Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Ertugliflozin/Sitagliptin

Proprietary Product Name: Steglujan

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

Date of first round report: 18 October 2017

Date of second round report: 18 January 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
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About the Extract from the Clinical Evaluation Report

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

Contents

List of common abbreviations

Abbreviation	Meaning
^{14}C-Total	Total amount of ^{14}C radioactivity recovered in urine
25-OH	25-hydroxy
A1c	Glycosylated haemoglobin (haemoglobin A1c; HbA1c)
AACE	American Association of Clinical Endocrinologists
ABPM	ambulatory blood pressure monitoring
ADA	American Diabetes Association
ADME	Absorption, distribution, metabolism and elimination
AE	Adverse event
Ae72%	Percent of dose recovered unchanged in urine from 0 to 72 hours post-dose
Ae96%	Percent of dose recovered unchanged in urine from 0 to 96 hours post-dose
AHA	Anti-hyperglycaemic agent
ALAG1	Absorption lag time
ALP	Alkaline phosphate
ALT	Alanine aminotransferase
ALT (SGPT)	Alanine aminotransferase
AMP	Adenosine monophosphate
ANOVA	Analysis of variance
AST (SGOT)	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{inf}	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time
$AUC_{inf(dn)}$	Dose normalized (to 1 mg) AUC_{inf}
AUClast	Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (Clast)
AV	Atrioventricular

Abbreviation	Meaning
BA	Bioavailability
BE	Bioequivalence
BID	Twice-daily
BMI	Body mass index
BP	Blood pressure
BSAP	Bone-specific alkaline phosphatase
Cav	Average concentration
CFB	Change from baseline
CI	Confidence interval
CKD	Chronic kidney disease
CL (IV)	CL; systemic clearance
CL/F (oral)	Apparent clearance; CL/F
cLDA	Constrained longitudinal data analysis
CLr	Renal clearance
C_{max}	Maximum observed plasma concentration
C_{max}(dn)	Dose normalized (to 1 mg) C_{max}
C_{min}	Lowest concentration observed during the dosing interval
CRU	Clinical research unit
CSR	Clinical study report
CT	Computed tomography
CTX1	C-terminal telopeptides of type-1 collagen
CV	Coefficient of variation
CV	Cardiovascular
CVOT	Cardiovascular outcome trial
CYP	Cytochrome P450
DBP	Diastolic blood pressure

Abbreviation	Meaning
DDI	Drug-drug interaction
DPM	Disintegrations per minute
DPP	Dipeptidyl peptidase
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
Emax	Maximum effect
ER	Excluding rescue
ESRD	End stage renal disease
EU	European union
F	Bioavailability
F1	Relative bioavailability
Fa	Fraction of dose absorbed
FAS	Full analysis set
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FME	Full model estimation
FOCE-I	First order conditional estimation method with interaction
FPG	Fasting plasma glucose
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
GMR	Geometric mean ratio

Abbreviation	Meaning
h	Hour/s
HbA1c	Haemoglobin 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
IPTH	Intact parathyroid hormone
IR	Immediate-release
IV	Intravenous
ka	First-order absorption rate constant
LDA	Longitudinal data analysis
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein-cholesterol
LLOQ	Lower limit of quantitation
L-PGA	L-pyroglutamic acid
LS	Least-squares
MACE	Major adverse cardiovascular event
MAR	Missing at random
MBMA	Model-based meta-analysis
MCAR	Missing completely at random
MedDRA	Medical Dictionary for Regulatory activities
min	Minute/s
MK-8335	Ertugliflozin/PF-04971729
MR	Modified-release
MRI	Magnetic Resonance Imaging

Abbreviation	Meaning
nCi	Nano Curie
NDA	New Drug Application
NONMEM	Non-linear mixed effects modelling
NTX-1	N-terminal telopeptide-1
OAD	Oral anti-diabetic
OC	Osteocalcin
P1NP	Procollagen type 1 amino-terminal propeptide
PD	Pharmacodynamics
PDLC	Pre-defined limit of change
P-gp	P-glycoprotein
PK	Pharmacokinetic
PO	Per os
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
RSE	Relative standard error
RTG	Renal threshold for glucose
SA	Specific activity
SAE	Serious adverse event

Abbreviation	Meaning
SBP	Systolic blood pressure
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	Standard deviation
SGLT1	Sodium-glucose co-transporter 1
SGLT2	Sodium glucose co-transporter 2
SMQ	Standardized MedDRA query
SOC	System organ class
SOP	Standard operating procedures
$t_{1/2}$	Terminal half-life
T2DM	Type 2 diabetes mellitus
TdP	Torsades de pointes
TEAE	Treatment-emergent adverse event
TECOS	Trial Evaluating Cardiovascular Outcomes with Sitagliptin
T_{max}	Time for C_{max}
TRAP5	Tartrate-resistant acid phosphatase isoform 5
UGE	Urinary glucose excretion
UGE0-24	Cumulative urinary glucose excretion over 24 hours
UGT	Uridine 5'-diphospho-glucuronosyltransferase
UK	United Kingdom
UKPDS	United Kingdom Prospective Diabetes Study
ULN	Upper limit of normal
US	United States
Vc/F	Apparent central volume of distribution
Vp/F	Apparent peripheral volume of distribution
Vss	Steady-state volume of distribution

Abbreviation	Meaning
Vz/F (oral)	Vz/F: apparent volume of distribution following oral administration

1. Submission details

1.1. Identifying information

Submission number	PM-2017-01329-1-5
Sponsor	Merck Sharpe and Dohme (Australia) Pty Ltd.
Trade name	Steglujan
Active substance	FDC tablets containing Ertugliflozin/ sitagliptin 5/50 mg, 15/50 mg, 5/100 mg and 15/100 mg.

1.2. Submission Type

This is an application to register ertugliflozin tablets (5 mg and 15 mg) for the treatment of type 2 diabetes mellitus (T2DM).

1.3. Drug class and therapeutic indication

MSD ertugliflozin-sitagliptin contains ertugliflozin pyroglutamic acid, a sodium-glucose co-transporter 2 (SGLT2) inhibitor and sitagliptin phosphate, a dipeptidyl peptidase 4 (DPP-4) inhibitor.

The proposed indication is:

> *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.*

1.4. Dosage forms and strengths

MSD-ertugliflozin-sitagliptin is available for oral use as film-coated tablets containing:

- 6.48 mg ertugliflozin pyroglutamic acid equivalent to 5 mg of ertugliflozin and 64.25 mg sitagliptin phosphate monohydrate equivalent to 50 mg of sitagliptin (MSD-ertugliflozin-sitagliptin 5 mg / 50 mg)
- 19.43 mg ertugliflozin pyroglutamic acid equivalent to 15 mg of ertugliflozin and 64.25 mg sitagliptin phosphate monohydrate equivalent to 50 mg of sitagliptin (MSD ertugliflozin-sitagliptin 15 mg / 50 mg)
- 6.48 mg ertugliflozin pyroglutamic acid equivalent to 5 mg of ertugliflozin and 128.5 mg sitagliptin phosphate monohydrate equivalent to 100 mg of sitagliptin (MSD-ertugliflozin-sitagliptin 5 mg / 100 mg)
- 19.43 mg ertugliflozin pyroglutamic acid equivalent to 15 mg of ertugliflozin and 128.5 mg sitagliptin phosphate monohydrate equivalent to 100 mg of sitagliptin (MSD ertugliflozin-sitagliptin 15 mg / 100 mg)

1.5. Dosage and administration

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

'General

The recommended starting dose of MSD-ertugliflozin-sitagliptin is 5 mg ertugliflozin/100 mg sitagliptin once daily, taken in the morning, with or without food. In patients tolerating MSD ertugliflozin-sitagliptin, 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 MSD-ertugliflozin-sitagliptin, the dose of ertugliflozin can be maintained.

In patients with volume depletion, correcting this condition prior to initiation of MSD ertugliflozin- sitagliptin is recommended (see PRECAUTIONS).

Renal Impairment

Assessment of renal function is recommended prior to initiation of MSD-ertugliflozin-sitagliptin and periodically thereafter (see PRECAUTIONS).

Initiation of MSD-ertugliflozin-sitagliptin is not recommended in patients with an eGFR less than 45 mL/min/1.73 m^2 (see PRECAUTIONS).

In patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 and tolerating MSD ertugliflozin-sitagliptin 5 mg, titrate to MSD-ertugliflozin-sitagliptin 15 mg once daily as 15 mg provided clinically meaningful reductions in HbA1c.

In patients with an eGFR less than 50 mL/min/1.73 m^2, MSD-ertugliflozin-sitagliptin containing 50 mg sitagliptin should be used.

Use of MSD-ertugliflozin-sitagliptin is not recommended in patients with eGFR persistently less than 45 mL/min/1.73 m^2.

Hepatic Impairment

No dosage adjustment of MSD-ertugliflozin-sitagliptin is necessary in patients with mild or moderate hepatic impairment. Benefit-risk for the use of MSD-ertugliflozin-sitagliptin in patients with severe hepatic impairment should be individually assessed since ertugliflozin has not been specifically studied in this population.

Paediatric Population

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

Elderly

No dosage adjustment is required based on age. Elderly patients are more likely to have decreased renal function. Because renal function abnormalities can occur after initiating ertugliflozin, and sitagliptin is known to be substantially excreted by the kidneys, care should be taken in dose selection in the elderly. (see Precautions).

Concomitant Use with Insulin or an Insulin Secretagogue

Coadministration of MSD-ertugliflozin-sitagliptin with insulin or an insulin secretagogue may require lower doses of insulin or the insulin secretagogue to reduce the risk of hypoglycaemia (see Precautions).

2. Background

2.1. Information on the condition being treated

The increasing worldwide prevalence of T2DM, along with its microvascular and macrovascular complications, is a major health issue and poses an increasing burden to health care systems around the world. The worldwide prevalence of diabetes in adults is expected to increase from 8.8% in 2015 (approximately 415 million people) to an estimated 10.4% (642 million people) by 2040; this represents a 55% increase in the number of people with diabetes relative to 2015.[1] There are 1.7 million Australians with diabetes (85% of these have T2DM).[2] Type 2 diabetes is associated with reduced life expectancy, significant morbidity due to the specific diabetes related microvascular complications (retinopathy, nephropathy and neuropathy), and the increased risk of macrovascular complications (ischemic heart disease, stroke and peripheral vascular disease). The development of these complications impacts on quality of life.

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

2.2. Current treatment options

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

A number of systematic reviews have examined the relationship between blood glucose control and long term complications in people with T2DM. These studies concluded that improved glycaemic control can reduce retinopathy, renal disease and neuropathy in T2DM. Long term data from the United Kingdom Prospective Diabetes Study (UKPDS; Stratton, 2000) also suggests that glycaemic control reduces the risk of macrovascular complications of T2DM.

[1] 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.
[2] www.diabetesaustralia.com.au

Although pharmacological intervention, either in the form of a single agent or in combination, may provide effective glycaemic control for some patients, many do not achieve their target A1c levels, and glycaemic control deteriorates over time.

The SGLT2 inhibitors are a new class of agents for T2DM therapy that have been shown to improve glycaemic control, reduce body weight and lower blood pressure. Agents of this class approved for use in Australia include empagliflozin (Jardiance, approved in April 2014), dapagliflozin (Forxiga in 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.

DPP-4 inhibitors act by increasing and prolonging the action of incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). By increasing and prolonging active incretin levels, sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner. The DPP-4 inhibitors approved in Australia include alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin; all of these DPP-4 inhibitors are also available as FDCs in combination with metformin.

Glyxambi was the first combination tablet of a DPP-4 inhibitor and an SGLT-2 inhibitor approved in USA in 2015 and is also available in Australia (2016); it is available in doses of 10 mg or 25 mg of empagliflozin with 5 mg of Linagliptin, to be taken once daily in the morning.

2.3. Clinical rationale

Ertugliflozin is an oral, highly selective SGLT2 inhibitor with greater than 2000-fold higher selectivity for SGLT2 compared to SGLT1. Under conditions of normoglycaemia, glucose is filtered in the glomerulus, with essentially all the filtered glucose being reabsorbed into the circulation in the early and late portion of the proximal tubule via the action of SGLT2 and SGLT1, respectively. Under conditions of hyperglycaemia, when the transporters reach their maximum reabsorptive capacity (referred to as the transport maximum for glucose) glucosuria ensues. Ertugliflozin inhibits renal glucose reabsorption, resulting in a lowering of the renal threshold for glucose and increased UGE, thereby reducing plasma glucose and A1C in subjects with T2DM. Ertugliflozin improves glycaemic control via a mechanism independent of insulin and pancreatic beta-cell function and its durability is not dependent on beta-cell function; it represents a potentially effective and durable therapy across the typical disease progression of T2DM. Furthermore, the extent of UGE is dependent on ambient glucose levels and as glucose levels decrease to normal, UGE also decreases, making hypoglycaemia unlikely.

Sitagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Concentrations of the active intact hormones are increased by sitagliptin, thereby increasing and prolonging the action of these hormones. Incretin hormones including GLP-1 and GIP are released by the intestine throughout the day, and levels are increased in response to a meal. These hormones are rapidly inactivated by DPP-4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic 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.

2.4. Formulation

2.4.1. Formulation development

Four strengths of film-coated, immediate release, FDC tablets containing ertugliflozin and sitagliptin for once daily (QD) administration have been developed and are proposed for commercialisation: ertugliflozin 5 mg/sitagliptin 100 mg; ertugliflozin 15 mg/sitagliptin 100 mg; ertugliflozin 5 mg/sitagliptin 50 mg; and ertugliflozin 15 mg/sitagliptin 50 mg.

The proposed FDC commercial formulations are identical to those used in the bioequivalence (BE) studies with the exception of debossing on the commercial tablets.

2.4.2. Excipients

In summary, each film-coated tablet of MSD-ertugliflozin-sitagliptin contains the following inactive ingredients: microcrystalline cellulose, dibasic calcium phosphate anhydrous, croscarmellose sodium, sodium stearyl fumarate, and magnesium stearate.

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

The film coating for the MSD-ertugliflozin-sitagliptin 5 mg / 100 mg and MSD-ertugliflozin-sitagliptin 15 mg / 100 mg tablets also contains iron oxide yellow.

2.5. Related submissions

Ertugliflozin and FDCs of ertugliflozin are being co-developed by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Merck), and Pfizer Inc, with Merck serving as the regulatory sponsor. Registration of ertugliflozin (Steglatro; PM-2017-01328-1-5), ertugliflozin/sitagliptin FDC (Steglujan; PM-2017-01329-1-5) and ertugliflozin/metformin FDC (Segluromet; PM-2017-01330-1-5) for the treatment of T2DM are being pursued concurrently.

2.6. Guidance

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

2.7. Evaluator's commentary on the background information

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

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

3.1.1. Clinical Pharmacology

The current submission comprises 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.

3.1.2. 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.

Comment: 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 bioequivalence (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 (Study P016/1006 and P042/1004) which have been discussed in the Steglatro evaluation report PM-2017-01328-1-5 [see Attachment 2].

3.2. Paediatric data

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

3.3. Good clinical practice

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

3.4. Evaluator's commentary on the clinical dossier

The submission was well-presented. For shortcomings of the concurrent ertugliflozin submission, please refer to the evaluation report for Steglatro.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic information

Table 1: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	Bioequivalence† Single dose	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
	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.

