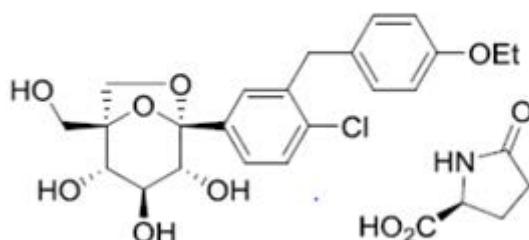
Drug substance (active ingredient)

Ertugliflozin

The following figures show the chemical structure of ertugliflozin pyroglutamic acid and ertugliflozin.

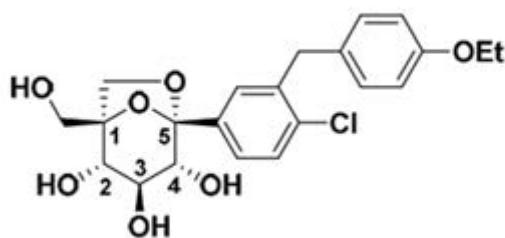
Figure 1: Chemical structure of ertugliflozin pyroglutamic acid; and ertugliflozin (active moiety)

A: Ertugliflozin pyroglutamic acid



$C_{27}H_{32}ClNO_{10}$ MW: 566.0

B: Ertugliflozin



$C_{22}H_{25}ClNO_7$ MW: 436.88

Ertugliflozin is the active moiety and ertugliflozin L-pyroglutamic acid (L-PGA) represents the co-crystal of ertugliflozin and L-PGA. Ertugliflozin in its free form is an amorphous solid.

Ertugliflozin L-pyroglutamic acid is a white to off-white powder which is soluble in ethanol and acetone, slightly soluble in ethyl acetate and acetonitrile and very slightly soluble in water. Ertugliflozin L-PGA co-crystal rapidly dissociates within one minute when in an aqueous environment; therefore, the thermodynamic solubility of the co-crystal cannot be determined. The amorphous ertugliflozin free form solubility was

determined to be 0.64 to 0.74 mg/mL throughout the physiological pH range. Solubility is pH-independent as ertugliflozin is non-ionisable under physiological conditions. Ertugliflozin L-PGA is classified as a BCS Class I substance.⁶

Ertugliflozin has five asymmetric centres (1S, 2S, 3S, 4R, and 5S). Ertugliflozin L-PGA has an additional stereo centre in the L-PGA molecule (2S configuration).

The drug substance has a melting point of approximately 142°C, it is not hygroscopic, and has an optical rotation of +8.8° in methanol at 25°C. Only one crystalline form of ertugliflozin L-PGA has been identified to date (Form A) and has been confirmed by powder x-ray diffraction (PXRD).

The quality control of the drug substance includes tests and limits for identification (by IR), ertugliflozin assay, L-PGA content, water content, particle size, residue on ignition, heavy metals, organic impurities (9 specified impurities) and residual solvents.

All tests and limits proposed for the drug specification are considered acceptable.

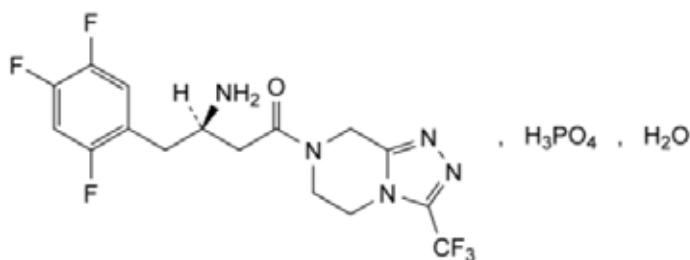
The tightening of the ertugliflozin Assay limits has been negotiated. The proposed limits are still wider than potency limits typically set for drug substances determined using High-performance liquid chromatography (HPLC) analysis. The wider potency limits do not pose a safety concern but is considered to be more of a quality issue. However, the sponsor has stated that the proposed specification will be reassessed and updated if warranted after data on additional commercial active pharmaceutical ingredient (API) batches are generated. It has been suggested to the Delegate that the sponsor's commitment to review the results of 20 commercial scale API batches and revise the ertugliflozin drug substance specification if warranted, be made a Condition of Registration to ensure that this course of action is taken.

The analytical methods used for the routine quality control assessment of the drug substance were all adequately validated and appropriate for use.

Sitagliptin (as phosphate monohydrate)

The following figure shows the chemical structure of sitagliptin.

Figure 2: Chemical structure of sitagliptin



C₆₃H₁₅F₆N₅O.H₃PO₄.H₂O MW: 523.32 CAS number: 654671-77-9

The sitagliptin drug substance is a white, crystalline powder, non-hygroscopic powder. It is soluble in water and *N,N*-dimethylformamide; slightly soluble in methanol; very slightly

⁶ The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

soluble in ethanol, acetone, and acetonitrile and insoluble in isopropanol and isopropyl acetate.

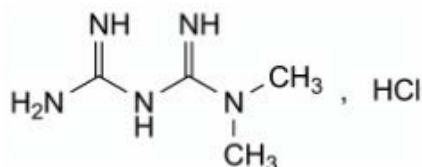
The proposed drug substance specifications applied by the finished product manufacturer include all tests stated in the Ph.Eur. monograph for sitagliptin as well as an additional test for residual solvents.

The quality control of the drug substance (including the drug substance specification) is acceptable.

Metformin hydrochloride

The following figure shows the chemical structure of metformin hydrochloride.

Figure 3: Chemical structure of metformin hydrochloride



C₄H₁₁N₅HCl MW: 165.63 CAS number: 1115-70-4

Metformin is a biguanide with anti-hyperglycaemic effects; lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia. Metformin hydrochloride is not chemically or pharmacologically related to any other classes of oral anti-hyperglycaemic agents.

The drug substance is a white to off-white powder that is odourless or almost odourless and is freely soluble in water and practically insoluble in acetone, ether and chloroform. The dissolution constant (pKa) of metformin is 12.4 and the pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

The proposed drug substance specifications applied by the finished product manufacturer include all tests stated in the Ph.Eur. monograph for metformin hydrochloride.

The quality control of the drug substance (including the drug substance specification) is acceptable.

Drug product

Ertugliflozin monotherapy tablets

Two strengths for the Steglatro/MSD-ertugliflozin immediate release tablets are proposed for registration, namely 5 mg and 15 mg. The tablet strengths are easily distinguishable from each other in terms of colour, size and debossing. Both tablets are film-coated and unscored. They are to be taken once a day.

The active ingredient, ertugliflozin (as ertugliflozin L-PGA) represents approximately 4.8% of the total tablet weight of both tablet strengths. The two tablet strengths are direct scales with the only differences between the strengths being the relative amounts of titanium dioxide and iron oxide red. No overages are used.

The two tablet strengths are manufactured from a common blend by a conventional dry granulation, direct compression process, utilising compendial excipients. The proposed

tablet formulations are identical to those used in the Phase III clinical studies, with the exception of the white film-coating used for the clinical batches. This difference was justified with acceptable comparative dissolution data.

As part of the product development, Study P011 compared the relative bioavailability of ertugliflozin tablet containing the amorphous form of ertugliflozin relative to tablets containing the ertugliflozin L-PGA co-crystal. The formulations were bioequivalent and therefore any dissociation to the amorphous form that does occur in tablets containing the co-crystal will not have any meaningful impact on the oral bioavailability of ertugliflozin.

The drug products are to be manufactured with quality control testing by one site with another site proposed for packaging/labelling and release for supply and another site proposed for stability testing. Good Manufacturing Practice (GMP) clearances for the drug product manufacturing sites are all currently valid past the expected decision date.

The quality of the drug products is controlled by acceptable specifications which include tests and limits for appearance, identification (HPLC and UV), assay, degradation products, uniformity of dosage units and disintegration. The assay limits comply with TGO 78;⁷ the individual degradant limits comply with Internal Conference on Harmonisation (ICH) qualification threshold limits, and 'Total Degradants' have been based upon batch analysis and stability data generated to date.

The replacement of the dissolution test with the disintegration test was justified, given the high aqueous solubility of ertugliflozin and rapid dissolution observed across the physiological pH range (1.2 to 6.8). Furthermore, a linear relationship was demonstrated between the disintegration and dissolution results.

The analytical methods used to analyse the product were adequately described and validated.

The drug product is to be packaged in Aluminium (Al)/Al blisters in packs of 7 and 28 tablets.

The stability data supplied supported a shelf life of 24 months for the unopened product when stored at or below 30°C. No other storage conditions are required.

Ertugliflozin sitagliptin FDC tablets

Two strengths for the Steglujan X /Y /MSD-ertugliflozin-sitagliptin X /Y immediate release FDC tablets are proposed for registration, namely 5 mg/100 mg and 15 mg/100 mg for ertugliflozin and sitagliptin respectively. The tablet strengths are easily distinguishable from each other in terms of colour and debossing. Both tablets are film-coated and unscored. They are to be taken once a day.

The active ingredient, ertugliflozin (as ertugliflozin L-PGA) represents around 1.6%, and 4.7 % of the total tablet weight of the 5 mg /100 mg, and 15 mg /100 mg tablet strengths, respectively.

The active ingredient, sitagliptin (as phosphate monohydrate) represents ca 31.2% of the total tablet weight of the 5 mg /100 mg and 15 mg /100 mg tablet strengths.

No overages are used.

As for the monotherapy tablets, the two tablet strengths are manufactured using a conventional dry granulation, direct compression process, utilising compendial excipients.

⁷ Therapeutic Goods Order 78 (TGO 78) describes the standards required for tablets and capsules.

The Phase III clinical studies used the monotherapy products for ertugliflozin and sitagliptin. The proposed commercial manufacturing process is the same as the process used to manufacture the bioequivalence study batches, except for an increase in batch size. This difference was justified with acceptable comparative dissolution data.

The drug products are to be manufactured with quality control testing, packaging/labelling and release for supply by one site and another site is proposed for stability testing. The GMP clearances for the drug product manufacturing sites are currently valid past the expected decision date.

The quality of the drug products is controlled by acceptable specifications that include tests and limits for appearance, identification of both actives (HPLC and UV), assay for both actives, degradation products, uniformity of dosage units, and disintegration. The assay limits of both drug substances comply with TGO 78;⁷ and the degradant limits of both drug substances ICH identification or qualification threshold limits and 'Total Degradants' have been based upon batch analysis and stability data generated to date.

The replacement of the dissolution test with the disintegration test was justified, given the high aqueous solubility of ertugliflozin and sitagliptin, and rapid dissolution observed across the physiological pH range (1.2 to 6.8) and the Disintegration test was shown to be more discriminating compared to the dissolution test with regard to changes in tablet properties. The disintegration limit is tighter than the Ph.Eur. general monograph for 'Tablets Coated tablets'.

The analytical methods used to analyse the product were adequately described and validated.

The drug product is to be packaged in Al/Al blisters in packs of 7 and 28 tablets.

The stability data supplied supported a shelf life of 24 months for the unopened product when stored at or below 30°C. No other storage conditions are required.

Ertugliflozin metformin FDC tablets

Four strengths for the Segluromet X /Y /MSD-ertugliflozin-metformin X /Y immediate release FDC tablets are proposed for registration, namely 2.5 mg/500 mg, 2.5 mg/1000 mg, 7.5 mg/500 mg, and 7.5/1000 mg for ertugliflozin and metformin hydrochloride respectively. The four tablet strengths are easily distinguishable from each other in terms of colour, size, and debossing. All tablets are film-coated and unscored. They are taken twice a day.

The active ingredient, ertugliflozin (as ertugliflozin L-PGA) represents approximately 0.5%, 0.25%, 1.45% and 0.73% of the total tablet weight of the 2.5 mg/500 mg, 2.5 mg/1000 mg, 7.5 mg/500 mg and 7.5 mg/1000 mg tablet strengths, respectively.

The active ingredient, metformin hydrochloride, represents approximately 74.6% of the total tablet weight of all tablet strengths. Except for the quantities of ertugliflozin L-PGA and the microcrystalline cellulose, the 2.5 mg/500 mg and 2.5 mg/1000 mg strengths and the 7.5 mg/500 mg and 7.5 mg/1000 mg strengths are direct scales.

No overages are used.

Differently from the other products, the proposed manufacturing process employs a granulation process (milling, mixing, granulation, drying and milling) to manufacture metformin granules. The metformin granules are then dry blended with ertugliflozin L-PGA and excipients, followed by a direct compression and coating process, using conventional techniques (for example, blending, lubrication, compression and film coating).

The Phase III clinical studies used the monotherapy products. Bioequivalence studies were performed comparing the proposed market formulation tablets for the highest (7.5/1000 mg) and lowest (2.5/500 mg) strengths and the ertugliflozin and metformin hydrochloride monotherapy tablets used in Phase III studies. The tablets administered in the bioequivalence study were identical to those of the proposed market formulation except the tablets were not debossed. This difference was justified with acceptable comparative dissolution data.

The drug products are to be manufactured with quality control testing at one site with an alternate site proposed for quality control testing, packaging/labelling, and release for supply; and another site proposed for stability testing. The GMP clearances for the drug product manufacturing and testing sites are currently valid past the expected decision date.

The quality of the drug products is controlled by acceptable specifications that include tests and limits for appearance, identification of both actives (HPLC and UV), assay for both actives, degradation products, uniformity of dosage units and disintegration.

The replacement of the dissolution test with the disintegration test was justified, given the high aqueous solubility of ertugliflozin and sitagliptin and rapid dissolution observed across the physiological pH range (1.2 to 6.8). A linear relationship between tablet disintegration and dissolution was demonstrated. The analytical methods used to analyse the product were adequately described and validated.

The drug product is to be packaged in Al/Al blisters in packs of 14 and 56 tablets.

The stability data supplied supported a shelf life of 24 months for the unopened product when stored at or below 30°C. No other storage conditions are required.

Biopharmaceutics

A large number of bioequivalence studies (18) were performed. Only those relating directly to the product development and relative bioavailability of the proposed product compared to the Phase III clinical studies were assessed by the TGA.

The results for the bioavailability/bioequivalence studies are currently in doubt as critical information relating to the work up of whole blood samples after sampling and the bioanalytical methods used in three evaluated clinical studies have not as yet been provided to for TGA review. The statistical analyses used for each of the evaluated studies were considered acceptable.

These matters have been brought to the attention of the sponsor and may be resolved prior to the expected decision phase for the submission.

Ertugliflozin monotherapy tablets

Absolute bioavailability Study P020/1043

Study title: A Phase I, open label, non-randomised, two period, fixed sequence, study to assess the absolute BA and fraction absorbed of ertugliflozin in healthy male subjects using a ¹⁴C-microdose approach.

Following oral administration of ertugliflozin, estimates of absolute bioavailability and fraction absorbed were approximately 100% (F = 105% and Fa = 111%), suggesting complete absorption.

Relative Bioequivalence Study P023/1037

Study title: A Phase I, single dose, open label, randomised, cross over bioequivalence study of ertugliflozin 15 mg commercial image tablet versus ertugliflozin Phase III tablets in healthy subjects.

The proposed 15 mg commercial and Phase III clinical tablet formulations were concluded to be bioequivalent. This is as expected given that ertugliflozin is BCS class 1.

Table 3: Pharmacokinetic parameters

| Single dose, prompt release | n | T _{max} (h) (range) | C _{max} (ng/mL) | AUC _{0-t} (ng.h/mL) | AUC _{0-∞} (ng.h/mL) |
|----------------------------------|----|------------------------------|--------------------------|------------------------------|------------------------------|
| Treatment A – Phase III | 16 | 1.00 (0.500, 2.00) | 272.3 | 1358 | 1380 |
| Treatment B – Commercial Product | 16 | 1.00 (0.500, 1.50) | 262.4 | 1334 | 1354 |
| Statistical analysis: | | Median diff. | Ratio (%) | Ratio (%) | Ratio (%) |
| B versus A Estimate | | 0.0 | 96.3 | 98.2 | 98.1 |
| 90% CI | | - | 86.3 to 107.6 | 95.6 to 101.0 | 95.4 to 100.8 |

Food effect Study P024/1048

Study title: A Phase I, randomised, open label, 2 sequence, 2 period crossover study to estimate the effect of food on the PK of an ertugliflozin commercial image tablet in healthy subjects.

Administration of the ertugliflozin 15 mg commercial image tablet with a high-fat meal resulted in no meaningful effect on Area under the plasma concentration-time profile from time 0 extrapolated to infinite time (AUC_{inf}).

Food delayed median T_{max} by 1 h and reduced mean maximum observed plasma concentration (C_{max}) by approximately 30% compared to fasted conditions. The decrease in ertugliflozin C_{max} with food was not anticipated to be clinically relevant by the sponsor and it was concluded that ertugliflozin may be administered without regard to meals.

PK/PD study of dosing regimen Study P040/1007

Study title: A Phase I randomised, double blind, placebo controlled, 2 period, cross over single day evaluation of the pharmacokinetic-pharmacodynamic effect of once and twice daily oral administration of PF-04971729 in patients with type 2 diabetes mellitus.

Doses administered were ertugliflozin 1 mg twice daily (BD), 2 mg once daily (QD), 2 mg BD, and 4 mg QD. Administration of oral doses of ertugliflozin up to 4 mg was considered to be safe and well tolerated. BD dosing of ertugliflozin resulted in delayed plasma T_{max}, lower C_{max} but similar Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (AUC_{0-last}) relative to QD administration of the same dose.

Ertugliflozin sitagliptin FDC tablets

In addition to the ertugliflozin monotherapy bioavailability (BA)/bioequivalence (BE) studies presented above, the following clinical studies were also applicable for consideration.

Relative bioequivalence Study P025/1038

Study title: A Phase I, single dose, open label, randomised, crossover bioequivalence study of a sitagliptin 100 mg/ertugliflozin 15 mg fixed dose combination tablet versus Co-administration of the individual components (sitagliptin (100 mg) and ertugliflozin (15 mg)) in healthy subjects.

The sponsor confirmed that the monotherapy, sitagliptin 100 mg film-coated tablets are identical to the Januvia sitagliptin 100 mg tablets marketed in Australia.

Bioequivalence of the monotherapy tablets and the proposed 15 mg/100 mg FDC tablets was concluded.

Table 4: Pharmacokinetics of ertugliflozin

| Ertugliflozin | | | | | |
|-----------------------------|--------|---------------------------------|--------------------------|---------------------------------|------------------------------|
| Single dose, prompt release | n | T _{max} (h) (range) | C _{max} (ng/mL) | AUC _{0-t} (ng.h/mL) | AUC _{0-∞} (ng.h/mL) |
| Treatment A Monotherapy | 18, 17 | 1.010 (0.500, 5.000) | 198.144 | 1183.849 | 1242.192 |
| Treatment B FDC | 18, 18 | 1.010 (0.500, 4.000) | 202.363 | 116.356 | 1187.932 |
| Statistical analysis: | | Median diff. | Ratio (%) | Ratio (%) | Ratio (%) |
| B versus A Estimate | | 0.0 | 102.1 | 98.2 | 95.6 |
| 90% CI | | - | 92.3 to 113.0 | 95.2 to 101.3 | 92.6 to 98.8 |

Table 5: Pharmacokinetics of sitagliptin

| Sitagliptin | | | | | |
|-----------------------------|-----------|---------------------------------|-----------------------|---------------------------|---------------------------|
| Single dose, prompt release | n | T _{max} (h) (range) | C _{max} (nM) | AUC _{0-t} (μM.h) | AUC _{0-∞} (μM.h) |
| Treatment A Monotherapy | 18, 17 | 3.980 (1.980, 5.000) | 579.175 | 7.058 | 7.239 |
| Treatment B FDC | 18, 18 | 3.000 (0.500, 6.020) | 661.066 | 7.241 | 7.343 |
| Statistical analysis: | | Median diff. | Ratio (%) | Ratio (%) | Ratio (%) |
| B versus A Estimate | | 1.0 | 114.1 | 102.6 | 101.4 |

| Sitagliptin | | | | | |
|------------------------------------|----------|------------------------------------|-----------------------------|---------------------------------|---------------------------------|
| Single dose, prompt release | n | T_{max} (h) (range) | C_{max} (nM) | AUC_{0-t} (μM.h) | AUC_{0-∞} (μM.h) |
| 90% CI | | - | 108.3 to 120.2 | 99.8 to 105.5 | 98.6 to 104.4 |

Relative bioequivalence Study P048/1056

A Phase I, single dose, open label, randomised, crossover bioequivalence study of a sitagliptin 100 mg/ertugliflozin 5 mg fixed dose combination tablet versus co-administration of the individual components [Sitagliptin (100 mg) and Ertugliflozin (15 mg)] in Healthy Subjects

The sponsor confirmed that the monotherapy, Sitagliptin 100 mg film-coated tablets are identical to the Januvia sitagliptin 100 mg tablets marketed in Australia.

Bioequivalence of the monotherapy tablets and the proposed 5 mg/100 mg FDC tablets was concluded.

Table6: Pharmacokinetics of ertugliflozin and sitagliptin

| Ertugliflozin | | | | | |
|------------------------------------|----------|------------------------------------|--------------------------------|------------------------------------|------------------------------------|
| Single dose, prompt release | n | T_{max} (h) (range) | C_{max} (ng/mL) | AUC_{0-t} (ng.h/mL) | AUC_{0-∞} (ng.h/mL) |
| Treatment A Monotherapy | 18, 17 | 1.010 (0.500, 4.000) | 71.19 | 364.3 | 382.1 |
| Treatment B FDC | 18, 18 | 1.010 (0.500, 3.000) | 73.44 | 371.7 | 386.8 |
| Statistical analysis: | | Median diff. | Ratio (%) | Ratio (%) | Ratio (%) |
| B versus A Estimate | | 0.0 | 103.17 | 102.01 | 101.23 |
| 90% CI | | - | 93.76 to 113.52 | 97.89 to 106.32 | 97.15 to 105.49 |
| Sitagliptin | | | | | |
| Single dose, prompt release | n | T_{max} (h) (range) | C_{max} (nM) | AUC_{0-t} (μM.h) | AUC_{0-∞} (μM.h) |
| Treatment A Monotherapy | 18, 17 | 2.98 (0.483 to 5.00) | 659.5 | 7.005 | 7.077 |
| Treatment B FDC | 18, 18 | 3.00 (1.00 to 4.08) | 673.8 | 7.061 | 7.136 |
| Statistical analysis: | | Median diff. | Ratio (%) | Ratio (%) | Ratio (%) |
| B versus A Estimate | | - | 99.76 | 99.77 | 99.80 |
| 90% CI | | - | 93.63 to 106.28 | 98.05 to 101.52 | 98.12 to 101.51 |

Food effect Study P026/1050

A Phase I, Randomised, Open label, 2 sequence, 2 period Crossover Study to Estimate the Effect of Food on the Pharmacokinetics of Sitagliptin and Ertugliflozin When Administered as a Fixed Dose Combination Tablet (15 mg/100 mg) to Healthy Subjects.

Single oral administration of ertugliflozin 15 mg/sitagliptin 100 mg FDC tablet with a high-fat meal resulted in no meaningful effect on AUC_{inf} of ertugliflozin. Food reduced mean ertugliflozin C_{max} by approximately 30% compared to fasted conditions and this decrease in ertugliflozin C_{max} is not anticipated to be clinically relevant by the sponsor.

Single oral administration of ertugliflozin 15 mg/sitagliptin 100 mg FDC tablet with a high-fat meal resulted in no meaningful effect on AUC_{inf} and C_{max} of sitagliptin.

Relative bioequivalence Study P044/1053

A Phase I, Single Dose, Open label, Randomised, Crossover Bioequivalence Study of a Sitagliptin 50 mg/Ertugliflozin 15 mg Fixed Dose Combination Tablet versus Co-Administration of the Individual Components [Sitagliptin (50 mg) and Ertugliflozin (15 mg)] in Healthy Subjects

The sponsor confirmed that the monotherapy, sitagliptin 50 mg film-coated tablets are identical to the Januvia sitagliptin 50 mg tablets marketed in Australia.

Bioequivalence of the monotherapy tablets and the proposed 15 mg/50 mg FDC tablets was concluded. Note: The 15 mg/50 mg FDC Tablet is not proposed by the sponsor.

Relative bioequivalence Study P049/1057

A Phase I, single dose, open label, randomised, crossover bioequivalence study of a sitagliptin 50 mg/ertugliflozin 5 mg fixed dose combination tablet versus co-administration of the individual components [sitagliptin (50 mg) and ertugliflozin (5 mg)] in healthy subjects.

The sponsor confirmed that the monotherapy, Sitagliptin 50 mg film coated tablets are identical to the Januvia sitagliptin 50 mg tablets marketed in Australia.

Bioequivalence of the monotherapy tablets and the proposed 5 mg/50 mg FDC tablets was concluded. Note: The 5 mg/50 mg FDC Tablet is not proposed by the sponsor.

Ertugliflozin metformin FDC tablets

The biowaiver for not submitting biopharmaceutical data for the ertugliflozin/metformin 2.5 mg/500 mg and 7.5 mg/500 mg strengths was provided and found to be acceptable from a pharmaceutical chemistry perspective.

The biowaiver for not using the Australian sourced reference products for the metformin hydrochloride monotherapy tablets was provided to support the use of USA, European and Canadian sourced Glucophage metformin hydrochloride 1000 mg tablets in the P027/1041, P047/1055, P050/1058 and P052/1060 bioequivalence studies. The biowaiver was found to be unacceptable from a pharmaceutical chemistry perspective, as comparative dissolution data for the Australian and European sourced Glucophage reference products across the physiological range was not located initially.

In addition to the ertugliflozin monotherapy bioavailability/bioequivalence studies presented above, the following clinical studies were also applicable for consideration.

Relative bioequivalence Study P027/1041

A Phase I, single dose, open label, randomised, crossover bioequivalence study of an ertugliflozin 7.5 mg/metformin 1000 mg fixed dose combination tablet versus co-administration of the individual components (ertugliflozin and US sourced metformin) in healthy subjects.

Bioequivalence of the ertugliflozin and metformin (US-sourced Glucophage) monotherapy tablets and the proposed 7.5 mg/1000 mg FDC tablets was concluded.

Table 6: Pharmacokinetics of ertugliflozin and metformin

| Ertugliflozin | | | | | |
|------------------------------------|----------|------------------------------------|--------------------------------|------------------------------------|------------------------------------|
| Single dose, prompt release | n | T_{max} (h) (range) | C_{max} (ng/mL) | AUC_{0-t} (ng.h/mL) | AUC_{0-∞} (ng.h/mL) |
| Treatment A Monotherapy | 32, 32 | 1.000 (0.500, 2.020) | 119.860 | 637.655 | 653.924 |
| Treatment B FDC | 32, 32 | 1.030 (1.000, 3.000) | 124.051 | 637.995 | 651.540 |
| Statistical analysis: | | Median diff. | Ratio (%) | Ratio (%) | Ratio (%) |
| B versus A Estimate | | 0.03 | 103.5 | 100.1 | 99.6 |
| 90% CI | | - | 97.8 to 109.5 | 97.3 to 102.9 | 97.0 to 102.3 |
| Metformin | | | | | |
| Single dose, prompt release | n | T_{max} (h) (range) | C_{max} (nM) | AUC_{0-t} (μM.h) | AUC_{0-∞} (μM.h) |
| Treatment A Monotherapy | 32, 26 | 1.980 (0.517, 3.980) | 1661.284 | 11127.539 | 11600.932 |
| Treatment B FDC | 32, 27 | 2.010 (1.000, 4.100) | 1648.013 | 10873.816 | 11179.148 |
| Statistical analysis: | | Median diff. | Ratio (%) | Ratio (%) | Ratio (%) |
| B versus A Estimate | | 0.03 | 99.2 | 97.7 | 96.4 |
| 90% CI | | - | 92.1 106.9 | 91.3 to 104.6 | 89.3 to 104.0 |

Relative bioequivalence Study P046/1054

A Phase I, single dose, open label, randomised, crossover bioequivalence study of an ertugliflozin 7.5 mg/metformin 850 mg fixed dose combination tablet versus co-administration of the individual components (ertugliflozin and EU sourced metformin) in healthy subjects.

Bioequivalence of the ertugliflozin and metformin (EU-sourced Glucophage) monotherapy tablets (EU-sourced) and the proposed 7.5 mg/850 mg FDC tablets was concluded. Note: The 7.5 mg/850 mg FDC Tablet is not proposed for registration in Australia.

Relative bioequivalence Study P047/1055

A Phase I, single dose, open label, randomised, crossover bioequivalence study of an ertugliflozin 7.5 mg/metformin 1000 mg fixed dose combination tablet versus co-administration of the individual components (ertugliflozin and EU sourced metformin) in healthy subjects.

Bioequivalence of the ertugliflozin and metformin (EU sourced Glucophage) monotherapy tablets (EU sourced) and the proposed 7.5 mg/1000 mg FDC tablets was concluded.

Table 7: Plasma exposure of ertugliflozin 90% Confidence intervals (CIs)

| Parameter (Units) | Adjusted (Least-Squares) Geometric Means | | Ratio (Test/Reference) of Adjusted Means ^a | 90% CI for Ratio |
|-------------------------------|--|---|---|------------------|
| | Ertugliflozin 7.5 mg/Metformin 1000 mg FDC Tablet (Test) | Ertugliflozin 7.5 mg + Metformin 1000 mg (EU) Co-administered (Reference) | | |
| AUC _{inf} (ng·h/mL) | 621.1 | 631.9 | 98.28 | 95.72, 100.91 |
| AUC _{last} (ng·h/mL) | 603.3 | 613.3 | 98.36 | 95.54, 101.27 |
| C _{max} (ng/mL) | 121.5 | 122.7 | 98.99 | 93.84, 104.42 |

Table 8: Plasma exposure of metformin 90% CIs

| Parameter (Units) | Adjusted (Least-Squares) Geometric Means | | Ratio (Test/Reference) of Adjusted Means ^a | 90% CI for Ratio |
|-------------------------------|--|---|---|------------------|
| | Ertugliflozin 7.5 mg/Metformin 1000 mg FDC Tablet (Test) | Ertugliflozin 7.5 mg + Metformin 1000 mg (EU) Co-administered (Reference) | | |
| AUC _{inf} (ng·h/mL) | 11150 | 10750 | 103.76 | 96.43, 111.65 |
| AUC _{last} (ng·h/mL) | 10940 | 10450 | 104.66 | 97.67, 112.14 |
| C _{max} (ng/mL) | 1749 | 1589 | 110.08 | 100.31, 120.79 |

Relative bioequivalence Study P050/1058

A Phase I, single dose, open label, randomised, crossover bioequivalence study of an ertugliflozin 2.5 mg/metformin 500 mg fixed dose combination tablet versus co-administration of the individual components (ertugliflozin and US sourced metformin) in healthy subjects.

Bioequivalence of the ertugliflozin and metformin (US-sourced Glucophage) monotherapy tablets and the proposed 2.5 mg/1000 mg FDC tablets was concluded.

Table 9: Plasma exposure of ertugliflozin 90% CIs

| Parameter (units) | Adjusted (Least-Squares) Geometric Means | | Ratio (Test/Reference) of Adjusted Means ^a | 90% CI for Ratio |
|--------------------------------|---|--|---|------------------|
| | Ertugliflozin 2.5 mg/Metformin 500 mg FDC tablet (Test) | Ertugliflozin 2.5 mg + Metformin 500 mg (US) Co-administration (Reference) | | |
| AUC _{inf} (ng·hr/mL) | 176.9 | 180.0 | 98.26 | 96.62, 99.94 |
| AUC _{last} (ng·hr/mL) | 165.3 | 167.6 | 98.62 | 96.82, 100.44 |
| C _{max} (ng/mL) | 34.94 | 34.86 | 100.22 | 94.76, 106.00 |

Table 10: Plasma exposure of metformin 90% CIs

| Parameter (units) | Adjusted (Least-Squares) Geometric Means | | Ratio (Test/Reference) of Adjusted Means ^a | 90% CI for Ratio |
|--------------------------------|---|--|---|------------------|
| | Ertugliflozin 2.5 mg/Metformin 500 mg FDC tablet (Test) | Ertugliflozin 2.5 mg + Metformin 500 mg (US) Co-administration (Reference) | | |
| AUC _{inf} (ng·hr/mL) | 6934 | 6717 | 103.24 | 96.16, 110.83 |
| AUC _{last} (ng·hr/mL) | 6819 | 6794 | 100.36 | 93.28, 107.98 |
| C _{max} (ng/mL) | 1030 | 1015 | 101.49 | 93.83, 109.76 |

Relative bioequivalence Study P052/1060

A Phase I, single dose, open label, randomised, crossover bioequivalence study of metformin in ertugliflozin 2.5 mg/metformin 500 mg fixed dose combination tablet versus Canadian sourced glucophage co-administered with ertugliflozin in healthy subjects in fasted and fed states.

The sponsor concluded that the metformin component of the ertugliflozin 2.5 mg/metformin 500 mg FDC tablet is bioequivalent to metformin in the metformin 500 mg (Canada sourced Glucophage) tablet co-administered with ertugliflozin 2.5 mg when administered under both fasted and fed conditions.

Table 11: Plasma exposure of ertugliflozin 90% Cis

| Parameter (units) | Adjusted (Least-Squares) Geometric Means | | Ratio (Test/Reference) of Adjusted Means ^a | 90% CI for Ratio |
|-----------------------------------|--|---|--|---------------------|
| | Ertugliflozin 2.5 mg/ Metformin 500 mg FDC Tablet - Fasted (Test) | Ertugliflozin 2.5 mg + Metformin 500 mg (CA) Co-administered - Fasted (Reference) | | |
| AUC _{inf} (ng•hr/mL) | 6840 | 6960 | 98.28 | 87.50, 110.38 |
| AUC _{last} (ng•hr/mL) | 6746 | 6316 | 106.80 | 96.17, 118.61 |
| C _{max} (ng/mL) | 1096 | 1012 | 108.27 | 95.69, 122.50 |

Table 12: Plasma exposure of metformin 90% CIs

| Parameter (units) | Adjusted (Least-Squares) Geometric Means | | Ratio (Test/Reference) of Adjusted Means ^a | 90% CI for Ratio |
|-----------------------------------|---|---|--|---------------------|
| | Ertugliflozin 2.5 mg/ Metformin 500 mg FDC Tablet - Fed (Test) | Ertugliflozin 2.5 mg + Metformin 500 mg (CA) Co-administered - Fed (Reference) | | |
| AUC _{inf} (ng•hr/mL) | 5182 | 5178 | 100.07 | 87.06, 115.03 |
| AUC _{last} (ng•hr/mL) | 5158 | 5228 | 98.65 | 92.79, 104.87 |
| C _{max} (ng/mL) | 641.7 | 632.5 | 101.46 | 97.54, 105.52 |

Relative bioequivalence Study P053/1061

A Phase I, single dose, open label, randomised, crossover bioequivalence study of metformin in ertugliflozin 7.5 mg/metformin 850 mg fixed dose combination tablet versus Canadian sourced glucophage co-administered with ertugliflozin in healthy subjects in fasted and fed states.

The sponsor concluded that the metformin component of the ertugliflozin 7.5 mg/metformin 850 mg FDC tablet is bioequivalent to metformin in the metformin 850 mg (CA-sourced Glucophage) tablet co-administered with ertugliflozin 7.5 mg when administered under both fasted and fed conditions. Note: The 7.5 mg/850 mg FDC Tablet is not proposed for registration in Australia.

Food effect study P028/1049

A Phase I, single dose, randomised, open label, crossover study to estimate the effect of food on the pharmacokinetics of ertugliflozin and metformin when administered as a fixed dose combination tablet (7.5 mg/1000 mg) to healthy subjects.

Administration of ertugliflozin 7.5 mg/metformin 1000 mg FDC tablet with a high fat meal resulted in no meaningful effect on AUC_{inf} of ertugliflozin and metformin.

Food reduced mean ertugliflozin C_{max} by approximately 41% and delayed median T_{max} by 1 h compared to the fasted condition (T_{max} 2.50 h fed versus 1.50 h fasted). These results are similar to those observed for the ertugliflozin monotherapy tablets.

Food also reduced metformin C_{max} by approximately 29% and delayed median T_{max} by 1.75 h compared to the fasted condition (T_{max} 4.00 h fed versus 2.25 h fasted).

The decreases in ertugliflozin and metformin C_{max} with food were not considered to be clinically relevant by the sponsor.

Quality summary and conclusions

Approval is recommended from a pharmaceutical chemistry and quality control perspective.

However, it should be noted that whilst the pharmaceutical aspects of the PI documents and product labelling for each submission are considered acceptable, they are yet to be finalised due to issues with the proposed trade names.

Whilst the inclusion of the tablet strengths in the trade names is desired, the sponsor has chosen to include the units (in 'mg') as part of the trade name, which is not desirable. The decision on the acceptability or not of the proposed trade names has been referred to the Delegate for consideration.

IV. Nonclinical findings

Steglatro

General comments

The nonclinical dossier was of good overall quality, with the package of studies conducted in accordance with relevant TGA adopted guidelines.⁸ All pivotal safety-related studies were conducted according to Good Laboratory Practice.

Pharmacology

Primary pharmacology

Ertugliflozin is an inhibitor of SGLT2. This transporter is expressed in proximal renal tubules where it is responsible for resorption of the majority of glucose filtered by the renal glomerulus. Inhibition of SGLT2 results in increased urinary glucose excretion, leading to lowered plasma glucose.

In vitro in transfected cells, ertugliflozin inhibited human SGLT2 with approximately nanomolar potency (50% inhibitory concentration (IC_{50}) 0.877 nM). The drug was also shown to be active against rat and dog SGLT2 (IC_{50} values of 1.15 and 0.118 nM in the respective species). In vivo, single oral administration of ertugliflozin was shown to produce a dose dependent increase in urinary glucose excretion in rats. With repeated administration (30 mg/kg/day PO for 8 days), reductions in plasma glucose and body weight were additionally shown, along with diuresis and activation of the renin-angiotensin-aldosterone system. Pharmacological activity was also evident in the dog, with increased urinary glucose concentration seen from the lowest dose tested in repeat-dose toxicity studies (≥ 1 mg/kg/day PO). There were no studies in an animal model of T2DM.

The two major human circulating metabolites of ertugliflozin (the glucuronides PF-06481944 (M5c) and PF-06685948 (M5a)) displayed only weak activity against human SGLT2 (approximately 540 and > 1140 times less potent than their parent).

Secondary pharmacodynamics and safety pharmacology

The other member of the sodium-glucose co-transporter family is SGLT1, which mediates glucose (and galactose) absorption from the gastrointestinal tract. The selectivity of ertugliflozin for inhibition of human SGLT2 over SGLT1 was > 2200 fold; similar selectivity was seen for dogs (approximately 2700 fold), but lower SGLT2/SGLT1 selectivity was

⁸ Including ICH M3 (R2) Nonclinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals.

evident in rats (approximately 300 fold). Other glucose transporters (GLUT1–4) were not or only very weakly inhibited by ertugliflozin (> 75000 fold lower potency compared to at SGLT2). In screening assays, ertugliflozin (10 μ M) did not exhibit significant affinity for/activity against a panel of 56 receptors, ion channels, amine transporters and enzymes.

The diuretic effect of ertugliflozin was accompanied by reduced blood pressure in hypertensive rats. Activation of the renin-angiotensin-aldosterone system was observed at the higher but not lower dose level tested (36 and 6 mg/kg/day), and this effect appears to be related to body weight loss rather than a direct pharmacological effect.

Specialised safety pharmacology studies with ertugliflozin covered the central nervous, cardiovascular and respiratory systems. They identified no clinically relevant effects on the core battery of physiological systems (based on consideration of animal: human plasma drug levels). Effects on central nervous system (CNS) function (decreased body temperature and locomotor activity) were observed in rats at 500 mg/kg PO, a dose associated with a peak plasma concentration of unbound ertugliflozin 170 times higher than in patients at the maximum recommended human dose (17.2 ng/mL).⁹ CNS function was unaffected in rats at 25 mg/kg PO, yielding 19 times the clinical peak plasma concentration (C_{max}) for unbound drug. Ertugliflozin inhibited a potassium (hERG K⁺) channel but not at clinically relevant concentrations; the IC_{50} of 59 μ M is approximately 100 times higher than the clinical C_{max} for total drug and approximately 1500 times higher than the clinical C_{max} for unbound ertugliflozin. The main cardiac voltage-gated sodium channel (Nav1.5 channel) was inhibited by ertugliflozin even more weakly (IC_{50} , 188 μ M). In vivo, cardiovascular function was unaffected in dogs at 5 mg/kg PO (12.5 times the clinical C_{max} for unbound ertugliflozin) while moderate effects (including decreases in heart rate, corrected QT interval;¹⁰ left ventricular contractility and increased systolic blood pressure) were observed at 50 mg/kg (83 times higher than the clinical C_{max} for unbound ertugliflozin). In rats, ertugliflozin increased respiratory rate and minute volume at \geq 25 mg/kg PO (19 times the clinical C_{max} for unbound drug); respiration was unaffected at 5 mg/kg (3.5 times the unbound clinical C_{max}).

Pharmacokinetics

Absorption after oral administration was rapid in mice, rats and dogs (time to C_{max} (T_{max}) approximately 0.5 to 2.5 h), as in humans (T_{max} , 1 h). Bioavailability was high in mice (75 to 87%) and dogs (approximately 95%), virtually complete in humans (approximately 100%), and moderate in rats (67%). Peak and overall exposure (C_{max} and AUC) were generally dose proportional but C_{max} increased in a less than dose proportional manner at the highest dose levels tested in rats (\geq 250 mg/kg/day) and dogs (\geq 150 mg/kg/day). Plasma half-life was shorter in laboratory animal species (2.7, 4.1 and 7.5 h in mice, rats and dogs, respectively) than in humans (16.6 h for type 2 diabetes mellitus patients with normal renal function). Consistent with this, no accumulation with repeat daily administration was evident in animals. Sex differences in exposure were seen in rodents, with C_{max} and AUC tending to be higher in females compared to males in mice and rats.

⁹ Comparisons in this section are based on C_{max} values for total ertugliflozin of 1.52 μ g/mL, 8.23 μ g/mL and 73.3 μ g/mL in rats at 5, 25 and 500 mg/kg (using day 1 values from Study TT097890), 6.71 μ g/mL and 44.7 μ g/mL in dogs at 25 and 50 mg/kg (from Studies TT097888 and TT097887), and 0.268 μ g/mL in humans at 15 mg/day PO (Study P035/1051), and plasma protein binding of 96.0%, 96.8% and 93.6% in the respective species (Study PK036-MK8835), equating to 60.8, 329, 2932, 215, 1430 and 17.2 ng/mL free ertugliflozin.

¹⁰ The QT interval is the time from the start of the Q wave to the end of the T wave. It represents the time taken for ventricular depolarisation and repolarisation, effectively the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation. The QT shortens at faster heart rates. An abnormally prolonged QT is associated with an increased risk of ventricular arrhythmias, especially Torsades de Pointes.

Plasma protein binding was high but variable in all species: 95.5% in mice, 96.0% in rats, 92.9% in rabbits, 96.8% in dogs and 93.6% in humans. Because the free fraction was lower in the key nonclinical species compared to humans, exposure comparisons made here are based on amount of unbound ertugliflozin rather than total drug. Red blood cell partitioning was similar across tested species (blood: plasma ratios of 0.66, 0.58 and 0.66 for rats, dogs and humans, respectively). Volume of distribution was moderate and exceeded total body water in animals and humans. Accordingly, widespread tissue distribution of radioactivity was observed in rats after oral administration of radiolabelled [¹⁴C]-ertugliflozin, with highest exposure in the bladder, liver and kidney. Distribution to reproductive tissues was low in males and moderate in females. Penetration of the blood-brain barrier was low; distribution to bone was also low, and there was no evidence of binding to melanin.

Metabolism of ertugliflozin chiefly involved glucuronidation on the hydroxy groups of its modified glucose moiety, with additional minor contributions from oxidation reactions. In vitro experiments with recombinant enzymes and human liver microsomes identified key roles for UGT1A9 and 2B7 in the glucuronidation of ertugliflozin, and CYP3A4, and to a much lesser extent, 3A5, 2D6 and 2C8, contributing to oxidation. Unchanged ertugliflozin was by far the dominant circulating species in humans and laboratory animal species. The 3-O- β and 2-O- β glucuronides of ertugliflozin (= metabolites M5c and M5a) were the major circulating metabolites in humans (accounting for approximately 24% and 12% of [¹⁴C]-ertugliflozin derived radioactivity in plasma over 0 to 24 h post-dose compared to approximately 50% for unchanged ertugliflozin). One or both of these were present in mouse, rat and dog plasma but at considerably lower levels. Given these metabolites have minimal primary pharmacological activity and glucuronidation can be considered a detoxification step, this is not of significant concern. No unique human metabolites were observed. Chiral inversion of ertugliflozin was not apparent in plasma obtained from humans given the drug.

Excretion of ertugliflozin and its metabolites was predominantly via the faecal route in rats (approximately 60%) and dogs (approximately 85%), with urine playing a more major role in humans (approximately 50%). Significant biliary excretion was demonstrated in both laboratory animal species.

The pharmacokinetic profile of ertugliflozin in the laboratory animal species is seen to be sufficiently similar to that in humans to allow them to serve as appropriate models for assessing ertugliflozin toxicity.

Pharmacokinetic drug interactions¹¹

Neither ertugliflozin nor its major glucuronide metabolites exhibited significant inhibitory activity against a sufficiently comprehensive set of cytochrome P450 system (CYP) isozymes and uridine diphospho-glucuronosyltransferase (UGT) isozymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5; UGT1A1, 1A4, 1A6, 1A9, 2B7 and (metabolites only) 2B15). The most sensitive target was UGT1A1, inhibited by ertugliflozin with an IC₅₀ of 39 μ M. This concentration is almost 1000 times higher than the peak plasma concentration of unbound ertugliflozin in patients at the maximum recommended human dose (17.2 ng/mL = 39.3 nM), indicating no clinical relevance. Experiments with cultured

¹¹ Assessment is based on the EMA guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2), using values of 436.88 for molecular weight, 15 mg for dose, 268 ng/mL for clinical plasma C_{max}, 93.6% for plasma protein binding, 0.25 L for intestinal volume, 0.329 h⁻¹ for absorption rate constant, 1 for fraction absorbed from gut to portal vein, and 97 L/h for total hepatic blood flow.

human hepatocytes and a human hepatocyte cell line showed no significant induction of CYPs 1A2, 2B6 or 3A4 by ertugliflozin, M5a or M5c.

Ertugliflozin was shown to be a substrate of P-glycoprotein and breast cancer resistance protein (BCRP) and to not be a substrate of human organic anion transporters (OAT) P1B1, OATP1B3, OATP2B1, organic cation transporters (OCT) 1 (hepatic uptake transporters), OAT1, OAT3 or OCT2 (renal transporters). Weak inhibition of various transporters by ertugliflozin was shown; the most sensitive target was OATP1B1 (IC_{50} , 35.4 μ M; > 750 times higher than the maximum expected unbound drug concentration in the portal vein, 47 nM). For inhibition of P-glycoprotein, the IC_{50} was 176 μ M (approximately 4500 times higher than the peak plasma concentration of unbound ertugliflozin). Metabolites M5a and M5c were weaker transporter inhibitors compared to their parent.

Toxicity

Acute toxicity

Single dose toxicity studies were conducted by the intravenous (IV) route in rats and by the PO route in dogs. There were no treatment-related deaths in either study (tested up to 100 mg/kg IV in rats and 500 mg/kg PO in dogs). Clinical signs were limited to white foamy emesis in dogs at the high dose level. The studies indicate a low order of acute toxicity for ertugliflozin.

Repeat dose toxicity

Repeat dose toxicity studies of up to 3 months duration were conducted in mice, 6 months in rats and 9 months in dogs. All involved once daily administration by the clinical route (oral). The pivotal studies were adequately conducted in terms of the species used (rats and dogs), duration, dose selection, and the monitoring and analyses performed.

Relative exposure

Exposure ratios have been calculated based on animal: human plasma AUC_{0-24h} for unbound ertugliflozin. Due to limited toxicokinetic sampling, AUC values for the mouse carcinogenicity study are from the 3 month repeat-dose toxicity study in the species (interpolated for the mid-dose level). Very high multiples of the clinical exposure to unbound ertugliflozin was obtained at the upper dose levels tested.

Table 13: Relative exposure in selected repeat-dose toxicity and rodent carcinogenicity studies

| Species | | Study | Dose mg/kg/day | AUC_{0-24h} (μ g·h/mL) [^] | | | | Exposure ratio [#] | |
|---------|-------------|------------------------|-------------------|--|------|---------|-------|--------------------------------|-----|
| | | | | Total | | Unbound | | | |
| | | | | M | F | M | F | M | F |
| Mouse | wt rasH2 | 1 month [TT137801] | 3 | 3.77 | 6.67 | 0.106 | 0.187 | 1.4 | 2.4 |
| | | | 15 | 19.6 | 40.6 | 0.549 | 1.14 | 7 | 15 |
| | | | 100 | 178 | 322 | 4.98 | 9.02 | 65 | 118 |
| | CD-1 | 3 months [TT137801] | 5 | 4.83 | 9.67 | 0.217 | 0.435 | 2.8 | 6 |
| | | | 40 | 53.0 | 87.2 | 2.39 | 3.92 | 31 | 51 |

| Species | Study | Dose | AUC _{0-24h} (µg·h/mL) [^] | | | | Exposure | | |
|---------------------------------|---|-----------|---|------|--------|-------|----------|-----|-----|
| | | | 100 | 152 | 245 | 6.84 | 11.0 | 90 | 144 |
| | Approx. 2 years carcinogenicity; TT141003 | 5 | 4.83 | 9.67 | 0.217 | 0.435 | 2.8 | 6 | |
| | | 15 | 17.2 | 30.9 | 0.774 | 1.39 | 10 | 18 | |
| | | 40 | 53.0 | 87.2 | 2.39 | 3.92 | 31 | 51 | |
| | | 5 | 8.40 | 14.9 | 0.378 | 0.671 | 5 | 9 | |
| Rat (SD) | 1 month [TT097890] | 25 | 69.3 | 93.0 | 3.12 | 4.19 | 41 | 55 | |
| | | 250 | 541 | 718 | 24.3 | 32.3 | 319 | 423 | |
| | | 5 | 15.2 | 24.5 | 0.608 | 0.980 | 8 | 13 | |
| | 3 months [TT097892] | 25 | 81.4 | 97.4 | 3.26 | 3.90 | 43 | 51 | |
| | | 250 | 694 | 781 | 27.8 | 31.2 | 364 | 409 | |
| | | 5 | 17.6 | 26.9 | 0.704 | 1.076 | 9 | 14 | |
| | 6 months pivotal; TT097894] | 25 | 128 | 167 | 5.12 | 6.68 | 67 | 87 | |
| | | 100 | 397 | 814 | 15.9 | 32.6 | 208 | 426 | |
| | | 1.5 | 6.69 | 9.27 | 0.268 | 0.371 | 3.5 | 5 | |
| | 2 years carcinogenicity TT137800] | 5 | 24.4 | 39.2 | 0.976 | 1.57 | 13 | 21 | |
| | | 15 | 91.0 | 102 | 3.64 | 4.08 | 48 | 53 | |
| | | 1 | 6.30 | | 0.202 | | 2.6 | | |
| Dog (Beagle) | 9 months pivotal; TT097895 | 10 | 70.6 | | 2.26 | | 30 | | |
| | | 150 | 904 | | 28.9 | | 379 | | |
| Human (healthy subjects) | steady state P035/1051 | 15 mg/day | 1.193 | | 0.0764 | | - | | |

= animal:human plasma AUC_{0-24h} for unbound ertugliflozin; ^ = values are for the last sampling occasion, and for the sexes combined in non-rodents; fraction unbound: 2.8% for rasH2 mouse, 4.5% for CD-1 mouse, 4.0% for rat, 3.2% for dog and 6.4% for human

Major toxicities and treatment related changes

Treatment with ertugliflozin was associated with effects on body weight, and renal, adrenal, gastrointestinal and bone changes.

Body weight gain was usually reduced in treated animals, accompanied by increased food consumption. This is seen to be related to the marked loss of glucose in the urine resulting from the drug's primary pharmacological activity, with food intake increased to (partly) compensate. Urinary glucose concentrations in rats and dogs in the pivotal studies were

increased by up to 450 and 250 times control levels, and serum glucose (in these normoglycaemic animals) was reduced by up to approximately 50% and approximately 30% in the respective species.

Glucosuria induced osmotic diuresis. This occurred at all dose levels in the pivotal studies, with urine volume increased by a minimum of 70% in rats and 40% in dogs and by up to 5 fold in both species (urinalysis was not performed in any of the studies in mice). Dehydration was frequently apparent in rats (as increases in blood urea nitrogen). Bodyweight relative kidney weight was increased in all species, from the lowest doses tested where measured (3 mg/kg/day in mice, 5 mg/kg/day in rats and 1 mg/kg/day in dogs). Treatment related microscopic changes in the kidney were limited to rodents, and included tubule dilatation, pelvis dilatation, mineral deposition, exacerbation of chronic progressive nephropathy and hypertrophy of the proximal tubule epithelium. The renal findings are seen to be related to the drug-induced diuresis, and mostly an adaptive response to increased fluid load within the nephron. The pivotal studies establish a no observable adverse effect level (NOAEL) for kidney microscopic changes of 5 mg/kg/day in rats (relative exposure, 9 to 14) and 150 mg/kg/day in dogs (relative exposure, approximately 380).

There was evidence of urinary tract infections in several studies in rats (3 month; impurity qualification; carcinogenicity), as kidney inflammation or pyelonephritis, and inflammation of the prostate, seminal vesicle, bladder and/or ureter. This is seen to be related to glucosuria.

Hypertrophy and/or vacuolation of the adrenal zona glomerulosa was commonly seen in treated rats, evident at all doses tested in 1, 3 and 6 month studies (≥ 5 mg/kg/day; relative exposure, ≥ 5). Bodyweight-relative adrenal weight was also sometimes increased. This is consistent with a compensatory response to diuresis: increased aldosterone secretion to counter increased sodium loss in urine. Adrenal changes were not observed in treated dogs (≤ 150 mg/kg/day in the pivotal study; relative exposure, ≤ 379).

Microscopic changes in the stomach were observed at ≥ 25 mg/kg/day in rats treated for 3 and 6 months. There were findings of erosion/ulceration in both the 3 and 6 month studies and additionally foveolar hyperplasia, crypt degeneration in the pylorus and glandular dilatation in the pivotal 6 month study (where a NOAEL of 5 mg/kg/day for stomach histopathological changes is established; relative exposure, 9 to 14). Decreased pancreatic zymogen granules occurred in rats at all doses (≥ 5 mg/kg/day). The stomach and pancreas findings are considered to be secondary to increased food consumption. Such microscopic changes were not seen in dogs, although emesis (white and foamy) and stool changes (soft, mucoid and watery) were observed in the species with treatment at 150 mg/kg/day for 1, 3 and 9 months (relative exposure, approximately 380 in the pivotal study), and to a lesser extent at 50 mg/kg/day in 1 week pilot studies.

Increased trabecular bone formation was noted in the femur and sternum in male rats at 100 mg/kg/day ertugliflozin in the pivotal 6 month study (relative exposure, > 200), and at ≥ 25 mg/kg/day in males and at 250 mg/kg/day in females (relative exposure 43 to 409) in a 3 month rat study. There were alteration in serum calcium (decreased) and urine calcium (increased) in the pivotal rat study. Effects on bone are likely to be related to increased calcium absorption, occurring secondary to carbohydrate malabsorption due to ertugliflozin inhibition of SGLT1. Despite the drug's approximately 300 fold selectivity for SGLT2 over SGLT1 in the rat and with bioavailability moderate in the species, high intraluminal concentrations of ertugliflozin sufficient to inhibit SGLT1 on the luminal surface of intestinal enterocytes are expected. The resulting inhibition of intestinal absorption of glucose and galactose will provide substrate for bacterial fermentation in the distal gastrointestinal (GI) tract, lowering the luminal pH and thereby increasing the

solubility (and absorption) of calcium. There were no effects on bone in dogs (relative exposure, ≤ 379 in the pivotal 9 month study).

Toxicity in combination with metformin and sitagliptin

Combination toxicity studies of up to 3 months duration were performed with ertugliflozin/metformin and ertugliflozin/sitagliptin in rats. These studies are described in more detail in separate evaluation reports for concurrent applications to register such fixed-dose combination products (Segluromet and Steglujan). No novel or additive toxicity was seen with co-administration.

Genotoxicity

The genotoxic potential of ertugliflozin was investigated in the standard battery of tests; a bacterial reverse mutation assay, an *in vitro* assay for clastogenicity using human peripheral lymphocytes, and a bone marrow micronucleus test in rats. The conduct of the definitive studies was in accordance with relevant guidelines. Concentrations/doses used were appropriate (up to maximum recommended levels, or limited by cytotoxicity or producing clinical signs and high exposure). All assays returned negative results.

Carcinogenicity

Lifetime (2 year) carcinogenicity studies were conducted with ertugliflozin by the oral route in mice and rats. The studies were appropriately designed and conducted, in accordance with relevant TGA adopted guidelines.¹² High dose levels yielded very high multiples of the clinical AUC for unbound ertugliflozin in both rodent species and did not adversely affect survival. The mouse study featured only limited toxicokinetic sampling but this was sufficient to demonstrate the relevance of toxicokinetic parameters obtained in an earlier 3 month mouse study.

No treatment related increase in tumour incidence was observed up to the highest dose level tested in mice (40 mg/kg/day; relative exposure, 31 for males and 51 for females). In rats, ertugliflozin was not carcinogenic in female animals (≤ 15 mg/kg/day; relative exposure, 53) but was seen to increase the incidence of benign phaeochromocytoma in males at 15 mg/kg/day (relative exposure 48). This was accompanied by increased adrenal medullary hyperplasia (present at ≥ 5 mg/kg/day). The particular sensitivity of the rat to increases in the incidence of these adrenal proliferative lesions (common age-related spontaneous findings in the species) following disturbances in calcium homeostasis (secondary, here, to carbohydrate malabsorption via SGLT1 inhibition) is well recognised. Analogous findings are seen with poorly absorbable sugars (such as lactose) and sugar alcohols in rats; lactose is not associated with increased tumours in humans. The no observable effect level (NOEL) for carcinogenicity in the rat is 5 mg/kg/day (relative exposure 13).

Reproductive and developmental toxicity

Reproductive toxicity studies submitted by the sponsor covered all stages (fertility, early embryonic development, embryofetal development, and pre and postnatal development). Adequate animal numbers were used in the pivotal studies, and the timing/duration of treatment was appropriate. Rats were used for all study types; the rabbit was used as the

¹² ICH S1A Need for carcinogenicity studies of pharmaceuticals. ICH S1B Carcinogenicity: testing for carcinogenicity of pharmaceuticals. ICH S1C Dose selection for carcinogenicity studies of pharmaceuticals.

second (non-rodent) species for embryofetal development. Toxicity in juvenile animals was additionally investigated (in rats). All studies were conducted by the oral route.

Table 14: Relative exposure in reproductive and developmental toxicity studies

| Species | Study | Dose mg/kg/day | AUC _{0-24h} (µg·h/mL) [^] | | | | Exposure ratio [#] | | |
|-----------------------------|---|---------------------------------|---|------|---------|-------|-----------------------------|------|-----|
| | | | Total | | Unbound | | | | |
| | | | M | F | M | F | M | F | |
| Rat (SD) | Fertility [TT107835] | 5 | 8.40 | 14.9 | 0.336 | 0.596 | 4.4 | 8 | |
| | | 25 | 69.3 | 93.0 | 2.77 | 3.72 | 36 | 49 | |
| | | 250 | 541 | 718 | 21.6 | 28.7 | 283 | 376 | |
| | Embryofetal development [TT107833] | 50 | - | 199 | - | 7.96 | - | 104 | |
| | | 100 | - | 457 | - | 18.3 | - | 239 | |
| | Pre/post-natal development [TT157803] | 250 | - | 975 | - | 39.0 | - | 510 | |
| | | Juvenile toxicity [TT157803] | 5 | 20.3 | 28.0 | 0.812 | 1.12 | 11 | 15 |
| | | | 25 | 116 | 97.1 | 4.64 | 3.88 | 61 | 51 |
| | | | 250 | 696 | 939 | 27.8 | 37.6 | 364 | 492 |
| Rabbit (NZW) | Embryofetal development [TT107834] | 50 | - | 207 | - | 14.7 | - | 192 | |
| | | 100 | - | 424 | - | 30.1 | - | 394 | |
| | | 250 | - | 1150 | - | 81.7 | - | 1069 | |
| Human (healthy subjects) | steady state [P035/1051] | 15 mg/day | 1.193 | | 0.0764 | | - | | |

= animal:human plasma AUC_{0-24 h} for unbound ertugliflozin; ^ = due to limited/absent toxicokinetic sampling, AUC values for the fertility study are from a 1-month rat repeat dose toxicity study (TT097890), and from the rat embryofetal development study for the pre-/postnatal development study; fraction unbound: 4.0% for rat, 7.1% for rabbit and 6.4% for human.

Male and female fertility were unaffected in rats up to the highest dose tested (250 mg/kg/day; relative exposure, 283 to 376).

Ertugliflozin and/or its metabolites were shown to cross the placenta and be excreted in milk in rats. While only [¹⁴C]-ertugliflozin derived radioactivity was measured (that is, representing unchanged drug and/or metabolites), excretion of unchanged ertugliflozin in milk is apparent from observations of pharmacologically-mediated effects in nursing pups.

Treatment with ertugliflozin was associated with embryo-lethality (increased post-implantation loss due to increased early resorptions and leading to decreased live litter size) and teratogenicity (increased incidence of cardiac malformation [membranous ventricular septal defect]) at 250 mg/kg/day in the rat embryofetal development study;

skeletal variations were also increased. This dose was maternotoxic. The NOEL for effects on embryofetal development in the rat is 100 mg/kg/day (relative exposure, approximately 240). No adverse effects on embryofetal development were observed in the rabbit (\leq 250 mg/kg/day; relative exposure, $>$ 1000).

In the pre-/postnatal development study in rats, treatment with ertugliflozin decreased pup body weight at all doses pre-weaning (\geq 50 mg/kg/day) and at \geq 100 mg/kg/day post-weaning. At 250 mg/kg/day, there were reductions in pup birth weight and perinatal survival (with no milk in stomach commonly seen at necropsy) and delays in male and female sexual maturation. Motor activity, sensory function, learning and memory, and reproductive function were unaffected in the offspring. The NOAEL for effects on pre/postnatal development is 50 mg/kg/day (relative exposure, $>$ 100), with the effects on body weight observed at this low dose level not as severe as to be considered as adverse. The adverse effects on pre/postnatal development observed in this study occurred in conjunction with maternotoxicity. Tissues of pups (most notably the kidney; see below) were not subjected to microscopic examination.

The juvenile toxicity study involved treatment of rats for 10 weeks from postnatal Day 21. Body weight gain was suppressed in males at \geq 25 mg/kg/day. At 250 mg/kg/day, there was transient inhibition of body weight gain in females, along with delays in sexual maturation in both sexes (in females, this was not secondary to lower body weight). Increased bodyweight relative kidney weight and microscopic renal changes were observed at all dose levels tested (\geq 5 mg/kg/day; relative exposure, 13 [mean for males and females]). While the histopathological findings were similar in nature to those seen in adult animals, comprising renal tubule dilatation, pelvis dilatation and mineralisation, the incidence was greater in the younger animals. This was most prominent for tubule dilatation, with 17/20 juvenile rats displaying the finding at 5 mg/kg/day compared to 2/20 adult animals treated at this dose level in a 13 week study (where exposure was similar). Increased bone was also observed (at 250 mg/kg/day in males and at \geq 25 mg/kg/day in females), in line with findings in adult animals.

The developing kidney is seen to be more sensitive to ertugliflozin than the mature organ, consistent with findings with other members of this pharmacological class (dapagliflozin, canagliflozin and empagliflozin). This is likely related to the reduced ability of the immature kidney to handle the increased urinary output that occurs as a consequence of SGLT2 inhibition.

Kidney anatomical maturation occurs postnatally in rats, with nephrogenesis continuing to 11 days from birth;¹³ and tubular differentiation continuing until the time of weaning (approximately 21 days of age); functional maturation occurs later still. Human anatomical renal maturation occurs in utero during the second and third trimesters and functional maturation continues for the first 2 years of life.¹⁴ The absence of microscopic examination of the kidneys in the pre/postnatal development study (beyond standard requirements) and the timing of the juvenile animal study means that effects of ertugliflozin exposure prior to anatomical maturation of the kidney have not been examined. Only limited reversibility of tubular dilatation was observed in juvenile male rats after a 4 week treatment-free period (still present in 4/5 animals), while recovery was more substantial in females. Pelvis dilatation was fully reversed in males and mostly reversed in females; renal mineralisation persisted. Irreversible kidney changes that may affect renal function are recognised for the pharmacological class, and concerns are greatest with drug exposure prior to anatomical maturation of the kidney.

¹³ Kavlock, R.J and J.A. Gray. (1982) Evaluation of renal function in neonatal rats. *Biol. Neonate* 41: 279–288.

¹⁴ Zoetis T. and Hurt M.E. (2003) Species comparison of anatomical and functional renal development. *Birth Defects Res. (Pt B)* 68: 111–120.

Pregnancy classification

The sponsor has proposed Pregnancy Category C.¹⁵ However, based on concerns for potential irreversible effects on the developing kidney an assignment to Pregnancy Category D;¹⁶ is warranted instead. This category is for drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage.

Phototoxicity

No phototoxicity studies were performed with ertugliflozin. This is acceptable under the relevant TGA-adopted guideline¹⁷, with its molar extinction coefficient $< 1000 \text{ L mol}^{-1} \text{ cm}^{-1}$ at wavelengths 290 to 700 nm. Tissue distribution studies in rats showed no particular distribution to skin or eye or binding to melanin.

Impurities

Proposed limits for ertugliflozin related impurities/degradants in the drug substance and drug product are considered to be toxicologically acceptable. Limits for three impurities that exceeded the applicable ICH Q3A threshold were adequately qualified.

Nonclinical summary

- The nonclinical dossier was of good quality, with the package of studies conducted in accordance with the relevant EU guideline.¹⁸ All pivotal safety-related studies were Good Laboratory Practice compliant.
- Ertugliflozin was shown to inhibit human SGLT2 in vitro with approximately nanomolar potency (50% inhibitory concentration (IC_{50}) = 0.877 nM). It inhibited the rat and dog forms of the transporter with comparable or higher potency compared to human, resulting in markedly increased urinary excretion of glucose in vivo in the laboratory animal species.
- The two major metabolites of ertugliflozin in humans (glucuronides) have much lower potency against SGLT2 cf. their parent, with no appreciable pharmacological activity expected at clinical concentrations.
- Ertugliflozin displays very high selectivity (> 2200 fold) for human SGLT2 over SGLT1. No notable secondary targets for ertugliflozin were identified among other glucose transporters (GLUT1–4) and various other unrelated receptors, ion channels, amine transporters and enzymes.
- Safety pharmacology studies identified no clinically relevant effects on central nervous, cardiovascular or respiratory function.
- Oral absorption of ertugliflozin was rapid in mice, rats and dogs, as in humans, with moderate (rats) or high (other species) bioavailability. Plasma protein binding was high in humans (93.6%) and laboratory animal species (92.9 to 96.8%); given the

¹⁵ Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

¹⁶ Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

¹⁷ ICH S10: Photosafety evaluation of pharmaceuticals

¹⁸ ICH Q3A (R2) Impurities in new drug substances Q3A

variability, exposure multiples in this report account for differences in the extent of plasma protein binding between animals and humans. Tissue distribution of radioactivity following oral administration of [¹⁴C]-ertugliflozin was wide in the rat, with distribution to the target organ (kidney) particularly high; penetration of the blood-brain barrier was low. Metabolism of ertugliflozin chiefly involved glucuronidation on the hydroxy groups of the molecule's modified glucose moiety (mediated by UGT1A9 and 2B7), generating two major circulating metabolites in humans. Excretion was predominantly via the faecal route in rats and dogs, with the renal route playing a more major role in humans (approximately 50%). Biliary excretion was demonstrated in animals.