4.2. Summary of pharmacokinetics

4.2.1. Analytic Methods

A validated, specific and sensitive high-performance liquid chromatography tandem mass spectrometric (HPLC-MS/MS) method was used to determine plasma sitagliptin levels. The lower limit of quantitation (LLOQ) was 1.00 ng/mL and the linear range of the assay was 1.00 to 1000 ng/mL.

Plasma concentrations of ertugliflozin were determined using validated, sensitive and specific HPLC-MS/MS methods with a LLOQ ranging from 0.020 to 0.50 ng/mL.

4.2.2. Pharmacokinetics in healthy subjects

Comment: A limited number of studies examined the PKs of the ertugliflozin/sitagliptin FDC and these primarily related to the bioequivalence between the FDC tablets and corresponding free combinations of the matching dose strengths of the individual tablets. In addition, a single study examined the effect of a high fat/high-calorie breakfast on the PKs of the FDC tablet with the strength of ertugliflozin 15 mg/sitagliptin 100 mg. Where no dedicated PK studies are available for the FDC tablets, the evaluator requests that the Delegate refers to the concurrent submission for Steglatro which describes the studies relating to ertugliflozin.

4.2.2.1. Absorption

Sites and mechanism of absorption

Ertugliflozin-sitagliptin film-coated FDC tablets are for oral administration. For the ertugliflozin 15 mg/sitagliptin 100 mg, ertugliflozin 15 mg/sitagliptin 50 mg, ertugliflozin 5 mg/sitagliptin 100 mg and ertugliflozin 5 mg/sitagliptin 50 mg FDC, the median ertugliflozin T_{max} value was approximately 1.0 h and it was 3.0 h for the sitagliptin component.

4.2.2.2. Bioavailability

Bioequivalence to relevant registered products

Comment: The 50 mg and 100 mg sitagliptin tablets administered as part of the free combination treatments described below were provided as commercially packaged Januvia tablets, which were sourced from the USA.

Ertugliflozin 15 mg/sitagliptin 100 mg

Study P025/1038 examined the BE of ertugliflozin 15 mg/sitagliptin 100 mg FDC tablet and the free combination following a single dose under fasted conditions in 18 healthy subjects.

Under these conditions the geometric mean ratios (GMRs) and 90% confidence intervals (90% CIs) for the comparison of the FDC to the free combination for ertugliflozin AUC_{inf}, AUC_{last} and C_{max} were 98.25% (95.07%, 101.54%), 98.18% (95.17%, 101.30%),and 102.13% (92.32%, 112.99%), respectively. Median ertugliflozin T_{max} was 1.01 h for both treatments and the mean $t_{1/2}$ values for the FDC and free combinations were 13.38 h and 13.84 h, respectively.

For the sitagliptin component, the GMRs (90%CIs) comparing the FDC/free for AUC_{inf}, AUC_{last}, and C_{max} were 102.40% (99.51%, 105.38%), 102.60% (99.78%, 105.50%), and 114.14% (108.35%, 120.24%), respectively. The median sitagliptin T_{max} for the fixed-dose and free combinations were 3.00 h and 3.98 h, respectively, and the mean $t_{1/2}$ values were 12.16 h and 12.53 h, respectively.

The results indicated ertugliflozin 15 mg/sitagliptin 100 mg FDC and free combinations were bioequivalent as 90% CIs for the AUC_{inf}, AUC_{last} and C_{max} GMRs for both active components were contained within the (80%, 125%) acceptance limits.

Ertugliflozin 15 mg/sitagliptin 50 mg

Study P044/1053 examined the BE of ertugliflozin 15 mg/sitagliptin 50 mg FDC tablet and the free combination following a single dose under fasted conditions in 19 healthy subjects.

Under these conditions, the GMRs (90% CIs) for the comparison of the FDC to the free combination for ertugliflozin AUC_{inf}, AUC_{last} and C_{max} were 98.40% (95.37%, 101.52%), 98.47% (95.49%, 101.54%) and 91.74% (84.65%, 99.43%), respectively. Median ertugliflozin T_{max} was 1.00 h for both treatments and the mean $t_{1/2}$ values for the FDC and free combinations were 12.80 h and 12.60 h, respectively.

For the sitagliptin component, the GMRs (90%CIs) comparing the FDC/free for AUC_{inf}, AUC_{last}, and C_{max} were 101.89% (99.73%, 104.10%), 102.20% (99.92%, 104.53%) and 103.02% (94.37%, 112.46%), respectively. The median sitagliptin T_{max} for the fixed-dose and free combinations were 3.00 h and 2.24 h, respectively, and the mean $t_{1/2}$ values were 11.68 h and 11.70 h, respectively.

The results indicated that the ertugliflozin 15 mg/sitagliptin 50 mg FDC and free combinations were bioequivalent as 90% CIs for the AUC_{inf}, AUC_{last} and C_{max} GMRs for both active components were contained within the (80%, 125%) acceptance limits.

Ertugliflozin 5 mg/sitagliptin 100 mg

Study P048/1056 examined the BE of ertugliflozin 5 mg/sitagliptin 100 mg FDC tablet and the free combination following a single dose under fasted conditions in 18 healthy subjects.

Under these conditions, the GMRs (90% CIs) for the comparison of the FDC to the free combination for ertugliflozin AUC_{inf}, AUC_{last} and C_{max} were 101.23% (97.15%, 105.49%), 102.01% (97.89%, 106.32%) and 103.17% (93.76%, 113.52%), respectively. Median ertugliflozin T_{max} was 1.01 h for both treatments and the mean $t_{1/2}$ values for the FDC and free combinations were 12.99 h and 11.84 h, respectively.

For the sitagliptin component, the GMRs (90%CIs) comparing the FDC/free for AUC_{inf}, AUC_{last}, and C_{max} were 99.80% (98.12%, 101.51%), 99.77% (98.05%, 101.52%) and 99.76% (93.63%, 106.28%), respectively. The median sitagliptin T_{max} for the fixed-dose and free combinations were 3.00 h and 2.98 h, respectively, and the mean $t_{1/2}$ values were 11.56 h and 11.18 h, respectively.

The results indicated that the ertugliflozin 5 mg/sitagliptin 100 mg FDC and free combinations were bioequivalent as 90% CIs for the AUC_{inf}, AUC_{last} and C_{max} GMRs for both active components were contained within the (80%, 125%) acceptance limits.

Ertugliflozin 5 mg/sitagliptin 50 mg

Study P049/1057 examined the BE of ertugliflozin 5 mg/sitagliptin 50 mg FDC tablet and the free combination following a single dose under fasted conditions in 19 healthy subjects.

Under these conditions, the GMRs (90% CIs) for the comparison of the FDC to the free combination for ertugliflozin AUC_{inf}, AUC_{last} and C_{max} were 101.61% (97.98%, 105.37%), 101.69% (97.81%, 105.73%) and 99.80% (91.21%, 109.20%), respectively. Median ertugliflozin T_{max} was 1.00 h for both treatments and the mean $t_{1/2}$ values for the FDC and free combinations were 12.05h and 11.16 h, respectively.

For the sitagliptin component, the GMRs (90%CIs) comparing the FDC/free for AUC_{inf}, AUC_{last}, and C_{max} were 104.34% (101.21%, 107.57%), 104.63% (101.43%, 107.93%) and 106.60% (99.32%, 114.40%), respectively. The median sitagliptin T_{max} values were 3.00 h for both treatments, respectively, and the mean $t_{1/2}$ values were 11.93 h and 11.56 h, respectively.

The results indicated that the ertugliflozin 5 mg/sitagliptin 50 mg FDC and free combinations were bioequivalent as 90% CIs for the AUC_{inf}, AUC_{last} and C_{max} GMRs for both active components were contained within the (80%, 125%) acceptance limits.

4.2.2.3. Influence of food

Study P026/1050 examined the relative bioavailability (BA) of ertugliflozin 15 mg/sitagliptin 100 mg FDC tablet under fasted conditions and following a standard high-fat, high-calorie breakfast in 14 healthy subjects.

When the FDC tablet was administered with a high-fat breakfast, ertugliflozin C_{max} was approximately 30% lower compared to when it was administered following an overnight fast and the median T_{max} was delayed from 1 h to 2 h. By contrast, ertugliflozin mean AUC_{inf}, AUC_{last} and $t_{1/2}$ values were similar under both conditions. The GMR (90% CIs) comparing fed relative to fasted conditions for ertugliflozin AUC_{inf}, AUC_{last} and C_{max} were 94.64% (91.62%, 97.75%), 94.81% (91.79%, 97.93%) and 70.47% (63.34%, 78.39%), respectively. The 90% CIs for AUC_{inf} and AUC_{last} were contained within the (80%, 125%) acceptance range for bioequivalence, indicating no meaningful effect of food on ertugliflozin AUC, whereas, ertugliflozin C_{max} was significantly lower; however, this decrease is unlikely to be clinically relevant.

For the sitagliptin component of the FDC, the C_{max} and AUC_{inf}, AUC_{last} and $t_{1/2}$ values were generally similar under both conditions. By contrast, the median T_{max} was 3.00 h in the fasted state and 1.77 h in the fed state. The GMRs (90%CIs) comparing sitagliptin AUC_{inf}, AUC_{last} and C_{max} under fed relative to fasted conditions were 96.64% (93.99%, 99.37%), 96.40% (93.79%, 99.08%) and 96.09% (82.38%, 112.09%), respectively and were contained within the (80%, 125%) acceptance range for bioequivalence, indicating no meaningful effect of food on sitagliptin AUC and C_{max}.

4.2.2.4. Distribution, metabolism and excretion

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

4.2.2.5. Intra and inter individual variability of pharmacokinetics

Following a single oral administration of the highest proposed dosage strength of the FDC tablet, containing sitagliptin 100 mg/ertugliflozin 15 mg, or co-administration of the corresponding free combination under fasted conditions the geometric CV% was 22% for ertugliflozin AUC_{inf}, and ranged from 24% to 34% for ertugliflozin C_{max}. For the sitagliptin component, the geometric CV% ranged from 14% to 15% for AUC_{inf}, and ranged from 20% to 22% for C_{max}.

4.2.3. Pharmacokinetics in the target population

No dedicated studies examined the PKs of the proposed FDC in the target population.

4.2.4. Pharmacokinetics in special populations

No dedicated studies examined the PKs of the FDC in special populations. However, as sitagliptin is excreted renally the following precaution regarding renal dysfunction is included in the PI for Januvia:

> *To achieve plasma concentrations of Januvia similar to those in patients with normal renal function, lower dosages are recommended in patients with moderate and severe renal insufficiency, as well as in ESRD patients requiring haemodialysis or peritoneal dialysis*.

For ertugliflozin, there is no clinical experience in patients with Child-Pugh class C (severe) hepatic impairment and its use is contraindicated in patients with chronic kidney disease (CKD) stage 4 or 5 (severely impaired renal function including patients receiving dialysis; eGFR < 30 mL/min/1.73 m^2 or creatinine clearance (CrCl) < 30 mL/min) or eGFR persistently < 45 mL/min/1.73m2 or CrCl persistently < 45 mL/min (CKD stage 3B).

4.2.5. Population pharmacokinetics

No dedicated popPK analyses were undertaken for the FDC tablets.

4.2.6. Pharmacokinetic interactions

No dedicated PK studies examined drug-drug interactions between the FDC and other drugs; however, the interaction between ertugliflozin and sitagliptin has been examined in the concurrent submission (for Steglatro). In summary, Study P022/1033 (submission for Steglatro) examined the PK interaction following co-administration of a single dose of 100 mg sitagliptin and 15 mg ertugliflozin in healthy volunteers. The results indicated that following co-administration there was no adverse DDI between the two drugs as the GMRs (90% CI) for ertugliflozin AUC_{inf} and C_{max} were 102.27% (99.72%, 104.89%) and 98.18% (91.20%, 105.70%), respectively (submission for Steglatro), and the GMRs (90% CIs) for sitagliptin AUC_{inf} and C_{max} were 101.67% (98.40%, 105.04%) and 101.68% (91.65%, 112.80%), respectively (submission for Steglatro).

Comment: The sponsor states that the drug-drug interaction potential for ertugliflozin and sitagliptin with other concomitant medications is low and therefore, no clinically meaningful interactions are expected when the ertugliflozin/sitagliptin FDC is administered with other medications. However, it should be noted that no DDI studies were undertaken using the proposed FDC and PK interactions between the FDC and other commonly administered drugs in this patient population such as diuretics, warfarin, digoxin, etc were not evaluated. In addition, the concurrent submission for ertugliflozin (Steglatro, one of the active components of the proposed FDC, only contained a limited number of DDI studies with drugs that are known to interact with the pathways via which ertugliflozin is metabolised (for example, CYP3A4-inhibitors).For instance, although ertugliflozin is in part metabolised by CYP3A4, no studies have examined the effects of a strong CYP3A-inhibitor on ertugliflozin PKs.

4.2.7. Clinical implications of in vitro findings

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

4.3. Evaluator's overall conclusions on pharmacokinetics

- The current submission contains four previously unevaluated studies, which examine the BE between the various strengths of the FDC proposed for marketing and the corresponding free 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 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.
- 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 (~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 (please see Section 12 of this report for further details). 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, digoxin, etc were not evaluated.

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

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic information

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

5.2. Summary of pharmacodynamics

5.2.1. Mechanism of action

5.2.1.1. Ertugliflozin

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

5.2.1.2. Sitagliptin

Sitagliptin is a dipeptidyl peptidase 4 (DPP-4) inhibitor and improves glycaemic control in patients with type 2 diabetes by enhancing the levels of active incretin hormones.

5.2.1.3. MSD-ertugliflozin-sitagliptin

MSD-ertugliflozin-sitagliptin is the fixed dose combination of the two active antihyperglycaemic agents, which are thought to have complementary mechanisms of action, thereby improving glycaemic control in patients with type 2 diabetes over that possible with a single agent.

5.2.2. Pharmacodynamic effects

No dedicated studies examined the primary, secondary, or the time-course of PD effects for the FDC tablets. In addition, none of the previously unevaluated studies examined the relationship between drug concentration and PD effect, PD effects in special populations or PD interactions between the FDC tablets and other drugs. However, these parameters are well-established for sitagliptin and the results for ertugliflozin are discussed in the concurrent submission for Steglatro (please see Attachment 2).

5.3. Evaluator's overall conclusions on pharmacodynamics

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

6. Dosage selection for the pivotal studies

6.1.1. Pharmacokinetic and pharmacodynamic dose finding studies

In the sitagliptin and ertugliflozin drug-drug interaction 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 pharmacokinetics (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.

6.2. Phase II dose finding studies

The two Phase II dose-ranging studies for ertugliflozin were evaluated in the Steglatro report (please see Attachment 2).

6.3. 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 m^2.

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.

6.4. 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 ESRD, no ertugliflozin/sitagliptin tablet containing sitagliptin 25 mg is planned for commercialization. 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.

7. Clinical efficacy

7.1. 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 antihyperglycaemic agents (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) (Table 2).