- Ertugliflozin and its two major glucuronide metabolites were only weak or very weak inhibitors of CYP and UGT isozymes and various transporters in vitro, with no relevant in vivo inhibition to cause pharmacokinetic drug interactions predicted in patients. The drug is a substrate for P glycoprotein and BCRP.
- Ertugliflozin had a low order of acute toxicity in animals by the PO and IV routes.
- Repeat dose toxicity studies by the oral route were conducted in mice (up to 3 months), rats (up to 6 months) and dogs (up to 9 months). Very high multiples of the clinical exposure was achieved at the upper dose levels tested. Major findings comprised changes in the kidneys (increased organ weight, tubule dilatation, pelvis dilatation, mineralisation, and proximal tubule epithelial hypertrophy), adrenal gland (hypertrophy and vacuolation of the zona glomerulosa), bone (hyperostosis) and stomach (erosion, ulceration, degeneration of pylorus crypts).
- Ertugliflozin was not genotoxic in the standard battery of tests.
- No treatment related increase in tumour incidence was observed in mice or female rats treated with ertugliflozin in 2 year oral carcinogenicity studies. In male rats, ertugliflozin increased the incidence of benign adrenal phaeochromocytoma at 15 mg/kg/day. The NOEL for carcinogenicity was 40 mg/kg/day in mice (relative exposure based on plasma AUC for unbound ertugliflozin 40) and 5 mg/kg/day in rats (relative exposure, 13).
- Male and female fertility were unaffected by ertugliflozin in rats. Embryo lethality (increased post implantation loss) and teratogenicity (cardiac malformation) were observed in the rat (occurring in the context of maternotoxicity), while no adverse effects on embryofetal development were seen in the rabbit. Reductions in birth weight, perinatal survival, postnatal body weight gain and delayed sexual maturation were observed in a pre /postnatal development study in rats (at a maternotoxic dose). Placental transfer and excretion in milk were demonstrated in the rat.
- A juvenile toxicity study in rats showed that the developing kidney is more sensitive to ertugliflozin related changes than the mature organ.

Nonclinical conclusions and recommendation

- The nonclinical dossier contained no critical deficiencies.
- Primary pharmacology studies, showing inhibition of SGLT2 in vitro and increased urinary glucose excretion in vivo, offer support for the proposed use of the drug in the treatment of T2DM.
- Ertugliflozin is not predicted to produce clinically significant enzyme or transporter inhibition in patients to give rise to pharmacokinetic drug interactions.
- The toxicological profile of ertugliflozin is typical of the SGLT2 inhibitor class.

- The kidney, adrenal gland, bone and stomach were identified as targets for toxicity in repeat-dose studies in rats. These effects are largely seen to be related to osmotic diuresis (caused by glucosuria due to SGLT2 inhibition) and altered calcium homeostasis (secondary to carbohydrate malabsorption due to SGLT1 inhibition in the intestine). Supporting limited human relevance, histopathological changes in these tissues were not seen in dogs at very high multiples of the clinical exposure (up to approximately 380 fold).
- Ertugliflozin was not genotoxic. The finding of increased phaeochromocytomas in male rats is not considered to indicate that ertugliflozin poses a particular carcinogenic risk to patients.
- Like other members of this class, concerns exist for potential irreversible effects of ertugliflozin on the developing kidney. Treatment in the juvenile animal study commenced after renal anatomical maturation; other earlier developmental studies did not include microscopic examination of the kidney. Concern is greatest for drug exposure prior to this stage (that is, in utero in humans and prior to postnatal Day 21 in rats). Ertugliflozin should be assigned Pregnancy Category D, rather than Category C as the sponsor proposes.
- There are no nonclinical objections to the registration of Steglatiro for the proposed indication provided that the Product Information is amended.

Steglujan

Introduction

The nonclinical submission contained repeat-dose toxicity studies (including toxicokinetic analyses) with ertugliflozin and sitagliptin in combination in rats. The scope of studies investigating the combination was in accordance with relevant TGA adopted guidelines.¹⁹ The pivotal study was conducted according to Good Laboratory Practice.

Pharmacology

Ertugliflozin is a new SGLT2 inhibitor and sitagliptin is an established DPP-4 inhibitor. This is a novel combination of pharmacological classes for a fixed-dose product but use of such agents in free combination is already approved.

No nonclinical efficacy studies with ertugliflozin and sitagliptin in combination were submitted.

Pharmacokinetics

The enzymes chiefly responsible for the metabolism of ertugliflozin and sitagliptin are distinct: UGT1A9 and 2B7 for ertugliflozin; and CYP3A4 and to a much lesser extent CYP2C8 for sitagliptin. In vitro studies showed that ertugliflozin (and its two major glucuronide metabolites) do not inhibit these CYP isoforms at clinically relevant concentrations.

Consistent with predictions from in vitro data, no pharmacokinetic interaction between ertugliflozin and sitagliptin was observed in rats nor is reported in humans.

¹⁹ EMA guideline on the nonclinical development of fixed combinations of medicinal products: EMEA/CHMP/SWP/258498/2005]; ICH M3 (R2) Nonclinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals.

Toxicology

Repeat dose toxicity studies of 2 and 13 weeks duration were conducted with ertugliflozin and sitagliptin in combination in rats. Administration was by the clinical route (PO) and single agent comparator groups were included in both studies. The duration of the pivotal study (3 months) and the use of a single species are consistent with relevant guidelines. Group size was appropriate.

Ertugliflozin: sitagliptin dose ratios used in rats were different from those proposed for patients (1:0.8, 1:2.4, 1:4 and 1:12 cf. 1:6.7 and 1:20) but the 5/60 mg/kg/day dose group did yield exposure multiples that were roughly equivalent for the two drugs (with respect to the maximum recommended human dose). Exposure ratios obtained in the pivotal study are calculated below based on animal: human plasma area under the plasma concentration versus time curve from time 0 to 24 h post dosing ($AUC_{0-24\text{h}}$) values for unbound ertugliflozin and for (total) sitagliptin. Human reference AUC values used are for the maximum dose level and are taken from the nonclinical evaluation reports for the two drugs as new chemical entities. Adequate multiples of the expected clinical exposure was achieved.

Relative exposures in the pivotal repeat-dose toxicity study are tabulated below.

Table 15: Relative exposure in the pivotal repeat-dose toxicity study

| Species | Study | Dose (mg/kg/day) | | $AUC_{0-24\text{h}} (\mu\text{g}\cdot\text{h}/\text{mL})$ | | Exposure ratio [#] | |
|-----------------|-----------------------------|-------------------------------|--------|---|-----------------|-----------------------------|-----|
| | | Ertugliflozin/ sitagliptin | | Ertugliflozin (E) | Sitagliptin (S) | E | S |
| Rat (SD) | 13 weeks [TT147808]] | 5 | 20 | 21.0 | 6.93 | 11 | 2.0 |
| | | 5 | 60 | 24.8 | 28.6 | 13 | 8 |
| | | 25 | 20 | 154 | 8.39 | 80 | 2.4 |
| | | 25 | 60 | 123 | 24.4 | 64 | 7 |
| | | 25 | - | 115 | - | 60 | - |
| | | - | 60 | - | 30.2 | - | 9 |
| Human | P035/1051 ; P033/P004 | 15 mg | 100 mg | 1.193 | 3.45 | - | - |

= animal: human plasma $AUC_{0-24\text{h}}$; for ertugliflozin, the exposure ratio is adjusted for cross-species differences in protein binding (fraction unbound: 4.0% for rat and 6.4% for human); animal AUC values are for the last sampling occasion, and for the sexes combined.

Findings with combination treatment in rats were almost entirely attributable to ertugliflozin. No novel or additive toxicity was seen. Histopathological changes involved the kidney (tubular dilatation and pelvic dilatation), adrenal (hypertrophy in the zona glomerulosa), stomach (erosion, submucosal inflammation, and haemorrhage), pancreas (zymogen depletion) and prostate (mixed cell inflammation [considered secondary to infections due to increased urinary excretion of glucose]) and were mostly graded minimal or slight.

Pregnancy classification

No embryofetal development studies have been performed with ertugliflozin and sitagliptin in combination. The sponsor proposes Pregnancy Category C.²⁰ This is not supported. Assignment to Pregnancy Category D²¹ is warranted instead due to concerns for potential irreversible effects on the developing kidney due to ertugliflozin. This is the more restrictive category for ertugliflozin (Category D recommended for Steglatiro) and sitagliptin (B3²²) as single agents.

Nonclinical summary and conclusions

- The set of nonclinical studies performed with ertugliflozin and sitagliptin in combination was suitably comprehensive.
- No nonclinical efficacy studies with the combination were submitted. Assessment of combination efficacy relies on clinical data only.
- In vitro data suggest no likely pharmacokinetic interaction between the two drugs. Consistent with this, no pharmacokinetic interaction with co-administration of ertugliflozin and sitagliptin was observed in rats, and no notable interaction was reported for humans.
- A Good Laboratory Practice compliant 3 month repeat-dose toxicity study revealed no novel or additive toxicity with ertugliflozin and sitagliptin in combination in rats.
- There are no nonclinical objections to the registration of Steglujan for the proposed indication provided that the Product Information document is amended as recommended. Of particular note, the product should be assigned Pregnancy Category D (rather than Category C as the sponsor proposes) due to concerns for irreversible effects on the developing kidney caused by ertugliflozin.

Segluromet

The nonclinical submission contained repeat-dose toxicity studies (including toxicokinetic analyses) with ertugliflozin and metformin in combination in rats. The scope of studies investigating the combination was in accordance with relevant TGA adopted guidelines.²³ The pivotal study was conducted according to Good Laboratory Practice.

Pharmacology

Ertugliflozin is a new SGLT2 inhibitor and metformin is a biguanide. This is not a novel combination of pharmacological classes, with fixed-dose combinations of other SGLT2

²⁰ Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

²¹ Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

²² Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

²³ EMA guideline on the nonclinical development of fixed combinations of medicinal products [EMEA/CHMP/SWP/258498/2005]; ICH M3 (R2) [Nonclinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals

inhibitors and metformin are already approved: Jardiamet (empagliflozin + metformin) and Xigduo XR (dapagliflozin + metformin).

No nonclinical efficacy studies with ertugliflozin and metformin in combination were submitted.

Pharmacokinetics

Ertugliflozin and metformin do not share metabolic pathways. Ertugliflozin is chiefly metabolised by UGT1A9 and 2B7 while metformin is not subject to hepatic metabolism being excreted unchanged in the urine and with no human metabolites identified.

A modest pharmacokinetic interaction was suggested in rats, with metformin appearing to reduce absorption/exposure of ertugliflozin when co-administered; no effect of ertugliflozin on metformin's kinetics was apparent. No pharmacokinetic interaction between ertugliflozin and metformin was reported in humans.

Toxicity

Repeat dose toxicity studies of 2 and 13 weeks duration were conducted with ertugliflozin and metformin in combination in rats. Administration was by the clinical route (PO) and single agent comparator groups were included in both studies. The duration of the pivotal study (3 months) and the use of a single species are consistent with relevant guidelines. Group size was appropriate.

Ertugliflozin: metformin dose ratios used in rats were mostly very different from those proposed for patients (1:4, 1:8, 1:24 and 1:120 compared with 1:67, 1:133, 1:200 and 1:400) but the 5/600 mg/kg/day dose group did yield exposure multiples that were very roughly parallel for the two drugs (with respect to the maximum recommended human dose). Exposure ratios obtained in the pivotal study are calculated below based on animal: human plasma $AUC_{0-24\text{h}}$ values for unbound ertugliflozin and for (total) metformin.

Human reference AUC values used are taken from the nonclinical evaluation report for ertugliflozin as a new chemical entity and from the literature for metformin: administration of metformin (immediate-release form) at 1000 mg twice a day (BD) was reported to be associated with a human plasma $AUC_{0-24\text{h}}$ of 20544 ng·h/mL by Timmins et al. (2005).²⁴ Adequate multiples of the clinical exposure was achieved.

²⁴ Timmins P., et al (2005) Steady-state pharmacokinetics of a novel extended-release metformin formulation. *Clin. Pharmacokinet.* 2005; 44: 721–729.

Relative exposure in the pivotal repeat dose toxicity study**Table 16: Relative exposure in the pivotal repeat-dose toxicity study**

| Species | Study | Dose (mg/kg/day) | | AUC _{0-24h} (µg·h/mL) | | Exposure ratio [#] | |
|-----------------|--|---------------------------------|------------|--------------------------------|--------|-----------------------------|-----|
| | | Ertugliflozin (E)/metformin (M) | | E | M | E | M |
| Rat (SD) | 13 weeks TT147809 | 5 | 200 | 21.2 | 48.1 | 11 | 2.3 |
| | | 5 | 600 | 19.2 | 123 | 10 | 6.0 |
| | | 25 | 200 | 120 | 53.8 | 63 | 2.6 |
| | | 25 | 600 | 91.5 | 135 | 48 | 6.5 |
| | | 25 | - | 145 | - | 76 | - |
| | | - | 600 | - | 138 | - | 6.7 |
| Human | P035/1051 [†] ; Timmins et al. 2005 | 7.5 mg BD | 1000 mg BD | 1.193 | 20.544 | - | - |

= animal: human plasma AUC₀₋₂₄ h; for ertugliflozin, the exposure ratio is adjusted for cross-species differences in protein binding (fraction unbound: 4.0% for rat and 6.4% for human); animal AUC values are for the last sampling occasion, and for the sexes combined; the human AUC for ertugliflozin was obtained with dosing at 15 mg QD, with BD administration at 7.5 mg seen to result in an equivalent plasma AUC₀₋₂₄ h.

Findings with combination treatment in rats were chiefly attributable to ertugliflozin. No novel or additive toxicity was seen. There were approximately additive increases in bodyweight-relative kidney, adrenal, liver and heart weights but microscopic correlates were either not increased in incidence or severity as compared to that with the single agents or absent. Histopathological changes involved the kidney (tubular dilatation), adrenal (hypertrophy in the zona glomerulosa), stomach (erosion, ulcer) and pancreas (zymogen depletion), attributable to ertugliflozin, and salivary glands (decreased cytoplasmic granules and hypertrophy of the duct epithelium), attributable to metformin.

Pregnancy classification

No embryofetal development studies have been performed with ertugliflozin and metformin in combination. The sponsor proposes Pregnancy Category C.²⁰ This is not supported. Assignment to Pregnancy Category D;²¹ is warranted instead due to concerns for potential irreversible effects on the developing kidney due to ertugliflozin. This is the more restrictive category for ertugliflozin (Category D recommended for Steglatiro) and metformin (C) as single agents.

Nonclinical summary, conclusions and recommendation

- The set of nonclinical studies performed with ertugliflozin and metformin in combination was suitably comprehensive.
- No nonclinical efficacy studies with the combination were submitted. Assessment of combination efficacy relies on clinical data only.
- Ertugliflozin and metformin do not share metabolic pathways. A modest pharmacokinetic interaction between the two agents was observed in rats (co-

administration of metformin acting to reduce ertugliflozin absorption/exposure) but no pharmacokinetic interaction was reported in humans.

- A Good Laboratory Practice compliant 3 month repeat-dose toxicity study revealed no novel or additive toxicity with ertugliflozin and metformin in combination in rats.
- There are no nonclinical objections to the registration of Segluromet for the proposed indication provided that the Product Information document is amended. Of particular note, the product should be assigned Pregnancy Category D (rather than Category C as the sponsor proposes) due to concerns for irreversible effects on the developing kidney caused by ertugliflozin.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachments 2 to 4 for the 3 submissions.

Steglatro

Clinical rationale

Only about half of patients with T2DM achieve glycaemic control as per treatment guidelines despite the availability of a broad array of AHAs. Furthermore, while new classes of AHA medications have been introduced over the last decade, the percentage of patients reaching glycaemic targets has not improved.²⁵

Some of the factors contributing to the low attainment of HbA1c goals are (1) patients with T2DM exhibit declining beta-cell function, which influences disease progression and leads to elevated HbA1c levels over time; (2) increased body weight leads to worsening insulin resistance; and (3) 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, (4) patient non-compliance.

The SGLT2 inhibitors are a new class of AHAs for T2DM therapy that when used as monotherapy or in combination with other AHAs are shown to improve glycaemic control, reduce body weight and lower blood pressure and also have tolerable safety profiles.

SGLT2 inhibitors have low rates of hypoglycaemia when used as monotherapy or in combinations with agents not associated with hypoglycaemia.²⁶ Due to the insulin independent mechanism of action, SGLT2 inhibitors may also provide durable glycaemic efficacy. Data from the cardiovascular outcome trial (CVOT) with the SGLT2 inhibitor empagliflozin;²⁷ demonstrated a significant reduction in major adverse cardiovascular (CV) events (MACE), as well as significant reductions in CV death and hospitalisation for worsening heart failure.²⁸

²⁵ Stark Casagrande S, et al. The prevalence of meeting HbA1c, blood pressure, and LDL goals among people with diabetes, 1988-2010. *Diabetes Care*. 2013; 36: 2271-2279.

²⁶ Cefalu WT, Riddle MC. SGLT2 inhibitors: the latest 'new kids on the block'! *Diabetes Care*. 2015; 38: 352-354.

²⁷ Zinman B, et al. Rationale, design, and baseline characteristics of a randomised, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME). *Cardiovasc Diabetol*. 2014; 13: 102.

²⁸ Fitchett D, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME trial. *Eur Heart J*. 2016; 37: 1526-1534.

Scope of the clinical dossier

The ertugliflozin clinical development program is intended to support the approval of ertugliflozin as a stand-alone product, as well as the ertugliflozin/metformin and ertugliflozin/sitagliptin FDCs, and consists of 29 Phase I studies, 2 Phase II studies and 9 Phase III studies.

Clinical pharmacology

There are 24 studies related to the pharmacokinetics (PK)/pharmacodynamics (PD) of ertugliflozin. Of these, 19 contain PK data and 10 contain data related to the PDs of ertugliflozin. One of the dedicated PK studies, Study PMAR-EQDD-B152a-DP4-403, represented a population PK (popPK) analysis, whereas 3 of the PD studies (Studies PMAR-EQDD-B152c-DP4-444; PMAR-EQDD-B152a-DP4-407 and ASR-EQDD-B152a-DP3-253), represented either population PD or dose-response analyses. All Phase I studies in support of this submission are complete.

Efficacy and safety

Pivotal phase III studies

One monotherapy, 5 combination therapy and 1 Phase III study in patients with moderate renal impairment (see table below).

Table 17: Overview of Phase III studies contributing to efficacy

| Protocol Number | Background AHA | A1C Criterion for Enrollment (Inclusive) | Study Duration/Design | Number of Randomized Subjects | Treatment Groups |
|---------------------------------------|---|--|---|-------------------------------|---|
| Monotherapy | | | | | |
| P003/1022 | None | 7.0-10.5% | 52 weeks Phase A: 26-week double-blind, placebo-controlled Phase B: 26-week active-controlled | 461 | 1) Placebo 2) Ertugliflozin 5 mg 3) Ertugliflozin 15 mg |
| Combination Therapy | | | | | |
| P007/1017 | Metformin | 7.0-10.5% | 104 weeks Phase A: 26-week double-blind, placebo-controlled Phase B: 78-week active-controlled | 621 | 1) Placebo 2) Ertugliflozin 5 mg 3) Ertugliflozin 15 mg |
| P002/1013 | Metformin | 7.0-9.0% | 104 weeks Phase A: 52-week double-blind, active-comparator-controlled Phase B: 52-week double-blind, active-comparator-controlled | 1326 | 1) Glimepiride 2) Ertugliflozin 5 mg 3) Ertugliflozin 15 mg |
| P005/1019 | Metformin | 7.5-11.0% | 52 weeks Phase A: 26-week double-blind, active-controlled Phase B: 26-week double-blind, active-controlled | 1233 | 1) Ertugliflozin 5 mg + Sitagliptin 100 mg 2) Ertugliflozin 15 mg + Sitagliptin 100 mg 3) Ertugliflozin 5 mg 4) Ertugliflozin 15 mg 5) Sitagliptin 100 mg |
| P006/1015 | Metformin and Sitagliptin | 7.0-10.5% | 52 weeks Phase A: 26-week double-blind, placebo-controlled Phase B: 26-week double-blind, placebo-controlled | 463 | 1) Placebo 2) Ertugliflozin 5 mg 3) Ertugliflozin 15 mg |
| P017/1047 | None | 8.0-10.5% | 26 weeks, double-blind, placebo-controlled | 291 | 1) Placebo 2) Ertugliflozin 5 mg + Sitagliptin 100 mg 3) Ertugliflozin 15 mg + Sitagliptin 100 mg |
| Special Populations | | | | | |
| P001/1016 (moderate renal impairment) | Allowable non-metformin AHA background therapy (including insulin and/or sulfonylureas) | 7.0-10.5% | 52 weeks Phase A: 26-week double-blind, placebo-controlled Phase B: 26-week double-blind, placebo-controlled | 468 | 1) Placebo 2) Ertugliflozin 5 mg 3) Ertugliflozin 15 mg |

Other studies

Phase II dose-finding studies

Phase II dose-finding studies P042/1004 and P016/1006 were submitted.

In addition, an integrated summary of efficacy and safety, and Phase I and II Safety analyses, were also submitted.

The Phase III studies investigated ertugliflozin as monotherapy or in combination with other AHAs across a broad and diverse population of subjects with T2DM. However, recruitment in 2 of the 9 Phase III Studies [a CVOT study (P004/1021) and an Asia Pacific regional study (P012/1045)] are ongoing and limited (CVOT) or no data (Asia Pacific)

from these studies are currently available. These studies will remain blinded until its completion according to agreement with the FDA and the EMA. Neither the detailed results of the CV meta-analysis report nor any other results from the CVOT study have been included in this submission. The CVOT study is estimated to complete in 2019, with the exact timing dependent on the accrual of CV events.

Paediatric data

There is no paediatric data in the current submission. The sponsor has submitted a PIP (Paediatric investigation plan) in the EU and the date on which the sponsors are first required to submit a report of a study conducted as part of the PIP is September 2026.

Good clinical practice

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

Pharmacokinetics

Studies providing pharmacokinetic information

The following table summarises the PK studies submitted.

Table 18: Submitted pharmacokinetic studies

| PK topic | Subtopic | Study ID | * |
|----------------------|---------------------------|-----------|--|
| PK in healthy adults | BE | P023/1037 | BE of the ertugliflozin 15 mg commercial image tablet and the 15 mg ertugliflozin dose studied in Phase III |
| | BA | P020/1043 | Absolute BA of ertugliflozin |
| | BA/BE | P011/1034 | Relative BA of ertugliflozin when administered as a tablet containing amorphous form versus tablets containing co-crystal |
| | Food | P024/1048 | The effect of food on the PKs of ertugliflozin 15 mg commercial image tablet. |
| | Escalating Single dose | P036/1001 | Ertugliflozin PKs following single oral doses ranging from 0.5 to 300 mg |
| | | P037/1002 | PKs of ertugliflozin and its metabolite M2 |
| | Mass balance | P038/1003 | Rate and extent of excretion of total radioactivity in urine and faeces, following a single oral dose of 25 mg [¹⁴ C]ertugliflozin |
| | Effect of timing of doses | P035/1051 | Equivalence of exposure following daily dosing with 5 mg QD versus BD. |
| PK in special | Target population§ | P040/1007 | Ertugliflozin PKs following administration QD and BD in adults with T2DM; and to |

| PK topic | Subtopic | Study ID | * |
|-------------------------------|--------------------------|-------------------------|---|
| populations | | | investigate the relationship between plasma concentrations and PD. |
| | Hepatic impairment | P014/1024 | Effect of moderate hepatic impairment on the ertugliflozin PKs following a single oral dose of 15 mg. |
| | Renal impairment | P009/1023 | Effect of renal impairment on ertugliflozin PKs and PDs following a single oral dose of 15 mg. |
| | Other special population | P041/1009 | Comparison of ertugliflozin PKs and PDs following single and multiple doses in healthy Japanese and Westerners. |
| PK interactions | Metformin | P019/1032 | Effect of 1000 mg metformin on the PKs of a 15 mg dose of ertugliflozin |
| | Sitagliptin | P022/1033 | Effect of 100 mg sitagliptin on the PKs of a 15 mg dose of ertugliflozin |
| | Simvastatin | P030/1036 | Effect of 40 mg simvastatin on the PKs of a 15 mg dose of ertugliflozin |
| | Rifampin | P021/1040 | Effect of steady-state rifampin on the PKs of a single 15 mg dose of ertugliflozin |
| | Glimepiride | P032/1044 | Effect of 1 mg glimepiride on the PKs of 15 mg ertugliflozin |
| Population PK analyses | Healthy and target pop | PMAR-EQDD-B152a-DP4-403 | To describe the structural PK model and quantify the population variability in ertugliflozin PKs |

* Indicates the primary PK aim of the study. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

One PK BA/BE study was excluded from consideration (Study P039/1005).

Evaluator's overall conclusions on pharmacokinetics

Overall, the conduct of the PK studies of ertugliflozin was satisfactory and was compliant with existing TGA guidelines, validated analytical methods were employed and the data analyses undertaken were appropriate.

ADME

- The absolute oral bioavailability of a single 15 mg dose of amorphous ertugliflozin was 104.7%. Following administration of a single oral 15 mg dose of the commercial image tablet the median T_{max} occurred 1 h after dosing and the mean $t_{1/2}$ was 12.6 h. A high-fat/high-calorie breakfast had no effect on the AUC_{inf} of a 15 mg dose and reduced C_{max} by 29%, which is unlikely to be clinically relevant. Hence, the proposed dosing with or without food is justified; however, dosing should be undertaken at the same time of day as indicated by the Phase III studies. The commercial image tablet (1 x 15 mg) and

Phase III tablets (administered as a 10 mg tablet + a 5 mg tablet) were bioequivalent, as were the tablets that contained the Phase III and amorphous formulations.

- Following administration of single 0.5 to 300 mg doses, ertugliflozin C_{max} and AUC_{inf} increased linearly with increasing dose. Similarly, following 14 days of treatment with QD doses ranging from 1 mg to 100 mg, mean C_{max} and AUC_{τ} values increased proportionally with dose and the relative accumulation ratios for the 1 mg, 5 mg, 25 mg and 100 mg doses were, 1.36, 1.25, 1.22 and 1.38, respectively.
- A study that compared the PKs of ertugliflozin following 6 days of dosing with either 7.5 mg BD or 15 mg QD identified that the AUC_{24} was similar following both treatments, whereas, C_{max} after the morning dose was higher following QD rather than BD dosing.
- The absolute volume of distribution (Vz/F) for a 15 mg dose of unlabelled ertugliflozin was 215.3 L. Plasma protein binding was high with in vitro studies indicating that 93.6% of a 2.3 μ M concentration being protein bound. In human whole blood, ertugliflozin distributed preferentially into plasma relative to red blood cells with a blood-to-plasma concentration ratio of 0.66.
- HPLC analysis identified 8 metabolites following dosing with ertugliflozin in humans. Glucuronidation, which accounts for approximately 86% of ertugliflozin metabolism, was identified as the major metabolic pathway and the glucuronides, M5a, M5b, M5c, and M6a, were identified as the major circulating metabolites. They were responsible for 12.2%, 4.1%, 24.1%, and 6.0% of total radioactivity in plasma, respectively. Following multiple QD doses of 1 to 100 mg of ertugliflozin, M2 exposure represented less than 2% of that of the parent compound. Following an oral dose of radioactive ertugliflozin, 50.2% of the radioactivity was recovered in the urine and 40.9% was recovered in the faeces. Ertugliflozin accounted for approximately 50% of the circulating radioactivity.
- The inter-individual variance on absolute clearance (CL/F) expressed as %CV was 32%, whereas, the residual error estimates were 38.7% for the Phase I studies and 83.6% for the Phase II and III studies.

Target population

- Population PK (popPK) analysis predicted that ertugliflozin CL/F was reduced by approximately 10% in patients with T2DM compared to healthy subjects; however, this difference is unlikely to be clinically relevant.
- Following QD administration of a range of ertugliflozin doses to subjects with T2DM manifesting inadequate glycaemic and blood pressure control ertugliflozin trough concentrations increased proportionally with increasing dose and appeared to be stable over time. Similarly, following QD doses to subjects with inadequately controlled T2DM who were receiving stable doses of metformin, ertugliflozin trough levels increased proportionally with increasing dose and appeared to be stable over time. It is important to note that none of the above Phase II dose ranging studies evaluated the proposed 15 mg dose of ertugliflozin.

Special populations

- The geometric mean ratios (GMRs) for AUC_{inf} and C_{max} in subjects with moderate hepatic impairment compared to subjects with normal hepatic function were approximately 12 and 22% lower, respectively.
- In subjects with normal renal function, either healthy or with T2DM, the AUC values for ertugliflozin were similar. In comparison to subjects with normal renal function,

AUC_{inf} values for subjects with T2DM and mild, moderate and severe renal impairment were 1.2, 1.4 and 1.7 fold higher, respectively.

- Following single doses of 1 mg, 5 mg and 25 mg in Japanese and Western males, the GMRs for AUC_{inf} ranged from 91.05% to 98.94%.

PopPK

- The popPK analysis identified that ertugliflozin plasma concentration data from patients with T2DM could be characterised by a 2-compartment model with lag time, first-order absorption, and first-order elimination. A number of significant covariates were identified for CL/F, AUC_t , relative bioavailability and ka ; however, the magnitude of the changes ($\leq 56\%$) induced by any one of the covariates could not be considered clinically relevant. By contrast, the covariate Asian race increased V_c/F by 112%.

Drug-drug interactions (DDIs)

- There was no DDI between ertugliflozin and metformin, sitagliptin or glimepiride.
- Although a single dose of simvastatin had no effect on ertugliflozin exposure, co-administration increased simvastatin AUC_{inf} by approximately 24%.
- Steady-state rifampin 600 mg QD reduced ertugliflozin AUC_{inf} and C_{max} following a single dose by approximately 39% and 15%, respectively.

Overall, the PK sections of the proposed PI accurately reflect the submitted data.

The following limitations have been identified in the PK data:

- The bioequivalence of the 5 mg commercial image tablet and 5 mg Phase III tablet has not been assessed.
- A limited number of DDI studies were undertaken with drugs that are known to interact with the pathways via which ertugliflozin is metabolised (for example, CYP3A4 inhibitors). Although ertugliflozin is in part metabolised by CYP3A4, no studies have examined the effects of a strong CYP3A inhibitor on ertugliflozin PKs.
- Pharmacokinetic interactions between ertugliflozin and other commonly administered drugs in this patient population such as diuretics, warfarin and digoxin and so on were not evaluated.

Pharmacodynamics

Studies providing pharmacodynamic information

A number of PD studies reported also contain PK data and have been previously summarised under Pharmacokinetics and therefore, they are not included in the table below.

Table 19: Submitted pharmacodynamic studies

| PD Topic | Subtopic | Study ID | * |
|-------------------------|------------------|---------------|---|
| Secondary Pharmacology | Healthy subjects | P010/10 25 | Effect of 100 mg ertugliflozin on QTc |
| Dose/response in target | Patients with | P042/10 04 | Ertugliflozin dose/response in patients with T2DM |

| PD Topic | Subtopic | Study ID | * |
|--|--------------------|-------------------------|--|
| population | T2DM | P016/10 06 | Dose-response of ertugliflozin QD in patients with T2DM on stable doses of metformin |
| Population PD and dose-response analyses | Patients with T2DM | PMAR-EQDD-B152c-DP4-444 | Model-based meta-analysis that attempts to quantify the relationship between urinary glucose excretion and HbA1c |
| | | PMAR-EQDD-B152a-DP4-407 | Ertugliflozin population dose-response analysis in subjects with T2DM |
| | | ASR-EQDD-B152a-DP3-253 | Characterisation of the relationship between UGE and ertugliflozin dose in subjects with T2DM |

* Indicates the primary PD aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

Evaluator's overall conclusions on pharmacodynamics

Mode of action ertugliflozin is an oral, selective inhibitor of SGLT2 that inhibits renal glucose reabsorption and results in increased UGE and reductions in plasma glucose and HbA1c in subjects with T2DM.

Primary PD in healthy subjects

For healthy subjects in the fasted state, increases in UGE₀₋₂₄ were dose dependent over the range of 0.5 mg to 30 mg. At doses \geq 30 mg UGE₀₋₂₄ plateaued between 58 and 65 grams/day. Following multiple QD doses of 1 mg to 100 mg ertugliflozin in otherwise healthy overweight or obese subjects the UGE increased and renal glucose reabsorption decreased dose dependently.

Primary PD in T2DM

Two Phase II studies (Studies P016/1006 and P042/1004) involving over 500 T2DM patients provided the main data to enable the dose-response modelling which was used to determine the doses to be evaluated in the Phase III studies. However, the proposed ertugliflozin dose of 15 mg QD was not evaluated in either of these studies and the choice of the 15 mg dose appears to be arbitrary in the materials provided regarding the modelling studies. The sponsors have been asked to provide further justification regarding the choice of the 15 mg dose for the pivotal studies.

PD modelling and analyses

For a typical patient with T2DM, MBMA predicted that following ertugliflozin doses of 2.5 mg BD or 5 mg QD and 7.5 mg QID or 15 mg BD there was little difference in effect of ertugliflozin on HbA1c.

Population dose-response analysis predicted that in a typical patient with T2DM on a background of metformin, the placebo-adjusted change from baseline in HbA1c following 26 weeks of treatment with either 5 mg or 15 mg ertugliflozin were -0.674% (-0.805% to -0.565%) and -0.735% (-0.869% to -0.626%), respectively. Whereas, for a typical patient with Stage 3a Chronic kidney disease (CKD) the predicted mean placebo-adjusted change

from baseline HbA1c response for the 5 mg and 15 mg ertugliflozin doses were -0.458% (-0.603% to -0.339%) and -0.518% (-0.681% to -0.393%), respectively.

Following 28 days of administration the predicted UGE (90% confidence interval (CI)) values for the 5 mg and 15 mg doses of ertugliflozin were 62.5 (54.9, 69.7) g/day and 68.9 (58.9, 78.7) g/day, respectively.

Rifampin co-administration induced a slight decrease in the ability of ertugliflozin to lower change from baseline HbA1c.

In patients with T2DM, UGE₀₋₂₄ was dose dependent with 70.4 g excreted following the 2 mg dose and 80.5 g following the 4 mg dose. By contrast, weighted mean plasma glucose over 24 h was similar following both the 2 mg (175.6 mg/dL) and 4 mg (170.4 mg/dL) doses.

Secondary pharmacodynamic effects

Healthy subjects

Unlike 400 mg moxifloxacin, 100 mg ertugliflozin had no effect on QTc interval in healthy subjects. Following multiple QD doses ranging from 1 mg to 100 mg to otherwise healthy overweight or obese subjects, ertugliflozin had no effect on serum sodium, potassium and calcium levels or magnesium and calcium excretion on either Day 1 or Day 14 of treatment and no clear dose related effect was identified for serum magnesium levels or iPTH AUC.

T2DM

Following co-administration of a range of oral doses of ertugliflozin and 12.5 mg QD hydrochlorothiazide (HCTZ) for 4 weeks in patients with T2DM, ertugliflozin had a mild diuretic effect. By contrast it had no effect on 24 h urinary aldosterone, urinary sodium or urinary potassium. In contrast to sitagliptin, ertugliflozin induced minor bone resorption, as indicated by increased levels of serum CTX1 and urinary NTX-1; however, these effects did not appear to be dose dependent. By contrast, no effects on markers of bone formation were identified.

Time course of PD effects: UGE₀₋₂₄ was similar following BD and QD doses of ertugliflozin, following the equivalent total daily dose, in healthy subjects and in subjects with T2DM.

The sponsor states the following in regards to the selection of doses for the Phase III studies:

Since single oral doses as high as 300 mg, multiple doses of 100 mg QD up to 14 days and 25 mg QD up to 12 weeks were associated with an acceptable safety profile in the Phase I and Phase II studies, the key drivers for Phase III dose selection were the dose-response relationships for the change from baseline in HbA1c, FPG, and body weight in T2DM subjects from the 12-week Phase II dose-ranging study (Study P016/1006). The relationship between change from baseline in HbA1c or FPG or body weight at Week 12 versus dose was described by a maximum effect (E_{max}) model that included dose as a continuous variable. Phase III dose selection was also supported by dose-response modelling of the PD marker, 24 hour UGE, in subjects with T2DM from the 4 week Phase II Study P042/1004.

The two Phase II studies mentioned (Studies P016/1006 and P042/1004) examined the following doses of ertugliflozin: 1 mg, 5 mg, 10 mg and 25 mg. Therefore as neither of the dose ranging/dose response Phase II studies directly examined the 15 mg dose and its choice appears to be arbitrary in the materials provided regarding the modelling studies, it is unclear why the 15 mg dose was chosen for the Phase III and additional Phase I trials.

Dosage selection for the pivotal studies

Pharmacokinetic and pharmacodynamic dose finding studies

Oral doses of ertugliflozin as high as 300 mg (single dose), 100 mg QD (up to 14 days), and 25 mg QD (up to 12 weeks) demonstrated appropriate safety and tolerability in the early Phase I and 2 studies. The selection of the 5 mg and 15 mg doses for the Phase III studies was also supported by the safety and tolerability profile for ertugliflozin in Phase I and II clinical studies up to 12 weeks in duration. When accounting for species differences in protein binding the highest Phase III dose of 15 mg QD represented an exposure approximately 12 fold (for C_{max} (maximum concentration)) and 11 fold (for area under curve over 24 hours (AUC_{0-24})) lower than exposure at the no observed adverse effect level (NOAEL) in the 6 month toxicology study in the most sensitive species (rat).

Phase II dose finding studies

The Phase II Study P016/1006 assessed dose-response following 12 weeks of treatment with ertugliflozin (1 mg, 5 mg, 10 mg and 25 mg QD) and sitagliptin 100 mg QD in 328 subjects with inadequately controlled T2DM who were receiving stable doses of metformin. Results from this study confirmed the minimally efficacious dose as 1 mg with the 2 highest doses (10 mg and 25 mg) offering little incremental increase in efficacy (that is, effect on HbA1c, Fasting plasma glucose (FPG) and body weight) relative to the 5 mg once-daily dose. The efficacy observed with the 5 mg QD represents greater than effective dose in 80% of subjects (ED80) for the endpoints of HbA1c, FPG and body weight. In addition to effect on glycaemic control and body weight, ertugliflozin was observed to result in a clinically meaningful decline in seated trough blood pressure. There was no overall dose related increase in the frequency of adverse events (AEs) across the 25 fold range of doses evaluated (1 mg QD to 25 mg QD).

Another Phase II Study P042/1004 evaluated dose response (in terms of reduction in systolic blood pressure (SBP), UGE and FPG) following 4 weeks treatment with ertugliflozin doses (1 mg, 5 mg or 25 mg) and HCTZ in 193 subjects with T2DM and inadequate glycaemic and blood pressure control. Consistent with the mechanism of ertugliflozin, there was a statistically significant increase in UGE_{24h} and decrease in FPG at Week 4 for all 3 dose groups of ertugliflozin versus placebo although the 25 mg dose did not lead to much greater increase in UGE or decrease in FPG compared to the 5 mg dose. These Phase II studies have been discussed in detail in Attachment 2. The above two Phase II studies provided the main data to enable the dose response modelling which was used to determine the dose selection for the pivotal Phase III studies.

However, the proposed ertugliflozin dose of 15 mg QD was not evaluated in either of these studies and the choice of the 15 mg dose appears to be arbitrary in the materials provided regarding the modelling studies. The sponsors have been asked to provide further justification regarding the choice of the 15 mg dose for the pivotal studies.

Phase III pivotal studies investigating more than one dose regimen

Ertugliflozin doses of 5 mg and 15 mg QD were evaluated in all seven Phase III studies. Both ertugliflozin 5 mg and 15 mg demonstrated clinical efficacy in the Phase III studies. The recommended starting dose is 5 mg and the 15 mg dose provides incremental glycaemic efficacy compared to the 5 mg dose. Although the studies were not powered for or designed to detect between dose differences, the effects on HbA1c, FPG, and 2 h Post-prandial glucose (PPG) were generally greater for 15 mg versus 5 mg ertugliflozin across the Phase III studies.

Evaluator's conclusions on dose finding for the pivotal studies

The doses of ertugliflozin evaluated in the Phase III clinical studies were 5 mg and 15 mg once daily (QD). Since oral doses of ertugliflozin as high as 300 mg (single dose), 100 mg

QD (up to 14 days) and 25 mg QD (up to 12 weeks) were safe and well tolerated in Phase I/II studies, dose selection was based on dose response modelling of efficacy endpoints (HbA1c, FPG, body weight) from Study P016/B1521006 (12 week Phase II dose ranging study) as well as UGE_{24h} (mechanism biomarker) in T2DM subjects from Study P042/B1521004 (4 week Phase II dose-ranging study). The sponsors have stated that for these endpoints, the 5 mg and 15 mg doses consistently elicited a response that was > 80% and > 90% of the maximum response, respectively. However, it is not clear how the results summarising the '*Estimated percent maximum response for various endpoints*' were calculated. Furthermore, it is important to note that neither of the Phase II studies evaluated the proposed 15 mg QD dose of ertugliflozin and the sponsors have been asked to provide further clarification regarding choice of the 15 mg QD dose for the pivotal Phase III studies.

Efficacy

Studies providing evaluable efficacy data

The Phase III program included 7 pivotal studies to support the efficacy of ertugliflozin as monotherapy and combination therapy. All Phase III studies evaluated 2 doses of ertugliflozin (15 mg and 5 mg QD).

Monotherapy

- Study P003/1022: A Phase III, randomised, double blind, placebo controlled, 26 week multicentre study with a 26 week extension to evaluate the efficacy and safety of ertugliflozin monotherapy in the treatment of subjects with T2DM and inadequate glycaemic control despite diet and exercise.
- Combination with other AHAs

Add-on to metformin

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

Add-on to metformin plus sitagliptin

- Study P006/1015: Phase III, multicentre, randomised, double blind, placebo controlled, parallel group clinical trial to evaluate the safety and efficacy of ertugliflozin (MK- 8835/PF-04971729) in the treatment of subjects with T2DM who have inadequate glycaemic control on metformin and sitagliptin.
- Co-administration with sitagliptin in subjects on diet and exercise alone.
- Study P017/1047: A Phase III, randomised, double blind, placebo controlled, parallel group, multicentre clinical trial to evaluate the efficacy and safety of the initial combination of ertugliflozin (MK-8835/PF-04971729) with sitagliptin in the

treatment of subjects with T2DM with inadequate glycaemic control on diet and exercise.

Studies in special populations

- Study P001/1016: A Phase III, multicentre, randomised, double blind, placebo controlled clinical trial to evaluate the efficacy and safety of ertugliflozin (MK-8835/PF-04971729) in subjects with T2DM with Stage 3 chronic kidney disease who have inadequate glycaemic control on background anti-hyperglycaemic therapy.

Evaluator's conclusions on clinical efficacy

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

A total of 4863 subjects were randomly assigned to study medication: 3413 subjects were randomly assigned to receive ertugliflozin (co-administered with sitagliptin in Studies P005/1019 and P017/1047), 766 subjects were randomly assigned to receive placebo, and 684 subjects were randomly assigned to receive active comparators (sitagliptin, glimepiride). With the exception of the moderate renal impairment study (Study P001/1016), the mean age of the subjects was similar across the Phase III studies, ranging from 55.1 to 59.1 years and the mean body mass index (BMI) was similar across all studies, ranging from 30.8 to 33.0 kg/m². The mean baseline HbA1c ranged from 7.8% to 8.9% and mean FPG ranged from 8.8 to 11.0 mmol/L in these studies. The subjects in the co-administration of ertugliflozin and sitagliptin study (Study P017/1047) had the highest baseline HbA1c and FPG. With the exception of Study P001/1016, the mean baseline estimated glomerular filtration rate (eGFR) was similar across the Phase III studies, ranging from 87.2 to 92.4 mL/min/1.73 m². The mean duration of T2DM ranged from 5.0 years in Study P003/1022 to 14.2 years in Study P001/1016. The proportion of subjects with microvascular complications was lowest in Study P003/1022 compared to the other studies; while the proportion of subjects with microvascular complications was highest in Study P001/1016. With the exception of Study P001/1016, the AHA usage at randomisation varied from none to 2 agents (metformin and sitagliptin) depending on the study design. Across the Phase III studies, a high proportion of subjects were receiving concomitant hypertension medication (ranging from 47.8% to 94.0%) and anti-dyslipidaemia medication (ranging from 32.0% to 77.5%). The proportion of subjects with a history of CV disease was lowest in Study P003/1022 compared to the other studies; while the proportion of subjects with a history of CV disease was highest in Study P001/1016. Overall, patients evaluated in the 7 Phase III studies were representative of the target population for ertugliflozin monotherapy and combination therapy.

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

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

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

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

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

Second line therapy as add-on to metformin

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

- Both ertugliflozin 15 mg and 5 mg produced robust, statistically and clinically significant greater reductions from baseline to Week 26 in HbA1c compared with placebo. Other measures of glycaemia also showed significant improvements with ertugliflozin, including reducing FPG and increasing the proportion of subjects reaching an HbA1c $< 7\%$.
- Ertugliflozin 5 mg and 15 mg treatment also produced significantly greater reductions in body weight and systolic and diastolic blood pressure.
- Although study was not designed to compare the two doses of ertugliflozin, the 15 mg dose showed greater improvements in HbA1c, FPG and proportion of subjects with HbA1c $< 7\%$ compared with the 5 mg dose.
- The multicentre, randomised, double blind, active-controlled, parallel group clinical Study P002/1013 compared the efficacy and safety of ertugliflozin to glimepiride (median dose of 3 mg) in 1,326 subjects with T2DM and inadequate glycaemic control on a stable dose of metformin monotherapy (≥ 1500 mg/day).
- Ertugliflozin 15 mg met the pre-specified criteria for non-inferiority to glimepiride (where the mean glimepiride dose was 3.0 mg daily) for HbA1c reduction at 52 weeks of treatment. A clinically meaningful reduction from baseline in HbA1c at Week 52 was observed with the 5 mg dose of ertugliflozin; however, this did not meet the non-inferiority requirements relative to glimepiride.
- The HbA1c reductions observed in both ertugliflozin groups were evident by Week 6 and glycaemic efficacy was durable through Week 52. Although the Week 52 HbA1c reductions in the ertugliflozin groups were numerically smaller relative to glimepiride, FPG was numerically lower with both ertugliflozin doses compared with glimepiride at Week 52.
- Ertugliflozin (5 mg and 15 mg) also led to greater reductions in body weight and SBP compared to glimepiride; bodyweight for 15 mg was formally tested and test was successful.
- The coefficient of durability (COD) (of the HbA1c response between Week 26 and Week 52) was used to assess durability of treatment with ertugliflozin after reaching peak efficacy; the COD was numerically higher in the glimepiride group compared with the ertugliflozin 5 mg and 15 mg groups indicating there was a more rapid loss of HbA1c response in the glimepiride group than in the ertugliflozin groups after Week 26.

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

- Treatment with the initial combination of ertugliflozin (5 mg QD or 15 mg QD) and sitagliptin 100 mg QD for 26 weeks provided clinically meaningful reductions from

baseline in HbA1c, FPG, and 2 h post-prandial glucose (PPG) and resulted in greater proportion of subjects with HbA1c < 7% relative to placebo.

- The initial ertugliflozin+sitagliptin combination therapy also led to significant reduction in body weight and sitting SBP relative to placebo.
- Although this study was not designed to formally compare the 5 mg and 15 mg ertugliflozin doses, there were numerically greater reductions in HbA1c, FPG, 2 h PMG, body weight and sitting SBP with the ertugliflozin 15 mg (E15)/sitagliptin 100 mg (S100) combination relative to the ertugliflozin 5 mg (E5)/S100 combination.

Ertugliflozin (5 mg and 15 mg QD) in combination with other AHAs: third line of therapy

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

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

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

- The least-squares (LS) mean reductions at Week 26 were robust, clinically meaningful and significantly greater in both combination groups (E15/S100 and E5/S100) relative to the individual component treatment groups at corresponding dose strengths.
- About 50% of the subjects achieved glycaemic goal (HbA1c < 7%) with combination treatment, relative to treatment with the individual components (about 26 to 33%).
- Marked reductions in FPG were also observed in all treatment groups, with significantly greater reductions in the combination groups relative to the individual component treatment groups at corresponding dose strengths. The LS mean reductions from baseline in 2 h PPG (assessed in a subset of subjects who participated in a mixed-meal tolerance tests (MMTT) at Week 26 were similar across the treatment groups, except for the E15/S100 group, where larger reductions were observed relative to the individual component treatments at corresponding dose strengths.
- The number of subjects who required glycaemic rescue therapy was lower in the combination therapy groups with no subjects in the E15/S100 requiring rescue therapy.
- Reductions in body weight and sitting SBP were observed in the 4 ertugliflozin treated groups.
- No meaningful difference was observed between the 2 co-administration groups (E15/S100 and E5/S100) for HbA1c related endpoints, although there was a trend toward better efficacy for E15/S100 relative to E5/S100 for FPG and 2 h PPG.

However, interpretation was limited as this study was not powered to detect differences between the 2 combination groups.

Efficacy in special populations

In the moderate renal impairment study (Study P001/1016) involving 468 T2DM patients, the within group change from baseline in HbA1c in the ertugliflozin groups was smaller than in other studies, as expected. However, interpretation was confounded by the placebo effect (due to use of metformin) and a post hoc analysis excluding subjects who had a positive metformin assay result showed that ertugliflozin 15 mg provides greater reductions in HbA1c than placebo (based on the nominal 95% CI) in subjects with Stage 3 CKD (overall cohort). Very similar results were observed in subjects with Stage 3A CKD. However, there were no significant differences between treatment groups for change from baseline in body weight, FPG, sitting SBP and proportion of subjects with HbA1c < 7% and no post hoc analysis was done for these parameters. Unlike in the Overall Cohort and Stage 3A CKD stratum, there was no early or sustained separation of the ertugliflozin and placebo groups excluding data from subjects with a positive metformin assay in the Stage 3B CKD stratum had little impact on HbA1c reductions with no notable differences in any treatment group.

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

Limitations of efficacy data

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

Safety

Studies providing evaluable safety data

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

Patient exposure

Overall 6,068 subjects were treated across the Phase I to Phase III studies of which 4,418 were exposed to ertugliflozin.

In the placebo pool 1,544 subjects were randomised and received at least 1 dose of study medication in the 3 studies. The mean observation period on study medication through 26 weeks was not notably different in the ertugliflozin 5 mg and 15 mg groups (174.8 and 172.6 days, respectively) relative to the placebo group (170.2 days).

Treatment compliance was similar and high across groups in the placebo pool and majority of subjects in all groups (99.0%) reported taking > 75% of study medication. The proportions of subjects who discontinued study medication were not notably different in the ertugliflozin 5 mg and 15 mg groups and the all ertugliflozin group relative to the placebo group. The most common reasons for discontinuation from study medication in the total group were discontinuation due to an AE and withdrawal by subject. Of the 1,545 randomised subjects, 94.2% completed Phase A while on study medication or after premature discontinuation of study medication. The proportion of subjects who completed Phase A was similar across the treatment groups with withdrawal by subject and lost to follow-up being most common reasons for study discontinuation.

Baseline demographic and anthropometric characteristics were similar between groups. The mean age, BMI and eGFR was 57.3 years, 31.5 kg/m² and 88.9 mL/min/1.73 m², respectively. The majority of subjects in the placebo pool were White (73.4%); 15.1% were Asian, and 6.6% were Black or African American. There were slightly more males (52.6%) than females (47.4%). The mean duration of T2DM for subjects in the placebo pool was 7.5 years. Baseline HbA1c and FPG were similar between groups, with a mean baseline HbA1c of 8.1% and mean FPG of (9.6 mmol/L) across all groups. Diabetic microvascular complications were included in the medical history of 19.4% of all subjects. Most subjects (70.2%) were on an AHA at the time of randomisation, reflecting the use of background AHA therapy in the designs of 2 of the 3 studies in the placebo pool, with the most common AHA therapy being metformin (70.1%), followed by DPP-4 inhibitors (29.9%). More subjects were on only 1 AHA therapy at the time of randomisation (40.3%), while 30.1% were on 2 AHA therapies. The proportion of subjects with a history of CV disease was similar between groups in the overall pooled population, 10.6% had a history of coronary artery disease, 2.1% had a history of peripheral vascular disease, 1.4% had a history of heart failure and 2.8% had a history of cerebrovascular disease. The proportion of subjects with a history of hypertension was high (68.1% of all subjects) and was similar between groups; the proportion of subjects with a history of hyperlipidaemia was also high (65.3%) and similar between groups.

The Broad Pool includes data through completion of Study P017/1047 and includes Phase A data and Phase B data up to the longitudinal data analysis (LDA) date for the other 6 studies. In the Broad Pool, 4,859 subjects were randomised and received at least 1 dose of study medication in the 7 studies. Of the 3,409 subjects who received at least 1 dose of ertugliflozin (5 or 15 mg), 3,128, 2,575 and 371 subjects received treatment with any dose

of ertugliflozin for at least 25 weeks, 50 weeks, and 76 weeks, respectively. The mean duration of treatment with ertugliflozin was 355.7 days. A total of 1,450 subjects were randomised to the non-ertugliflozin group and 867 of these subjects received treatment for at least 50 weeks, with a mean duration of 354.9 days. Treatment compliance was similar and high across groups in the Broad Pool. The majority of subjects in all groups (98.8%) reported taking > 75% of study medication. More subjects were randomised and treated in the ertugliflozin 5 mg and 15 mg groups relative to the non-ertugliflozin group. Of the 4864 randomised subjects, 48.1% of subjects completed the study; most studies were ongoing in Phase B at the time of the data cut-off. The proportion of subjects who completed the study was numerically higher in the ertugliflozin 5 mg and 15 mg groups relative to the non-ertugliflozin group. The proportion of subjects who discontinued study medication was not notably different in the ertugliflozin 5 mg and 15 mg groups and the all ertugliflozin group relative to the non-ertugliflozin group. The most common reasons for discontinuation from study medication in all groups were withdrawal by subject, lost to follow-up, hyperglycaemia and discontinuation due to an AE with no notable differences between the groups.

In the Broad pool, the mean age was 57.8 years, 25.8% of subjects were > 65 years, and 4.5% were > 75 years of age. The mean BMI and eGFR was 31.7 kg/m² and 85.3 mL/min/1.73 m² respectively; 47.0% had an eGFR in the range of 60 to < 90 mL/min/1.73 m² and 41.2% of subjects had an eGFR > 90 mL/min/1.73 m². The majority of subjects were White (76.8%), 13.3% were Asian, and 5.0% were Black or African American; there were slightly more males (51.8%) than females (48.2%). The mean duration of T2DM for subjects Broad Pool was 7.9 years and numerically higher proportion of subjects (38.8%) had T2DM duration of < 5 years, relative to those with duration of T2DM from 5 to < 10 years (31.2%), or > 10 years (30.0%). Baseline HbA1c and FPG were similar between groups, the mean baseline HbA1c was 8.2% and the mean FPG was 171.4 mg/dL (9.5 mmol/L) across all groups. Diabetic microvascular complications were included in the medical history of 26.6% of all subjects. Most subjects (83.9%) were on an AHA at the time of randomisation, with the most common AHA therapy being metformin (74.9%), followed by DPP-4 inhibitors (10.9%), insulin (5.5%) and sulfonylurea (4.3%). Most subjects were on 1 AHA therapy at the time of randomisation (71.7%), while 12.0% were on 2 AHA therapies. The proportion of subjects with a history of CV disease was similar between groups; in the overall pooled population, 14.3% had a history of coronary artery disease, 3.3% had a history of peripheral vascular disease, 4.0% had a history of heart failure, and 4.8% had a history of cerebrovascular disease. The proportion of subjects with a history of hypertension was high (69.7%) and similar between groups. Similarly, the proportion of subjects with a history of hyperlipidaemia was high (62.1%) and similar between groups.

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

Evaluator's overall conclusions on clinical safety

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

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

Comprehensive evaluation of safety and tolerability was performed in 6,068 subjects in Phase I, II and III studies and 4,418 subjects were exposed to ertugliflozin.

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

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

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

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

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

Among the potential or established SGLT2 class related safety topics, ertugliflozin treatment was associated with an increased incidence of AEs for osmotic diuresis; volume depletion in subjects with moderate renal impairment, the elderly and those using

diuretics. In the general population, small transient reductions in eGFR were observed that generally resolved by Week 26. In subjects with moderate renal impairment, the reductions in eGFR were slightly greater (approximately 1 mL/min/1.73 m²) compared to the general population and there was not a complete return to baseline at Week 26. The moderate renal impairment study is continuing to Week 52 and will measure eGFR 2 weeks following discontinuation of study medication. The risk of renal related AEs was increased with ertugliflozin treatment in subjects with moderate renal impairment.

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

Ketoacidosis was confirmed as certain or possible in 3 ertugliflozin subjects compared to none in the non-ertugliflozin group. Patients treated with ertugliflozin who present with signs and symptoms consistent with severe metabolic acidosis should be promptly assessed for ketoacidosis regardless of presenting blood glucose levels as ketoacidosis associated with SGLT2 inhibitors may be present even if blood glucose levels are < 250 mg/dL (14 mmol/L).

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

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

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

Treatment with ertugliflozin did not result in a clinically meaningful increase in the risk of hypoglycaemia. Proportions of subjects with documented and severe hypoglycaemia were low across all groups. The incidence of hypoglycaemia may be increased when ertugliflozin is used in combination with insulin and/or insulin secretagogues.

Approximately 90% of subjects in the moderate renal impairment study (Study P001/1016) used insulin and/or sulfonylurea as background therapy. As such, the incidence of hypoglycaemia in this study was higher relative to the other Phase III studies, yet was similar across the treatment groups.

There was no evidence for increased risk of pancreatitis, hepatic injury, hypersensitivity, or venous thromboembolic events with ertugliflozin use. The overall incidence of malignancies was low in all groups but was more frequent in the ertugliflozin groups relative to the non-ertugliflozin group. Eleven out of 31 ertugliflozin treated subjects with

a malignancy had the malignancy detected within the first 6 months of randomisation, with several events diagnosed within 1 month following randomisation. There were no specific types of malignancies for which there was any notable imbalance. The more frequent occurrence of events in ertugliflozin treated subjects reflected a wide range of unrelated types of neoplasm, both solid and haematological, with no notable temporal pattern of onset.

Regarding laboratory parameters, small increases in haemoglobin and phosphate relative to placebo was observed in the ertugliflozin 5 mg and 15 mg groups. In both the Broad Pool and in subjects with moderate renal impairment, there was no evidence of an increased risk for hyperkalaemia either in the evaluation of mean changes in potassium over time or by the pre-defined limit of change (PDLC) analyses.

Limitations

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

Steglatro benefit-risk assessment

Second round assessment of benefits

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

Table 20: First round assessment of benefits

| Indication | |
|---|--|
| Benefits | Strengths and Uncertainties |
| Evidence to support use as monotherapy provided by pivotal Phase III placebo-controlled Study P003/1022 in 461 adult T2DM patients who had inadequate glycaemic control on diet and exercise. Ertugliflozin 5 mg and 15 mg once daily provided statistically significant and clinically relevant improvements in glycaemic control (HbA1c, FPG and proportion of subjects with HbA1c <7%) and body weight at Week 26 compared with placebo. | Only data up to 26 weeks submitted. Phase B results (Weeks 26 to 52) to be provided when available to ascertain long term efficacy of ertugliflozin as monotherapy in treatment of T2DM. |
| Evidence to support use of ertugliflozin (as adjunct to diet and exercise) with other anti-hyperglycaemic agents; mainly metformin and DPP-4 inhibitors (sitagliptin). | Ertugliflozin in combination with sulphonylurea, insulin and GLP-1 analogues was not evaluated. Results of long term maintenance of efficacy of |

| Indication | |
|--|---|
| Benefits | Strengths and Uncertainties |
| Ertugliflozin 15 mg and 5 mg, as add-on to metformin (alone or in combination with sitagliptin) provides clinically meaningful improvements in glycaemic control (HbA1c, proportion of subjects with HbA1c < 7.0%, FPG, 2 h PPG), as well as body weight reduction and SBP reduction in subjects with T2DM. | ertugliflozin in combination with other AHAs was not provided in this submission although data from the ongoing Phase B of the pivotal studies should help to address this. |
| Ertugliflozin 15 mg plus metformin provides non-inferior HbA1c reduction compared to glimepiride plus metformin. Ertugliflozin 5 mg and 15 mg once daily was associated with greater reduction in FPG, body weight and SBP compared with glimepiride. Significantly lower incidence of hypoglycaemia with ertugliflozin compared with glimepiride. | Non-inferiority of ertugliflozin 5 mg and glimepiride was not established. Although these differences were not tested formally since prior hypothesis in the ordered sequence were not met. |
| Simple once daily oral dosing. | |
| Insulin independent mechanism of action. | Efficacy of ertugliflozin is dependent on renal function. |
| Overall, ertugliflozin 5 mg and 15 mg QD was safe and well tolerated | Dose dependent increase in incidence of genital mycotic infections and elevated LDL-C. |

Second round assessment of risks

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

Table 21: Second round assessment of benefits

| Risks | Strengths and Uncertainties |
|---|---|
| Incidence of deaths was low, but numerically higher in ertugliflozin groups. | Deaths occurred in 10 (0.6%), 8 (0.5%) and 3 (0.2%) of subjects in ertugliflozin 5 mg, 15 mg and non-ertugliflozin groups, respectively; majority of fatal events were related to CV deaths. |
| The CV safety data (from 7 Phase III studies in nearly 5,000 subjects) included in the original submission and the 4 month SUR (provided in the sponsor's response to the TGA's request for further information) were based on preferred terms from investigator AE reporting and do not reflect the results of adjudication which remain firewalled. | The sponsor also conducted a CVMA of adjudicated, confirmed CV events from the Phase II/III studies in the submission and from the CV outcome study (P004/1021) which is ongoing and not included in the dossier. Access to the CVMA data including Study P004/1021 data and results is governed by a Data Access Plan and limited to a small firewalled team as was agreed with US FDA and discussed with the CHMP before submission to the EMA. |
| Increased risk of lower limb amputations; of | 12 subjects with non-traumatic limb |

| Risks | Strengths and Uncertainties |
|---|--|
| the 10 reported amputations in the Broad Pool with highest incidence in the ertugliflozin 15 mg group; 8 subjects in the ertugliflozin 15 mg group and 1 subject each in the ertugliflozin and non ertugliflozin groups. This is especially important in light of current findings of increased risk of lower limb amputations associated with another SGLT2 inhibitor canagliflozin. | amputation and peripheral revascularisation reported in the Broad Pool; all 12 subjects had baseline risk factors for amputation (for example, peripheral neuropathy, peripheral artery disease) or peripheral revascularisation (for example, hypertension and hyperlipidaemia). |
| Reduction in eGFR observed following ertugliflozin treatment with greater reduction in patients with moderate renal impairment. Incidence of renal related AEs also higher. | |
| The incidence of volume depletion events was numerically higher in both ertugliflozin groups relative to the non ertugliflozin group especially among subjects aged > 65 years, with renal impairment and those on diuretics. | Incidence of volume depletion AEs in subgroup of subjects aged > 65 years was 2.2%, 2.6% and 1.1% in the ertugliflozin 5 mg, 15 mg and non ertugliflozin groups, respectively. |
| The incidence of genital mycotic infections was higher in the ertugliflozin groups than in the non ertugliflozin groups in both men and women. In female subjects, there was a modest dose relationship. | Incidence of complicated infections was low (< 1%) but still higher in the ertugliflozin groups. |
| Lack of evaluation of efficacy/ safety of ertugliflozin in combination with insulin, SUs and GLP-1 analogues. | |
| None of the Phase II dose ranging studies evaluated the proposed 15 mg dose of ertugliflozin. | Data from the 2 Phase II dose ranging studies was used for the model based analysis which suggested that a 15 mg dose would provide additional HbA1c lowering relative to 5 mg, and that no further efficacy was to be expected from the 25 mg dose. |
| Lack of evidence to support long term maintenance of efficacy of ertugliflozin beyond 26 weeks with exception of one study (P002/1013) comparing ertugliflozin with glimepiride in patients with inadequate glycaemic control on metformin monotherapy which provided data up to 52 weeks. | Phase B of most of the studies (except the initial combination therapy study (P017/1047) with ertugliflozin+sitagliptin) should provide data on long term efficacy and these results should be made available for evaluation in order to confirm long term maintenance of efficacy in proposed indication. |

Second round assessment of benefit-risk balance

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

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

Second round recommendation regarding authorisation

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

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

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

Approval for the above indication is subject to the following:

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

Steglujan

Clinical rationale

For a summary of ertugliflozin please see Clinical findings Steglatro and Product background above.

Sitagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones 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 beta-cells by intracellular signalling pathways involving cyclic adenosine monophosphate (cAMP). GLP-1 also lowers glucagon secretion from pancreatic beta-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.

The ertugliflozin/sitagliptin FDC combines 2 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.

Scope of the clinical dossier

Clinical pharmacology

The current submission comprises five new Phase I PK studies, none of which include PD data. Four of the studies examine the BE between the various strengths of the FDC proposed for marketing and the corresponding free combination. In addition, a single study examined the effect of a high-fat/high-calorie breakfast on the PKs of the active

components of the FDC tablets. No new popPK or modelling studies were undertaken as part of the present submission.

Efficacy and safety

Three of the seven Phase III studies (submitted for the ertugliflozin submission) were conducted in support of the ertugliflozin/sitagliptin submission; including 1 active controlled factorial study (Study P005/1019) and 2 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.

Data from the 3 individual studies were not pooled for analysis due to differences in study designs.

No Phase II studies of ertugliflozin in combination with sitagliptin were conducted.

The three Phase III studies supporting this FDC were conducted using ertugliflozin and sitagliptin administered as separate tablets, and bridging to the FDC formulation is therefore provided via BE studies comparing the FDC to co-administration of individual components. The only Phase II dose response studies were those submitted in the ertugliflozin dossier (P016/1006 and P042/1004) which were discussed in the Steglatiro evaluation report (see above and Attachment 2).

Paediatric data

There is no paediatric data in the current submission. The sponsors have submitted a PIP (Paediatric investigation plan) in the EU and the date on which the sponsors are first required to submit a report of a study conducted as part of the PIP is September 2026.

Good clinical practice

All studies were conducted in accordance with Guidelines for Good Clinical Practice (GCP) and the Declaration of Helsinki.

Pharmacokinetics

Studies providing pharmacokinetic information

The following table summarises the PK studies submitted.

Table 22: Submitted pharmacokinetic studies

| PK topic | Subtopic | Study ID | * |
|----------------------|--------------------------------|-----------|---|
| PK in healthy adults | Bioequivalence† Single dose | P025/1038 | BE of ertugliflozin 15 mg/sitagliptin 100 mg FDC and the free combination |
| | | P044/1053 | BE of ertugliflozin 15 mg/sitagliptin 50 mg FDC and the free combination |
| | | P048/1056 | BE of ertugliflozin 5 mg/sitagliptin 100 mg FDC tablet and the free combination |
| | | P049/1057 | BE of ertugliflozin 5 mg/sitagliptin 50 mg FDC tablet and the free combination |

| PK topic | Subtopic | Study ID | * |
|----------|-------------|-----------|--|
| | Food effect | P026/1050 | Relative BA of ertugliflozin 15 mg/sitagliptin 100 mg FDC tablet under fasted and fed conditions |

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

Evaluator's overall conclusions on pharmacokinetics

The current submission contains four previously unevaluated studies, which examine the BE between the various strengths of the FDC proposed for marketing and the corresponding free combination. In addition, a single new study examined the effect of a high fat/high calorie breakfast on the PKs of the active components of the FDC tablets.

In regards to the tablets containing a single active component, the PKs of sitagliptin are well-established and the PKs of ertugliflozin are described in detail in the concurrent TGA submission (Attachment 2).

Overall, the conduct of the previously unevaluated studies was satisfactory and was compliant with existing TGA guidelines, validated analytical methods were employed and the data analyses undertaken were appropriate.

Each of the proposed dose strengths of the ertugliflozin/sitagliptin FDC tablets were bioequivalent with their matching dose of the free combination of ertugliflozin and sitagliptin tablets given in combination.

Compared to fasted conditions, a high fat breakfast had no effect on ertugliflozin AUC_{inf} and AUC_{last} and sitagliptin AUC_{inf} , AUC_{last} and C_{max} following a single dose of the ertugliflozin 15 mg/sitagliptin 100 mg FDC tablet. By contrast, ertugliflozin C_{max} was significantly lower (approximately 30%); however, this decrease is unlikely to be clinically relevant.

Overall, the PK sections of the proposed PI accurately reflect the submitted data; however, the section related to Cardiac Physiology will need correction. In addition, a number of limitations in the provided dataset were identified:

- No dedicated studies examined the PKs of the FDC combinations in either the target or special populations.
- No DDI studies were undertaken using the proposed FDC.
- Pharmacokinetic interactions between the FDC and other commonly administered drugs in this patient population such as diuretics, warfarin and digoxin and so on were not evaluated.