Table 2: 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 (1:1:1:1:1), double-blind, factorial	Sitagliptin 100 mg (n=247) Ertugliflozin 15 mg (n=248) Ertugliflozin 5 mg (n=250) Ertugliflozin 15 mg/sitagliptin 100 mg (n=245) Ertugliflozin 5 mg/sitagliptin 100 mg (n=243)	52 Weeks Phase A: 26 weeks Phase B: 26 weeks
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	Placebo (n=97) 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=glycosylated 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

7.2. Pivotal or main efficacy studies

Comments: The 3 pivotal studies to support the proposed ertugliflozin-sitagliptin FDC have been evaluated and discussed in detail in the Steglatro report (submission PM-2017-01328-1-5, see Attachment 2) and only the main efficacy results will be discussed below. 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 A1C, FPG and 2 h PPG;[3] the proportion of subjects with A1c < 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 DBP (Table 3).

Table 3: Overview of efficacy endpoints across the Phase III studies supporting the ertugliflozin / sitagliptin FDC

	P005/1019 Ertugliflozin Plus Sitagliptin Factorial	P017/1047 Ertugliflozin Plus Sitagliptin	P006/1015 Add-On to Metformin Plus Sitagliptin
Change from baseline in A1C	P	P	P
Change from baseline in FPG	S	S	S
2-hour post-prandial glucose[†,‡]	O	S	-
Proportion of subjects with A1C <7.0%	S	S	S
Proportion of subjects receiving glycemic rescue therapy	O	O	O
Time to glycemic rescue	O	O	O
Change from baseline in body weight	S	S	S
Change from baseline in SBP	S	S	S
Change from baseline in DBP	O	S	O
Change from baseline in β-cell responsivity static component (Φ_s)[‡]	S	-	-

[†] Also referred to as post-meal glucose.
[‡] Captured as part of the MMTT.
P=primary efficacy endpoint; S=key secondary efficacy endpoint included in pre-specified testing sequence controlling for Type I error; O=other efficacy endpoint not in testing sequence
Abbreviations: A1C=glycosylated hemoglobin A_{1c}; DBP=diastolic blood pressure; FDC= fixed-dose combination; FPG=fasting plasma glucose; MMTT= mixed meal tolerance test; SBP=systolic blood pressure

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+sitagliptin 100 mg treatment and 497 subjects to the ertugliflozin 5 mg+sitagliptin 100 mg treatment, either as co-

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

administration (Studies P005/1019 and P017/1047) or add-on therapy (Study P006/1015) (Table 4).

Table 4: Number of subjects randomised in ertugliflozin / sitagliptin studies

Study	Ertugliflozin 5 mg +Sitagliptin 100 mg	Ertugliflozin 15 mg +Sitagliptin 100 mg	Ertugliflozin 5 mg alone	Ertugliflozin 15 mg alone	Sitagliptin	Placebo	Total
P005/1019 Ertugliflozin plus sitagliptin factorial	243	245	250	248	247	--	1233
P017/1047 Ertugliflozin plus sitagliptin	98	96	--	--	--	97	291
P006/1015 Add-on to metformin plus sitagliptin	--	--	156	154	--	153	463
Total	341	341	406	402	247	250	1987

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/m^2. The two ertugliflozin and sitagliptin co-administration studies (P005/1019 and P017/1047) had higher baseline A1C (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 A1C values in Studies P005/1019 and P017/1047 compared to Study P006/1015 were the result of the study-specific A1C entry criteria which were appropriate given the initiation of 2 agents simultaneously. The mean baseline eGFR was similar across the 3 studies, ranging from 87.9 to 92.4 mL/min/1.73 m^2. The average duration of T2DM was 9.5 years for the subjects in the add-on to metformin and sitagliptin study (Study P006/1015), 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 (Table 5). 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.

Table 5: Baseline characteristics; study by study comparison all subjects treated ertugliflozin / sitagliptin studies

	P005/1019 Ertugliflozin+Sitagliptin factorial n (%)	P017/1047 Ertugliflozin+Sitagliptin n (%)	P006/1015 Add-on to Metformin+Sitagliptin n (%)
Baseline BMI (kg/m2)			
<25	136 (11.0)	24 (8.2)	70 (15.2)
25 to <30	410 (33.3)	81 (27.8)	153 (33.1)
30 to <35	360 (29.2)	113 (38.8)	141 (30.5)
>=35	326 (26.5)	73 (25.1)	98 (21.2)
Subjects with data	1232	291	462
Mean	31.9	32.2	30.8
SD	6.3	6.1	6.0
Median	30.7	31.6	30.3
Range	18.4 to 64.6	20.9 to 57.4	17.5 to 67.1
Baseline A1C (%)			
<8.0	363 (29.5)	32 (11.0)	249 (53.9)
8.0 to <9.0	458 (37.2)	113 (38.8)	134 (29.0)
>=9.0	390 (31.7)	145 (49.8)	76 (16.5)
Unknown [1]	21 (1.7)	1 (0.3)	3 (0.6)
Subjects with data	1211	290	459
Mean	8.6	8.9	8.0
SD	1.0	0.9	0.9
Median	8.4	9.0	7.9
Range	5.1 to 12.3	6.2 to 10.9	5.7 to 11.1
Baseline A1C (mmol/mol)			
<63.94	363 (29.5)	32 (11.0)	249 (53.9)
63.94 to <74.86	458 (37.2)	113 (38.8)	134 (29.0)
>=74.86	390 (31.7)	145 (49.8)	76 (16.5)
Unknown [1]	21 (1.7)	1 (0.3)	3 (0.6)
Subjects with data	1211	290	459
Mean	70.0	74.2	64.3
SD	11.0	9.4	9.6
Median	68.3	74.3	62.8
Range	32.2 to 110.9	44.3 to 95.6	38.8 to 97.8
Baseline FPG (mg/dL)			
Subjects with data	1224	290	460
Mean	180.4	197.8	169.7
SD	47.8	47.0	38.2
Median	173.5	193.0	165.0
Range	38.0 to 401.0	78.0 to 316.0	82.0 to 337.0
Baseline FPG (mmol/L)			
Subjects with data	1224	290	460
Mean	10.0	11.0	9.4
SD	2.7	2.6	2.1
Median	9.6	10.7	9.2
Range	2.1 to 22.3	4.3 to 17.5	4.6 to 18.7
SD	47.8	47.0	38.2
Median	173.5	193.0	165.0
Range	38.0 to 401.0	78.0 to 316.0	82.0 to 337.0
Baseline FPG (mmol/L)			
Subjects with data	1224	290	460
Mean	10.0	11.0	9.4
SD	2.7	2.6	2.1
Median	9.6	10.7	9.2
Range	2.1 to 22.3	4.3 to 17.5	4.6 to 18.7

Table 5 Baseline characteristics; study by study comparison all subjects treated ertugliflozin / sitagliptin studies

	P005/1019 Ertugliflozin+Sitagliptin factorial n (%)	P017/1047 Ertugliflozin+Sitagliptin n (%)	P006/1015 Add-on to Metformin+Sitagliptin n (%)
Baseline eGFR (mL/min/1.73m2)			
<30	0 (0.0)	0 (0.0)	0 (0.0)
30 to <45	2 (0.2)	0 (0.0)	0 (0.0)
45 to <60	25 (2.0)	4 (1.4)	8 (1.7)
60 to <90	588 (47.7)	155 (53.3)	257 (55.6)
>=90	616 (50.0)	131 (45.0)	197 (42.6)
Unknown [1]	1 (0.1)	1 (0.3)	0 (0.0)
Subjects with data	1231	290	462
Mean	92.4	90.7	87.9
SD	20.0	19.0	16.9
Median	90.0	88.0	86.0
Range	35.0 to 196.0	55.0 to 171.0	51.0 to 145.0
Duration of Type 2 Diabetes Mellitus (years)			
<5	540 (43.8)	148 (50.9)	106 (22.9)
5 to <10	404 (32.8)	76 (26.1)	159 (34.4)
>=10	288 (23.4)	67 (23.0)	197 (42.6)
Subjects with data	1232	291	462
Mean	6.9	6.3	9.5
SD	5.4	6.0	5.7
Median	5.7	4.9	8.8
Range	0.2 to 35.5	0.0 to 40.4	0.2 to 34.3
Diabetic Microvascular Complications[2]			
Yes	213 (17.3)	45 (15.5)	116 (25.1)
No	1019 (82.7)	246 (84.5)	346 (74.9)
AHA (alone or in combination) at Randomization[3]			
Currently on AHA therapy	1232 (100.0)	0 (0.0)	462 (100.0)
Insulin	1 (0.1)	0 (0.0)	0 (0.0)
Metformin	1232 (100.0)	0 (0.0)	461 (99.8)
Sulfonylurea	1 (0.1)	0 (0.0)	0 (0.0)
Thiazolidinediones	0 (0.0)	0 (0.0)	0 (0.0)
DPP4	0 (0.0)	0 (0.0)	460 (99.6)
Other AHA	0 (0.0)	0 (0.0)	0 (0.0)
Number of AHA therapies at Randomization			
1	1230 (99.8)	0 (0.0)	3 (0.6)
2	2 (0.2)	0 (0.0)	459 (99.4)
3 or more	0 (0.0)	0 (0.0)	0 (0.0)
None	0 (0.0)	291 (100.0)	0 (0.0)
History of Cardiovascular Disease			
CAD	145 (11.8)	34 (11.7)	59 (12.8)
PAD	38 (3.1)	15 (5.2)	17 (3.7)
Heart Failure	48 (3.9)	16 (5.5)	6 (1.3)
Cerebrovascular	52 (4.2)	11 (3.8)	17 (3.7)
History of Hypertension			
Yes	760 (61.7)	173 (59.5)	339 (73.4)
No	472 (38.3)	118 (40.5)	123 (26.6)
Related Concomitant Medication			
Hypertensives	729 (59.2)	139 (47.8)	322 (69.7)
ACE/ARB	658 (53.4)	120 (41.2)	288 (62.3)
Dyslipidemia Medication	535 (43.4)	93 (32.0)	286 (61.9)
Statin	468 (38.0)	79 (27.1)	257 (55.6)
Diuretic	253 (20.5)	57 (19.6)	113 (24.5)
Loop Diuretic	14 (1.1)	5 (1.7)	13 (2.8)

[illegible]

[1] Not included in summary statistics

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

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

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

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

All 3 studies achieved statistical significance for the primary endpoint of A1c reduction from baseline at Week 26 (Table 6).

Table 6: HbA1c (%); Change from Baseline at primary time-point by study. FAS: excluding rescue approach; ertugliflozin / sitagliptin studies

	N	Baseline Mean ± SD	LS Mean Change ± SE	LS Mean Difference (95% CI)	p-value
P005/1019 (Week 26) Ertugliflozin+Sitagliptin factorial					
Sitagliptin 100 mg	247	8.5 ± 1.03	-1.05 ± 0.062		
Ertugliflozin 5 mg	250	8.6 ± 1.05	-1.02 ± 0.061		
Ertugliflozin 15 mg	248	8.6 ± 1.01	-1.08 ± 0.062		
Ertugliflozin 5 mg + Sitagliptin 100 mg	243	8.6 ± 0.99	-1.49 ± 0.062	-0.43† (-0.60,-0.27)	<0.001†
				-0.46‡ (-0.63,-0.30)	<0.001‡
Ertugliflozin 15 mg + Sitagliptin 100 mg	244	8.6 ± 0.97	-1.52 ± 0.062	-0.47† (-0.63,-0.30)	<0.001†
				-0.49‡ (-0.66,-0.33)	<0.001‡
P017/1047 (Week 26) Ertugliflozin+Sitagliptin					
Placebo	96	8.9 ± 0.86	-0.44 ± 0.127		
Ertugliflozin 5 mg + Sitagliptin 100 mg	98	8.9 ± 0.87	-1.60 ± 0.110	-1.16 (-1.49,-0.84)	<0.001
Ertugliflozin 15 mg + Sitagliptin 100 mg	96	9.0 ± 0.87	-1.68 ± 0.112	-1.24 (-1.57,-0.91)	<0.001
P006/1015 (Week 26) Add-on to Metformin+Sitagliptin					
Placebo	153	8.0 ± 0.93	-0.09 ± 0.070		
Ertugliflozin 5 mg	156	8.1 ± 0.86	-0.78 ± 0.067	-0.69 (-0.87,-0.50)	<0.001
Ertugliflozin 15 mg	153	8.0 ± 0.83	-0.86 ± 0.068	-0.76 (-0.95,-0.58)	<0.001

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

In the ertugliflozin plus sitagliptin factorial study in subjects with mean baseline A1C of 8.6% and on background metformin monotherapy (Study P005/1019), co-administration of E15/S100 and E5/S100 provided A1C 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 (Study P017/1047) in subjects who were on diet and exercise alone with mean baseline A1C of 8.9%, co-administration of E15/S100 and E5/S100 provided significantly greater ($p < 0.001$) A1C 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 (Study P006/1015) in subjects who were on metformin and sitagliptin dual therapy and had mean baseline A1C of 8.0%, ertugliflozin 15 mg and 5 mg provided significantly greater ($p < 0.001$) A1C 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 A1C < 7.0% at Week 26 was analysed in all studies as a secondary efficacy endpoint (Table 7). 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 A1C 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 (Study P017/1047), co-administration of E5/S100 and E15/S100 resulted in significantly higher proportions of subjects with A1C < 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 A1C < 7.0% compared to placebo (32.1%, 39.9% and 17.0% in ertugliflozin 5 mg, 15 mg and placebo groups, respectively).

Table 7: Analysis of subjects with HbA1c < 7.0% at primary time-point by study; FAS: excluding rescue approach; ertugliflozin / sitagliptin studies

	N	Number (%) of Subjects With A1C<7.0% (Raw Proportion)	Adjusted Odds Ratio[†]	
			Point Estimate	95% CI
P005/1019 (Week 26) Ertugliflozin+Sitagliptin factorial				
Sitagliptin 100 mg	247	81 (32.8)		
Ertugliflozin 5 mg	250	66 (26.4)		
Ertugliflozin 15 mg	248	79 (31.9)		
Ertugliflozin 5 mg + Sitagliptin 100 mg	243	127 (52.3)	2.95[‡] 4.14[§]	(1.92, 4.54)[‡] (2.68, 6.40)[§]
Ertugliflozin 15 mg + Sitagliptin 100 mg	244	120 (49.2)	2.56[‡] 2.53[§]	(1.69, 3.89)[‡] (1.68, 3.83)[§]
P017/1047 (Week 26) Ertugliflozin+Sitagliptin				
Placebo	96	8 (8.3)		
Ertugliflozin 5 mg + Sitagliptin 100 mg	98	35 (35.7)	6.88	(2.81, 16.83)
Ertugliflozin 15 mg + Sitagliptin 100 mg	96	30 (31.3)	7.39	(2.98, 18.31)
P006/1015 (Week 26) Add-on to Metformin+Sitagliptin				
Placebo	153	26 (17.0)		
Ertugliflozin 5 mg	156	50 (32.1)	3.16	(1.74, 5.72)
Ertugliflozin 15 mg	153	61 (39.9)	4.43	(2.44, 8.02)

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

Comment: It is important to note that the only study which showed higher proportion of subjects with A1C < 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 A1C compared to the other two studies. The 2 studies which involved combination treatment with ertugliflozin+sitagliptin and involved subjects with higher baseline A1C 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 (Table 8).