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

Pharmacodynamics

Studies providing pharmacodynamic information

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

Evaluator's overall conclusions on pharmacodynamics

No studies have specifically examined the PDs of the FDC tablets.

Dosage selection for the pivotal studies

Pharmacokinetics and pharmacodynamics: dose finding studies

In the sitagliptin and ertugliflozin DDI study (Study P022/1033), co-administration of single doses of ertugliflozin 15 mg and sitagliptin 100 mg had no meaningful effect on ertugliflozin or sitagliptin PK when compared to ertugliflozin and sitagliptin administered alone. The effect of a standard high fat meal on the PK of ertugliflozin and sitagliptin was evaluated using the highest strength ertugliflozin 15 mg/sitagliptin 100 mg tablet. Similar to the effect of food on the ertugliflozin commercial tablet, administration of the FDC with food decreased ertugliflozin C_{max} by approximately 30% but had no meaningful effect on ertugliflozin AUC_{inf} .

The decrease in ertugliflozin C_{max} is not considered clinically relevant. For sitagliptin administration of the FDC with food resulted in no meaningful effect on sitagliptin AUC_{inf} or C_{max} which is consistent with the lack of food effect reported for sitagliptin tablets. Therefore, the ertugliflozin/sitagliptin FDC can be administered without regard to food, similar to how ertugliflozin and sitagliptin were co-administered in Phase III trials.

Phase II dose finding studies

The two Phase II dose ranging studies for ertugliflozin were evaluated in the Steglatiro report (Attachment 2).

Phase III pivotal studies investigating more than one dose regimen

The proposed dose strengths of ertugliflozin in the ertugliflozin/sitagliptin FDC of 15 mg and 5 mg are consistent with the ertugliflozin doses evaluated in the Phase III program. Ertugliflozin is contraindicated in subjects with an eGFR < 45 mL/min/1.73 m².

In the Phase III studies, ertugliflozin and sitagliptin were co-administered as individual tablets. The proposed ertugliflozin/sitagliptin FDC was not evaluated in any Phase III studies.

Bridging to the FDC tablets was accomplished through bioequivalence studies (Studies P025/1038, P044/1053, P048/1056 and P049/1057). Ertugliflozin 15 mg/sitagliptin 100 mg FDC and ertugliflozin 5 mg/sitagliptin 100 mg FDC are bioequivalent with the corresponding doses of ertugliflozin and sitagliptin tablets co-administered as individual components in the Phase III studies. Bioequivalence of ertugliflozin 15 mg/sitagliptin 50 mg FDC and ertugliflozin 5 mg/sitagliptin 50 mg FDC was also established.

Evaluator's conclusions on dose finding for the pivotal studies

The proposed doses of sitagliptin in the ertugliflozin/sitagliptin FDC are consistent with the approved sitagliptin label. The recommended doses of sitagliptin are 100 mg, 50 mg and 25 mg once daily for patients with mild, moderate and severe renal impairment (CrCL ≥ 50mL/min, 30 to < 50mL/min and < 30mL/min, respectively). As ertugliflozin is contraindicated in patients with severe renal impairment or end stage renal disease, no ertugliflozin/sitagliptin tablet containing sitagliptin 25 mg is planned for commercialisation. Hence, the sponsor has proposed 4 strengths of the ertugliflozin/sitagliptin FDC (ertugliflozin/ sitagliptin: 15/100 mg; 5/100 mg; 15/50 mg and 5/50 mg) to enable use over the T2DM spectrum of disease and range of renal function for which use of ertugliflozin and sitagliptin would be appropriate.

Efficacy

Studies providing evaluable efficacy data

Seven Phase III studies in the ertugliflozin clinical development program (including placebo controlled and active-controlled studies) evaluated ertugliflozin as monotherapy,

as well as add-on therapy to single and dual oral AHAs including sitagliptin, across a broad population of subjects with T2DM. Three of the 7 studies specifically support the efficacy of the proposed ertugliflozin/sitagliptin fixed dose combination (FDC) (see Table 23, below).

Table 23: Overview of Phase III studies supporting the ertugliflozin/sitagliptin FDC

| Study | Randomized Population | N | Study Design | Treatment Groups and Number of Subjects Randomized | Treatment Duration |
|---|---|------|---|--|--|
| P005/1019 Ertugliflozin plus sitagliptin factorial | Adult subjects ≥ 18 years of age with T2DM and inadequate glycemic control (A1C 7.5% to 11.0%, inclusive) on background of metformin | 1233 | Multicenter, randomized (1:1:1:1), double-blind, factorial | Sitagliptin 100 mg (n=247) Ertugliflozin 15 mg (n=248) Ertugliflozin 5 mg (n=250) Ertugliflozin 15 mg/sitagliptin 100 mg (n=245) Ertugliflozin 5 mg/sitagliptin 100 mg (n=243) Placebo (n=97) | 52 Weeks Phase A: 26 weeks Phase B: 26 weeks |
| P017/1047 Ertugliflozin plus sitagliptin initial combination | Adult subjects ≥ 18 years with T2DM and inadequate glycemic control (A1C 8.0% to 10.5%, inclusive) on diet and exercise | 291 | Multicenter, randomized (1:1:1), double-blind, placebo-controlled | Ertugliflozin 15 mg/sitagliptin 100 mg (n=96) Ertugliflozin 5 mg/sitagliptin 100 mg (n=98) | 26 weeks |
| P006/1015 Ertugliflozin add-on to metformin and sitagliptin | Adult subjects ≥ 18 years of age with T2DM and inadequate glycemic control (A1C 7.0% to 10.5%, inclusive) on background of metformin and sitagliptin | 463 | Multicenter, randomized (1:1:1), double-blind, placebo-controlled | Placebo (n=153) Ertugliflozin 15 mg (n=154) Ertugliflozin 5 mg (n=156) | 52 Weeks Phase A: 26 weeks Phase B: 26 weeks |

Abbreviations: A1C=glycated hemoglobin A_{1c}; FDC= fixed-dose combination; n=number of subjects randomly assigned to study medication; N=overall number of subjects randomly assigned to study medication; T2DM=type 2 diabetes mellitus

Pivotal or main efficacy studies

The 3 pivotal studies to support the proposed ertugliflozin-sitagliptin FDC have been evaluated and discussed in detail in the Steglatiro report (see Attachment 2) and only the main efficacy results will be discussed in Attachment 3. The efficacy endpoints used in these studies complied with TGA adopted EMA guidelines for evaluation of drugs used in treatment of T2DM.

All studies evaluated glycaemic efficacy (change from baseline in HbA1c, FPG and 2 h PPG²⁹, the proportion of subjects with HbA1c < 7.0%, the proportion of subjects receiving glycaemic rescue therapy, and the time to glycaemic rescue) of proposed ertugliflozin/sitagliptin combination and also evaluated impact of ertugliflozin/ sitagliptin or ertugliflozin on change from baseline in body weight, SBP and diastolic blood pressure (DBP).

A total of 1987 subjects were randomly assigned to study medication in the 3 pivotal FDC studies: 495 subjects were randomly assigned to receive ertugliflozin 15 mg with sitagliptin 100 mg treatment and 497 subjects to the ertugliflozin 5 mg with sitagliptin 100 mg treatment, either as co-administration (Studies P005/1019 and P017/1047) or add-on therapy (Study P006/1015). The mean age of the subjects was similar across the Phase III studies, ranging from 55.1 to 59.1 years (16.2% to 29.9% were ≥ 65 years of age and 2.3% to 2.8% of subjects were ≥ 75 years of age). Majority of subjects were males (53.9% to 57.4%), White (72.9% to 90.4%) and from either North America (excluding Central America) or Europe (including Russia). At baseline, the mean BMI was similar across all studies, ranging from 30.8 to 32.2 kg/m². The two ertugliflozin and sitagliptin co-administration studies (P005/1019 and P017/1047) had higher baseline HbA1c (8.6% and 8.9%, respectively) and FPG (10 mmol/L and 11.0 mmol/L, respectively), compared to the add-on to metformin and sitagliptin study (Study P006/1015) (8.0% and 9.4 mmol/L). The higher mean baseline HbA1c values in Studies P005/1019 and P017/1047 compared to Study P006/1015 were the result of the study specific HbA1c 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 m². The average duration of T2DM was 9.5 years for the subjects in the add-

²⁹ Obtained from the 120-minute time point after administration of a mixed meal tolerance test (MMTT) challenge (in selected studies)

on to metformin and sitagliptin study (Study P006/1015), which was 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. Overall, the demographics and baseline characteristics of the subjects across the 3 studies generally reflect the target patient population of patients with T2DM who may require ertugliflozin and sitagliptin combination treatment.

All 3 studies achieved statistical significance for the primary endpoint of HbA1c reduction from baseline at Week 26. In the ertugliflozin plus sitagliptin factorial study in subjects with mean baseline HbA1c of 8.6% and on background metformin monotherapy (Study P005/1019), co-administration of E15/S100 and E5/S100 provided HbA1c reduction from baseline of 1.52% and 1.49%, respectively, which was significantly greater ($p < 0.001$) compared to each corresponding ertugliflozin dose alone or sitagliptin alone. In the ertugliflozin plus sitagliptin initial combination study (P017/1047) in subjects who were on diet and exercise alone with mean baseline HbA1c of 8.9%, co-administration of E15/S100 and E5/S100 provided significantly greater ($p < 0.001$) HbA1c reductions from baseline compared with placebo (-0.44%, -1.60 and -1.68% with placebo, E5/S100 mg and E15/S100 mg, respectively). In the add-on to metformin and sitagliptin study (P006/1015) in subjects who were on metformin and sitagliptin dual therapy and had mean baseline HbA1c of 8.0%, ertugliflozin 15 mg and 5 mg provided significantly greater ($p < 0.001$) HbA1c reductions from baseline compared with placebo (-0.09%, -0.78 and -0.86% with placebo, ertugliflozin 5 mg and 15 mg, respectively).

The proportion of subjects with HbA1c < 7.0% at Week 26 was analysed in all studies as a secondary efficacy endpoint. In the ertugliflozin plus sitagliptin factorial study (Study P005/1019), co-administration of E5/S100 and E15/S100 resulted in 52.3% and 49.2% of subjects, respectively, reaching the HbA1c goal of < 7.0% which was significantly higher than those in each corresponding ertugliflozin or sitagliptin alone group (ranging from 26.4% to 32.8%). In the ertugliflozin plus sitagliptin initial combination study (P017/1047), co-administration of E5/S100 and E15/S100 resulted in significantly higher proportions of subjects with HbA1c < 7.0% compared to placebo (35.7%, 31.3%, and 8.3% with E5/S100, E15/S100 and placebo, respectively). In the add-on to metformin and sitagliptin study (Study P006/1015), ertugliflozin 5 mg and 15 mg resulted in significantly higher proportions of subjects with HbA1c < 7.0% compared to placebo (32.1%, 39.9% and 17.0% in ertugliflozin 5 mg, 15 mg and placebo groups, respectively).

It is important to note that the only study which showed higher proportion of subjects with HbA1c < 7% for the ertugliflozin 15 mg compared to the 5 mg dose was the add-on to metformin and sitagliptin study (Study P006/1015) which enrolled subjects with lower mean baseline HbA1c compared to the other two studies. The 2 studies which involved combination treatment with ertugliflozin with sitagliptin and involved subjects with higher baseline HbA1c did not show a dose response for ertugliflozin.

Significant FPG reductions from baseline were observed with ertugliflozin co-administration with or as add-on to sitagliptin treatment groups in all 3 studies. In the ertugliflozin plus sitagliptin factorial study (Study P005/1019), the LSM reductions from baseline in FPG at Week 26 were significantly greater in the E15/S100 and E5/S100 groups than in the placebo group ($p < 0.001$ for both comparisons) and were numerically greater in the E15/S100 group than in the E5/S100 group. Similar significant reductions in FPG compared with placebo were observed in the add-on to metformin and sitagliptin and the ertugliflozin plus sitagliptin initial combination studies (Studies P005/1006 and P017/1047), with numerically greater reductions in FPG observed with the higher ertugliflozin 15 mg dose compared to the 5 mg dose.

In Study P017/1047, reductions from baseline in 2 h PPG at Week 26 were observed with ertugliflozin 15 mg and 5 mg in combination with sitagliptin.

Across the 3 studies, ertugliflozin resulted in body weight comparator adjusted reductions of 1.72 kg to 2.27 kg. The body weight reductions were generally consistent whether ertugliflozin was co-initiated with sitagliptin or added on to a sitagliptin containing regimen. Significant SBP reductions from baseline were observed with ertugliflozin in all 3 studies despite different background medications and independent of whether ertugliflozin was added on to or co-initiated with sitagliptin. In all 3 studies, the proportions of subjects receiving glycaemic rescue therapy in the ertugliflozin and sitagliptin combination groups were low, ranging from 0% to 6.1%. In the 2 placebo controlled studies (Studies P006/1015 and P017/1047), higher proportions of subjects were rescued in the placebo arms.

Other efficacy studies

Refer to the Steglatiro report for details regarding the other four Phase III studies in the ertugliflozin clinical program (see Attachment 2).

Evaluator's conclusions on clinical efficacy

Dual therapy with ertugliflozin and sitagliptin provides two AHAs with different mechanisms of action neither of which are associated with hypoglycaemia nor weight gain. Ertugliflozin inhibits renal glucose reabsorption, resulting in urinary glucose excretion, and thereby reducing plasma glucose and HbA1c. Sitagliptin enhances the incretin axis, thereby increasing insulin secretion and reducing glucagon concentrations and in turn lowering hepatic glucose production. Combining these agents provides complementary mechanisms leading to robust glucose lowering efficacy, with low risk for hypoglycaemia.

The efficacy of proposed FDC of ertugliflozin+sitagliptin was evaluated in 3 pivotal Phase III studies involving 1987 subjects (495 and 497 received combination treatment with E5/S100 and E15/S100, respectively). The three Phase III studies supporting this FDC were conducted using ertugliflozin and sitagliptin administered as separate tablets, and bridging to the FDC formulation is therefore provided via BE studies comparing the FDC to co-administration of individual components. Extrapolation of the results obtained from the 3 Phase III studies as evidence for proposed FDC formulation is justified as bioequivalence between the proposed FDCs and co-administration of ertugliflozin+sitagliptin was proven. All 3 studies were well conducted according to TGA adopted EMEA guidelines for evaluation of drugs for treatment of T2DM as well as guidelines related to development of FDCs. The target population evaluated in the 3 studies was representative of the proposed target patient population of T2DM patients who may require treatment with ertugliflozin and sitagliptin.

Co-administration of ertugliflozin (15 mg and 5 mg) with sitagliptin provides clinically meaningful improvements in glycaemic parameters (HbA1c, FPG, and proportion of patients with HbA1c < 7.0%) compared to either sitagliptin alone or the corresponding dose of ertugliflozin alone in 1233 subjects with inadequate control on metformin. Co-administration of ertugliflozin (15 mg and 5 mg) with sitagliptin provides greater body weight and SBP reductions, compared to sitagliptin alone in subjects with inadequate control on metformin. No meaningful difference was observed between the 2 co-administration groups (E15/S100 and E5/S100) for HbA1c-related endpoints, although there was a trend toward better efficacy for E15/S100 relative to E5/S100 for FPG and 2 h PPG. However, interpretation was limited as this study was not powered to detect differences between the 2 combination groups.

Treatment with the initial combination of ertugliflozin (5 mg QD or 15 mg QD) and sitagliptin 100 mg QD for 26 weeks provides clinically meaningful improvements in

glycaemic parameters (HbA1c, FPG, 2 h PPG, and proportion of patients with HbA1c < 7.0%) as well as greater body weight and SBP reductions, compared to placebo in 291 T2DM subjects with inadequate control on diet and exercise alone (Study P017/1047). This study was not designed to formally compare the 5 mg and 15 mg ertugliflozin doses, there were numerically greater reductions in HbA1c, FPG, 2 h PMG, body weight and sitting SBP with the E15/S100 combination, relative to the E5/S100 combination, although the differences between the 2 co-administration groups were small for these endpoints.

Study P006/1015 was a well conducted pivotal Phase III study which evaluated the efficacy and safety of the addition of ertugliflozin (5 mg and 15 mg QD) compared with the addition of placebo to combination therapy with metformin \geq 1500 mg/day and sitagliptin 100 mg QD in 463 subjects with T2DM and inadequate glycaemic control. Ertugliflozin 15 mg and 5 mg, as add-on to sitagliptin and metformin dual therapy provided clinically meaningful improvements in glycaemic control (HbA1c, FPG and proportion of patients with HbA1c < 7.0%), as well as body weight and SBP reductions compared to placebo. Single-agent or dual therapies are often found to be insufficient to control blood glucose over time due to the progressive nature of diabetes. The addition of a third oral antidiabetic agent, with a different mechanism of action is often needed at a certain point of disease progression. Ertugliflozin, with a distinct mechanism of action relative to DPP-4 inhibitors and metformin, is a reasonable choice as a third-line therapy. The study population, with a mean duration of diabetes of 9.5 years and mean HbA1c of 8% despite combination therapy with metformin and sitagliptin, was representative of patients who may need an additional third-line therapy.

Dose response

Ertugliflozin 15 mg demonstrated a consistent numerically greater glycaemic efficacy compared to ertugliflozin 5 mg. In the add on to metformin and sitagliptin (Study P006/1015), ertugliflozin 15 mg provided numerically greater HbA1c and FPG reductions and resulted in a greater proportion of subjects with an HbA1c < 7.0% at Week 26 compared to the ertugliflozin 5 mg. A clear difference on HbA1c lowering between ertugliflozin 15 mg with sitagliptin 100 mg and ertugliflozin 5 mg with sitagliptin 100 mg was not observed in the 2 studies where sitagliptin and ertugliflozin were co-initiated and in fact the proportion of subjects with HbA1c < 7% was numerically greater with the lower 5 mg ertugliflozin dose compared to the 15 mg dose. A dose response for weight loss was not clearly observed between co-administration of ertugliflozin 15 mg/sitagliptin 100 mg and ertugliflozin 5 mg/sitagliptin 100 mg.

However, reductions in FPG and 2 h PPG were numerically greater for E15/S100 compared to E5/S100 in both Studies P005/1019 and P017/1047. Furthermore, ertugliflozin 15 mg/sitagliptin 100 mg also showed a numerically greater SBP reduction compared to ertugliflozin 5 mg/sitagliptin 100 in the 2 studies where the drugs were co-initiated. When added on to metformin and sitagliptin, ertugliflozin 15 mg resulted in numerically greater reductions in SBP than ertugliflozin 5 mg.

Long term maintenance of efficacy

The persistence of efficacy for sitagliptin has been demonstrated in a number of clinical studies. A 52 week study showed that efficacy of sitagliptin was sustained for 52 weeks and is presented in the sitagliptin label. The extension of this study showed that the efficacy of sitagliptin was sustained for 104 weeks.³⁰ Ertugliflozin co-administered with

³⁰ Seck T1, et al. (2010) Safety and efficacy of treatment with sitagliptin or glipizide in patients with type 2 diabetes inadequately controlled on metformin: a 2-year study. *Int J Clin Pract.* 2010; 64: 562-576. doi: 10.1111/j.1742-1241.2010.02353.x.

sitagliptin demonstrated stable HbA1c lowering over a period of 26 weeks when compared to placebo (Study P017/1047) and when compared to each individual agent (ertugliflozin alone or sitagliptin alone; Study P005/1019). Similar observations were made for FPG and lowering of body weight and SBP in these studies. These data combined with the efficacy durability data for sitagliptin suggest that co-administration of ertugliflozin and sitagliptin will have beneficial effects on glycaemic parameters and other endpoints such as reduction in body weight and SBP to at least 26 weeks. However, there is no evidence to confirm efficacy of proposed FDC beyond 26 weeks at this stage.

Safety

Studies providing evaluable safety data

Data for the safety and tolerability of the ertugliflozin/sitagliptin FDC was based upon 3 Phase III clinical studies of ertugliflozin administered in combination with sitagliptin, including one factorial study (Study P005/1019) and two placebo controlled studies (Studies P006/1015 and P017/1047).

Due to differences in study design and patient populations, safety data from the 3 individual studies were not pooled for analysis and therefore data are presented from the individual studies.

Patient exposure

Overall, 1985 subjects were randomised and received at least 1 dose of study medication, including 990 subjects randomised 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). In these 3 studies, the number of subjects randomised to treatment with ertugliflozin 5 mg (497 subjects) or ertugliflozin 15 mg (493 subjects) in co-administration with sitagliptin or as add-on therapy was evenly distributed. 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).

Over the 26 week treatment period for each study (reflecting Phase A of Studies P005/1019 and P006/1015 and the completed treatment period of Study P017/1047), the mean duration of exposure in each treatment group across the 3 studies was similar (170.9 days to 174.0 days), with the exception of the placebo group in Study P017/1047 in which the mean duration of exposure was 157.8 days, primarily due to a numerically higher proportion of subjects in this study who prematurely discontinued study medication. The subject disposition and baseline characteristics of the patients in the three Phase III studies have been summarised in the Steglatiro report (see Attachment 2).

In the ertugliflozin+sitagliptin factorial study P005/1019, a numerically higher proportion of subjects in the E15/S100 group discontinued study medication for an AE relative to the 4 other groups; the proportions of subjects who discontinued study medication for other reasons were generally similar between groups. In the add-on to metformin+sitagliptin Study P006/1015, A numerically higher proportion of subjects discontinued study medication for an adverse event in the ertugliflozin 5 mg group (3.2%) than in the ertugliflozin 15 mg and placebo groups (1 subject in each group (0.6% and 0.7%, respectively)). In the ertugliflozin+sitagliptin initial combination Study P017/1047, proportion of subjects who discontinued study medication was numerically lower in the E5/S100 (8.2%) and E15/S100 (8.3%) groups than in the placebo group (21.6%), primarily due to a numerically larger proportion of subjects in the placebo group who discontinued study medication for withdrawal by subject and for lost to follow-up.

Post marketing experience

Not applicable as the ertugliflozin/sitagliptin FDC has not been approved for use in any country. Ertugliflozin has also not received marketing approval to date.

The following information regarding post-marketing experience for sitagliptin has been included in the proposed PI for Steglujan:

'Additional adverse reactions have been identified during postmarketing use of sitagliptin as monotherapy and/or in combination with other antihyperglycaemic agents. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.'

Infections and infestations: upper respiratory tract infection; nasopharyngitis; nervous system disorders; headache.

Gastrointestinal disorders: acute pancreatitis, including fatal and non-fatal haemorrhagic and necrotising pancreatitis (see PRECAUTIONS, Pancreatitis); constipation; vomiting.

Musculoskeletal and connective tissue disorders: arthralgia; myalgia; pain in extremity; back pain.

Renal and urinary disorders: worsening renal function, including acute renal failure (sometimes requiring dialysis).

Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, pruritus, bullous pemphigoid (see Precautions, Bullous Pemphigoid), and exfoliative skin conditions, including Stevens-Johnson syndrome have been reported with use of sitagliptin (see Contraindications and Precautions, Hypersensitivity Reactions).'

Evaluator's overall conclusions on clinical safety

The safety of the proposed co-administration of ertugliflozin+sitagliptin was evaluated in 1987 patients in 3 pivotal Phase III studies with about 992 patients receiving ertugliflozin+sitagliptin combination treatment. Although the proposed FDC was not used in any of the Phase III studies, use of safety data from these studies is justified as bioequivalence between the proposed FDC and co-administration of individual tablets of ertugliflozin+sitagliptin was adequately established.

Study P005/1019 ertugliflozin +sitagliptin factorial study

The incidence of AEs overall was not notably different between the co-administration groups and the individual treatment groups. The incidence of SAEs in the E5/S100 and E15/S100 groups (2.5% and 1.6%, respectively) was similar relative to the E5, E15, and S100 groups (3.2%, 1.2%, and 1.6% respectively). No deaths were reported. The incidence of subjects who discontinued study medication due to an AE was higher in the E15/S100 group (2.9%) relative to the S100 group (0.4%) and not notably different relative to the E5/S100, E5, and the E15 groups (1.2%, 2.4%, and 1.2%, respectively).

Study P006/1015 add-on to metformin and sitagliptin study

The overall incidence of AEs was numerically lower in the ertugliflozin 5 mg and 15 mg groups (41.7% and 45.1%, respectively) compared with the placebo group (50.3%). The incidence of SAEs was not notably different across the ertugliflozin 5 mg and 15 mg treatment groups (4.5% and 2.0%, respectively) and the placebo group (3.3%). No deaths were reported. There was a numerically higher incidence of subjects who discontinued due to an AE in the ertugliflozin 5 mg group (3.2%) relative to the placebo and

ertugliflozin 15 mg groups (0.7% in each); the only notable pattern of discontinuation for an adverse event was the observation that 2 subjects in the ertugliflozin 5 mg group discontinued due to genital mycotic infections, which is a known class effect for SGLT2 inhibitors.

Study P017/1047 ertugliflozin +sitagliptin initial combination study

The overall incidence of AEs was slightly lower in the E5/S100 and E15/S100 groups (44.9% and 44.8%, respectively) than in the placebo group (42.3%). The incidence of SAEs was generally similar in the E5/S100 and E15/S100 groups (2.0% and 3.1%, respectively) relative to the placebo group (5.2%). No deaths were reported. AEs that led to discontinuation of study medication were experienced by 2 subjects each in the E5/S100 group (2.0%) and the E15/S100 group (2.1%) and 3 subjects (3.1%) in the placebo group. No specific AE that resulted in discontinuation from study medication was reported for more than 1 subject.

In the 3 Phase III studies, genital mycotic infections also occurred more frequently in men and in women treated with ertugliflozin, with no evidence of a further increase in incidence with ertugliflozin and sitagliptin combination therapy. AEs associated with osmotic diuresis and hypovolemia occurred infrequently, with no evident increase in incidence of events occurring with ertugliflozin and sitagliptin combination therapy.

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

In the ertugliflozin Phase III program and in the 3 studies that are the focus of this submission, examination of clinical laboratory results revealed small increases in haemoglobin, magnesium, and phosphate, and decreases in liver transaminases and uric acid levels. There were few AEs related to these changes, suggesting that the levels were generally not of clinical concern to investigators. There were no meaningful changes noted in serum potassium levels. There were also small to modest changes in the serum lipid profile, including increases in LDL-C, total cholesterol (TC) and High-density lipoprotein-cholesterol (HDL-C) with decreases in triglycerides.

Ertugliflozin treatment in the 3 studies in this submission was associated with decreases in systolic and diastolic blood pressure. There was no increase in heart rate or measures of orthostatic hypotension. There were no clinically meaningful differences in ECG parameters (heart rate, PR, QRS, QT, QTcB, and QTcF interval) between treatment groups in the 3 studies. These results were consistent with those in the ertugliflozin Phase III program. However, results of the CV meta-analysis in the ertugliflozin clinical program were not provided and CV safety of ertugliflozin has not yet been established.

The combination of ertugliflozin and sitagliptin was generally safe and well-tolerated. In a large factorial study on a background of metformin therapy, there were no notable risks associated with co-administration of ertugliflozin and sitagliptin relative to treatment with the individual components. The safety of the combination was also established in 2 additional settings, when ertugliflozin was added to background therapy with metformin and sitagliptin and when ertugliflozin and sitagliptin were co-administered as initial therapy after diet and exercise alone. These results suggest that the safety and tolerability of the ertugliflozin/sitagliptin FDC can be described based on those of the individual components.

Steglujan Benefit-risk balance

Second round assessment of benefit-risk balance

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

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

Second round recommendation regarding authorisation

Approval of Steglujan (ertugliflozin and sitagliptin FDC) is recommended for the following indication:

MSD-ertugliflozin-sitagliptin (ertugliflozin and sitagliptin phosphate monohydrate) is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate (refer Clinical Trials, Precautions).

Approval for the above indication is subject to the following:

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

Segluromet

Clinical rationale

As the pathogenesis of T2DM involves multiple metabolic defects, combination therapy with AHA agents that have different mechanisms of action can achieve robust reductions in HbA1c enabling patients to reach treatment goals. A FDC therapy may also help to improve treatment adherence.

The ertugliflozin/metformin FDC combines two AHAs with complementary mechanisms of action to improve glycaemic control in patients with T2DM. Ertugliflozin is a highly selective SGLT2 inhibitor that increases UGE via inhibition of renal tubular urinary glucose reabsorption. In subjects with T2DM, ertugliflozin lowers plasma glucose, achieves clinically significant reductions in HbA1c; ertugliflozin also achieves clinically significant reductions in body weight and SBP. Metformin hydrochloride is an AHA that improves glucose tolerance in patients with T2DM by lowering both basal and PPG. It is not chemically or pharmacologically related to any other class of oral AHA. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilisation. Metformin is approved for use in the US, EU, Australia and other countries and has an established safety and tolerability profile.

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

Observational studies demonstrate that treatment modification or intensification in patients with inadequate glycaemic control on monotherapy is frequently delayed.^{31 32} Furthermore, patients with very high HbA1c levels are also unlikely to attain HbA1c treatment goals with just a single agent. Current guidelines from the ADA and the EASD state that initial combination therapy with metformin and a second agent may allow some patients with baseline HbA1c levels well above target to more quickly achieve their HbA1c goal than sequentially adding on a second agent following metformin failure. The ADA/EASD guidelines state that a reasonable threshold for initial dual combination therapy with metformin and a second agent is for subjects with an HbA1c > 9%. Guidelines from the American Association of Clinical Endocrinologists (AACE) recommend initiation of dual anti-hyperglycaemic therapy in patients presenting with an HbA1c between 7.6% to 9.0%, because monotherapy is unlikely to result in the AACE goal attainment of an HbA1c < 6.5% (AACE guidelines, 2002).

Guidance

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

Prospective guidance over the course of the clinical development program supporting the proposed indication has been received from Health Authorities in the US and EU. Much of the feedback has focused on the Phase III program, and has been followed the BE and food effect studies to support registration of the ertugliflozin/metformin FDC were conducted in accordance with feedback from both agencies.

Contents of the clinical dossier

Scope of the clinical dossier

Pharmacology

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

Efficacy/ Safety

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

- Study P007/1017: A Phase III randomised double blind, placebo controlled, 26 week multicentre study with a 78 week extension to evaluate the efficacy and safety of ertugliflozin in subjects with T2DM and inadequate glycaemic control on metformin monotherapy.
- Study P002/1013: A Phase III, multicentre, randomised, double blind, active-comparator controlled clinical trial to study the safety and efficacy of the addition of

³¹ Khunti K, et al. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80 000 people. *Diabetes Care*. 2013; 36: 3411–3417

³² Fu AZ, et al. Treatment intensification in patients with type 2 diabetes who failed metformin monotherapy. *Diabetes Obes Metab*. 2011; 13: 765–769.

ertugliflozin (MK-8835/PF-04971729) compared with the addition of glimepiride in subjects with T2DM who have inadequate glycaemic control on metformin.

- Study P005/1019: A Phase III randomised, double blind, multicentre study to evaluate the efficacy and safety of the combination of ertugliflozin (MK- 8835/PF-04971729) with sitagliptin compared with ertugliflozin alone and sitagliptin alone, in the treatment of subjects with T2DM with inadequate glycaemic control on metformin monotherapy.
- Study P006/1015: A Phase III, multicentre, randomised, double blind, placebo controlled, parallel group clinical trial to evaluate the safety and efficacy of ertugliflozin (MK- 8835/PF-04971729) in the treatment of subjects with T2DM who have inadequate glycaemic control on metformin and sitagliptin.

Three other supportive Phase III studies:

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

Other studies

- Phase II dose-finding studies
 - Study P042/1004 and Study P016/100
- Integrated summary of efficacy and safety
- Phase I and II Safety analyses.

Paediatric data

There is no paediatric data in the current submission. The sponsors have submitted a PIP in the EU and the date on which the sponsors are first required to submit a report of a study conducted as part of the PIP is September 2026

Good clinical practice

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

Pharmacokinetics

Studies providing pharmacokinetic data

Submitted studies with pharmacokinetic data are listed in the in the table below.

Table 24: Submitted pharmacokinetic studies

| PK topic | Subtopic | Study ID | * |
|----------------------|---------------------------------|-----------|---|
| PK in healthy adults | Bioequivalence † Single dose | P027/1041 | BE between ertugliflozin 7.5 mg/metformin 1000 mg FDC tablet and the free combination (US) under fasted conditions |
| | | P046/1054 | BE between ertugliflozin 7.5 mg/metformin 850 mg FDC tablet and the free combination (EU) under fasted conditions |
| | | P047/1055 | BE between ertugliflozin 7.5 mg/metformin 1000 mg FDC tablet and the free combination (EU) under fasted conditions |
| | | P050/1058 | BE between ertugliflozin 2.5 mg/metformin 500 mg FDC tablet and the free combination (US) under fasted conditions |
| | Food effect | P028/1049 | Relative BA of ertugliflozin 7.5 mg/metformin 1000 mg FDC tablet under fasted and fed conditions |
| | | P052/1060 | BE of metformin component following administration of ertugliflozin 2.5 mg/metformin 500 mg FDC tablet or the free combination (CA) under fasted and fed conditions |
| | | P053/1061 | BE of metformin component following administration of ertugliflozin 7.5 mg/metformin 850 mg FDC tablet or the free combination (CA) under fasted and fed conditions |

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

Evaluator's conclusions on pharmacokinetics

- The current submission contains four previously unevaluated studies, which examine the BE between the various strengths of the FDC proposed for marketing and the corresponding free combinations. In addition, a further 3 new studies examined the effect of a high fat/high calorie breakfast on the PKs of the active components of the FDC tablets.
- In regards to the tablets containing a single active component, the PKs of metformin are well-established and the PKs of ertugliflozin are described in detail in the concurrent TGA submission for Steglatro.
- Overall, the conduct of the previously unevaluated studies was satisfactory and was compliant with existing TGA guidelines, validated analytical methods were employed and the data analyses undertaken were appropriate.