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 (Table 9).

Table 8: Change from Baseline in FPG (mmol/L) in the 3 pivotal Phase III studies

Study P005/1019¶

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

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

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

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

Study P006/1015¶

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

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

[†] Based on cLDA model with fixed effects for treatment, time, prior antihyperglycemic medication (metformin + DPP-4 inhibitor /metformin + SU), baseline eGFR (continuous) and the interaction of time by treatment. Time was treated as a categorical variable.

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

Study P017/1047¶

	Baseline		Week 26		Change from Baseline at Week 26		
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)[†]
Placebo	96	11.52 (2.494)	49	9.57 (1.967)	96	-0.82 (2.310)	-0.52 (-1.03, -0.00)
Ertugliflozin 5 mg + Sitagliptin 100 mg	98	10.99 (2.649)	85	8.06 (1.817)	98	-2.77 (2.538)	-2.68 (-3.11, -2.24)
Ertugliflozin 15 mg + Sitagliptin 100 mg	96	10.42 (2.590)	84	7.71 (1.628)	96	-2.75 (2.676)	-3.07 (-3.51, -2.63)
Pairwise Comparison						Difference in LS Means (95% CI)[†]	p-Value
Ertugliflozin 5 mg + Sitagliptin 100 mg vs. Placebo						-2.16 (-2.77, -1.55)	<0.001
Ertugliflozin 15 mg + Sitagliptin 100 mg vs. Placebo						-2.56 (-3.17, -1.94)	<0.001
Conditional Pooled SD of Change from Baseline							1.84

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

[†] Based on cLDA model with fixed effects for treatment, time, antihyperglycemic medication wash-off status (yes, no), baseline eGFR (continuous) and the interaction of time by treatment. Time was treated as a categorical variable.

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

Table 9: Study P017/1047 Change in 2 hours PPG (mmol/L) at Week 26

	Baseline		Week 26		Change from Baseline at Week 26		
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)[†]
Placebo	88	15.95 (4.108)	59	14.46 (3.778)	91	-0.48 (3.601)	-1.13 (-1.98, -0.29)
Ertugliflozin 5 mg + Sitagliptin 100 mg	93	15.61 (4.808)	85	11.08 (3.459)	97	-4.61 (4.405)	-4.60 (-5.33, -3.86)
Ertugliflozin 15 mg + Sitagliptin 100 mg	95	15.63 (4.258)	81	10.86 (2.900)	95	-5.16 (4.223)	-5.00 (-5.74, -4.26)
Pairwise Comparison						Difference in LS Means (95% CI)[†]	p-Value
Ertugliflozin 5 mg + Sitagliptin 100 mg vs. Placebo						-3.46 (-4.47, -2.46)	<0.001
Ertugliflozin 15 mg + Sitagliptin 100 mg vs. Placebo						-3.87 (-4.87, -2.86)	<0.001
Conditional Pooled SD of Change from Baseline							2.97

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

[†] Based on cLDA model with fixed effects for treatment, time, antihyperglycemic medication wash-off status (yes, no), baseline eGFR (continuous) and the interaction of time by treatment. Time was treated as a categorical variable.

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

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 (Table 10). 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 (Table 11). 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 (Table 12).

Table 10: Body weight (kg); Change from Baseline at primary time-point by study; FAS: excluding rescue approach; ertugliflozin / sitagliptin studies

	N	Baseline Mean ± SD	LS Mean Change ± SE	LS Mean Difference (95% CI)	p-value
P005/1019 (Week 26) Ertugliflozin+Sitagliptin factorial					
Sitagliptin 100 mg	247	89.8 ± 23.46	-0.67 ± 0.229		
Ertugliflozin 5 mg	250	88.6 ± 22.19	-2.69 ± 0.225		
Ertugliflozin 15 mg	248	88.0 ± 20.33	-3.74 ± 0.227		
Ertugliflozin 5 mg + Sitagliptin 100 mg	243	89.5 ± 20.85	-2.52 ± 0.228	-1.85† (-2.48,-1.22)	<0.001†
Ertugliflozin 15 mg + Sitagliptin 100 mg	244	87.5 ± 20.48	-2.94 ± 0.228	-2.27† (-2.90,-1.64)	<0.001†
P017/1047 (Week 26) Ertugliflozin+Sitagliptin					
Placebo	97	95.0 ± 20.53	-0.94 ± 0.386		
Ertugliflozin 5 mg + Sitagliptin 100 mg	98	90.8 ± 20.72	-2.94 ± 0.334	-2.00 (-2.99,-1.01)	<0.001
Ertugliflozin 15 mg + Sitagliptin 100 mg	96	91.2 ± 22.47	-3.04 ± 0.338	-2.10 (-3.10,-1.11)	<0.001
P006/1015 (Week 26) Add-on to Metformin+Sitagliptin					
Placebo	153	86.5 ± 20.82	-1.32 ± 0.229		
Ertugliflozin 5 mg	156	87.6 ± 18.62	-3.35 ± 0.221	-2.03 (-2.65,-1.40)	<0.001
Ertugliflozin 15 mg	153	86.6 ± 19.48	-3.04 ± 0.223	-1.72 (-2.35,-1.09)	<0.001

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

Table 11: Sitting SBP (mmHg); Change from Baseline at primary time-point by study; FAS: excluding rescue approach; rtugliflozin / sitagliptin studies

	N	Baseline Mean ± SD	LS Mean Change ± SE	LS Mean Difference (95% CI)	p-value
P005/1019 (Week 26) Ertugliflozin+Sitagliptin factorial					
Sitagliptin 100 mg	247	128.3 ± 12.21	-0.66 ± 0.721		
Ertugliflozin 5 mg	250	129.7 ± 12.48	-3.89 ± 0.709		
Ertugliflozin 15 mg	248	128.9 ± 12.51	-3.69 ± 0.708		
Ertugliflozin 5 mg + Sitagliptin 100 mg	243	130.2 ± 12.63	-3.42 ± 0.711	-2.76† (-4.69,-0.83)	0.005†
Ertugliflozin 15 mg + Sitagliptin 100 mg	244	129.1 ± 13.27	-3.67 ± 0.707	-3.01† (-4.94,-1.09)	0.002†
P017/1047 (Week 26) Ertugliflozin+Sitagliptin					
Placebo	97	127.4 ± 14.05	2.41 ± 1.392		
Ertugliflozin 5 mg + Sitagliptin 100 mg	98	130.7 ± 12.74	-2.04 ± 1.115	-4.44 (-7.87,-1.01)	0.011
Ertugliflozin 15 mg + Sitagliptin 100 mg	96	129.2 ± 12.17	-3.98 ± 1.119	-6.39 (-9.83,-2.95)	<0.001
P006/1015 (Week 26) Add-on to Metformin+Sitagliptin					
Placebo	153	130.2 ± 13.31	-0.88 ± 0.926		
Ertugliflozin 5 mg	156	132.1 ± 12.45	-3.81 ± 0.871	-2.93 (-5.36,-0.49)	0.019
Ertugliflozin 15 mg	153	131.6 ± 13.16	-4.82 ± 0.880	-3.94 (-6.39,-1.50)	0.002

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

Table 12: Analysis of time to glycaemic rescue at primary time-point by study All Subjects Treated Ertugliflozin / sitagliptin studies

	N	Number (%) of Subjects Rescued	Time to Rescue (days)		p-value
			Minimum	Maximum	
P005/1019 (Week 26) Ertugliflozin+Sitagliptin factorial					
Sitagliptin 100 mg	247	16 (6.5)	53	191	
Ertugliflozin 5 mg	250	16 (6.4)	5	156	
Ertugliflozin 15 mg	248	7 (2.8)	1	133	
Ertugliflozin 5 mg + Sitagliptin 100 mg	243	6 (2.5)	50	196	0.036[†] 0.042[‡]
Ertugliflozin 15 mg + Sitagliptin 100 mg	244	0 (0.0)	N/A	N/A	<0.001[†] 0.009[‡]
P017/1047 (Week 26) Ertugliflozin+Sitagliptin					
Placebo	97	31 (32.0)	9	166	
Ertugliflozin 5 mg + Sitagliptin 100 mg	98	6 (6.1)	79	148	<0.001
Ertugliflozin 15 mg + Sitagliptin 100 mg	96	0 (0.0)	N/A	N/A	<0.001
P006/1015 (Week 26) Add-on to Metformin+Sitagliptin					
Placebo	153	25 (16.3)	26	212	
Ertugliflozin 5 mg	156	2 (1.3)	135	141	<0.001
Ertugliflozin 15 mg	153	3 (2.0)	43	147	<0.001

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

7.3. Other efficacy studies

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

7.4. Analyses performed across trials pooled and meta-analyses

Data from the 3 individual studies were not pooled for analysis due to differences in study designs and patient populations. In study-specific subgroup analyses for Studies P005/1019 and P017/1047, the A1c reduction with ertugliflozin in combination with sitagliptin was consistent across age, gender, race, ethnicity and baseline A1c subgroups.

7.5. 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 A1c. 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 bioequivalence (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 (A1C, FPG, and proportion of patients with A1C < 7.0%) compared to either sitagliptin alone or the corresponding dose of ertugliflozin alone in 1233 subjects with inadequate control on metformin (P005/ 1019). 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 A1C 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 (A1C, FPG, 2 h PPG, and proportion of patients with A1C < 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 A1c, FPG, 2 hour PMG, body weight and sitting SBP with the E15/S100 combination, relative to the E5/S100 combination, although the differences between the 2 co-administration groups were small for these endpoints.

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 ≥ 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 (A1c, FPG, and proportion of patients with A1c < 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 A1c of 8% despite combination therapy with metformin and sitagliptin, was representative of patients who may need an additional third-line therapy.

7.5.1. 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 A1C and FPG reductions and resulted in a greater proportion of subjects with an A1c < 7.0% at Week 26 compared to the ertugliflozin 5 mg. A clear difference on A1c lowering between ertugliflozin 15 mg + sitagliptin 100 mg and ertugliflozin 5 mg + 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 A1c < 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.

7.5.2. 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 (Seck, 2010). Ertugliflozin co-administered with sitagliptin demonstrated stable A1c 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.

8. Clinical safety

8.1. 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.

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

None.

8.3. Pivotal and/or main efficacy studies

Safety evaluations in all three Phase III studies included the collection of adverse events (AEs), laboratory tests (haematology, chemistry and urinalysis), sitting blood pressure, orthostatic blood pressure (supine to standing), pulse rate (sitting, supine and standing), centrally-read 12-lead ECGs, physical examinations, and self-monitored blood glucose. CV, fracture, pancreatitis, renal and hepatic events in the 3 Phase III studies as well as in the broader ertugliflozin development program, were subject to adjudication by 5 separate clinical adjudication committees.

Study P005/1019, afactorial study, which directly compared the safety and tolerability of ertugliflozin and sitagliptin co-administration therapy to each individual treatment on a background of metformin. Studies P006/1015 and P017/1047 provide safety and tolerability data in 2 additional settings: the use of ertugliflozin on a background of dual therapy with metformin and sitagliptin (Study P006/1015) and as initial combination therapy with sitagliptin (Study P017/1047) in subjects with inadequate control on diet and exercise alone.

Analyses were performed in the All Subjects as Treated (ASaT) population, consisting of all randomised subjects who received at least 1 dose of study medication. Since initiation of glycaemic rescue therapy had the potential to confound certain safety assessments, some analyses were approached in 2 ways, excluding and including data after initiation of glycaemic rescue therapy. The excluding rescue approach censors data collected after the initiation of glycaemic rescue therapy, whereas the including rescue approach includes data regardless of glycaemic rescue therapy initiation. Except for assessments of hypoglycaemia, the 'including rescue approach' was the primary approach for all safety endpoints. In each of the 3 Phase III studies in this SCS, the analysis of safety data followed a tiered approach. The tiers differed with respect to the analyses that were performed. Tier 1 AEs were pre-specified and included symptomatic hypoglycaemia, AEs associated with urinary tract infection, male and female genital mycotic infection and hypovolemia. For these Tier 1 events, inferential testing provided statistical significance levels for between-group comparisons. Other safety parameters were considered Tier 2 or Tier 3. Tier 2 parameters were assessed via point estimates with 95% CIs provided for between-group comparisons; only point estimates by treatment group were provided for Tier 3 AEs and PDLC laboratory parameters (Table 13).

Table 13: Studies P005/1019, P006/1015 and P017/1047 Analysis strategy for safety parameters

Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1[†]	Urinary tract infection	X	X	X
	Genital mycotic infection (gender specific)	X	X	X
	Symptomatic hypoglycemia[‡]	X	X	X
	Hypovolemia	X	X	X
Tier 2[§]	Percent change from baseline in lipids (TG, LDL-C, HDL-C, Non-HDL-C, total cholesterol)		X	X
	Adverse event summary measures		X	X
	Specific adverse events[‖], SOCs, and PDLC		X	X
	Documented hypoglycemia		X	X
	Severe hypoglycemia		X	X
	Any			
	Requiring medical assistance			
	Requiring non-medical assistance			
Tier 3	All endpoints listed under Tier 2 (above) that have incidence <4 subjects in all treatment groups			X
	Additional hypoglycemia adverse event endpoints			X
	Change from baseline results (laboratory measurements, ECG, and vital signs)			X

[†] Urinary tract infections, genital mycotic infections, and hypovolemia events were defined by CMQs. The specific terms included in these definitions are provided in Appendix 2.
[‡] All symptomatic hypoglycemia episodes were classified by the investigator as adverse events and, thus, any episodes that were not classified as adverse events were asymptomatic episodes.
[§] Non-continuous endpoints listed here qualified for Tier 2 only if the incidence was ≥4 subjects in at least one of the treatment groups.
[‖] Among those endpoints not pre-specified as Tier 1 endpoints.
CI=confidence interval; ECG=electrocardiogram; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; PDLC=Pre-defined limit of change; SOC=System Organ Class; TG=triglycerides; X=results provided

8.4. Other studies

8.4.1. Studies evaluable for safety only

None.

8.5. Studies that assessed safety as the sole primary outcome

None.

8.6. 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 (Table 14), 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 Steglatro report.

Table 14: Exposure to study medication by study, in all subjects as treated population, including rescue approach

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

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.

8.7. Adverse events

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

8.7.1.1. Study P005/1019: Ertugliflozin +Sitagliptin Factorial Study

The overall incidence of AEs was similar in the E5/S100 and E15/S100 combination groups relative to the E5, E15 and S100 groups (52%, 43.5%, 42.1%, 45.7% and 46.7% in the E5, E15, S100, E5/S100 and E15/S100 groups, respectively). However, Gastrointestinal disorders; Respiratory, thoracic and mediastinal disorders; and Skin and subcutaneous tissue disorders SOCs showed higher incidence of AEs in the combination (E5/S100 and E15/S100) groups relative to the individual treatment groups (Table 15). Among AEs that occurred in ≥ 2% of subjects in any group, those that occurred at a higher incidence (that is, 95% CI excluded 0) in a co-administration group relative to the individual treatments at corresponding doses were vulvovaginal mycotic infection (higher incidence for E5/S100 versus S100) and hypoglycaemia (higher incidence for E15/S100 versus S100 in analyses including and excluding results after glycaemic rescue). The incidence of AEs of gastroenteritis was higher in the E5/S100 group (4 subjects (1.6%)) than in the E5 group, in which no cases were reported. However, the incidence of AEs of gastroenteritis in the 3 other groups (2 subjects (0.8%) in the E15 group and 3 subjects (1.2%) each in the E15/S100 and S100 groups) were similar to that in the E5/S100 group. Adverse events of gastroenteritis in the E5/S100 group, as well as in the 3 other groups with at least 1 event reported, were all mild or moderate, non-serious, and none resulted in discontinuation of study medication. The incidence of hyperuricemia was higher in the E5/S100 group (4 subjects (1.6%)) than in the E5 group, in which no cases were reported, but similar to the S100 group (3 subjects (1.2%)). No events of hyperuricemia were reported in the E15/S100 group and 1 subject (0.4%) in the E15 group had an AE of hyperuricaemia. Other conditions associated with increased uric acid, such as blood uric acid increased, gout, and gouty arthritis occurred infrequently and was balanced across groups.