- The proposed 7.5 mg/1000 mg ertugliflozin/metformin FDC tablet was bioequivalent with the free combinations, which contained commercially available metformin tablets sourced from either the US or EU. In addition, the 2.5 mg/500 mg FDC tablet was bioequivalent with the matching dose strength of the free combination, which contained US sourced metformin tablets. Given that the sponsor has demonstrated that the lowest and the highest dose strength of the FDC tablets are bioequivalent with the matching dose strengths of the relevant free combination tablets and the dose adjusted AUC for the doses examined meet the criterion of $\pm 25\%$ as per the relevant guideline;³³ it can be assumed that the other proposed strengths of the FDC tablets will be bioequivalent with the relevant free combinations.
- Compared to fasted conditions, a high fat breakfast had no effect on ertugliflozin or metformin AUC_{inf} and AUC_{last} values following a single dose of the ertugliflozin 7.5 mg/metformin 1000 mg FDC tablet. By contrast, ertugliflozin and metformin C_{max} values were approximately 40% and 30% lower, respectively, however, these decreases in C_{max} are unlikely to be clinically relevant.
- Overall, the PK sections of the proposed PI accurately reflect the submitted data; however, a number of limitations in the provided dataset were identified:
 - Although metformin formulations from the US, EU and Canadian markets have been examined, none of the BE studies included any of the approved Australia metformin formulations.
 - No dedicated PK studies examined the PKs of the FDC combinations in either the target or special populations.
 - No DDI studies were undertaken using the proposed FDC.
 - Pharmacokinetic interactions between the FDC and other commonly administered drugs in this patient population such as diuretics, warfarin, digoxin and so on was not evaluated.
 - Studies examining the effect of food on ertugliflozin PKs have not been performed in two of the previously unevaluated food studies, when plasma samples were available and this should have been a routine and relatively easy task to undertake.

The limitations regarding DDI studies are also present in the concurrent TGA submission for Steglatiro.

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

Pharmacodynamics

Studies providing pharmacodynamic (PD) data

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

Evaluator's conclusions on pharmacodynamics

No studies have specifically examined the PD of the FDC tablets. However, the results of the concurrent submission for Steglatiro, indicate that following matched total daily doses

³³ Guideline On The Investigation Of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr)

of ertugliflozin alone to subjects with T2DM administered either BD or QD the effects on UGE₀₋₂₄; mean plasma glucose and HbA1c³⁴ were similar.

Dosage selection for the pivotal studies

Pharmacokinetics and pharmacodynamics dose finding studies

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

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

The four Phase III studies supporting this FDC were conducted using ertugliflozin and metformin administered as separate tablets and bridging to the FDC formulation is provided via BE studies comparing the FDC to co-administration of the individual components. The clinical studies were also supported by repeat dose toxicology studies performed with the co-administration of ertugliflozin and metformin. In addition, ertugliflozin was dosed QD in all the Phase III studies. In order to bridge the QD dosing regimen of ertugliflozin administered in Phase III with the BD dosing regimen in the ertugliflozin/metformin FDC, a Phase I study (Study P035/1051) was conducted to demonstrate equivalence of steady state AUC₀₋₂₄ and similarity in steady state PD (cumulative UGE₀₋₂₄) for ertugliflozin between the QD and BD regimens at the same total daily dose (2.5 mg BD versus 5 mg QD and 7.5 mg BD versus 15 mg QD). Further, a model based meta-analysis was conducted to link the PD endpoint (UGE₀₋₂₄) with the clinical endpoint (HbA1c) in T2DM patients.

Phase II dose finding studies

The doses of ertugliflozin evaluated in the Phase III clinical studies were 5 mg and 15 mg once daily (QD). Dose selection was based on dose-response modelling of efficacy endpoints (HbA1c, FPG and body weight) from Study P016/B1521006 (12 week Phase II dose-ranging study) as well as UGE_{24h} (mechanism biomarker) in T2DM subjects from Study P042/B1521004 (4 week Phase II dose-ranging study) (refer to Steglatro report, Attachment 2). However, the proposed 15 mg QD dose of ertugliflozin was not evaluated in both Phase II studies and the sponsors have been asked to provide further clarification regarding choice of the 15 mg QD dose for the pivotal Phase III studies.

Phase III pivotal studies investigating more than one dose regimen

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

³⁴ HbA1c measures glycated haemoglobin.

Evaluator's conclusions on dose finding for the pivotal studies

The proposed doses of metformin used in the proposed ertugliflozin+metformin FDC are consistent with approved the metformin label. Clarification regarding choice of the 15 mg dose for ertugliflozin has been sought in the Steglatro report. The doses of ertugliflozin evaluated in the Phase III clinical studies were 5 mg and 15 mg QD but the proposed dosing for the ertugliflozin+metformin FDC is BD. However, equivalence was demonstrated for ertugliflozin between the QD and BD regimens at the same total daily dose (2.5 mg BD versus 5 mg QD and 7.5 mg BD versus 15 mg QD) with regards to steady state PK (AUC₀₋₂₄) and PD (UGE₀₋₂₄) in the Phase I Study P035/1051.

Efficacy

Studies providing efficacy data

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

- StudyP007/1017: A Phase III, randomised, double blind, placebo controlled, 26 week multicentre study with a 78 week extension to evaluate the efficacy and safety of ertugliflozin in subjects with T2DM and inadequate glycaemic control on metformin monotherapy (refer Steglatro evaluation report Attachment 2).
- StudyP005/1019: A Phase III, randomised, double blind, multicentre study to evaluate the efficacy and safety of the combination of ertugliflozin (MK- 8835/PF-04971729) with sitagliptin compared with ertugliflozin alone and sitagliptin alone, in the treatment of subjects with T2DM with inadequate glycaemic control on metformin monotherapy (refer Steglatro evaluation report Attachment 2).
- Study P002/1013: A Phase III, multicentre, randomised, double blind, active comparator controlled clinical trial to study the safety and efficacy of the addition of ertugliflozin (MK-8835/PF-04971729) compared with the addition of glimepiride in subjects with T2DM who have inadequate glycaemic control on metformin (refer Steglatro evaluation report Attachment 2).
- Study P006/1015: Phase III, multicentre, randomised, double blind, placebo controlled, parallel group clinical trial to evaluate the safety and efficacy of ertugliflozin (MK-8835/PF-04971729) in the treatment of subjects with T2DM who have inadequate glycaemic control on metformin and sitagliptin (refer Steglatro evaluation report Attachment 2).

Evaluator's conclusions on efficacy

Seven Phase III studies support the initial regulatory submission for ertugliflozin alone. Four of the 7 Phase III studies were submitted to support the ertugliflozin/metformin FDC submission, including 2 active controlled studies (Studies P005/1019 and Study P002/1013) and 2 placebo controlled studies (Studies P006/1015 and P007/1017) that evaluated the safety and efficacy of ertugliflozin in combination with metformin in 3,643 adult subjects with T2DM. Efficacy data were pooled for the 2 placebo controlled studies to assess efficacy on a background of metformin (ertugliflozin /metformin FDC Pool).

No Phase III studies have been performed with the proposed ertugliflozin/metformin FDC tablet. The studied doses of the FDC tablets (ertugliflozin 7.5 mg/metformin 1000 mg, ertugliflozin 7.5 mg/metformin 850 mg and ertugliflozin 2.5 mg/metformin 500 mg) are bioequivalent under fasted conditions to the corresponding doses of ertugliflozin and metformin tablets (US or EU sourced Glucophage) when co-administered. The metformin component of the studied doses of the FDC tablets (ertugliflozin 7.5 mg/metformin

850 mg and ertugliflozin 2.5 mg/metformin 500 mg) is also bioequivalent to the corresponding doses of metformin tablets (Canadian sourced Glucophage) when co-administered with corresponding doses of ertugliflozin tablets under fasted and fed conditions. These clinical data, along with the in vitro multi-media dissolution data, support the bridging of pharmacokinetic, pharmacodynamic, efficacy and safety data obtained in the Phase III studies to the proposed FDC commercial tablets. Hence, data obtained from the 4 Phase III studies (Studies P006/1015, P007/1017, P002/1013 and P005/1019) that assessed the use of ertugliflozin on a background of metformin (≥ 1500 mg/day) can be bridged to the FDC tablet based on established bioequivalence.

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

A total of 3,643 subjects were randomised in the 4 Phase III studies in support of this submission, including 2,597 who received ertugliflozin in combination with metformin. Demographic and baseline characteristics were similar across the 2 studies included in the ertugliflozin/metformin FDC Pool (Studies P007/1017 and P006/1015) and was representative of the target patient population for the proposed ertugliflozin+metformin FDC (46 to 57% males, mean age of 55 to 59 years, mean BMI of 31 to 32kg/m²), mean duration of diabetes of 7 to 9.5 years, mean baseline HbA1c of 7.8% to 8.6% and mean baseline eGFR of 87 to 92 mL/min/1.73 m²).

Ertugliflozin 15 mg or 5 mg as add-on to metformin (alone or in combination with sitagliptin) provides a clinically meaningful improvements in glycaemic control (HbA1c, proportion with HbA1c < 7.0%, FPG and 2 h PPG) as well as body weight reduction and SBP reduction in subjects with T2DM. Ertugliflozin 15 mg plus metformin provides non-inferior HbA1c reduction compared to glimepiride plus metformin.

Treatment with ertugliflozin 15 mg and 5 mg, compared with placebo, resulted in significant and clinically meaningful reductions from baseline in HbA1c and FPG at Week 26, as add-on therapy to metformin (Study P007/1017; add-on to metformin study), and as add-on therapy to metformin plus sitagliptin (Study P006/1015; add-on to metformin plus sitagliptin study). In both of these studies, treatment with ertugliflozin (both doses) added to metformin resulted in a higher proportion of subjects meeting the glycaemic goal of HbA1c < 7.0% (< 53 mmol/mol). In both the add-on to metformin study (Study P007/1017) and the add-on to metformin and sitagliptin study (Study P006/1015), treatment with both doses of ertugliflozin as add-on to metformin resulted in significant reductions from baseline in body weight and SBP at Week 26, compared with placebo. Significant reductions from baseline in DBP were observed in Study P007/1017.

Efficacy of combination of ertugliflozin and metformin was also evaluated using pooled data from 2 placebo controlled studies: Studies P007/1017 (add-on to metformin study) and P006/1015 (add-on to metformin plus sitagliptin study). The reductions from baseline in HbA1c and body weight and the proportions of subjects meeting the HbA1c goal of < 7.0% in the pool were greater in the ertugliflozin groups compared to the placebo group. In subgroup analyses of the pool, the addition of treatment with ertugliflozin 15 mg and 5 mg to metformin therapy resulted in a reduction from baseline in HbA1c and body weight compared with placebo across subgroups including age, gender, race, geographic region, baseline BMI and duration of T2DM.

Dose response

Both ertugliflozin 15 mg and 5 mg have demonstrated clinical efficacy in the Phase III studies when dosed in combination with metformin. Although the studies were not powered or designed to detect between-dose differences, the HbA1c reductions from baseline were numerically greater for ertugliflozin 15 mg compared to 5 mg in all 4 studies and the pooled analysis. In the pooled analysis ertugliflozin 15 mg provided a numerically greater reduction in HbA1c (approximately 0.14%) compared to ertugliflozin 5 mg. A dose response model was used to support predictions of the efficacy of the 2 ertugliflozin doses for a typical patient on metformin background therapy. The predictions suggest that ertugliflozin 15 mg provides approximately 0.1% greater HbA1c reduction compared to ertugliflozin 5 mg.

In all four Phase III studies, a numerically greater proportion of subjects reached HbA1c < 7.0% with ertugliflozin 15 mg compared with 5 mg.

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

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

Persistence of efficacy and/or tolerance effects

The persistence of efficacy of metformin has been demonstrated in clinical practice as well as in the literature. For example, in the A Diabetes Outcome Progression Trial, although the glycaemic control with metformin monotherapy gradually deteriorated in the course of 5 years of observation, consistent with the natural progression of the disease, it was generally sustained in the first 2 or 3 years with treatment failure below 10%.

Ertugliflozin used as add-on to metformin has been shown to deliver efficacy in HbA1c lowering over a period of 26 weeks; 3 different studies (Studies P007/1017, P005/1019 and P006/1015) demonstrated sustained clinically meaningful efficacy up to 26 weeks and 1 study (Study P002/1013) demonstrated non-inferiority for ertugliflozin 15 mg compared to sulfonylurea add-on to metformin up to 52 weeks. Stable lowering of FPG was also observed over the same study periods.

Limitations

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

Safety

Studies providing safety data

There were 4 pivotal Phase III studies from the ertugliflozin development program which provided the main safety data for the proposed ertugliflozin-metformin FDC.

No Phase III studies have been performed with the proposed ertugliflozin/metformin FDC tablet; however, data obtained from the 4 Phase III studies (Studies P006/1015, P007/1017, P002/1013 and P005/1019), that assessed the use of ertugliflozin on a

background of metformin (≥ 1500 mg/day) can be bridged to the FDC tablet based on established bioequivalence. Two of the studies (Studies P006/1015 and P007/1017) were placebo controlled and had a common study design that allowed the data to be pooled (Ertugliflozin/metformin Pool) for review of safety.

Patient exposure

The ertugliflozin/metformin Pool includes 1083 subjects who were randomised and received at least 1 dose of study medication; 363, 358 and 362 received ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, respectively. The mean observation period on study medication was similar in the ertugliflozin 5 mg and 15 mg groups (177.7 days and 174.2 days, respectively) and the placebo group (174.4 days), with 665 subjects receiving ertugliflozin in combination with metformin for > 26 weeks. The proportion of subjects who discontinued study medication within 26 weeks was numerically lower in the ertugliflozin 5 mg and 15 mg groups (5.2% and 7.8%, respectively) compared to the placebo group (8.6%). The most common reason for discontinuation in all groups was withdrawal by subject. Demographic and baseline characteristics were generally similar across groups.

Post-marketing data

Not applicable as the ertugliflozin/metformin FDC had not been approved for use in any country at the time of this evaluation.

Evaluator's conclusions on safety

The safety and tolerability profile of ertugliflozin, 5 mg QD and 15 mg QD, has been presented in a separate submission (refer to Safety section of the Steglatiro report in Attachment 2). Metformin, including the proposed daily doses, has an established safety and tolerability profile. The main AEs associated with metformin use are diarrhoea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, metallic taste and headache. Lactic acidosis is a rare but serious metabolic complication that can occur due to metformin accumulation during treatment.³⁵ The following conditions and situations can result in lactic acidosis: impaired renal function, concomitant medication(s) that may affect renal function, impaired hepatic function, excessive alcohol intake, poorly controlled diabetes, ketosis, prolonged fasting and any condition associated with hypoxia. Therefore, patients experiencing these conditions should avoid taking metformin.

Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Hypoxic states, including cardiovascular (CV) collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotaemia.

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

Ertugliflozin treatment, in the overall Phase III program and in the Ertugliflozin/metformin Pool, led to small mean changes from baseline in the serum lipid profile including increased LDL-C, total cholesterol and HDL-C and decreases in

³⁵ Lactic acidosis is fatal in approximately 50% of cases. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years).

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

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

Benefit-risk assessment

See also Attachment 4 for more details of the First and Second round Benefit risk assessments.

First round assessment of benefit-risk balance

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

In all 4 studies, clinically meaningful HbA1C reductions were observed when ertugliflozin 5 mg or 15 mg was added on to metformin (second line use) or metformin and sitagliptin (third line use). On a background of metformin, ertugliflozin 5 mg and 15 mg resulted in reductions in HbA1C that were generally greater than the results in the placebo group at Week 26, irrespective of gender, age, sex, race, ethnicity, geographic region, baseline BMI, baseline HbA1C, baseline eGFR, and duration of T2DM. The results of Study P002/1013 demonstrate that ertugliflozin offers several clinically relevant advantages to glimepiride

as an add-on to metformin with regards to safety/ tolerability (that is, lower rates of hypoglycaemia) and reductions in SBP and body weight.

In the Ertugliflozin/metformin FDC Pool, ertugliflozin 15 mg provided a numerically greater reduction in HbA1C (approximately 0.14%) compared to ertugliflozin 5 mg. In all 4 Phase III studies, a numerically greater proportion of subjects reached A1C < 7.0% with ertugliflozin 15 mg compared with 5 mg. The small but consistently greater HbA1C reduction from baseline with ertugliflozin 15 mg over ertugliflozin 5 mg may have an impact on the ability of patients to reach their HbA1C goal.

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

The ertugliflozin/metformin FDC will contain an immediate-release formulation of metformin, which requires twice daily dosing. Therefore, the ertugliflozin/metformin FDC also requires twice daily dosing. Bridging of the once daily ertugliflozin dosing regimen used in the Phase III studies to the proposed bid regimen for the FDC was shown through a Phase 1 PK/PD study (Study P035/1051) which showed equivalence of steady-state ertugliflozin AUC₀₋₂₄ on Day 6, and similarity in steady state PD (UGE₀₋₂₄ after the morning dose on Day 6), between the qd and BD regimens at the same total daily dose (2.5 mg BD versus 5 mg QD and 7.5 mg BD versus 15 mg QD). This study supports BD dosing of the ertugliflozin-metformin FDC. However, it is important to note that there was no clinical study to compare the clinical efficacy/safety of once versus twice daily ertugliflozin dosing. Furthermore, two FDCs containing a SGLT-2 inhibitor and metformin are already available in Australia: Xigduo-XR: FDC of dapagliflozin+metformin which requires once daily dosing, and Jardiamet: FDC containing empagliflozin and metformin which requires twice daily dosing. It is important to note that empagliflozin has added advantage of being approved in adults with T2DM and established cardiovascular disease to reduce the risk of cardiovascular death. This is especially important in light of the fact that no CV data was submitted for ertugliflozin. There is also lack of adequate evidence for long term efficacy/safety of ertugliflozin (refer to Steglatiro report submission).

Overall, the benefit-risk profile Segluromet (FDC of ertugliflozin + metformin) in the proposed usage is not currently favourable but may become favourable if the changes recommended to Steglatiro are resolved, the PI recommendations are adopted and the Clinical questions satisfactorily responded to.

Second round assessment of benefit-risk balance

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

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

Second round recommendation regarding authorisation

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

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

when treatment with both ertugliflozin and metformin is appropriate. (Refer Clinical Trials, Dosage and Administration).

Approval for the above indication is subject to the following:

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

VI. Pharmacovigilance findings

Steglatro risk management plan

- Steglatro is proposed to be used as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM as monotherapy when metformin is considered inappropriate due to intolerance or in combination with other anti-hyperglycaemic agents.
- The proposed dosing regimen of Steglatro involves oral administration of one tablet (5 mg) once daily which can be increased to 15 mg once daily if additional glycaemic control is needed.
- The sponsor has submitted EU-RMP version 1.0 (dated 22 December 2016; Data Lock Point (DLP) 31 May 2016 and Australian Specific Annex (ASA) version 1.0 (dated April 2017) in support of this application. The sponsor later submitted EU-RMP version 1.1 (dated 15 August 2017; DLP 31 May 2016) and ASA version 1.1 (dated 24 November 2017) in support of this application.
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies for Steglatro are summarised in Table 25, below.

Table 25: Summary of ongoing safety concerns for Steglatro

| Summary of safety concerns | | Pharmacovigilance | | Risk Minimisation | |
|----------------------------|--|-------------------|----------------|-------------------|---|
| | | Routine (R) | Additional (A) | R | A |
| Important Identified Risks | Volume depletion | ü | ü | ü | - |
| | Diabetic ketoacidosis with atypical presentation | ü | ü | ü | - |
| Important Potential Risks | Renal impairment | ü | ü | ü | - |
| | Bone fracture | ü | ü | - | - |
| | Lower limb amputation* | ü | ü | - | - |
| Missing information | Use in paediatric patients | ü | ü | ü | - |
| | Use in elderly patients (≥ 75 | ü | ü | ü | - |

| Summary of safety concerns | | Pharmacovigilance | | Risk Minimisation | |
|----------------------------|--------------------------------------|-------------------|---|-------------------|---|
| years) | | | | | |
| | Use in pregnancy and breastfeeding | Ü | - | Ü | - |
| | Use in patients with CHF Class II-IV | Ü | Ü | - | - |
| | Long-term CV Safety | Ü | Ü | - | - |

*Recommended by the RMP evaluator for all products at the first round and added in EU-RMP version 1.1 as well as the ASAs for the all the products which were submitted at the second round.

- Additional pharmacovigilance activities include two ongoing clinical trials (Study 8835-004/B1521021 and Study 8835-007/B1521017) and two planned paediatric investigational plans (PIPs), which is acceptable.
- There are no additional risk minimisation activities which is acceptable.

Outstanding recommendations

There is one outstanding issue which applies to all three products containing ertugliflozin (Steglatro, Steglujan and Segluromet):

Advice to the delegate

The Delegate may wish to consider if a warning should be added under Precautions regarding the Important Potential Risk (recommended by the RMP evaluator): Lower limb amputations; similar to the canagliflozin PI and consistent with the recommendation by the Pharmacovigilance Risk Assessment Committee (PRAC) regarding the SGLT2 inhibitors and special warnings and precautions in the EU Summary of Product Characteristics (SmPC).

'Lower Limb amputations: An increase in cases of lower limb amputation (primarily of the toe) has been observed in ongoing long-term, clinical studies with another SGLT2 inhibitor. It is unknown whether this constitutes a class effect. Like for all diabetic patients it is important to counsel patients on routine preventative foot-care.'

The Delegate should note that the PI for empagliflozin (and associated combination products) now includes a warning under Precautions about lower limb amputations.

If the Delegate considers that a warning under Precautions should be added to the PI regarding lower limb amputation (similar to the recommendation by PRAC for the SmPC) then the sponsor should align the Consumer Medicine Information (CMI) with the PI.

'Lower limb amputations' has been added as a safety concern (important potential risk) in the EU-RMP and ASA for all products.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

The Steglatro EU-Risk Management Plan (RMP) (version 1.1, dated 15 August 2017, data lock point 31 May 2016), with Australian Specific Annex (version 1.1, dated 24 November 2017), included with submission PM-2017-01328-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

The following wording is recommended for the Periodic Safety Update Report (PSUR) requirement:

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

As Steglatro is a new chemical entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

Steglattro (Ertugliflozin) is to be included in the Black Triangle Scheme. The PI and CMI for Steglattro must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

Steglujan risk management plan (abridged)

- The sponsor has submitted EU-RMP version 1.0 (dated 11 January 2017; DLP 31 May 2016 and ASA version 1.0 (dated April 2017) in support of this application. The sponsor later submitted EU-RMP version 1.1 (dated 15 August 2017; DLP 31 May 2016) and ASA version 1.1 (dated 24 November 2017) in support of this application.
- The proposed Summary of Safety Concerns for Steglujan and their associated risk monitoring and mitigation strategies are summarised in Table 26, below.

Table 26: Summary of ongoing safety concerns for Steglujan

| Summary of safety concerns | | Pharmacovigilance | | Risk Minimisation | |
|----------------------------|----------------------------|-------------------|----------------|-------------------|---|
| | | Routine (R) | Additional (A) | A | R |
| Important identified risks | Volume depletion | ü | ü | ü | - |
| | Diabetic ketoacidosis with | ü | ü | ü | - |

| Summary of safety concerns | Pharmacovigilance | Risk Minimisation | | |
|--|-------------------|-------------------|---|---|
| atypical presentation | | | | |
| Hypersensitivity reactions, including anaphylactic reaction, angioedema, rash, urticaria, cutaneous vasculitis, skin exfoliation, and Stevens-Johnson syndrome | ü | - | ü | - |
| Gastrointestinal disorders: nausea, vomiting, constipation, diarrhoea, abdominal pain, flatulence, abdominal pain upper, and related terms (dyspepsia and gastritis) | ü | - | ü | - |
| Musculoskeletal disorders: osteoarthritis, pain in extremity, and related terms (for example, arthralgia, myalgia, myopathy) | ü | - | ü | - |
| Pancreatitis | ü | - | ü | - |
| Infections: URTI, nasopharyngitis, and related terms (bronchitis, acute bronchitis, pharyngitis, sinusitis, and rhinitis) | ü | - | ü | - |
| Impaired renal function, including acute renal failure (sometimes requiring dialysis) | ü | ü | ü | - |
| Lower Limb Amputations | ü | ü | ü | - |
| Bone fracture | ü | ü | - | - |
| Neurotoxicity: tremor, ataxia, and balance disorders | ü | - | - | - |
| Suicidal ideation, suicide and depression | ü | - | - | - |
| Skin reactions: contact dermatitis | ü | - | - | - |

| Summary of safety concerns | | Pharmacovigilance | | Risk Minimisation | |
|----------------------------|---|-------------------|---|-------------------|---|
| | Pancreatic cancer | ü | - | - | - |
| | Rhabdomyolysis | ü | - | - | - |
| Missing information | Use in paediatric patients (patients below 18 years of age) | ü | ü | ü | - |
| | Use in elderly patients (≥75 years) | ü | ü | ü | - |
| | Use in pregnancy and breastfeeding | ü | - | ü | - |
| | Use in patients with CHF Class II-IV | ü | ü | - | - |
| | Long-term CV Safety | ü | ü | - | - |
| | Theoretic carcinogenic potential | ü | - | - | - |

- The additional pharmacovigilance activities are the same as what is proposed for ertugliflozin (two ongoing clinical trials and two planned PIPs; Steglatiro).
- There are no additional risk minimisation activities as per the application for ertugliflozin.

Outstanding recommendations

There are no other outstanding issues at the second round.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

The Steglujan EU-Risk Management Plan (RMP) (version 1.1, dated 15 August 2017, data lock point 31 May 2016), with Australian Specific Annex (version 1.1, dated 24 November 2017), included with submission PM-2017-01329-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

The following wording is recommended for the PSUR requirement:

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be

submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

As Steglujan is a new chemical entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

Steglujan (Ertugliflozin with sitagliptin) is to be included in the Black Triangle Scheme. The PI and CMI for Steglujan must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

Segluromet risk management plan (abridged)

- The proposed dosing regimen involves twice daily oral administration with individualisation of the starting dose of Segluromet based on the patient's current regimen.
 - In patients on metformin, switch to Segluromet tablets containing 2.5 mg ertugliflozin, with a similar total daily dose of metformin.
 - In patients on ertugliflozin, switch to Segluromet tablets containing 500 mg metformin, with a similar total daily dose of ertugliflozin.
 - In patients already treated with ertugliflozin and metformin, switch to Segluromet tablets containing the same total daily dose of ertugliflozin and a similar daily dose of metformin.
- The proposed Summary of Safety Concerns for Segluromet and their associated risk monitoring and mitigation strategies are summarised in Table 27 below.

Table 27: Summary of ongoing safety concerns for Segluromet

| Summary of safety concerns | | Pharmacovigilance | | Risk Minimisation | |
|----------------------------|--|-------------------|----------------|-------------------|---|
| | | Routine (R) | Additional (A) | R | A |
| Important identified risks | Volume depletion | ü | ü | ü | - |
| | Diabetic ketoacidosis with atypical presentation | ü | ü | ü | - |
| | Lactic acidosis | ü | - | ü | - |
| Important | Renal Impairment | ü | ü | ü | - |

| Summary of safety concerns | | Pharmacovigilance | | Risk Minimisation | |
|----------------------------|--|-------------------|---|-------------------|---|
| potential risks | Lower limb amputations | ü | ü | ü | - |
| | Bone fracture | ü | ü | - | - |
| Missing information | Use in paediatric patients | ü | ü | ü | - |
| | Use in elderly patients (≥ 75 years) | ü | ü | ü | - |
| | Use in pregnancy and breastfeeding | ü | - | ü | - |
| | Use in patients with CHF Class II-IV | ü | ü | - | - |
| | Long-term CV Safety | ü | ü | - | - |

VII. Overall conclusion and risk/benefit assessment

The main submission (Steglatro) was summarised in the following Delegate's overview and recommendations:

Quality

Approval is recommended from a pharmaceutical chemistry and quality control perspective.

However, it should be noted that whilst the pharmaceutical aspects of the PI documents and Product labelling for each submission are considered acceptable, they are yet to be finalised due to issues with the proposed trade names.

Whilst the inclusion of the tablet strengths in the trade names is desired, the sponsor has chosen to include the units (in 'mg') as part of the trade name, which is not desirable.

Nonclinical

- The nonclinical dossier contained no critical deficiencies.
- Primary pharmacology studies, showing inhibition of SGLT2 in vitro and increased urinary glucose excretion in vivo, offer support for the proposed use of the drug in the treatment of T2DM.
- Ertugliflozin is not predicted to produce clinically significant enzyme or transporter inhibition in patients to give rise to pharmacokinetic drug interactions.
- The toxicological profile of ertugliflozin is typical of the SGLT2 inhibitor class.

- The kidney, adrenal gland, bone and stomach were identified as targets for toxicity in repeat-dose studies in rats. These effects are largely seen to be related to osmotic diuresis (caused by glucosuria due to SGLT2 inhibition) and altered calcium homeostasis (secondary to carbohydrate malabsorption due to SGLT1 inhibition in the intestine). Supporting limited human relevance, histopathological changes in these tissues were not seen in dogs at very high multiples of the clinical exposure (up to approximately 380 fold).
- Ertugliflozin was not genotoxic. The finding of increased phaeochromocytomas in male rats is not considered to indicate that ertugliflozin poses a particular carcinogenic risk to patients.
- Like other members of this class, concerns exist for potential irreversible effects of ertugliflozin on the developing kidney. Treatment in the juvenile animal study commenced after renal anatomical maturation; other earlier developmental studies did not include microscopic examination of the kidney. Concern is greatest for drug exposure prior to this stage (that is, in utero in humans and prior to postnatal Day 21 in rats). Ertugliflozin should be assigned Pregnancy Category D, rather than Category C as the sponsor proposes.
- There are no nonclinical objections to the registration of Steglatiro for the proposed indication provided that the Product Information is amended as directed.

Clinical

Pharmacology

Ertugliflozin tablets contain 6.48 or 19.43 mg of ertugliflozin pyroglutamic acid, which is equivalent to 5 and 15 mg of the active ingredient ertugliflozin.

Ertugliflozin tablets contain the inactive ingredients: microcrystalline cellulose, lactose monohydrate, sodium starch glycolate Type A and magnesium stearate. The film coating contains hypromellose, lactose monohydrate, macrogol 3350, triacetin, titanium dioxide and iron oxide red.

Pharmacokinetics

Following oral administration, the mean T_{max} was 1 h and $T_{1/2}$ 12.2 to 12.6 h.

The oral bioavailability was 100%.

Food had no effect on AUC but C_{max} was reduced by 29%.

The pharmacokinetics was linear in the dose range 0.5 to 300 mg in healthy subjects.

The AUC was similar when dosed daily or twice daily, but C_{max} higher when given daily.

Volume of distribution was 215.3L. Ertugliflozin is highly bound to plasma proteins. There are 8 metabolites. Phase I metabolism was minimal. The two main metabolites are pharmacologically inactive. About 50% of the oral dose is recovered from the urine.

There was no difference in plasma concentration when ertugliflozin was co-administered with metformin or sitagliptin or glimepiride.

In patients with moderate hepatic impairment, there was a 13% decrease in AUC and 22% decrease in C_{max} . Ertugliflozin has not been studied in severe hepatic impairment.

In popPK studies, the AUC for ertugliflozin in mild, moderate and severe renal impairment was estimated using log-linear regression to be approximately 1.2, 1.4 and 1.7 fold higher than AUC_{inf} values in subjects with normal renal function.

The evaluator noted that although ertugliflozin did not induce or inhibit a range of CYP enzymes, it is in part a substrate for both CYP3A4 and CYP3A5; however, no studies have examined the effects of a strong CYP3A inhibitor, such as clarithromycin or itraconazole, on the PKs of ertugliflozin. Furthermore, pharmacokinetic interactions between ertugliflozin and other commonly administered drugs in this patient population such as diuretics, warfarin, and digoxin and so on were not evaluated. The effect of smoking and alcohol use on ertugliflozin PKs was also not specifically studied.

Pharmacodynamics

In healthy subjects, there was a plateau of urinary glucose excretion of around 58-65 grams/day for doses of > 30 mg ertugliflozin in a fasted state. UGE increased when patients were fed a high caloric meal. There was no change in serum glucose levels.

In patients with T2DM, Phase II studies examined 2 and 4 mg doses and found cumulative increase in AUC of UGE of 70g and 80.5g respectively. The 5 mg and 15 mg doses were not evaluated.

No effect on QTc or urinary electrolytes. Markers of bone resorption increased.

There was a similar UGE with 5 and 15 mg in patients with T2DM. Urinary glucose excretion decreases with decreasing eGFR. The UGE_{0.24} values on Day 1 in the mild, moderate and severe renal impairment groups were 49.75% (90% CI: 27.22%, 90.93%), 38.10% (90% CI: 20.85%, 69.64%), and 13.95% (90% CI: 7.32%, 26.58%) compared to subjects with T2DM but normal function group (72.31 g).

Efficacy (monotherapy)

Study P003/1022

A Phase III, randomised, double blind, placebo controlled, 26 week multicentre study with a 26 week extension to evaluate the efficacy and safety of ertugliflozin monotherapy in the treatment of subjects with T2DM and inadequate glycaemic control despite diet and exercise.

Only 26 week placebo controlled part of the study was complete at the time of submission. The study had a 1 week screening period, 8 week diet/exercise period where other medication was discontinued and 2 week placebo run in period.

Inclusion criteria were patients with T2DM aged > 18 years and BMI > 18kg/m², HbA1c 7 to 10.5% on no medicines or 6.5 to 9.5% on metformin, DPP-4, glinide or alpha glucosidase inhibitor (stopped prior to treatment).

Treatment was 5 or 15 mg ertugliflozin or placebo. Glycaemic rescue was given with metformin if fasting BGL was > 15 mmol/L from baseline to Week 6, fasting BGL > 13.3mmol/L from Weeks 6 to 12, fasting BGL > 11.1 after Week 12.

The primary efficacy analyses compared the efficacy of ertugliflozin relative to placebo in change from baseline in HbA1c at Week 26, excluding data obtained after the initiation of glycaemic rescue therapy or after bariatric surgery.

The mean changes from baseline in HbA1c at Week 26 for the ertugliflozin groups were compared to the mean changes in the placebo group using the estimated treatment differences via a constrained LDA (cLDA) model, proposed by Liang and Zeger. The statistical model included terms for treatment (categorical), time (categorical), the

treatment by time interaction, AHA status at study entry (binary; yes/no), and baseline eGFR (continuous). No imputation of missing data was performed. (This form of analysis is similar to ANOVA but also adjusts for baseline risk factors).