Table 15: Study P005/1019 Subjects with AEs by SOC (incidence > 0% in 1 or more treatment groups); All subjects as treated. Phase A: Including rescue approach

	Ertugliflozin 5 mg		Ertugliflozin 15 mg		Sitagliptin 100 mg		Ertugliflozin 5 mg + Sitagliptin 100 mg		Ertugliflozin 15 mg + Sitagliptin 100 mg	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	250		248		247		243		244	
with one or more adverse events	130	(52.0)	108	(43.5)	104	(42.1)	111	(45.7)	114	(46.7)
with no adverse events	120	(48.0)	140	(56.5)	143	(57.9)	132	(54.3)	130	(53.3)
Blood and lymphatic system disorders	2	(0.8)	1	(0.4)	1	(0.4)	3	(1.2)	2	(0.8)
Cardiac disorders	8	(3.2)	3	(1.2)	3	(1.2)	2	(0.8)	2	(0.8)
Congenital, familial and genetic disorders	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)
Ear and labyrinth disorders	3	(1.2)	1	(0.4)	1	(0.4)	2	(0.8)	2	(0.8)
Eye disorders	2	(0.8)	0	(0.0)	2	(0.8)	3	(1.2)	2	(0.8)
Gastrointestinal disorders	29	(11.6)	16	(6.5)	12	(4.9)	23	(9.5)	18	(7.4)
General disorders and administration site conditions	3	(1.2)	5	(2.0)	5	(2.0)	3	(1.2)	9	(3.7)
Hepatobiliary disorders	3	(1.2)	1	(0.4)	1	(0.4)	0	(0.0)	1	(0.4)
Immune system disorders	2	(0.8)	0	(0.0)	1	(0.4)	2	(0.8)	2	(0.8)
Infections and infestations	51	(20.4)	54	(21.8)	45	(18.2)	50	(20.6)	43	(17.6)
Injury, poisoning and procedural complications	10	(4.0)	6	(2.4)	7	(2.8)	7	(2.9)	4	(1.6)
Investigations	14	(5.6)	18	(7.3)	12	(4.9)	11	(4.5)	11	(4.5)
Metabolism and nutrition disorders	19	(7.6)	23	(9.3)	18	(7.3)	21	(8.6)	22	(9.0)
Musculoskeletal and connective tissue disorders	21	(8.4)	8	(3.2)	17	(6.9)	20	(8.2)	7	(2.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.4)	2	(0.8)
Nervous system disorders	10	(4.0)	12	(4.8)	13	(5.3)	11	(4.5)	11	(4.5)
Psychiatric disorders	3	(1.2)	1	(0.4)	4	(1.6)	6	(2.5)	4	(1.6)
Renal and urinary disorders	9	(3.6)	6	(2.4)	6	(2.4)	13	(5.3)	12	(4.9)
Reproductive system and breast disorders	8	(3.2)	6	(2.4)	1	(0.4)	4	(1.6)	5	(2.0)
Respiratory, thoracic and mediastinal disorders	2	(0.8)	11	(4.4)	7	(2.8)	8	(3.3)	7	(2.9)
Skin and subcutaneous tissue disorders	8	(3.2)	2	(0.8)	4	(1.6)	4	(1.6)	12	(4.9)
Social circumstances	0	(0.0)	0	(0.0)	1	(0.4)	0	(0.0)	0	(0.0)
Vascular disorders	8	(3.2)	3	(1.2)	3	(1.2)	5	(2.1)	8	(3.3)

Every subject is counted a single time for each applicable row and column.
A system organ class appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
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8.7.1.2. Study P006/1015 add-on to metformin and sitagliptin study

The overall incidence of AEs was numerically lower in the ertugliflozin groups compared with placebo (48.4%, 41.7% and 43.8% in placebo, ertugliflozin 5 mg and 15 mg groups, respectively) (Table 16). Numerically higher incidences of AEs of vulvovaginal mycotic infection (0.7%, 2.6% and 3.3% in placebo, ertugliflozin 5 mg and 15 mg groups, respectively), balanoposthitis, constipation and cystitis was reported among the 2 ertugliflozin groups compared with the placebo group. Only small numeric differences were seen in the incidence of other specific AEs, with no evident pattern observed (Table 17).

Table 16: Study P006/1015 Analysis of AE summary measures; All subjects as treated, Phase A: excluding rescue approach

Treatment	n	(%)	Difference in % vs Placebo Estimate (95% CI)†
Subjects in population			
Placebo	153		
Ertugliflozin 5 mg	156		
Ertugliflozin 15 mg	153		
with one or more adverse events			
Placebo	74	(48.4)	
Ertugliflozin 5 mg	65	(41.7)	-6.7 (-17.6, 4.4)
Ertugliflozin 15 mg	67	(43.8)	-4.6 (-15.6, 6.6)
with no adverse events			
Placebo	79	(51.6)	
Ertugliflozin 5 mg	91	(58.3)	6.7 (-4.4, 17.6)
Ertugliflozin 15 mg	86	(56.2)	4.6 (-6.6, 15.6)
with drug-related‡ adverse events			
Placebo	13	(8.5)	
Ertugliflozin 5 mg	17	(10.9)	2.4 (-4.4, 9.3)
Ertugliflozin 15 mg	22	(14.4)	5.9 (-1.3, 13.3)
with serious adverse events			
Placebo	4	(2.6)	
Ertugliflozin 5 mg	7	(4.5)	1.9 (-2.6, 6.7)
Ertugliflozin 15 mg	3	(2.0)	-0.7 (-4.8, 3.3)
with serious drug-related adverse events			
Placebo	0	(0.0)	
Ertugliflozin 5 mg	0	(0.0)	
Ertugliflozin 15 mg	1	(0.7)	
who died			
Placebo	0	(0.0)	
Ertugliflozin 5 mg	0	(0.0)	
Ertugliflozin 15 mg	0	(0.0)	
discontinued study medication due to an adverse event			
Placebo	1	(0.7)	
Ertugliflozin 5 mg	5	(3.2)	2.6 (-0.7, 6.7)
Ertugliflozin 15 mg	1	(0.7)	0.0 (-3.0, 3.0)
discontinued study medication due to a drug-related adverse event			
Placebo	0	(0.0)	
Ertugliflozin 5 mg	2	(1.3)	
Ertugliflozin 15 mg	0	(0.0)	
discontinued study medication due to a serious adverse event			
Placebo	1	(0.7)	
Ertugliflozin 5 mg	0	(0.0)	
Ertugliflozin 15 mg	0	(0.0)	
discontinued study medication due to a serious drug-related adverse event			
Placebo	0	(0.0)	
Ertugliflozin 5 mg	0	(0.0)	
Ertugliflozin 15 mg	0	(0.0)	

† Based on Miettinen & Nurminen method.

‡ Determined by the investigator to be related to the drug.

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

Table 17: Analysis of subjects with AEs (incidence ≥ 4 subjects in 1 or more treatment groups); All subjects as treated Phase A: excluding rescue approach

Treatment	n	(%)	Difference in % vs Placebo Estimate (95% CI)*
Subjects in population			
Placebo	153		
Ertugliflozin 5 mg	156		
Ertugliflozin 15 mg	153		
with one or more adverse events			
Placebo	74	(48.4)	
Ertugliflozin 5 mg	65	(41.7)	-6.7 (-17.6, 4.4)
Ertugliflozin 15 mg	67	(43.8)	-4.6 (-15.6, 6.6)
with no adverse events			
Placebo	79	(51.6)	
Ertugliflozin 5 mg	91	(58.3)	6.7 (-4.4, 17.6)
Ertugliflozin 15 mg	86	(56.2)	4.6 (-6.6, 15.6)
Gastrointestinal disorders			
Constipation			
Placebo	2	(1.3)	
Ertugliflozin 5 mg	0	(0.0)	-1.3 (-4.6, 1.1)
Ertugliflozin 15 mg	5	(3.3)	2.0 (-1.8, 6.3)
Diarrhoea			
Placebo	5	(3.3)	
Ertugliflozin 5 mg	1	(0.6)	-2.6 (-6.9, 0.6)
Ertugliflozin 15 mg	1	(0.7)	-2.6 (-6.9, 0.7)
Infections and infestations			
Cystitis			
Placebo	1	(0.7)	
Ertugliflozin 5 mg	1	(0.6)	-0.0 (-3.0, 3.0)
Ertugliflozin 15 mg	4	(2.6)	2.0 (-1.3, 6.0)
Upper respiratory tract infection			
Placebo	7	(4.6)	
Ertugliflozin 5 mg	3	(1.9)	-2.7 (-7.5, 1.5)
Upper respiratory tract infection			
Ertugliflozin 15 mg	4	(2.6)	-2.0 (-6.9, 2.6)
Viral infection			
Placebo	5	(3.3)	
Ertugliflozin 5 mg	0	(0.0)	-3.3 (-7.4, -0.8)
Ertugliflozin 15 mg	0	(0.0)	-3.3 (-7.4, -0.8)
Vulvovaginal mycotic infection			
Placebo	1	(0.7)	
Ertugliflozin 5 mg	4	(2.6)	1.9 (-1.3, 5.8)
Ertugliflozin 15 mg	5	(3.3)	2.6 (-0.7, 6.9)
Metabolism and nutrition disorders			
Hypoglycaemia			
Placebo	4	(2.6)	
Ertugliflozin 5 mg	6	(3.8)	1.2 (-3.2, 5.9)
Ertugliflozin 15 mg	1	(0.7)	-2.0 (-6.0, 1.3)
Musculoskeletal and connective tissue disorders			
Back pain			
Placebo	4	(2.6)	
Ertugliflozin 5 mg	4	(2.6)	-0.1 (-4.3, 4.1)
Ertugliflozin 15 mg	2	(1.3)	-1.3 (-5.4, 2.3)

* Based on Miettinen & Nurminen method.

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

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

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

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8.7.1.3. Study P017/1047 ertugliflozin +sitagliptin initial combination study

The incidence of AEs was similar across treatment groups: 42.3%, 44.9% and 44.8% in placebo, E5/S100 and E15/S100 groups, respectively (Table 18). The differences in incidences of AEs by SOC were generally small between the coadministration and placebo groups. The only SOC where the 95% CI for the between-group difference excluded 0 was the Nervous system disorders SOC with higher incidence in the combination treatment groups (1%, 8.2% and 10.4% in placebo, E5/S100 and E15/S100 groups, respectively). The higher incidence of AEs in the E5/S100 group relative to the placebo group was primarily due to headaches (4.1% and 0.0%, respectively). The higher incidence of AEs in the E15/S100 group relative to the placebo group was primarily due to headaches (3.1% and 0.0%, respectively) and dizziness (4.2% and 1.0%, respectively, which includes 1 event of postural dizziness in the E15/S100 group). All AEs of headache were mild or moderate in intensity and non-serious. None resulted in discontinuation of study medication. The 95% CIs for between-group differences also excluded 0 for 3 specific AEs for which the incidences in the placebo group were higher relative to those in the E5/S100 group (hyperglycaemia) and in the E15/S100 group (blood glucose increased and back pain). AEs associated with osmotic diuresis have been associated with SGLT2 inhibition but such events were infrequent in this study. One subject in the E5/S100 group had an AE of polyuria, and 1 subject in the E15/S100 group had an AE of micturition urgency. All the AEs associated with hypovolemia were non-serious, and none led to discontinuation of study medication. One subject in the placebo group had an AE of dehydration, 2 subjects in the E5/S100 group and 1 subject in the E15/S100 group had an AE of hypotension, and 1 subject in the E15/S100 group had an AE of dizziness postural. All but one of the AEs associated with hypovolaemia were mild; the AE of hypotension in the subject in the E15/S100 group was moderate in intensity.

Table 18: Study P017/1047 Analysis of AE summary measures; All subjects as treated: excluding rescue approach

Treatment	n	(%)	Difference in % vs Placebo Estimate (95% CI)[†]
Subjects in population			
Placebo	97		
Ertugliflozin 5 mg + Sitagliptin 100 mg	98		
Ertugliflozin 15 mg + Sitagliptin 100 mg	96		
with one or more adverse events			
Placebo	41	(42.3)	
Ertugliflozin 5 mg + Sitagliptin 100 mg	44	(44.9)	2.6 (-11.2, 16.4)
Ertugliflozin 15 mg + Sitagliptin 100 mg	43	(44.8)	2.5 (-11.4, 16.4)
with no adverse events			
Placebo	56	(57.7)	
Ertugliflozin 5 mg + Sitagliptin 100 mg	54	(55.1)	-2.6 (-16.4, 11.2)
Ertugliflozin 15 mg + Sitagliptin 100 mg	53	(55.2)	-2.5 (-16.4, 11.4)
with drug-related[‡] adverse events			
Placebo	8	(8.2)	
Ertugliflozin 5 mg + Sitagliptin 100 mg	9	(9.2)	0.9 (-7.5, 9.4)
Ertugliflozin 15 mg + Sitagliptin 100 mg	13	(13.5)	5.3 (-3.7, 14.7)
with serious adverse events			
Placebo	4	(4.1)	
Ertugliflozin 5 mg + Sitagliptin 100 mg	2	(2.0)	-2.1 (-8.4, 3.5)
Ertugliflozin 15 mg + Sitagliptin 100 mg	3	(3.1)	-1.0 (-7.4, 5.2)
with serious drug-related adverse events			
Placebo	0	(0.0)	
Ertugliflozin 5 mg + Sitagliptin 100 mg	0	(0.0)	
Ertugliflozin 15 mg + Sitagliptin 100 mg	0	(0.0)	
who died			
Placebo	0	(0.0)	
Ertugliflozin 5 mg + Sitagliptin 100 mg	0	(0.0)	
Ertugliflozin 15 mg + Sitagliptin 100 mg	0	(0.0)	
discontinued study medication due to an adverse event			
Placebo	2	(2.1)	
Ertugliflozin 5 mg + Sitagliptin 100 mg	2	(2.0)	
Ertugliflozin 15 mg + Sitagliptin 100 mg	2	(2.1)	
discontinued study medication due to a drug-related adverse event			
Placebo	2	(2.1)	
Ertugliflozin 5 mg + Sitagliptin 100 mg	2	(2.0)	
Ertugliflozin 15 mg + Sitagliptin 100 mg	0	(0.0)	
discontinued study medication due to a serious adverse event			
Placebo	0	(0.0)	
Ertugliflozin 5 mg + Sitagliptin 100 mg	0	(0.0)	
Ertugliflozin 15 mg + Sitagliptin 100 mg	1	(1.0)	
discontinued study medication due to a serious drug-related adverse event			
Placebo	0	(0.0)	
Ertugliflozin 5 mg + Sitagliptin 100 mg	0	(0.0)	
Ertugliflozin 15 mg + Sitagliptin 100 mg	0	(0.0)	

[†] Based on Miettinen & Nurminen method.