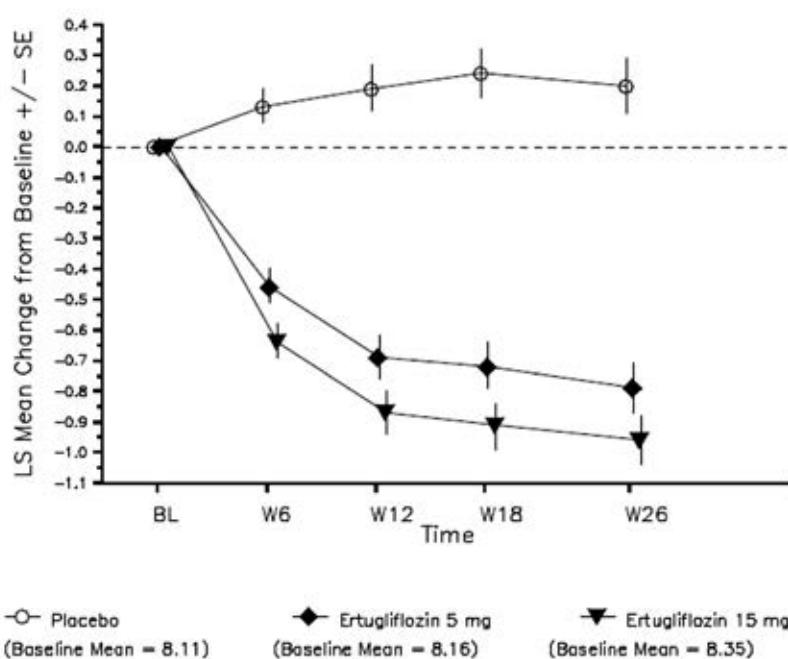
Results

More patients discontinued in the placebo group due to hyperglycaemia or lack of efficacy.

Mean age was 56.4 years, 14.3% were < 45 years and 26% were > 65 years; 84% White, 8.5% Asian and 6.3% Black or African American. Mean BMI 33kg/m². Mean HbA1c 8.2%. Mean duration of diabetes 5 years. 52% were on previous anti-hyperglycaemic therapy.

Compared with placebo, the LS mean reductions from baseline in HbA1c at Week 26 were significantly greater in the ertugliflozin 5 mg (-0.99, 95% CI: -1.22, -0.76) and 15 mg (-1.16, 95% CI: -1.39, -0.93) groups (p < 0.001 for both comparisons).

Figure 4: Mean change in HbA1c from baseline from Baseline to Week 26



Abbreviations: A1C = hemoglobin A_{1c}; BL = baseline; cLDA = constrained longitudinal data analysis; LS = least squares; SE = standard error; W = week.

Compared with placebo, the raw proportions of subjects with an HbA1c < 7.0% were 2 and 3 times greater in the ertugliflozin 5 mg and 15 mg groups, respectively (28.2%, 35.8% and 13.1% in the ertugliflozin 5 mg, 15 mg and placebo groups, respectively).

The LS mean reductions from baseline in FPG at Week 26 were significantly (p < 0.001 for both comparisons) greater in the ertugliflozin 5 mg and 15 mg groups compared to the placebo group (-1.88, -2.41 and +0.03mmol/L, respectively).

At Week 26, 25.5% of patients in the placebo group, 1.9% of patients in the 5 mg group and 2.6% of patients in the 15 mg were taking rescue medication.

Efficacy (combination with other anti-hyperglycaemic agents)

Add-on to metformin

Study P007/1017

A Phase III, randomised, double blind, placebo controlled, 26 week multicentre study with a 78 week extension to evaluate the efficacy and safety of ertugliflozin in subjects with T2DM and inadequate glycaemic control on metformin monotherapy.

This is a 104 week, multicentre, randomised, parallel group study with a 26 week, double blind, placebo controlled treatment period (Phase A) followed by a 78 week active controlled treatment period (Phase B) in adults with T2DM, diagnosed in accordance with the ADA guidelines and inadequate glycaemic control (HbA1c 7.0 to 10.5% inclusive) on metformin monotherapy at a dose \geq 1500 mg/day. The study includes a screening period of 1 week, a minimum 8 week metformin stable dose period (when subjects discontinued and remained off any previous allowable background diabetes therapy except for metformin), and a 2 week single blind placebo run-in period prior to randomisation. Only the 26 week treatment phase was available for evaluation.

Patients were included if they were $>$ 18 years, BMI 18 to 40 kg/m² and had an HbA1c within the following range (see Table 28, below):

Table 28: HbA1c inclusion criteria

| Diabetes Medication at Screening Visit (S1) | A1C Inclusion Criterion at S1 |
|--|---|
| Metformin monotherapy, \geq 1500 mg/day | 7.0%–10.5% (53-91 mmol/mol) inclusive |
| Metformin monotherapy, $<$ 1500 mg/day | 7.5% - 11.0% (58-97 mmol/mol) inclusive |
| Dual combination therapy with metformin + sulfonylurea, DPP-4 inhibitor, meglitinide, or alpha-glucosidase inhibitor | 6.5%–9.5% (48-80 mmol/mol), inclusive |

Subjects were prescribed open label glycaemic rescue therapy and dosed according to physician judgment if they met specific, progressively more stringent, glycaemic criteria based on a repeated, confirmed FPG or HbA1c measured by the central laboratory. Glycaemic rescue therapy was initially with glimepiride and if that was insufficient basal insulin.

Randomisation was stratified so that at least 50% of the population was post-menopausal (so as to get sufficient high risk patients for fracture outcomes).

Patients were censored if they had glycaemic rescue therapy or bariatric surgery (except for glycaemic control endpoints).

The overall mean and median dose of metformin at randomisation was approximately 2000 mg/day and was similar across all groups. In this study there were a greater proportion of subjects of Asian 16% or Black 10.3% racial origin. Mean BMI 30.9kg/m². Mean HbA1c 8.2%. Mean duration of diabetes was 8 years.

Compared with placebo, the LS mean reduction from baseline in HbA1c at Week 26 was significantly greater ($p < 0.001$) for both ertugliflozin 5 mg (placebo subtracted difference (-0.70, 95% CI: -0.87, -0.53) and 15 mg (-0.88, 95% CI: -1.05, -0.71) groups.

The raw proportions of subjects with anHbA1c $<$ 7.0% were approximately 2.5-times greater in the ertugliflozin 5 mg and 15 mg groups than in the placebo group (35.3%, 40% and 15.8% in the ertugliflozin 5 mg, 15 mg and placebo group, respectively).

Compared with placebo, the LS mean reductions from baseline in FPG at Week 26 were significantly ($p < 0.001$) greater in the 5 mg and 15 mg ertugliflozin groups (-1.5, -2.2 and -0.05mmol/L, respectively).

Compared with placebo, the LS mean reductions from baseline in body weight at Week 26 were significantly ($p < 0.001$) greater in the ertugliflozin groups (-3.0, -2.9 and -1.3kg, respectively).

Compared with placebo, the LS mean reductions from baseline in sitting SBP at Week 26 were significantly greater in the ertugliflozin 5 mg and 15 mg groups (-4.4, -5.2 and -0.7 mmHg). The LS mean reductions from baseline in sitting DBP at Week 26 were also significantly greater in the ertugliflozin 5 mg and 15 mg groups (-1.6, -2.2 and +0.23 mmHg.).

Study P002/1013

A Phase III, multicentre, randomised, double blind, active comparator controlled clinical trial to study the safety and efficacy of the addition of ertugliflozin (MK-8835/PF-04971729) compared with the addition of glimepiride in subjects with T2DM who have inadequate glycaemic control on metformin.

The study population included in adults with T2DM and inadequate glycaemic control, defined as $\text{HbA1c} \geq 7.0\%$ and $\leq 9.0\%$ on ≥ 1500 mg/day metformin monotherapy for at least 8 weeks. The double blind treatment period was 104 weeks in duration and divided into two 52 week phases (Phase A; Weeks 0 to 52; Phase B; Weeks 52 to 104) and only Phase A results were provided in submitted dossier.

The comparative treatments were ertugliflozin 5 mg, 15 mg and glimepiride (1 to 8 mg). Open labelled sitagliptin was used for patients who had poor glycaemic control. The study was designed as a non-inferiority study.

There was a high drop-out rate for a non-inferiority study. Overall, 448, 441 and 437 subjects were randomised to ertugliflozin 5 mg, ertugliflozin 15 mg and glimepiride, respectively. The proportion of subjects who discontinued study medication in Phase A was 24.1%, 18.8% and 20.4% in ertugliflozin 5 mg, 15 mg and glimepiride groups, respectively, primarily related to discontinuations for hyperglycaemia and non-compliance with study drug. In addition, there were a significant number of protocol deviations. 23 subjects were randomised at more than 1 site. Overall, 31% of subjects were reported to have more than 1 major protocol variation. These factors potentially impact on the interpretation of results.

The mean duration of diabetes was 7 years. Mean dose of metformin was 2000 mg. mean HbA1c 7.8%.

At Week 52, there were clinically meaningful LS mean reductions from baseline in HbA1c in the ertugliflozin 5 mg group (-0.56%), 15 mg group (-0.64%) and the glimepiride group (-0.74%). The LS mean difference (95% CI) between ertugliflozin 15 mg and glimepiride at Week 52 was 0.10% (-0.02, 0.22); non-inferior. The LS mean difference (95% CI) between ertugliflozin 5 mg and glimepiride at Week 52 was 0.18% (0.06, 0.30) and not non-inferior.

Fewer subjects in the ertugliflozin 5 mg and 15 mg groups had a Week 52 HbA1c value $< 7\%$ compared with the glimepiride group (34.4%, 38% and 43.5%, respectively).

The LS mean reductions from baseline in FPG at Week 52 were greater in the ertugliflozin groups (-1.04, -1.32 versus 0.90 mmol/L for glimepiride).

Compared with glimepiride, the LS mean reduction from baseline in body weight was significantly greater in the ertugliflozin 5 mg and 15 mg groups (-3.0, -3.4 and +0.91kg, respectively).

Compared with glimepiride, the LS mean reductions from baseline in sitting SBP at Week 52 were greater in the ertugliflozin 5 and 15 mg groups (-2.3, -3.8 versus +0.95 mmHg, respectively). Similarly, LS mean reductions from baseline in sitting DBP at

Week 52 were greater in the ertugliflozin 5 and 15 mg groups (-0.92, -1.22 versus +0.32mmHg, respectively). The cumulative percentage of subjects who received glycaemic rescue medication through Week 52 was low: ertugliflozin 5 mg 5.6%, ertugliflozin 15 mg 3.6% and glimepiride 3.2% groups.

The proportion of subjects who met the composite endpoint of > 0.5% decrease from baseline in HbA1c at Week 52, no symptomatic hypoglycaemia between baseline and Week 52, and no increase in body weight at Week 52, excluding data after initiation of rescue therapy was higher in the ertugliflozin 5 mg and 15 mg groups relative to the glimepiride group (45.5%, 48.5% and 21.4%, respectively).

The Delegate commented that the high dropout rate and number of protocol deviations create some question on the quality of the study. Non-inferiority of the 15 mg dose to glimepiride was demonstrated but not the 5 mg dose. However ertugliflozin caused less weight gain and hypoglycaemia.

Study P005/1019

A Phase III, randomised, double blind, multicentre study to evaluate the efficacy and safety of the combination of ertugliflozin (MK- 8835/PF-04971729) with sitagliptin compared with ertugliflozin alone and sitagliptin alone, in the treatment of subjects with T2DM with inadequate glycaemic control on metformin monotherapy.

This was factorial study was to evaluate the efficacy and safety of the addition of dual combination therapy with ertugliflozin and sitagliptin compared with the addition of ertugliflozin alone or sitagliptin alone, in subjects with T2DM and inadequate glycaemic control on metformin monotherapy over 26 weeks. Subjects were on \geq 1500 mg/day of metformin for \geq 8 weeks with an HbA1c of \geq 0.5 and \leq 11%. There were 5 treatment arms. Patients who had inadequate glycaemic control on treatment received rescue therapy with glimepiride.

The main efficacy endpoint was HbA1c, safety and tolerability.

Data obtained after the initiation of rescue therapy was censored. The study was designed as a superiority study to detect difference of HbA1c of 0.4% with 94% power.

At baseline, the mean duration of diabetes was 7 years, HbA1c 8.5%, 70% had HbA1c $>$ 8%, mean dose of metformin 2000 mg.

The LS mean reductions from baseline in HbA1c at Week 26 were significantly greater in the E15/S100 group relative to the individual component treatment groups (S100 group and E15 group), and in the E5/S100 group relative to the individual component treatment groups (S100 group and E5 group) (-1.02, -1.08, -1.05, -1.49 and -1.52 in the E5, E15, S100, E5/S100 and E15/S100 groups, respectively; $p < 0.001$ for all pre-specified comparisons). There was little difference in the addition of 15 mg over 5 mg in combination with sitagliptin. An analysis of change from baseline in HbA1c at Week 26, including data after initiation of glycaemic rescue therapy (which included more subjects with HbA1c data at Week 26, particularly in the E5 and S100 groups) also showed results which were consistent with the primary analysis. Both combination therapy groups had a larger change in FPG, body weight and BP. No subjects received glycaemic rescue therapy in the E15/S100 group, as opposed to 2.5% of subjects who received treatment in the E5/S100 group. Urinary glucose was excreted by a similar amount in all ertugliflozin treatment groups.

Add ertugliflozin in patients on metformin plus sitagliptin

Study P006

This was a multicentre, randomised, double blind, placebo controlled, parallel group clinical trial of ertugliflozin in subjects with T2DM on stable treatment with metformin ≥ 1500 mg/day and sitagliptin 100 mg daily. Only the results of the 26 week component were evaluated. There were three treatment arms: E5, E15 and placebo. Open labelled glimepiride was given for patients with poor glycaemic control on treatment.

At baseline, 66% of patients were on metformin and a DPP-4 inhibitor, 34% were on metformin and a sulfonylurea. The median dose of metformin was 2000 mg. The mean duration of diabetes was 9.5 years.

The LS mean reductions from baseline in HbA1c at Week 26 were significantly greater in the ertugliflozin 5 mg and 15 mg groups compared with the placebo group (-0.78% and -0.86% versus placebo -0.09%). The addition of ertugliflozin was associated with greater decrease in the proportion of patients with HbA1c $< 7\%$, a greater reduction in FPG, body weight and SBP. Less than 2% of patients received glycaemic rescue therapy in the ertugliflozin groups, compared to 16.3% of those in the placebo group.

Study P017 Co-administration of ertugliflozin and sitagliptin

This was a multicentre, randomised, double blind, placebo controlled, parallel group, clinical trial of ertugliflozin co-administered with sitagliptin in 291 adults with T2DM and inadequate glycaemic control (HbA1c $\geq 8.0\%$ and $\leq 10.5\%$) while on diet and exercise.

Subjects with an HbA1c of $\geq 8.0\%$ and $\leq 10.5\%$ at screening while on diet and exercise and not on AHA treatment for ≥ 8 weeks were eligible to directly enter a 2 week, single blind placebo run-in period. Subjects on monotherapy or low dose dual combination therapy with an allowable AHA who had an HbA1c of $\geq 7.5\%$ and $\leq 10\%$ at screening entered a diet/exercise and AHA wash-off period ≥ 8 weeks in duration. Allowable AHAs prior to screening were metformin, alpha-glucosidase inhibitors, sulfonylureas and glinides. Glycaemic rescue therapy with glimepiride was given. At baseline, 52% were currently on AHA, 12% had received previous AHA, and 36% were treatment naïve. The baseline HbA1c was 8.9%.

The LS mean reduction from baseline in HbA1c at Week 26 was significantly greater in the E5/S100 and E15/S100 groups (-1.60 and -1.68 versus placebo -0.44). Changes in FPG were supportive. Glycaemic rescue therapy was required by no patients in the E15/S100 group, 0.1% in the E5/S100 group and 32% in the placebo group.

Safety

In the initial dossier, the safety data included a total of 4,418 subjects with an average duration of exposure was 174 days. This was a major limitation of the safety data. There are a number of studies with 52 week data that are near completion as well as a long term cardiovascular study due for completion in 2019.

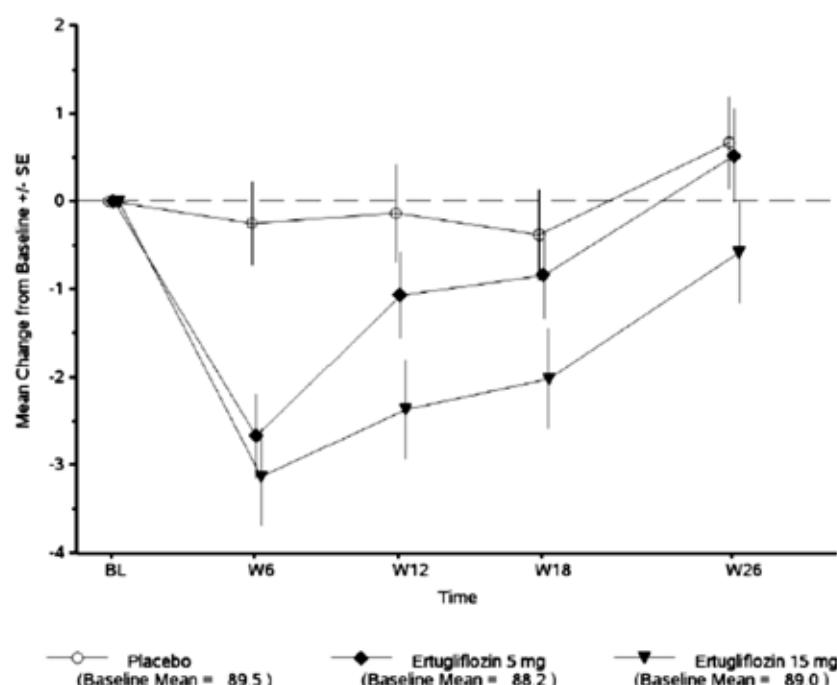
The sponsor pooled safety data from Phase II and II clinical studies where patients were exposed to ertugliflozin for > 12 weeks. The following comments refer mainly to the Broad Pool of safety data which includes all ertugliflozin treated patients and a non-ertugliflozin group that includes a range of other comparators.

The overall rate of adverse events among ertugliflozin and non-ertugliflozin groups was around 62%. The most commonly reported AEs with ertugliflozin were URTI, hypoglycaemia, UTI and headache. Hypoglycaemia was more commonly seen with the non-ertugliflozin treated patients. More patients treated with ertugliflozin had vulvovaginal infections, balanitis, dry mouth, thirst, polyuria and decreased BP.

Overall, there were more deaths with ertugliflozin (0.5% and 0.6% with 5 mg and 15 mg) than the comparator arms (0.2%). However the number of SAEs was similar (5 to 6%). There was a low rate of discontinuation due to AEs.

Patients treated with ertugliflozin had a greater decrease in eGFR at week 6 compared to comparators. However this returned to baseline or above baseline by Week 26 (it is unclear if this measurement is on or off therapy). By Week 26 there was no difference in the number of patients with a decrease of eGFR of > 30% (overall around 2.8%). There were a greater number of patients treated with ertugliflozin who had an increase in urea nitrogen, this may be more representative of volume depletion than renal impairment. There was no imbalance in the number of subjects who discontinued due to renal problems.

Figure 5: eGFR (mL/min/1.73 m²) Mean change from baseline over time (mean ±SE) all subjects as treated. Placebo controlled pool, including rescue approach



In subjects with renal impairment, the decrease in eGFR was greater and did not return to baseline at Week 26. The decrease in eGFR relative to placebo was -2.6 and -2.8% in the ertugliflozin 15 mg and 5 mg groups, compared to -0.54% in the comparator group. There was a dose dependent increase in the number of patients with a decrease in eGFR of > 30%.

Ertugliflozin had an adverse effect on lipid profile and positive effect on BP. There was no meta-analysis of cardiovascular studies included with the dossier, due to concerns that the release of such information may adversely affect the integrity of the long term CV safety study. However the 95% confidence interval for the risk of MACE+ was stated to be less than 1.8.

Cases of ketoacidosis were reported in the clinical development program, however these were rare. There were slightly more amputations with ertugliflozin than comparators.

There was no imbalance in the rate of fracture, change in BMD or calcium.

Long term safety data

In the their response, the sponsor submitted a safety update report (SUR) which contained cumulative safety data, including information that was collected after the reporting dates

established in the original marketing application, through the SUR cut-off dates for the Broad Pool. Broad Pool, included 7 Phase III studies of subjects with T2DM including a study of subjects with moderate renal impairment.

The Broad Pool also includes the Phase III studies that supported the ertugliflozin/sitagliptin and ertugliflozin/metformin FDCs.

The mean exposure was approximately 391 days in those treated with ertugliflozin.

Table 29: Mean exposure to ertugliflozin

| Treatment | < 25 wks | ≥ 25 wks to 50 wks | ≥ 50 wks to 76 wks | ≥ 76 wks to 102 wks | ≥ 102 wks | Total Subjects | Duration Range | Mean Duration |
|---------------------|----------|--------------------|--------------------|---------------------|-----------|----------------|----------------|---------------|
| Non-Ertugliflozin | 155 | 184 | 689 | 344 | 78 | 1450 | 1 to 768 days | 396.0 days |
| Ertugliflozin 5 mg | 130 | 218 | 949 | 337 | 82 | 1716 | 1 to 758 days | 391.5 days |
| Ertugliflozin 15 mg | 151 | 204 | 919 | 332 | 87 | 1693 | 1 to 754 days | 391.0 days |
| All Ertugliflozin | 281 | 422 | 1868 | 669 | 169 | 3409 | 1 to 758 days | 391.2 days |

Table 30: Subjects with AE resulting in death; cumulative exposure

| Cause | Ertugliflozin 5 mg | Ertugliflozin 15 mg | Placebo |
|-------------------|--------------------|---------------------|---------|
| N | 1716 | 1693 | 1450 |
| Cardiac disorders | 1 | 3 | 2 |
| Infections | 0 | 1 | 1 |

Table 31: Subjects with serious AEs; cumulative exposure

| Cause | Ertugliflozin 5 mg | Ertugliflozin 15 mg | Placebo |
|-----------------------------|--------------------|---------------------|---------|
| N | 1716 | 1693 | 1450 |
| Cardiac disorders | 25 | 24 | 14 |
| Neoplasms | 12 | 18 | 7 |
| Renal and urinary disorders | 6 | 4 | 6 |

Table 32: Adverse events leading to treatment discontinuation

| Cause | Ertugliflozin 5 mg | Ertugliflozin 15 mg | Placebo |
|-----------------------------|--------------------|---------------------|---------|
| N | 1716 | 1693 | 1450 |
| Infections | 15 | 12 | 5 |
| Renal and urinary disorders | 7 | 12 | 4 |

The cumulative incidence of genital mycotic infections in female and male subjects in the Broad Pool was higher in ertugliflozin treated subjects. More patients in the ertugliflozin treatment arms discontinued study due to infection.

The cumulative incidence of non-traumatic limb amputation in the Broad Pool was 0.2% ertugliflozin 5 mg, 0.5% ertugliflozin 15 mg, and 0.1% and non ertugliflozin group.

The cumulative incidence of adjudication-confirmed fracture was similar across the ertugliflozin 5 mg, ertugliflozin 15 mg and non ertugliflozin groups (0.6%, 0.5%, and 0.7%, respectively).

The cumulative incidence of malignancies in the Broad Pool was low across all groups, although the point estimate was higher in the ertugliflozin 15 mg group (1.3%) compared to the ertugliflozin 5 mg group (0.6%) and the non ertugliflozin group (0.6%). During the SUR period, no malignancies were reported in the ertugliflozin 5 mg group, 1 malignancy was reported in the ertugliflozin 15 mg group (basal cell carcinoma), and 4 malignancies were reported in the non ertugliflozin group (squamous cell carcinoma of the skin, colorectal cancer, basal cell carcinoma and hepatic cancer).

The cumulative rate of volume depletion in the broad pool was 1.9% with ertugliflozin 5 mg, 1.6% with ertugliflozin 15 mg and 1.2% with comparator.

Study P001/1016 moderate renal impairment

Study P001/1016 was a 52 week study that evaluated the efficacy and safety of ertugliflozin compared to placebo in subjects with inadequately controlled T2DM and Stage 3 chronic kidney disease (CKD). Subjects were randomised within 2 strata based on their screening eGFR:

1. eGFR \geq 45 to < 60 mL/min/1.73 m² (Stage 3A CKD) or
2. eGFR \geq 30 to < 45 mL/min/1.73 m² (Stage 3B CKD).

Although the LS mean reduction from baseline in HbA1c at Week 26 in the ertugliflozin 15 mg group was numerically greater than in the placebo group, the between group difference was not statistically significant; the LS mean reduction in the ertugliflozin 5 mg group was similar to that of the placebo group (-0.26%, -0.29 and -0.41% in placebo, ertugliflozin 5 mg and 15 mg groups, respectively). The sponsors have attributed this difference to the (prohibited) use of metformin during the study however the number of positive metformin assays was similar for all groups. When patients with a positive metformin assay were excluded from the study there was a statistically significant improvement in the E15 group but this was less than the 0.4% considered to be clinically relevant.

Table33: HbA1c change from baseline at Week 26 cLDA Subgroup with positive metformin assay results Full analysis set excluding rescue approach

| Treatment | Baseline | | Week 26 | | Change from Baseline at Week 26 | | |
|---|----------|--------------|---------|--------------|---------------------------------|---------------|--|
| | N | Mean (SD) | N | Mean (SD) | N | Mean (SD) | LS Mean (95% CI) [†] |
| Placebo | 126 | 8.01 (0.861) | 92 | 7.90 (0.972) | 128 | -0.13 (0.899) | -0.14 (-0.31, 0.02) |
| Ertugliflozin 5 mg | 131 | 8.24 (1.003) | 104 | 7.79 (1.115) | 134 | -0.31 (0.752) | -0.28 (-0.44, -0.13) |
| Ertugliflozin 15 mg | 123 | 8.16 (0.909) | 99 | 7.56 (0.793) | 127 | -0.52 (0.937) | -0.47 (-0.63, -0.31) |
| Estimated Difference | | | | | | | Difference in LS Means (95% CI) [†] |
| Ertugliflozin 5 mg vs Placebo | | | | | | | -0.14 (-0.36, 0.08) |
| Ertugliflozin 15 mg vs Placebo | | | | | | | -0.33 (-0.55, -0.11) |
| Conditional Pooled SD of Change from Baseline | | | | | | | 0.83 |

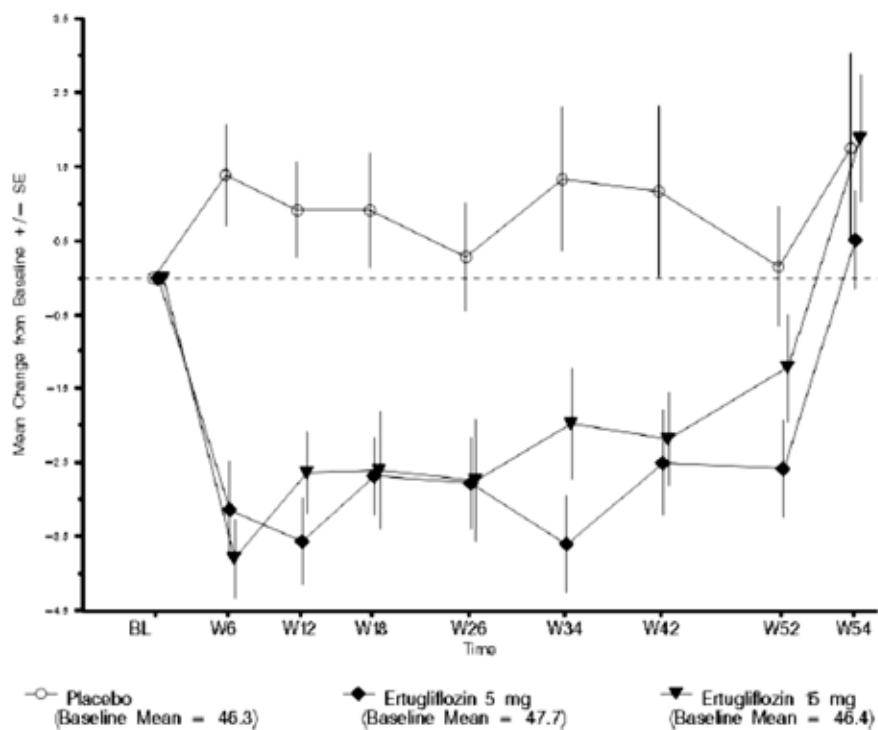
For baseline and Week 26, N is the number of subjects with non-missing assessments at the specific timepoint; for Change from Baseline at Week 26, N is the number of subjects in the FAS (i.e., randomized subjects who took at least 1 dose of study medication and had at least one assessment at or after 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/1.73m²), 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.

Treatment was ceased at 52 weeks.

Figure 6: Change in eGFR

Risk management plan

See *pharmacovigilance findings* above.

Ongoing studies

- Study 8835-004/B1521021; A randomised, double blind, placebo controlled, parallel group study to assess cardiovascular outcomes following treatment with ertugliflozin in subjects with T2DM and established vascular disease.
- Study 8835-007/B1521017; A safety and efficacy of the addition of ertugliflozin compared with the addition of placebo in subjects with T2DM on metformin (including data on fractures).
- There are two planned paediatric studies for patients aged 10 to 18 years.

Risk-benefit analysis

Delegate's considerations

Efficacy

Use as monotherapy

The sponsor has submitted data to demonstrate the efficacy of ertugliflozin compared to placebo in improving glycaemic control. There was no comparator trial to metformin. The proposed indication as use as monotherapy when metformin is not indicated or tolerated is appropriate.

Use in combination therapy

The sponsor has demonstrated efficacy in improving glycaemic control as add on treatment to metformin. The study evaluating the relative efficacy of ertugliflozin compared to glimepiride showed that the 5 mg dose was not non inferior to glimepiride alone. However ertugliflozin had other benefits in terms of reducing body weight and blood pressure, with a low rate of hypoglycaemia.

The sponsor has included studies using ertugliflozin in combination with sitagliptin. Basal insulin and sulphonylureas were used as rescue therapy in the clinical trials, however there were no studies evaluating the efficacy and safety of this combination.

The sponsor has not submitted studies to support use with GLP-1 receptor agonists, thiazolidinediones or alpha glucosidase inhibitors.

Other SGLT-2 inhibitors have an indication for use as combination therapy.

Empagliflozin has been studied with metformin, sulphonylureas, basal insulin, DPP-4 inhibitors and pioglitazone. Canagliflozin has been studied with metformin, sulphonylureas, pioglitazone and insulin. Dapagliflozin has been studied with metformin, sulphonylureas, DPP-4 inhibitors, insulin and exenatide.

There is no contraindication for use with other AHAs.

Based on the data submitted, indication for combination therapy with metformin or DDP-4 inhibitor would be more appropriate than the proposed for use with other hypoglycaemic data. Although the later scientifically reasonable based on extrapolation from other drugs of this class, other sponsors of SGLT-2 inhibitors have data to support a broader range of products in combination with their medicine.

Safety

The Delegate is concerned about the imbalance in cardiac AE between groups and lack of data about cardiovascular events. It is noted a long term safety study is underway. Other drugs of this class are associated with reduced risk of cardiovascular events and heart failure. However there are a number of examples of drugs within a class that have divergent adverse event profile and have subsequently been discontinued.

Activation of the renin-angiotensin system associated with volume depletion was seen in animal studies. Most other AEs noted in the clinical development program are consistent with the AEs of the other drugs of this class. However the rate of volume depletion and renal AEs for the 15 mg dose appears to be higher than other drugs of this class.

There was an imbalance in amputations in the clinical development program. An increased rate of toe amputations was also noted in the long term cardiovascular study for canagliflozin but not the clinical studies. There has been no risk of amputations identified for dapagliflozin or empagliflozin. This increased risk of amputation may be due to more vigilant monitoring in the clinical trial given the known safety profile of these agents however an inherent increased risk of amputations with ertugliflozin cannot be excluded. The risk of foot problems and amputations needs to be included in the PI, consistent with other medicines of this class.

A possible increased risk of fracture has been identified with canagliflozin but no other SGLT-2 inhibitor. There was no signal for fracture or reduced BMD in the clinical development program for ertugliflozin. Fractures are listed in the summary of safety concerns. There is no need for these to be included in the PI.

There was an imbalance in the number of malignancies in the clinical development program. Toxicology studies did not suggest an increased risk of malignancy. This should be included in the RMP.

There was no information about the efficacy or safety of ertugliflozin when used in combination with diuretics.

Use in renal insufficiency

The Delegate does not support the use of ertugliflozin in moderate renal insufficiency (eGFR 30 to 60mL/min/1.73 m²). The clinical study failed the primary endpoint of reduction in HbA1c compared to placebo in this group. In addition, treatment with ertugliflozin resulted in a decrease in eGFR which persisted until treatment was ceased. There were more AE in those with renal impairment.

The pharmacodynamic studies showed less urinary glucose excretion with increasing renal impairment; thus reduced efficacy in this group is not surprising. The increased risk of adverse events is also not surprising as patients with diabetes and renal disease are also likely to have other microvascular complications which impair their ability to compensate for excessive fluid loss or changes in BP.

Dosing instructions

The current recommendation is to start at a dose of 5 mg and increase to 15 mg if additional glycaemic control is needed. Some (but not all) of the clinical studies showed a numerically greater reduction in HbA1c and percent of patients with HbA1c in the target range with a higher dose, however the studies were not designed to compare relative efficacy of 5 mg versus 15 mg tablets. In the pharmacodynamic studies, there was increased UGE with increasing doses below 4 mg in healthy subjects but no increase in UGE in patients with T2DM at the doses proposed. In addition, the studies did not evaluate the effect of increasing the dose from 5 mg to 15 mg in patients with poor glycaemic control on 5 mg. And the rate of AEs was higher for the patients taking a 15 mg dose.

The Delegate would not recommend approving the 15 mg dose until the results of the cardiovascular study is available.

Use with sitagliptin

There was no benefit of 15 mg over 5 mg in the clinical trials of combination therapy with sitagliptin. The combination ertugliflozin 15 mg/sitagliptin 100 mg is not recommended for approval.

Use with metformin

The Delegate would not recommend approval of the ertugliflozin 7.5 mg/metformin 500 mg or ertugliflozin 7.5 mg/metformin 1000 mg tablets as a total daily dose of 15 mg ertugliflozin appears to have minimal gains in efficacy but more risk of adverse effects.

Use in pregnancy and children

The sponsor has amended the use in pregnancy section in line the recommendations from the nonclinical evaluator. The Delegate would also recommend the Pregnancy category to be changed to a D¹⁶.

Conclusion and recommendations

This will be the fourth registered SGLT-2 inhibitor. The evidence submitted to support registration in the initial dossier was somewhat limited in terms of comparators for efficacy and long term safety. This is somewhat mitigated by the safety update report in the sponsor's response. However the Delegate remains concerned about the lack of transparency with meta-vascular meta-analysis. The Delegate's preference would be to reject the application until this data is available. However the Delegate is aware that this medicine is approved by the FDA and a positive recommendation has been received by the CHMP. The Delegate has been unable to review the EMA reports about their consideration

of the 15 mg dose or use in renal impairment. The Delegate has been unable to review the PI from either regulator.

An alternative approach would be to approve a more limited indication and dose, conditional on amendments to the PI and RMP and a commitment to long providing the long term safety data and making the TGA aware safety concerns that arise in the interim.

Summary of issues

- The clinical dossier includes combination with sitagliptin and metformin and clinical studies. Use with sulphonylureas and insulin has occurred in the context of rescue therapy. Use with GLP-1, alpha glucosidase inhibitors and thiazolidinediones is not studied.
- The Delegate has concerns about use of the 15 mg dose in renal impairment. Lower GFR leads to increase AUC. Higher AUC does not lead to greater efficacy. The efficacy of SGLT-2 inhibitors decreases with decreased renal function.
- The recommendation to increase the dose to from 5 mg to 15 mg in patients with poor glycaemic control is not supported by evidence. There is a small benefit in average decrease in HbA1c and % of patients in the target range with 15 mg versus 5 mg but no statistical difference calculated. The correct study design would be to test if increasing dose from 5 to 15 mg led to a greater response in patients with inadequate glycaemic control on 5 mg.
- Use in moderate renal impairment is not justified. There is decreased efficacy with more adverse effects.
- Overall, AE profile consistent with other SGLT-2 inhibitors. It is however noted that the rates of AEs tended to be higher for 15 mg dose relative to other drugs of this class.
- There was an imbalance in CV deaths, CV events and amputations in the clinical studies. No meta-analysis of CV safety was available. A long term cardiovascular trial underway but not complete until 2019.

Proposed action

The Delegate had no reason to say, at this time, that the application for ertugliflozin 5 mg should not be approved for registration, conditional on changes to the indications, PI and RMP.

The Delegate would not recommend approval of the 15 mg tablet.

Proposed conditions

Clinical

To submit the results of Study 8835-004/B1521021: A randomised, double blind, placebo controlled parallel group study to assess cardiovascular outcomes following treatment with ertugliflozin in subjects with T2DM and established vascular disease.

RMP

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system. The suggested wording is:

The Steglatro EU-Risk Management Plan (RMP) (version 1.1, dated 15 August 2017, data lock point 31 May 2016), with Australian Specific Annex (version 1.1, dated

24 November 2017), included with submission PM-2017-01328-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

The following wording is recommended for the PSUR requirement:

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs).

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter. The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

As Steglatiro is a new chemical entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

Steglatiro (Ertugliflozin) is to be included in the Black Triangle Scheme. The PI and CMI for Steglatiro must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

Request for ACM advice

Questions for the ACM:

1. Should the 15 mg dose be approved? Although there was some benefit of 5 mg over 15 mg clinical trials, this does not mean an individual patient will respond better to 15 mg than 5 mg. There were more AEs with 15 mg.
2. Should we need to wait for the results of the cardiovascular meta-analysis or long term cardiovascular study before approval?
3. Is use with 'other anti-hyperglycaemic agents' appropriate when the clinical studies are limited to combination with metformin, and sitagliptin.

Response from sponsor

Comments on proposed regulatory action

The sponsor submitted 3 related applications to register ertugliflozin, a new chemical entity, and 2 FDC tablets for the treatment of patients with T2DM.

Ertugliflozin 15 mg

The Delegate expressed concern with regard to the benefits of ertugliflozin 15 mg versus 5 mg dose strength. The sponsor notes that in all 7 Phase III ertugliflozin studies, the point estimates for HbA1c and FPG lowering were greater with ertugliflozin 15 mg versus 5 mg.

These results support the efficacy of ertugliflozin when used in first, second and third line treatment settings in subjects with T2DM.

None of the individual ertugliflozin Phase III studies were powered to compare the ertugliflozin doses with regard to glycaemic efficacy. Indeed, Phase III development programs studying more than 1 dose strength for an investigational product are generally powered to detect differences relative to the comparator(s) and are not powered to detect differences between doses. This is consistent with the EMA guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus.³⁶

Therefore, the most relevant population for the assessment of ertugliflozin dose response is the placebo pool. The results from this pool are a direct determination of the efficacy of both doses of ertugliflozin in the intended population. In this pool with data from greater than 1500 subjects, the placebo-adjusted LS mean changes (95% CI) from baseline in HbA1c were -0.76% (-0.87, -0.65) and -0.91% (-1.02, -0.80) for the ertugliflozin 5 mg and 15 mg groups, respectively. Thus, ertugliflozin 15 mg resulted in an incremental HbA1c reduction of 0.15% relative to ertugliflozin 5 mg.

The sponsor also notes that the difference in glycaemic efficacy between the 15 mg and 5 mg doses of ertugliflozin were similar to those seen between the 25 mg and 10 mg doses of empagliflozin. In the empagliflozin monotherapy study, the 25 mg dose achieved an incremental HbA1c lowering of 0.11% (placebo-adjusted) relative to the 10 mg dose (see Table 1 from the empagliflozin label).

The proposed posology recommends a titration dose of ertugliflozin 15 mg once daily in those tolerating ertugliflozin 5 mg and needing additional glycaemic control. This dosing recommendation is further supported by the subgroup analysis in the placebo pool, where subjects with a baseline HbA1c \geq 7.9%, which is the population for whom dose titration would more likely to be considered, had a greater incremental difference in HbA1c lowering (placebo-adjusted) between ertugliflozin 15 mg and 5 mg than those with HbA1c < 7.9% (0.3% versus 0.03%, respectively).

With regard to safety, overall, ertugliflozin was safe and well tolerated at both the 5 mg and 15 mg doses, which demonstrated generally similar safety profiles. In the placebo pool, the overall percentage of subjects with 1 or more AEs was not notably different in the ertugliflozin 5 mg (45.5%), ertugliflozin 15 mg (50.4%), and placebo (51.1%) groups. The incidence of drug related AEs was similar in both ertugliflozin 5 mg and 15 mg groups (14.3% and 14.7%, respectively) and slightly higher than the placebo group (9.3%). The incidence of non-fatal SAEs was also slightly higher in the ertugliflozin 5 mg group (3.3%) compared with the 15 mg (2.4%) and placebo groups (2.9%). Similarly, the AEs resulting in discontinuation were slightly higher in the ertugliflozin 5 mg group (2.3%) compared with the 15 mg (1.4%) and placebo groups (1.7%). Similar findings were seen in the Broad Pool.

The findings at the time of the 4 month SUR confirmed the conclusions of the original application; there were similar safety profiles at both doses. The cumulative incidence of non-fatal SAEs in the Broad Pool was 6.8%, 6.0%, and 6.1% in the ertugliflozin 5 mg, 15 mg, and non-ertugliflozin groups, respectively. The cumulative incidence of death in the All Post Randomisation Follow-up period was 0.6%, 0.5%, and 0.7% in the ertugliflozin 5 mg, 15 mg, and non ertugliflozin groups, respectively.

In regard to specific AEs, evidence for a dose response was observed only for increases in LDL-C and female genital mycotic infections. There were no clinically meaningful differences between the 5 mg and 15 mg doses with regard to other special safety topics.

³⁶ CPMP/EWP/1080/00 Rev.1

Based on the totality of the data, the sponsor respectfully disagrees that there is a higher incidence of AEs with the ertugliflozin 15 mg compared to 5 mg.

The sponsor believes that the efficacy and safety results from the ertugliflozin development program demonstrate a favourable benefit: risk profile for both the 5 mg and 15 mg doses. Both dose strengths were approved by US FDA, and recommended by CHMP for approval in the EU (European Commission decision anticipated by the end of March 2018). Finally, the sponsor notes that approval of both ertugliflozin doses would necessitate the approval of both strengths in the FDC with sitagliptin, as well as the 7.5 mg strength in the metformin FDC.

Cardiovascular, death and amputation data

The Delegate expressed concern with regard to an imbalance in CV events, death and amputations in clinical studies and that no meta-analysis of the CV safety was available.

As noted with the sponsor's responses to the TGA's request, the 4 month SUR provided a substantial increase in long term exposure relative to the original submission (approximately 2 times the number of subjects with \geq 76 weeks to 102 weeks exposure, and approximately 5 times the number of subjects with \geq 102 weeks exposure), and summarised complete or nearly complete cumulative Phase A+B data for 4 of the 6 studies with Phase A+B designs. Data in the SUR showed similar incidences of non-fatal SAEs across groups in the cardiac disorders System Organ Class (SOC) (ertugliflozin 5 mg: 1.5%; ertugliflozin 15 mg: 1.4%, non ertugliflozin: 1.0%) and the nervous system disorder SOC (ertugliflozin 5 mg: 0.8%; ertugliflozin 15 mg: 0.2%; non-ertugliflozin: 0.6%).

Further analysis of CV events from the SUR Broad Pool that were potentially submitted for CV adjudication (using the preferred terms in the Cardiovascular Adjudication Charter plus all reported 'death' terms) was provided. The results from this analysis showed that the incidence of CV AEs was similar across groups (ertugliflozin 5 mg: 4.2%; ertugliflozin 15 mg: 2.8%; non-ertugliflozin: 4.4%), suggesting that there is no excess CV risk with ertugliflozin and is supportive of the information provided in the DMC attestation letter. In conclusion, based on the totality of the data, the sponsor believes there is no imbalance suggesting a safety concern for CV events. Therefore, the sponsor does not agree that information on CV events or that lack of CV safety data should be included in the PI. Results from the final analysis of adjudication-confirmed CV events will be provided after the completion of the CVOT (Study P004/1021).

The sponsor also conducted a CVMA of adjudicated, confirmed CV events from the Phase II/III studies in the submission and from the CV outcome study (P004/1021) which is ongoing and not included in the dossier. Data from the CVMA were submitted only to the US FDA by a separate firewalled team in order to not jeopardize the ongoing CVOT trial by disclosure of the interim results from this study. The CHMP also agreed that submission of unblinded interim outcome data from the CVOT could give rise to concern over trial integrity and therefore CHMP did not require that the CVMA be submitted. The CHMP agreed to evaluate the overall data package of nonclinical and clinical data for a conclusion on CV safety, considering also the scientific knowledge and clinical experience on the whole substance class and how similar the mechanism of action and receptor specificity are relative to other SGLT2 inhibitors. For these reasons, the CVMA was not submitted to the TGA. However, the sponsor believes that the data provided in the original submission, including the DMC attestation letter confirming that the Stage 1 CV risk assessment criterion has been met and responses to the TGA's request for information, which included the SUR, provided adequate information on CV safety to support the initial registration of ertugliflozin. The EMA's CHMP reviewed the same data as TGA and issued a positive opinion for ertugliflozin in January 2018 with a commitment by the sponsor to provide final results from the CVOT after its completion.

In the 4 month SUR, the cumulative incidence of AEs resulting in death in the Broad Pool was low and similar across groups; the cumulative incidence in the All Post Randomisation Follow-up period was 0.6%, 0.5%, and 0.7% in the ertugliflozin 5 mg, 15 mg, and non-ertugliflozin groups, respectively. Based on these data, the sponsor respectfully disagrees that there is an imbalance in death with ertugliflozin and does not agree with adding wording to the PI.

Although there was a small imbalance in the incidence of amputations in the SUR Broad Pool (ertugliflozin 5 mg: 0.2%; ertugliflozin 15 mg: 0.5%; non-ertugliflozin: 0.1%), the limited number of cases (12 subjects) makes assessment of a causal association with ertugliflozin difficult. In addition, the assessment is confounded by the fact that all subjects had baseline risk factors for amputation, as noted by TGA clinical evaluator. VERTIS- CV is a large, ongoing CVOT in subjects with established CV disease. Interim amputation data from the ongoing CVOT, that were previously available to only the sponsor's firewalled team, were recently released to the public by the US FDA. Compared to the SUR Broad Pool, where there were 12 subjects with 1 or more amputations, there were 61 (on-treatment analysis) and 72 (all follow-up analysis) subjects with 1 or more amputations in the analyses released by the US FDA. The data show that the magnitude of the differences in event rates are small and not dose dependent further supporting the sponsor's position that a causal association with ertugliflozin has not been established. Nevertheless, the sponsor agrees to update the PI to include the requested warning language describing an increased risk of amputation with another SGLT2 inhibitor. With regard to amputation incidence data, the sponsor is aware that the empagliflozin PI contains such data but notes that it is based on a relatively large number of cases from a completed study in subjects at higher risk for amputation. This is in contrast to the sponsor's data which are limited and/or interim in nature. Considering this, and the sponsor's position that a causal association with ertugliflozin has not been established, the sponsor does not agree to add these data to the PI. Of note, the US FDA informed the sponsor that they '*do not believe that the disclosure of the amputation data from the ongoing CVOT trial endangers the integrity of the trial.*' Access to interim data from the ongoing CVOT remains limited to the firewalled team per the Data Access Plan agreed with the US FDA.

Proposed indication for ertugliflozin use with other antihyperglycaemic agents

The Delegate expressed concern with regard to the degree of experience with ertugliflozin as combination therapy with insulin, sulfonylureas, GLP-1 receptor agonists, thiazolidinediones and alpha glucosidase inhibitors. However, the sponsor notes that the Delegate stated in the request for ACM advise that it is scientifically reasonable to extrapolate from the data generated for other medicines in this class to support a broader range of products in combination with ertugliflozin. The clinical evaluator recommended that the approval can be granted by qualifying the indication with reference to the Clinical trials, Precaution section for available data on the different add-on combination therapies. The sponsor has accepted the clinical evaluator's recommendation as outlined below.

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

- *Monotherapy when metformin is considered inappropriate due to intolerance or*
- *In combination with other anti-hyperglycaemic agents (see 5.1 Pharmacodynamic Properties, Clinical trials and 4.4 Special Warnings and Precautions for Use for available data on different add-on combination therapies).*

Use in subjects with moderate renal impairment

The Delegate expressed concern with regard to the use of ertugliflozin in subjects with renal insufficiency. The sponsor believes that the totality of the data for ertugliflozin in subjects with moderate renal impairment, together with data from other studies with

SGLT2 inhibitors in this population, show that ertugliflozin has the expected degree of pharmacodynamic activity (effects on HbA1c, FPG, body weight, blood pressure, eGFR) and an acceptable safety profile for an SGLT2 inhibitor in patients with Stage 3A CKD.

In the Overall Cohort (including subjects who used prohibited metformin), the change from baseline in HbA1c with ertugliflozin is nearly identical to the change from baseline observed with canagliflozin and empagliflozin. The sponsor believes that these changes from baseline with ertugliflozin (0.3% to 0.4% in the overall population for ertugliflozin 5 mg and 15 mg) are clinically relevant, particularly given the limitations of other AHAs in this patient population (for example, hypoglycaemia with sulfonylureas, fluid retention, and fracture risk with TZDs).

Evidence for HbA1c lowering comes not only from the post hoc analyses in Study P001/1016, which excluded subjects who tested positive for metformin use but also from an analysis of a moderate renal impairment subgroup of the placebo pool which did not include subjects from Study P001/1016. Moreover, data from the ertugliflozin Phase I study (Study P009/1023) demonstrated effects on UGE24 that were approximately half of those observed in subjects with normal renal function. Taken together, this profile is consistent to that of other SGLT2 inhibitors in subjects with moderate renal impairment.

Nevertheless, the sponsor acknowledges that the success criterion for the primary hypothesis in Study P001/1016 was not met, most likely because of the confounding effects of surreptitious metformin use among some subjects, which primarily impacted the placebo response. While the proportion of subjects who had a positive assay for metformin was similar, there was a larger HbA1c effect in placebo than in ertugliflozin subjects as reflected by the attenuation of the placebo response when excluding subjects who tested positive for metformin, with more minimal effects on HbA1c in the ertugliflozin groups.

Ertugliflozin causes an osmotic diuresis that leads to a transient decrease in eGFR, which is slightly greater in subjects with moderate renal impairment. However, in these subjects, the eGFR decrease was fully reversible following treatment discontinuation, providing evidence that acute haemodynamic changes play a role in the renal function abnormalities observed with ertugliflozin. With regard to safety, despite potentially greater exposure, ertugliflozin was well tolerated in subjects with moderate renal impairment with a similar safety profile at both doses. Since the selected ertugliflozin doses are near the top of the dose response curve and provide near maximal pharmacodynamic effect, any increase in exposure that might occur as a result of renal impairment is not expected to drive any meaningful increase in pharmacodynamic activity, especially given that less glucose is filtered in renally impaired patients. Although the incidence of volume depletion and renal related AEs is higher in subjects with moderate renal impairment, this would be anticipated based on the mechanism of action and is consistent with the findings of other SGLT2 inhibitors.

The sponsor believes that the totality of the pharmacodynamic, efficacy and safety data presented in subjects with moderate renal impairment supports use of ertugliflozin in subjects with eGFR \geq 45 to 60 mL/min/1.73 m².

Volume depletion and renal adverse events

The Delegate expressed concern with regard to the incidence of volume depletion and renal AEs with the 15 mg dose of ertugliflozin relative to other agents in the same class. The sponsor would like to clarify that the incidences of volume depletion and renal AEs (which may not be uniformly defined across agents) with the ertugliflozin 15 mg dose were not higher than those reported with the high dose strength of other agents in the SGLT2 inhibitor class.

The correct incidence of volume depletion AEs in the placebo pool was 1.7%, 0.8%, and 1.0% in the placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg groups, respectively (error in the Delegate's Overview which suggested that the incidence was 1.0% and 1.7% in the ertugliflozin 5 mg and 15 mg groups, respectively). With respect to other SGLT2 inhibitors, the incidence of volume depletion AEs was 1.3%, 0.4%, and 1.1% for the high dose of canagliflozin, empagliflozin and dapagliflozin, respectively. Thus, the incidence of volume depletion AEs for ertugliflozin 15 mg was consistent with incidences reported for the high dose strength of other SGLT2 inhibitors.

Similarly, the incidence of renal (renal related) AEs in the Broad Pool (including subjects with moderate renal impairment) was 0.4%, 0.6%, and 0.8% in the non-ertugliflozin, ertugliflozin 5 mg, and ertugliflozin 15 mg groups, respectively. With respect to other SGLT2 inhibitors, the incidence of renal AEs was 0.9%, 1.3%, and 4.0% (all Phase IIb/III study pool) for the high dose of canagliflozin, empagliflozin, and dapagliflozin, respectively. Thus, there was not an increase in the incidence of renal AEs with ertugliflozin 15 mg relative to the high dose strength of other SGLT2 inhibitors.

Other issues

The sponsor wishes to address other issues raised by the Delegate in the 'Request for ACM Advice.'

Biopharmaceutics

The sponsor addressed TGA questions concerning the biowaiver and bioanalytical methods on 23 February 2018 and was subsequently advised that these matters were considered resolved.

Drug interactions

The Delegate noted that the issue of certain drug interactions not studied remains unresolved. Although ertugliflozin did not induce or inhibit a range of CYP enzymes, it is in part a substrate for both CYP3A4 and CYP3A5; however, no studies have examined the effects of a strong CYP3A inhibitor, such as clarithromycin or itraconazole, on the PKs of ertugliflozin. Furthermore, pharmacokinetic interactions between ertugliflozin and other commonly administered drugs in this patient population such as diuretics, warfarin, and digoxin and so on were not evaluated. The effect of smoking and alcohol use on ertugliflozin PKs was also not specifically studied.

The sponsor clarifies that the primary clearance mechanism of ertugliflozin is glucuronidation by UGT1A9 and UGT2B7 (86%), with minor contributions from oxidative metabolism (12%). The sponsor clarifies that the minor oxidative pathway of ertugliflozin is catalysed primarily by CYP3A4, with lesser involvement of CYP3A5 and CYP2C8. Therefore, no specific drug interaction study with a strong CYP3A inhibitor, such as clarithromycin or itraconazole was considered necessary.

Across the Phase III studies, a high proportion of subjects were receiving concomitant antihypertension medication (ranging from 50.5% to 96.6%), including concomitant diuretic medication (ranging from 15.7% to 24.0%) and anti-dyslipidaemia medication (ranging from 32.0% to 77.3%). Thus, there is a large clinical experience with use of these concomitant medications.

Moreover, there was no supportive evidence that smoking and alcohol induces or inhibits UGT1A9, major enzyme for ertugliflozin metabolism, and hence were not studied.

RMP Risk of malignancy

The Delegate expressed concern with regard to malignancies in the ertugliflozin clinical development program and has requested that malignancy be added as an important potential risk in the RMP.

Malignancies reported in ertugliflozin groups reflected a wide range of unrelated types of neoplasms, both solid and haematological, with no notable temporal pattern of onset and no notable difference in neoplasm type relative to the non-ertugliflozin group. To date, there has been no reported plausible mechanism of action to support a causal relationship between SGLT2 inhibition and tumour promotion and the nonclinical data with ertugliflozin also do not support a relevant risk to humans for tumour development with ertugliflozin. At this time, the sponsor does not believe that the data with ertugliflozin warrant adding an additional risk to the RMP related to malignancy.

Use with diuretics

The Delegate's overview suggested that there is no efficacy or safety data for ertugliflozin when used in combination with a diuretic. The sponsor notes that subjects taking diuretics were included in the clinical trials and safety data were included in the original submission. There is no reason to expect that the glucose lowering effects of SGLT2 inhibitors, including ertugliflozin, are impacted when used in combination with diuretics.

Conclusion

In the general population with T2DM, both ertugliflozin 5 mg and 15 mg once daily provide clinically meaningful improvement in glycaemia. The incremental improvement with ertugliflozin 15 mg over 5 mg, as well as the acceptable and similar safety profiles of both doses supports the dosing recommendation to increase ertugliflozin dose from 5 mg to 15 mg in subjects who are tolerating 5 mg and need additional glycaemic control.

The glycaemic efficacy of the SGLT2 inhibitors is related to renal function, with attenuated glycaemic efficacy as renal function declines. Based on the totality of evidence available, ertugliflozin 15 mg provides clinically meaningful efficacy in subjects with Stage 3A CKD with an acceptable safety profile.

Based on the totality of the efficacy and safety data, the sponsor believes that there is a positive benefit: risk profile for ertugliflozin 5 mg and 15 mg, as well as the FDCs ertugliflozin/sitagliptin and ertugliflozin/metformin.

Advisory Committee Considerations³⁷

Three related applications: a new chemical entity ertugliflozin (Steglatro), as well as 2 new combination products ertugliflozin/sitagliptin (Steglujan) and ertugliflozin/metformin (Segluromet) were submitted.

The ACM taking into account the submitted evidence of efficacy, safety and quality, the ACM considered Steglato tablets containing 5 mg and 15 mg of Ertugliflozin to have an overall positive benefit-risk profile for the proposed amended indication:

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

³⁷ The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.

The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

- *Monotherapy when metformin is considered inappropriate due to intolerance; or*
- *In combination with other anti-hyperglycaemic agents (see 5.1 Pharmacodynamic Properties, Clinical Trials and 4.4 Special Warnings and Precautions for Use for available data on different add-on combination therapies).*

In providing this advice, the ACM noted that:

- There is an on-going long term cardiovascular trial currently underway and due to be completed in 2019.
- There are three other registered SGLT-2 inhibitors: empagliflozin, dapagliflozin and canagliflozin.
- Ertugliflozin, ertugliflozin/metformin and ertugliflozin/sitagliptin were approved by the FDA in December 2017.
- Ertugliflozin, ertugliflozin/metformin and ertugliflozin/sitagliptin were given a positive recommendation by the CHMP in January 2018.

Proposed conditions of registration

- Timely submission of the results of on-going trials and making TGA aware of safety concerns that arise in the interim;
- Implementation of the Risk Management Plan version most recently approved by the TGA's Pharmacovigilance and Special Access Branch;
- Finalisation of the Product Information to the satisfaction of the TGA.

Proposed amendments to the PI/CMI

- ACM noted that the PI recommends that patient discuss the diabetic ketoacidosis (DKA) risks with their doctor, including symptoms, treatment management before, during and after surgery where necessary.
- Reference to the importance of proper routine preventative foot care.
- A statement in the Dosage and Administration section of the PI and relevant sections of the CMI to ensure the reference of the impact of food and dosing.
- The terminology for Chronic Kidney Disease stages should be included in the PI when referring to degrees of renal impairment.
- Amendments to the PI and CMI as proposed in details by the Delegate and evaluators to be finalised in negotiations with the Delegate.

Specific Advice

The ACM advised the following in response to the Delegate's specific questions on the submission:

1. *Should the 15 mg dose be approved? Although there was some benefit of 15 mg over 5 mg in clinical trials, this does not mean an individual patient will respond better to 15 mg than 5 mg. There were more AEs with 15 mg.*

The ACM noted that the use of ertugliflozin 15 mg resulted in an incremental HbA1c reduction of 0.15% relative to ertugliflozin 5 mg. Taken together with the no long-term cardiovascular studies, the clinical importance of the 15 mg dose was questioned.

- As a long-term cardiovascular study is currently underway and there appeared to be no safety signals at present, the ACM was of the view that the 15 mg dose could be approved.
- Patients with renal impairment had a numerically greater improvement with 15 mg than 5 mg.

2. *Should we need to wait for the results of the cardiovascular meta-analysis or long term cardiovascular study before approval?*

The ACM noted that a cardiovascular outcomes trial is still on-going, and that the timely presentation of results of CVOT should be a condition of registration.

3. *Is use with 'other anti-hyperglycaemic agents' appropriate when the clinical studies are limited to combination with metformin, and sitagliptin.*

That the proposed indication would create consistency among drugs of this class, and including a reference to the clinical trial, warnings and precautions sections would provide more detail on the combinations studied for health professionals.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Post-ACM deliberations

The Delegate reviewed the sponsor's pre-ACM response and considered the recommendations of the ACM and responded as follows:

Regarding Steglatro

The proposed indication:

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

is accepted.

In relation to the statement '*see 5.1 Pharmacodynamic Properties, Clinical trials and 4.4 Special Warnings and Precautions For Use for available data on different add-on combination therapies*' please note that references to other sections of the PI under the indications section are not part of the indication. This reference is acceptable to aid reader's understanding however it would be preferable if this were formatted on the next line so as not to detract from the main indication.

Doses

The ACM were of the view that although there was only a marginal improvement in HbA1c with the bigger dose, the margin of improvement was similar to other larger doses of drugs in this class. Overall, the safety of the two doses was similar. It appears the larger dose may be more efficacious in renal impairment. Thus, at this stage the Delegate accepts both the 5 mg and 15 mg dose for registration. However, if in a post- market setting more AEs occur with the larger dose this may need to be reconsidered.

Use in renal impairment

The ACM noted the transient decrease in eGFR on initiating treatment with this class of medicines, which may be a PD effect related to the effects of renal vasculature. Although there is yet no data for ertugliflozin, other drugs of this class have an overall positive effect on renal function.

Thus, the Delegate accepts the current recommendations in the PI in relation to renal impairment.

Please see amendments recommended in PI

Regarding Steglujan

The proposed indication is acceptable.

Regarding Segluromet

The proposed indication is acceptable.

The metformin black box warning needs to be included in the Precautions section.

Outcome

Based on a review of quality, safety and efficacy, TGA approve the registration of

Steglatro application PM-2017-1328-1-5

- *Steglatro 5 ertugliflozin 5 mg film-coated tablet blister pack*
- *Steglatro 15 ertugliflozin 15 mg film-coated tablet blister pack*
- *MSD-Ertugliflozin 5 ertugliflozin 5 mg film-coated tablet blister pack*
- *MSD-Ertugliflozin 15 ertugliflozin 15 mg film-coated tablet blister pack.*

The approved indications for these therapeutic goods are:

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

- *monotherapy when metformin is considered inappropriate due to intolerance; or*
- *in combination with other anti-hyperglycaemic agents [see 5.1 Pharmacodynamic Properties, Clinical trials and 4.4 Special Warnings and Precautions for Use for available data on different add-on combination therapies].*

Specific conditions of registration applying to these goods

1. Steglatro 5 and 15; MSD-Ertugliflozin 5 and 15 ertugliflozin are to be included in the Black Triangle Scheme. The PI and CMI documents for Steglatro 5 and 15; MSD-Ertugliflozin 5 and 15 must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the products.
2. Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.
3. The ertugliflozin EU-Risk Management Plan (EU-RMP), version 1.1, dated 15 August 2017, (data lock point 31 May 2016), with Australian Specific Annex, version 1.1, dated 24 November 2017, included with submission PM-2017-01328-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
4. Submit the results of Study 8835-004/B1521021 Randomised, Double-blind, Placebo-Controlled, Parallel-Group Study To Assess Cardiovascular Outcomes Following Treatment with Ertugliflozin in Subjects with T2DM and Established Vascular Disease.

5. You [the sponsor] should review the results of 20 commercial scale API batches and revise the ertugliflozin drug substance specification if warranted.

Steglujan application PM-2017-1329-1-5

- *Steglujan 5/100 ertugliflozin/sitagliptin (as phosphate monohydrate) 5 mg/100 mg film-coated tablet blister pack*
- *Steglujan 15/100 ertugliflozin/sitagliptin (as phosphate monohydrate) 15 mg/100 mg film-coated tablet blister pack*
- *MSD-Ertugliflozin-Sitagliptin 5/100 ertugliflozin/sitagliptin (as phosphate monohydrate) 5 mg/100 mg film-coated tablet blister pack*
- *MSD-Ertugliflozin-Sitagliptin 15/100 ertugliflozin/sitagliptin (as phosphate monohydrate) 15 mg/100 mg film-coated tablet blister pack*

The approved indications for these therapeutic goods are:

<TRADENAME> (ertugliflozin and sitagliptin phosphate monohydrate) is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and sitagliptin is appropriate.[see 5.1 Pharmacodynamic Properties, Clinical trials, and 4.4 Special Warnings and Precautions for Use]

Specific conditions of registration applying to these goods

1. Steglujan 5/100 and 15/100 and MSD-Ertugliflozin-Sitagliptin 5/100 and 15/100 (ertugliflozin/sitagliptin phosphate monohydrate) is to be included in the Black Triangle Scheme. The PI and CMI documents for Steglujan 5/100 and 15/100 and MSD-Ertugliflozin-Sitagliptin 5/100 and 15/100 must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
2. Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The ertugliflozin/sitagliptin phosphate monohydrate EU-Risk Management Plan (EU-RMP), version 1.1, dated 15 August 2017 (data lock point 31 May 2016), with Australian Specific Annex, version 1.1, dated 24 November, included with submission PM-2017-01329-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

3. Submit the results:
 - a. From the ongoing Phase B of all 7 Phase III studies to enable assessment of long-term efficacy and safety of ertugliflozin component of the proposed FDC.
 - b. Of the cardiovascular meta-analysis (CVMA) of adjudicated, confirmed CV events from the Phase II/III studies and from the ongoing CV outcome study (P004/1021) upon completion.
4. You [the sponsor] should review the results of 20 commercial scale API batches and revise the ertugliflozin drug substance specification if warranted.

Segluromet application PM-2017-1330-1-5

- *Segluromet 2.5/500 ertugliflozin/metformin hydrochloride 2.5 mg/500 mg film-coated tablet blister pack*

- *Segluromet 2.5/1000 ertugliflozin/metformin hydrochloride 2.5 mg/1000 mg film-coated tablet blister pack*
- *Segluromet 7.5/500 ertugliflozin/metformin hydrochloride 7.5 mg/500 mg film-coated tablet blister pack*
- *Segluromet 7.5/1000 ertugliflozin/metformin hydrochloride 7.5 mg/1000 mg film-coated tablet blister pack*
- *MSD-Ertugliflozin-Metformin 2.5/500 ertugliflozin/metformin hydrochloride 2.5 mg/500 mg film-coated tablet blister pack*
- *MSD-Ertugliflozin-Metformin 2.5/1000 ertugliflozin/metformin hydrochloride 2.5 mg/1000 mg film-coated tablet blister pack*
- *MSD-Ertugliflozin-Metformin 7.5/500 ertugliflozin/metformin hydrochloride 7.5 mg/500 mg film-coated tablet blister pack*
- *MSD-Ertugliflozin-Metformin 7.5/1000 ertugliflozin/metformin hydrochloride 7.5 mg/1000 mg film-coated tablet blister pack*

The approved indications for these therapeutic goods are:

<TRADENAME> (ertugliflozin and metformin hydrochloride) is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both ertugliflozin and metformin is appropriate [see 5.1 Pharmacodynamic Properties, Clinical trials and 4.2 Dose and Method of Administration].

Specific conditions of registration applying to these goods

1. To be included in the Black Triangle Scheme. The PI and CMI documents for Segluromet 2.5/500, 2.5/1000, 7.5/500 and 7.5/1000 and MSD-Ertugliflozin-Metformin 2.5/500, 2.5/1000, 7.5/500 and 7.5/1000 must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
2. Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system. The ertugliflozin/metformin hydrochloride EU-Risk Management Plan (EU-RMP), version 1.1, dated 15 August 2017 (data lock point 31 May 2016), with Australian Specific Annex, version 1.1, dated 24 November, included with submission PM-2017-01330-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
3. Submit the results:
 - a. From the ongoing Phase B of all 7 Phase III studies to enable assessment of long-term efficacy and safety of ertugliflozin component of the proposed FDC.
 - b. Of the cardiovascular meta-analysis (CVMA) of adjudicated, confirmed CV events from the Phase II/III studies and from the ongoing CV outcome study (P004/1021) upon completion.
4. You [the sponsor] should review the results of 20 commercial scale API batches and revise the ertugliflozin drug substance specification if warranted.

Attachments 1A-C. Product Information

The PI for Steglatro approved with the submission which is described in this AusPAR is at Attachment 1A. The PI for Steglujan approved with the submission which is described in this AusPAR is at Attachment 1B. The PI for Segluromet approved with the submission which is described in this AusPAR is at Attachment 1C. For the most recent PIs, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>> .

Attachment 2. (Parts 1 and 2) Extract from the Clinical Evaluation Report for Steglatro

Attachment 3. Extract from the Clinical Evaluation Report for Steglujan

Attachment 4. Extract from the Clinical Evaluation Report for Segluromet

Therapeutic Goods Administration

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