[‡] Determined by the investigator to be related to the drug.

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

This table contains events that occurred between the first dose of treatment and 14 days after the final dose of treatment, excluding events after initiation of glycemic rescue medication.

8.7.2. Treatment related adverse events (adverse drug reactions)

8.7.2.1. Study P005/1019 ertugliflozin + sitagliptin factorial study

The incidence of drug related AEs was higher in the E5/S100 and E15/S100 groups than in the S100 group, but was not notably different relative to the E5 and E15 groups (16.8%, 12.1%, 4.9%, 11.1% and 16% in the E5, E15, S100, E5/S100 and E15/S100 groups, respectively). AEs associated with genital mycotic infections were the most frequently reported drug related AEs in the E5/S100 and E15/S100 groups, and in the E5 and E15 groups, with none reported in the S100 group. The incidence of other specific drug related AEs was low (occurring in 3 or fewer subjects) and not notably different across groups, except for hypoglycaemia, which was reported in 2.9% of subjects in the E15/S100 group and 0.4% to 1.2% of subjects in the 4 other groups. The incidence of drug related hypoglycaemia was the same using the including and excluding rescue approaches.

8.7.2.2. Study P006/1015 Add-on to metformin and sitagliptin study

Compared with placebo, the incidence of drug related AEs was numerically higher in the ertugliflozin 5 mg and 15 mg groups (8.5%, 10.9% and 14.4% in the placebo, ertugliflozin 5 mg and 15 mg groups, respectively). The most frequently reported drug related AEs in the ertugliflozin groups were those associated with genital mycotic infections. The only other specific drug related AEs reported in > 2 subjects in a group were dry mouth in the ertugliflozin 5 mg group and weight decreased in the ertugliflozin 5 mg and placebo groups. These events were both reported in 3 subjects. One subject in the ertugliflozin 15 mg group had a SAE of transient ischemic attack that was considered related to study medication by the investigator.

8.7.2.3. Study P017/1047 ertugliflozin + sitagliptin initial combination study

The incidence of drug related AEs was numerically higher in the E15/S100 group (13.5%) and similar in the E5/S100 group (9.2%), relative to the placebo group (9.3%). AEs associated with UTI and genital mycotic infections were among the drug related AEs in the coadministration groups**.** Drug-related AEs occurring in > 1 subject were urinary tract infection, pruritus genital, and hypoglycaemia in the coadministration groups and back pain in the placebo group. These events were reported in 2 subjects each. The incidence of drug related AEs of hypoglycaemia was the same for the excluding and including glycaemic rescue approaches. No subject had an SAE that was considered related to study medication.

8.7.3. Deaths and other serious adverse events

8.7.3.1. Study P005/1019 ertugliflozin + sitagliptin factorial study

No deaths were reported during Phase A. SAEs occurred at a low incidence across groups (<4%) and small numeric differences in the incidence of SAEs were not due to an increased incidence of any particular SAE term. The only SAE that occurred in > 1 subject in a treatment group was acute myocardial infarction, which occurred in 2 subjects (0.8%) in the E15/S100 group. Only 1 SAE was considered by the investigator to be related to study medication.[4] Two subjects, both in the E5/S100 group, discontinued study medication due to SAEs, 1 due to an event of myocardial infarction and 1 due to nodal marginal zone B-cell lymphoma stage III. Both SAEs were assessed as severe in intensity and not related to study medication. Two subjects had a SAE after the last dose of study medication: an event of pancreatic carcinoma was reported for 1 subject in the E15/S100 group and an event of acute myocardial infarction was reported for 1 subject in the S100 group. Both SAEs occurred 28 days after the last dose of study medication

8.7.3.2. Study P006/1015 Add-on to metformin and sitagliptin study

No deaths were reported during Phase A. The incidence of SAEs was low and similar in the ertugliflozin 5 mg (4.5%), ertugliflozin 15 mg (2.0%) and placebo (3.3%) groups. No specific

[4] A [information redacted] patient in the E5/S100 group, experienced a SAE of pyelonephritis acute on Day 64

SAE term was reported for > 1 subject in the ertugliflozin or placebo groups, and no notable difference in the incidence of SAEs by SOC, was observed. No SAE was reported after a subject discontinued study medication. Across the 3 treatment groups, 1 subject had a SAE that was considered related to study medication by the investigator (a SAE of transient ischemic attack in a subject in the ertugliflozin 15 mg group).

8.7.3.3. Study P017/1047 Ertugliflozin + sitagliptin initial combination study

No deaths were reported in this study. The incidence of SAEs was similar in the E5/S100 group (2.0%), E15/S100 group (3.1%), and placebo group (5.2%). No specific SAE term was reported for > 1 subject in the ertugliflozin or placebo groups, and no notable difference in the incidence of SAEs by SOC, was observed. No SAE was reported after a subject discontinued study medication. Across the 3 treatment groups, no SAE was considered related to study medication. Two subjects had a SAE that led to discontinuation of study medication.[5]

8.7.4. Discontinuations due to adverse events

8.7.4.1. Study P005/1019 ertugliflozin +sitagliptin factorial study

AEs resulting in discontinuation from study medication, although infrequent across groups, occurred at a higher incidence in the E15/S100 group (2.9%) relative to the S100 group (0.4%); incidences in the 3 other groups (6 subjects (2.4%) in the E5 group and 3 subjects (1.2%) each in the E15 and E5/S100 groups) were similar to the E15/S100 group. There was no discernible pattern in the AEs resulting in discontinuation from study medication in the E15/S100 group, or in the E5/S100 group. The only AEs that resulted in discontinuation from study medication in > 1 subject across the 5 groups were dizziness and balanoposthitis (each resulted in discontinuation of 2 subjects in the E5 group Two subjects, both in the E5/S100 group, discontinued study medication due to a SAE; 1 due to an event of myocardial infarction and 1 due to an event of nodal marginal zone B-cell lymphoma stage III (both were assessed as severe in intensity and not related to study medication).

8.7.4.2. Study P006/1015 Add-on to metformin and sitagliptin study

The incidence of AEs resulting in discontinuation from study medication was numerically higher in the ertugliflozin 5 mg group (3.2%) than in the ertugliflozin 15 mg or placebo groups (0.7% each). The only AEs that resulted in discontinuation from study medication in more than 1 subject were those related to genital mycotic infection, involving 2 subjects in the ertugliflozin 5 mg group (1 female subject with an AE of vulvovaginal candidiasis and 1 male subject with an AE of balanoposthitis) both of which were considered drug related by investigators. Three subjects in the ertugliflozin 15 mg group were discontinued from study medication for meeting the protocol-specified discontinuation thresholds for eGFR and/or serum creatinine.

8.7.4.3. Study P017/1047 ertugliflozin + sitagliptin initial combination study

The incidence of AEs resulting in discontinuation from study medication was low and similar in the E5/S100 (2.0%), E15/S100 (2.1%), and placebo (3.1%) groups. No specific AE resulted in discontinuation from study medication in more than 1 subject in the co-administration or placebo groups. AEs resulting in discontinuation were dispersed across multiple SOCs, with no clear pattern.

[5] Subject in the E15/S100 group with an SAE of endometrial adenocarcinoma and subject in the placebo group with an SAE of ischemic stroke

8.8. Evaluation of issues with possible regulatory impact

8.8.1. Liver function and liver toxicity

8.8.1.1. Study P005/1019 ertugliflozin + sitagliptin factorial study

In Study P005/1019, decreases from baseline in ALT (baseline values ranging from 26.6 IU/L to 28.9 IU/L) at Week 26 in the E5/S100 and E15/S100 groups (-4.2 IU/L and -5.1 IU/L, respectively) and in the E5 and E15 groups (-4.4 IU/L and -4.9 IU/L, respectively) were similar, and greater in magnitude than the decrease in the S100 group (-1.6 IU/L). Decreases from baseline in AST (baseline values ranging from 21.4 IU/L to 22.4 IU/L) at Week 26 in the E5/S100 and E15/S100 groups (-1.8 IU/L and -1.9 IU/L, respectively) and in the E5 and E15 groups (-2.2 IU/L and -2.3 IU/L, respectively) were also similar, and greater in magnitude than the decrease in the S100 group (-0.5 IU/L).

ALT and/or AST elevations ≥ 3 x ULN were infrequent, occurring in just 1 subject in the E15/S100 group (who had ALT and AST ≥ 3 x ULN), 2 subjects in the S100 group (who both had ALT ≥ 3 x ULN), and no subjects in the 3 other groups. The ALT/AST elevations resolved while treatment with study medication continued in the subject in the E15/S100 group and in 1 subject in the S100 group, but was unresolved in the other subject in the S100 group when he completed Phase A. The ALT/AST elevations in these 3 subjects were not associated with a concurrent increase > 2 x ULN in total bilirubin, and no subject had an ALT or AST value > 5 x ULN. No subject in the E5/S100 or E15/S100 groups had an adverse event of ALT or AST increased compared with the E5, E15, and S100 groups, where 3, 3, and 2 subjects, respectively, had an adverse event of ALT increased, and 3, 0, and 1 subjects, respectively, had an AE of AST increased.

8.8.1.2. Studies P006/1015 and P017/1047

Reductions from baseline in ALT and AST, which were generally similar in magnitude to those seen in the ertugliflozin-treated groups in Study P005/1019, were also observed at Week 26 in the ertugliflozin groups in Study P006/1015 and in the co-administration groups in Study P017/1047.

In Study P006/1015, ALT and AST elevations ≥ 3 x ULN were also infrequent, occurring in no subject in the ertugliflozin 5 mg group, 1 subject in the ertugliflozin 15 mg group (who had an ALT ≥ 3X ULN), and 2 subjects in the placebo group (1 with ALT ≥ 3 x ULN and 1 with AST ≥ 3 x ULN). The ALT/AST elevations resolved in the ertugliflozin 15 mg subject while treatment with study medication continued, but remained ≥ 3 x ULN for 1 subject in the placebo group through her last evaluation before discontinuation, and elevated, but <3 x ULN, for the other subject in the placebo group when he completed Phase A. The ALT/AST elevations in the ertugliflozin 15 mg and placebo subjects were not associated with a concurrent increase > 2x ULN in total bilirubin, and no subject had an ALT or AST value > 5 x ULN. No subject in the ertugliflozin 5 mg or 15 mg groups had an AE of ALT or AST increased. In the placebo group, 1 subject had an adverse event of AST increased, and none had an AE of ALT increased.

In Study P017/1047, no subject had an ALT or AST elevation ≥ 3 x ULN, and no subject had an AE of ALT or AST increased.

8.8.2. Renal function and renal toxicity

8.8.2.1. Study P005/1019 ertugliflozin + sitagliptin factorial study

There were modest reductions from baseline in eGFR (baseline mean values ranging from 91.9 to 92.8 mL/min/1.73 m^2) at Week 6 in the 4 ertugliflozin-treated groups. The magnitude of the reductions were greater in the E5/S100 and E15/S100 groups (-3.5 and -5.1 mL/min/1.73 m^2, respectively) relative to the E5 and E15 groups (-2.4 and -3.4 mL/min/1.73 m^2, respectively). There was a subsequent return of eGFR to baseline (E5/S100 and E5 groups), or toward baseline (E15/S100 and E15 groups) at Week 26. In the S100 group, a small decrease in eGFR

through Week 12 (-1.4 mL/min/1.73 m^2) was followed by a slight increase toward baseline at Week 26.

The proportion of subjects with at least 1 decrease in eGFR > 30% from baseline was numerically greater in the E5/S100 group (5.9%) than in the E5 group (2.8%), but was similar in the E15/S100 (3.8%) and E15 (4.1%) groups, with 2.9% of subjects in the S100 group meeting this criterion. There were modest increases from baseline (baseline values approximately 0.8 mg/dL) in serum creatinine at Week 6 in the 4 ertugliflozin-treated groups. An AE of eGFR decreased or blood creatinine increased was reported for: 4 (1.6%) and 2 (0.8%) subjects in the E5/S100 and E15/S100 groups, respectively; 3 (1.2%) and 6 (2.4%) subjects in the E5 and E15 groups, respectively; and 1 subject (0.4%) in the S100 group. None of these events was severe or serious and only 1 led to discontinuation of study medication (eGFR decreased reported for subject in the E15/S100 group); although, 1 subject (in the E5/S100 group) discontinued study medication for meeting protocol-specified eGFR/serum creatinine discontinuation criteria.

An AE of acute kidney injury, chronic kidney disease, renal impairment, or nephropathy was reported for 3 (1.2%), 1 (0.4%), 2 (0.8%) and 2 (0.8%) and 0 subjects in the E5/S100, E15/S100; E5, E15 and S100 groups, respectively. Among these subjects, 1 subject[6] in the E5 group had an event that was severe in intensity.

8.8.2.2. Study P006/1015 Add-on to metformin and sitagliptin study

An AE of renal failure was reported for 1 subject in each ertugliflozin group, an AE of blood creatinine increased was reported for 1 subject in the ertugliflozin 15 mg group, and an AE of renal impairment was reported for 1 subject in the placebo group. None of these events was an SAE and none led to discontinuation of study medication. Six (3.9%), 3 (2.0%), and 7 (4.7%) subjects in the ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo groups, respectively, met the PDLC criterion of a decrease from baseline in eGFR > 30% (at least one occurrence) (excluding data after initiation of glycaemic rescue therapy. Additionally, evaluation of changes over time in mean eGFR showed a modest decrease from baseline in both ertugliflozin groups at Week 6 which returned to baseline in the ertugliflozin 5 mg group and increased toward baseline in the ertugliflozin 15 mg group at Week 26. The proportion of subjects meeting PDLC criterion for BUN increase ≥ 50% and value > ULN was numerically greater in the ertugliflozin groups compared with placebo (7.2%, 13.3% and 5.4% in ertugliflozin 5 mg, 15 mg and placebo groups, respectively) during the double-blind treatment period. . A mean increase from baseline in BUN was seen at the first measurement at Week 6, persisting through Week 26 in both ertugliflozin groups.

8.8.2.3. Study P017/1047 ertugliflozin + sitagliptin initial combination study

At Week 6, there were modest reductions from baseline in mean eGFR in all 3 treatment groups. The mean change in the E5/S100 group (-4.3 mL/min/1.73 m^2) was greater than in the other 2 treatment groups (approximately -2.0 mL/min/1.73 m^2 in both groups). In the E5/S100 group, the decrease in mean eGFR at Week 6 was followed by a return to baseline at Week 26. In the E15/S100 group, mean eGFR returned to baseline at Week 18 and was slightly below baseline at Week 26. Two subjects (2.1%) in each coadministration group and 2 (2.3%) subjects in the placebo group met the PDLC criterion of at least one decrease in eGFR > 30% from baseline. No subjects were discontinued from study medication for meeting the protocol-specified discontinuation threshold for eGFR or serum creatinine. There were no AEs reflecting events of acute or chronic renal dysfunction in the Renal and urinary disorders SOC.

[6] This subject, a [information redacted] with a baseline eGFR of 58 mL/min/1.73 m^2, had an eGFR of 12 mL/min/1.73 m^2 on Day 98, a concurrent serious adverse event of pancreatitis, and concurrent non-serious adverse events of urinary tract infection and cholecystitis acute, for which a laparoscopic cholecystectomy was performed. The eGFR on Day 103 was 104 mL/min/1.73 m^2. The investigator considered the event of acute kidney injury to be secondary to dehydration and use of angiotensin-converting inhibitors.

8.8.3. Other clinical chemistry

In the 3 Phase III studies, changes in the serum lipid profile seen with ertugliflozin and sitagliptin combination therapy were generally similar to those seen in the ertugliflozin Phase III program and in the individual ertugliflozin groups in Study P005/1019, including small increases in LDL-C, total cholesterol, and HDL-C, and small decreases in triglycerides. In Study P006/1015, lipid effects with ertugliflozin treatment were generally similar to those observed with placebo, except for high-density lipoprotein cholesterol (HDL-C) which increased at Week 26 in the ertugliflozin groups. In study O017/1047, LDL-C, HDL-C and total cholesterol increased in both ertugliflozin groups compared with placebo.

The PDLC criterion for phosphate increase ≥ 0.5 mg/dL and value > ULN was met by 29 (19.1%), 28 (18.7%), and 12 (8.1%) subjects in ertugliflozin 5 mg, 15 mg and placebo groups, respectively during the double blind treatment period. Small (< 0.5 mg/dL) mean increases from baseline in serum phosphate were seen in both ertugliflozin groups, with no notable change from baseline in the placebo group.

The incidence of subjects with a potassium value > 5.4 mEq/L and 15% above baseline at the last on-treatment assessment was higher in the ertugliflozin 5 mg group (4 subjects; 2.6%) relative to the placebo group (no subjects); 1 subject (0.7%) met this PDLC criterion in the ertugliflozin 15 mg group and no subjects in the study had a potassium value > 6 mEq/L at the last on-treatment visit; the proportions of subjects with any potassium value > 6 mEq/L during the double-blind treatment period were low and similar in the 3 treatment groups (1 (0.7%), 2 (1.3%) and 2 (1.3%) in the ertugliflozin 5 mg, ertugliflozin 15 mg and placebo groups, respectively, including data after initiation of glycaemic rescue therapy. No meaningful differences in changes over time in mean potassium were observed through Week 26 in the ertugliflozin groups relative to the placebo group, excluding and including data after initiation of glycaemic rescue therapy.

Decreases from baseline in uric acid that were observed with ertugliflozin and sitagliptin combination therapy in the 3 studies was similar to those seen with the individual ertugliflozin groups in Study P005/1019, and with ertugliflozin treatment in the Phase III development program.

In the 3 Phase III studies, small increases from baseline over time in phosphate and magnesium, and fluctuations in calcium were observed in the ertugliflozin-treated groups relative to non-ertugliflozin-treated groups (that is, placebo or sitagliptin). More subjects in the ertugliflozin-treated groups than in the non-ertugliflozin groups met PDLC criteria for an increase in phosphate. Increases meeting PDLC criteria for magnesium and calcium were infrequent. Changes over time and proportions of subjects meeting PDLC criteria for phosphate, magnesium, and calcium with ertugliflozin and sitagliptin combination treatment were consistent with those seen in the individual ertugliflozin groups in Study P005/1019, and with ertugliflozin treatment in the Phase III development program.

There were no meaningful changes associated with ertugliflozin and sitagliptin combination treatment in potassium, bicarbonate or sodium.

No subjects had a laboratory-related SAE or discontinued study medication due to a laboratory-related AE, with the exception of a subject in the E15/S100 group, who discontinued study medication due to asymptomatic hypoglycaemia (glucose 3.1 mmol/L).

8.8.4. Haematology and haematological toxicity

8.8.4.1. Study P005/1019 ertugliflozin + sitagliptin factorial study

Small increases in haemoglobin (≤ 0.63 g/dL, from baseline values ranging from 13.89 g/dL to 14.22 g/dL) were observed at Weeks 12 and 26 in the co-administration and individual ertugliflozin treatment groups, relative to a slight decline (≤ 0.28 g/dL) in the sitagliptin group. The proportions of subjects with at least 1 haemoglobin value meeting the PDLC c criterion for

an increase > 2.0 g/dL from baseline were similar in the E5/S100 and E15/S100 groups (3.1% and 2.2%, respectively) relative to the E5 and E15 groups (3.4% in both groups). The incidence in the S100 group (1.3%) was numerically lower than in the 4 ertugliflozin-treated groups.

8.8.4.2. Study P006/1015 Add-on to metformin and sitagliptin study

Mean changes over time in most haematology parameters were generally small with no meaningful differences between the ertugliflozin and placebo groups. A small mean increase from baseline in haemoglobin was observed in the ertugliflozin 5 mg and 15 mg groups at Week 12 which persisted through Week 26. No subjects across the 3 treatment groups had an AE reported that was associated with a change in haemoglobin. Six (4.0%), 2 (1.4%), and 1 (0.7%) subjects in the ertugliflozin 5 mg, ertugliflozin 15 mg, and placebo groups, respectively, met the PDLC criterion of an increase from baseline in haemoglobin > 2 g/dL (at least 1 occurrence) (excluding data after initiation of glycaemic rescue therapy.

8.8.4.3. Study P017/1047 ertugliflozin + sitagliptin initial combination study

Small mean increases from baseline in haemoglobin observed at Week 12 persisted through Week 26 in the coadministration groups Four (4.3%), 3 (3.3%), and 0 (0.0%) subjects in the E5/S100, E15/S100, and placebo groups, respectively, met the PDLC criterion of an increase from baseline in haemoglobin > 2.0 g/dL, and one subject in the E15/S100 group met the criterion of an increase from baseline in haemoglobin > 2.0 g/dL and value > ULN.

8.8.5. Other laboratory tests

Not applicable.

8.8.6. Electrocardiograph findings and cardiovascular safety

In each of the 3 Phase III studies, 12-lead ECGs were performed at Week -2 (regarded as the baseline measurement for ECG endpoints) and Week 26. Summary statistics for mean changes over time in ECG parameters (PR interval, QRS interval, QT, QTcB, QTcF, and heart rate) were evaluated for each study. No meaningful changes from baseline in ECG parameters were observed in the co-administration groups relative to the individual treatments in Study P005/1019, in the ertugliflozin groups relative to the placebo group in Study P006/1015, or in the co-administration groups relative to the placebo group in Study P017/1047.

In Study P005/1019, 1 subject;[7] in the E5/S100 group and no subject in the 4 other groups met the criterion for a QTcF value ≥ 500 ms. The proportions of subjects who met the QTcF criteria for increase ≥ 30 ms and value above gender specific ULN was not notably different in the E5/S100 and E15/S100 groups (2 (0.9%) and 4 (1.8%) subjects, respectively) relative to the E5 and E15 groups (1 (0.5%) and 1 (0.5%) subjects, respectively) and the S100 group (6 subjects (2.8%)).

In Study P006/1015, no subjects in the ertugliflozin 5 mg, 15 mg, or placebo groups met the criterion for a QTcF value ≥ 500 ms, or had a QTcF increase ≥ 60 ms and value above gender specific ULN. The proportions of subjects who met the QTcF criteria for increase ≥ 30 ms and value above the gender specific ULN was not notably different in the ertugliflozin 5 mg and 15 mg groups (2 (1.5%) and 3 (2.2%), respectively) relative to the placebo group (0.0%).

In Study P017/1047, no subject in the E5/S100, E15/S100, or placebo groups met the criterion for a QTcF value ≥ 500 ms, or had a QTcF increase ≥ 60 ms and value above gender specific ULN. One subject each in the E5/S100 group (1.2%) and the E15/S100 group (1.2%), and none in the placebo group, met the criteria for QTcF increase ≥ 30 ms and value above gender specific ULN.

[7] The subject who met this criterion in the E5/S100 group had a QTcF interval on Day 183 (Week 26) of 520 ms; however, the subject's pre-treatment result (501 ms) also met this PDLC criterion, and was consistent with the result on Day 183.

Comment: It is important to note that results of the CV meta-analysis for ertugliflozin were not provided (please refer to the evaluation report for the submission for Steglatro, available as Attachment 2).

8.8.7. Vital signs and clinical examination findings

8.8.7.1. Study P005/1019 ertugliflozin + sitagliptin factorial study

There were no meaningful differences between treatment groups in the proportions of subjects who met the pre-specified criteria for orthostatic changes in systolic blood pressure or diastolic blood pressure. No meaningful differences in sitting pulse rate were observed over time in the co-administration groups relative to the individual treatments in Study P005/1019.

8.8.7.2. Study P006/1015 Add-on to metformin and sitagliptin study

Mean changes in pulse rate were either similar to or slightly lower than baseline at all time points through Week 26 in the ertugliflozin groups and fluctuated above and below baseline in the placebo group. Small numeric increases in the proportion of subjects who met the pre-specified criterion for orthostatic change in SBP were observed in the ertugliflozin groups relative to the placebo group. The increases in the ertugliflozin groups were not dose-dependent or clinically meaningful. Relative to the placebo group, numeric increases in the proportion of subjects who met the pre-specified criterion for orthostatic change in DBP were observed at Week 6 in both ertugliflozin groups, and at Week 26 in the ertugliflozin 15 mg group. The increases in the ertugliflozin groups were not dose-dependent or clinically meaningful.

8.8.7.3. Study P017/1047 ertugliflozin + sitagliptin initial combination study

At both the Weeks 6 and 26 time points, there were no meaningful differences in the proportions of subjects who met the pre-specified criterion for orthostatic change in systolic or diastolic blood pressure between the 3 treatment groups. No meaningful differences in mean supine pulse rate were observed between the coadministration and placebo groups through Week 26.

8.8.8. Immunogenicity and immunological events

There have been postmarketing reports;[8] of serious hypersensitivity reactions in patients treated with sitagliptin and may include anaphylaxis, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin with some reports occurring after the first dose.

8.8.9. Serious skin reactions

Exfoliative skin conditions including Stevens-Johnson syndrome have been reported with sitagliptin. Postmarketing cases of bullous pemphigoid requiring hospitalisation have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor.

The following is included in the proposed PI for Steglujan: *'Patients to report development of blisters or erosions while receiving MSD- ertugliflozin-sitagliptin. If bullous pemphigoid is suspected, MSD-ertugliflozin-sitagliptin should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.'*

[8] 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.

8.9. Special safety topics for FDC of ertugliflozin-sitagliptin

Special safety topics identified for review in the ertugliflozin program were discussed in detail in the Steglatro report. Among these topics, 3 overlapped with regard to labelled safety or dosing topics for sitagliptin and include changes in renal function, pancreatitis, and hypersensitivity. Hence, these topics, along with hypoglycaemia, an important safety concern for all AHAs, were identified as Special safety topics for the ertugliflozin-sitagliptin FDC. AEs specific to ertugliflozin including urinary, genital mycotic infections and hypovolema/osmotic diuresis are also discussed in the following section.

8.9.1. Hypoglycaemia

8.9.1.1. Study P005/1019 ertugliflozin + sitagliptin factorial study

Documented hypoglycaemia (symptomatic and asymptomatic together) was reported most frequently in the E15/S100 group, with a similar frequency in the E5/S100 group relative to the E5 and E15 groups, and least frequently in the S100 group (Table 19). Two subjects,[9] 1 in the E15/S100 group and 1 in the E15 group, had AEs of severe hypoglycaemia. The incidence of symptomatic hypoglycaemia was similar in the E5/S100 group, and numerically higher in the E15/S100 group in the pre-specified comparisons with the E15, E5 and S100 groups (Table 20).

Table 19: Documented (symptomatic and asymptomatic) and severe hypoglycaemia by study (ertugliflozin / sitagliptin)

P005/1019 (26 weeks) Ertugliflozin + Sitagliptin Factorial	**Sitagliptin (N=247)**	**Ertugliflozin 5 mg (N=250)**	**Ertugliflozin 15 mg (N=248)**	**Ertugliflozin 5 mg + Sitagliptin 100 mg (N=243)**	**Ertugliflozin 15 mg + Sitagliptin 100 mg (N=244)**
Documented, n (%) Severe, n (%)	9 (3.6) 0 (0)	14 (5.6) 0 (0)	13 (5.2) 1 (0.4)	13 (5.3) 0 (0)	22 (9.0) 1 (0.4)
P006/1015 (26 weeks) Add-on to Metformin and Sitagliptin	**Placebo (N=153)**	**Ertugliflozin 5 mg (N=156)**	**Ertugliflozin 15 mg (N=153)**		
Documented, n (%) Severe, n (%)	5 (3.3) 1 (0.7)	7 (4.5) 1 (0.6)	3 (2.0) 0 (0)		
P017/1047 (26 weeks) Ertugliflozin + Sitagliptin Initial Combination	**Placebo (N=97)**			**Ertugliflozin 5 mg + Sitagliptin 100 mg (N=98)**	**Ertugliflozin 15 mg + Sitagliptin 100 mg (N=96)**
Documented, n (%) Severe, n (%)	1 (1.0) 0 (0)			6 (6.1) 0 (0)	3 (3.1) 2 (2.1)

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

[9] The subject in the E15/S100 group had 2 events of severe hypoglycaemia (associated glucose values per event were [3.3 mmol/L and 2.8 mmol/L which were each categorized as requiring non-medical assistance. The event for the subject in the ertugliflozin 15 mg group (associated glucose of 3.4 mmol/L, which was reported to have resulted in a markedly depressed level of consciousness, was categorized as requiring medical assistance.

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

P005/1019 (26 weeks) Ertugliflozin + Sitagliptin Factorial Study	Sitagliptin 100 (N=250)	Ertugliflozin 5 mg (N=248)	Ertugliflozin 15 mg (N=247)	Ertugliflozin 5 mg + Sitagliptin 100mg (N=243)	Ertugliflozin 15 mg + Sitagliptin 100 mg (N=244)
Symptomatic Events, n(%)	6 (2.4)	6 (2.4)	6 (2.4)	6 (2.5)	12 (4.9)
P006/1015 (26 weeks) Add-on to Metformin and Sitagliptin Study	Placebo (N=153)	Ertugliflozin 5 mg (N=156)	Ertugliflozin 15 mg (N=153)		
Symptomatic Events, n(%)	4 (2.6)	6 (3.8)	1 (0.7)		
P017/1047 (26 weeks) Ertugliflozin + Sitagliptin Initial Combination Study	Placebo (N=97)			Ertugliflozin 5 mg + Sitagliptin 100 mg (N=98)	Ertugliflozin 15 mg + Sitagliptin100 mg (N=96)
Symptomatic Events, n(%)	1 (1.0)			3 (3.1)	3 (3.1)
N = number of subjects in the ASaT population, n = number of subjects with 1 or more events					

8.9.1.2. Study P006/1015 Add-on to metformin and sitagliptin study

The incidence of documented hypoglycaemia (symptomatic and asymptomatic together) was low and similar between the ertugliflozin groups and the placebo group (Table 19). Two subjects, 1 in the ertugliflozin 5 mg group;[10] and 1 in the placebo group;[11] had an AE of severe hypoglycaemia. The incidence of symptomatic hypoglycaemia was similar in the ertugliflozin 5 mg group (3.8%), and numerically lower in the ertugliflozin 15 mg group (0.7%), relative to the placebo group (2.6%) (Table 20). One subject in the placebo group and 1 subject in the ertugliflozin 5 mg group experienced an episode of severe hypoglycaemia. Among subjects with documented hypoglycaemia, the majority experienced a single episode. Two (1.3%) subjects in the ertugliflozin 5 mg group, 1 (0.7%) subject in the ertugliflozin 15 mg group, and no subjects in the placebo group experienced 3 or more episodes of documented hypoglycaemia. For 2 of the 3 ertugliflozin subjects with 3 or more episodes of documented hypoglycaemia, the hypoglycaemia episodes were symptomatic.

8.9.1.3. Study P017/1047 ertugliflozin +sitagliptin initial combination study

The incidence of overall documented hypoglycaemia in the E5/S100 group (6.1%) was numerically higher than in the E15/S100 (3.1%) and placebo (1.0%) groups (Table 19). However, two subjects;[12] in the E15/S100 group, experienced an AE of severe hypoglycaemia. The incidence of symptomatic hypoglycaemia was not notably different in the E5/S100 and E15/S100 groups relative to the placebo group (Table 20). The incidence of symptomatic hypoglycaemia was low and not notably different between the E5/S100 and E15/S100 groups (both 3.1% (3 subjects)) and the placebo group (1.0% (1 subject)). Two subjects in the E15/S100 group and none in the other treatment groups experienced an episode of severe hypoglycaemia. One subject in the E15/S100 group experienced multiple episodes of documented hypoglycaemia; all other subjects with documented hypoglycaemia in the E15/S100 group, as well as in the E5/S100 group, experienced a single episode.

8.9.2. Pancreatitis

Events of potential pancreatitis were evaluated by a blinded adjudication committee for confirmation. In the Broad Pool of the ertugliflozin SCS there were no cases of confirmed

[10] This event resulted in a seizure (associated glucose of 3.6 mmol/L was categorized as requiring medical assistance.
[11] The event resulted in a markedly depressed level of consciousness (associated glucose of 3.8 mmol/L, was categorised as requiring medical assistance.
[12] Both severe events were reported as requiring non-medical assistance. One of the 2 subjects had no associated glucose value reported, and the other subject had an associated glucose value of 5.1 mmol/L.

pancreatitis in subjects treated with ertugliflozin, with or without combination treatment with sitagliptin.

8.9.3. Hypersensitivity

Hypersensitivity reactions, including anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome, are included in labelling of sitagliptin based upon post-marketing reports. In the Broad Pool of 7 Phase III studies in the ertugliflozin SCS, the incidence of hypersensitivity-related events was low and similar in the ertugliflozin 5 mg and 15 mg dose groups (3.3% and 2.4%, respectively) and the non-ertugliflozin group (2.5%). Only 1 event, in a non-ertugliflozin treated subject, was serious. Four events in ertugliflozin treated subjects and 1 event in a non-ertugliflozin treated subject led to discontinuation of treatment. All were mild or moderate events of rash, rash maculopapular, or dermatitis allergic. One of these subjects was in the E15/S100 group in Study P005/1019.[13]

8.9.4. Urinary tract infection (UTI)

In the ertugliflozin /sitagliptin factorial Study P005/1019, the incidence of UTI was similar in the E5/S100 and E15/S100 groups (3.3% and 3.7%, respectively) relative to the S100 group (3.2%), but were numerically lower than the incidence in the E5 and E15 groups (6.0% and 5.6%, respectively). There were 2 reports of complicated UTI (1 each in the E5/S100 and the E15 group, both of which resolved); only 1 AE of UTI led to discontinuation in the E15/S100 group.

In Study P006/1015, the incidence of UTI was numerically higher in the ertugliflozin 15 mg group (5.2%) relative to the ertugliflozin 5 mg and placebo groups (2.6% in both groups). Across the 3 groups, AEs of UTI were all non-serious, mild or moderate in intensity, and none led to discontinuation of study medication and there were no reports of complicated UTI.

In the initial combination Study P1017/1047, the incidence of urinary tract infections was numerically lower in the E15/S100 group (3.1%) relative to the E5/S100 (8.2%) and placebo (6.2%) groups; 1 subject in the E5/S100 group had an event that resulted in discontinuation from study medication and 1 subject in the E15/S100 group had a complicated UTI (which resolved 1 week later).

8.9.5. Genital mycotic infections

In the ertugliflozin /sitagliptin factorial Study P005/1019, the incidence of genital mycotic infections in male subjects in the E5/S100 and E15/S100 groups (4.1% and 2.4%, respectively) was similar to those in the E5 and E15 groups (4.7% and 3.7%, respectively), but was significantly higher ($p = 0.012$) and numerically higher, respectively, relative to the S100 group, where no cases were reported. Similar results were observed in females E5/S100 and E15/S100 groups (5.0% and 7.6%, respectively) was similar to those in the E5 and E15 groups (4.9% and 7.0%, respectively), but was numerically higher and significantly higher ($p = 0.027$), respectively, relative to the S100 group (1.1%).

In Study P006/1015, the incidence of genital mycotic infections in male subjects was significantly higher in the ertugliflozin 5 mg group (4.9%; $p = 0.025$) and numerically higher in the ertugliflozin 15 mg group (3.7%) than in the placebo group, where no events were reported Similarly, incidence of genital mycotic infections in female subjects was numerically higher in the ertugliflozin 5 mg group (8.0%) and significantly higher in the ertugliflozin 15 mg group (12.7%; $p = 0.030$) than in the placebo group (1.9%).

[13] A [information redacted] subject who experienced a non-serious, moderate adverse event of dermatitis allergic on Day 105, reported as not related to study medication by the investigator. The event duration was 2.57 weeks and the last dose of study medication was on Day 121

In the initial combination study P1017/1047, the incidence of genital mycotic infections in males was higher in the E5/S100 and E15/S100 groups compared with placebo (5.3%, 1.9% and 0% in the E5/S100, E15/S100 and placebo groups, respectively). However, incidence of genital mycotic infections was numerically higher in the placebo group in females (4.9%, 7.0% and 10.0%, respectively.

Across all 3 studies, majority of the AEs of genital mycotic infection in both male and female subjects were non-serious and mild or moderate in intensity.

8.9.6. Hypovolemia and osmotic diuresis

In Study P005/1019, there were no adverse events related to hypovolemia in the E5/S100 or E15/S100 groups, or in the S100 group. Four subjects (1.6%) in the E5 group (2 with syncope, 1 with hypotension, and 1 with orthostatic hypotension) and 2 subjects (0.8%) in the E15 group (1 with dehydration and 1 with orthostatic hypotension) had AEs related to hypovolemia. Except for the SAE of syncope reported for 1 subject in the E5 group, adverse events of hypovolemia in the E5 and E15 groups were all non-serious and mild or moderate in intensity. None resulted in discontinuation from study medication.

The incidence of AEs related to osmotic diuresis was low across groups (≤ 2.1%), without any notable pattern of occurrence in the co-administration groups relative to the ertugliflozin alone and sitagliptin alone groups.

In Study P006/1016, AEs related to hypovolemia were reported for 1 subject (0.6%) in the ertugliflozin 5 mg group (syncope), no subjects in the ertugliflozin 15 mg group, and 1 subject (0.7%) in the placebo group (hypotension). The incidence of AEs related to osmotic diuresis was 1.3%, 3.2% and 2.6% in the placebo, ertugliflozin 5 mg and 15 mg groups, respectively. All AEs related to hypovolemia or osmotic diuresis were mild, non-serious and none resulted in discontinuation from study medication.

In Study P1017/1047, AEs related to hypovolemia were reported for 2 subjects (2.0%) in the E5/S100 group (hypotension for each), 2 subjects (2.1%) in the E15/S100 group (dizziness postural and hypotension), and 1 subject (1.0%) in the placebo group (dehydration). One subject in each co-administration group and none in the placebo group had an AE related to osmotic diuresis. An event of polyuria, reported for a subject in the E5/S100 group, was severe and resulted in discontinuation of study medication. No other AEs related to osmotic diuresis, increased urination, or thirst were severe or resulted in discontinuation of study medication, and none was serious.

8.10. Other safety issues

8.10.1. Safety in special populations

No specific analyses to assess intrinsic factors were performed for subjects taking the combination of ertugliflozin and sitagliptin. Formal subgroup analyses for safety were not performed in the 3 individual Phase III studies given the smaller subgroup sizes. However, safety of individual components of the proposed FDC (ertugliflozin and sitagliptin) in patients with renal/hepatic impairment and elderly patients has been adequately covered in the proposed PI.

8.10.1.1. Pregnancy/lactation

There are no adequate and well-controlled studies in pregnant women with the ertugliflozin/sitagliptin FDC or its individual components. This FDC should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Based on results from animal studies, ertugliflozin may affect renal development and maturation, therefore the ertugliflozin/sitagliptin FDC is not recommended during the second and third trimesters of pregnancy. There is no information regarding the presence of the ertugliflozin/sitagliptin FDC

or its individual components in human milk, the effects on the breastfed infant, or the effects on milk production. Ertugliflozin and sitagliptin are present in the milk of lactating rats. Since human kidney maturation occurs in utero and during the first 2 years of life when locational exposure may occur, there may be risk to the developing human kidney, based on data with ertugliflozin. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from the ertugliflozin/ sitagliptin FDC, a decision should be made whether to discontinue nursing or to discontinue the FDC, taking into account the importance of the drug to the mother.

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

In the 3 Phase III studies, 7 subjects randomised to combination therapy with ertugliflozin and sitagliptin had an AE of accidental overdose of study medication. None of these overdoses was reported to be associated with a clinical adverse event or an abnormal laboratory result.

The drug abuse and dependence potential of ertugliflozin has not been characterised, but given the mechanism of action, it is not expected to be subject to drug abuse and dependence. The pharmacodynamic profile of sitagliptin does not suggest any potential for drug abuse.

There are no non-clinical or clinical data that would suggest a potential for withdrawal or rebound effects after discontinuing ertugliflozin.

As with any AHA, it is expected that blood glucose levels could increase upon discontinuation of the AHA. However, based on the mechanism of action of ertugliflozin and sitagliptin, any increase in blood glucose levels would not be expected to be precipitous.

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

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

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

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

All of the known DDI interactions for each of the active agents contained in the FDC are adequately addressed in the proposed PI.

8.12. 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 postmarketing 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).'

8.13. Evaluator's overall conclusions on clinical safety

The safety of the proposed coadministration 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.

8.13.1. 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).

8.13.2. 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.

8.13.3. 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, TC and 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.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

Table 21: First round assessment of benefits

Benefits	Strengths and Uncertainties
Combination of ertugliflozin+sitagliptin provides greater improvements (reductions) in HbA1c, FPG, body weight and SBP compared to individual agents.	Efficacy only established up to 26 weeks.
In subjects with T2DM and inadequate glycaemic control on diet and exercise, treatment with the initial combination of	

Benefits	Strengths and Uncertainties
ertugliflozin (5 mg QD or 15 mg QD) and sitagliptin 100 mg QD for 26 weeks provides clinically meaningful reductions from baseline in A1c, FPG, and 2-hour PMG relative to placebo.	
Initial combination treatment with ertugliflozin (5 mg QD or 15 mg QD) and sitagliptin 100 mg QD for 26 weeks In subjects with T2DM and inadequate glycaemic control on diet and exercise, treatment provides clinically meaningful reductions from baseline in A1c, FPG, and 2 hour PMG, body weight and SBP relative to placebo.	
Simple once daily oral dosing may improve treatment compliance.	Actual effect on treatment compliance not assessed.
Insulin independent mechanism of action	Efficacy of ertugliflozin is dependent on renal function.
Overall, ertugliflozin 5 mg and 15 mg od was safe and well tolerated	Dose-dependent increase in incidence of genital mycotic infections and elevated LDL-C.

9.2. First round assessment of risks

The risks associated with ertugliflozin, the NCE in the proposed FDC of ertugliflozin+sitagliptin were discussed in the Steglatro report (PM-2017-01328-1-5, see Attachment 2). However, main aspects have been mentioned below.

Table 22: First round assessment of risks

Risks	Strengths and Uncertainties
Although CV meta-analysis of CV events in the Phase III studies was conducted, results were not presented.	The sponsor has initiated a CV outcome Study P004/1021 to assess CV risks of ertugliflozin and it is expected to complete in 2019.
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.	
The incidence of genital mycotic infections was	Incidence of complicated infections was low

Risks	Strengths and Uncertainties
higher in the ertugliflozin groups than in the non-ertugliflozin groups in both men and women. In female subjects, there was a modest dose-relationship.	(< 1%) but still higher in the ertugliflozin groups.
Lack of evaluation of efficacy/ safety of ertugliflozin in combination with insulin, SUs and GLP-1 analogues.	
None of the Phase II dose ranging studies evaluated the proposed 15 mg dose of ertugliflozin.	
Lack of evidence to support long term maintenance of efficacy of ertugliflozin + sitagliptin beyond 26 weeks.	Phase B of 2 of the 3 studies submitted to support proposed FDC should help address lack of data on long term efficacy.

9.3. First round assessment of benefit-risk balance

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 A1c. 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.

Three of the 7 Phase III studies (Studies P005/1019, P006/1015, and P017/1047) evaluated the safety and efficacy of combination therapy with ertugliflozin and sitagliptin in adult subjects with T2DM in support of the ertugliflozin/sitagliptin FDC. The proposed FDC of ertugliflozin+sitagliptin was not evaluated in any of the Phase III studies as ertugliflozin and sitagliptin were co-administered as individual tablets in all Phase III studies in the ertugliflozin clinical development program including the 3 pivotal Phase III studies submitted to support this FDC submission. Bridging to the FDC tablets was accomplished through bioequivalence studies (Studies P025/1038, P044/1053, P048/1056, and P049/1057).

Efficacy of ertugliflozin and sitagliptin combination therapy was evaluated in the ertugliflozin plus sitagliptin factorial study (Study P005/1019), in the ertugliflozin plus sitagliptin initial combination study (Study P017/1047) and in the add-on to metformin and sitagliptin study (Study P006/1015). Both doses of the combination, ertugliflozin 15 mg/sitagliptin 100 mg and ertugliflozin 5 mg/sitagliptin 100 mg, led to significant and clinically meaningful reductions in A1C, FPG, and 2 h PPG, and a greater proportion of subjects reaching A1c < 7.0% compared to placebo or each corresponding dose of ertugliflozin or sitagliptin alone. In addition, ertugliflozin in combination with sitagliptin, either when co-initiated with or as add-on therapy, provided reductions in body weight and SBP compared to placebo and sitagliptin alone.

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.

There is lack of evidence to support long-term efficacy/safety of proposed co-administration of ertugliflozin+sitagliptin beyond 26 weeks. CV safety of ertugliflozin has not been established and there were other limitations of the ertugliflozin submission (please refer to the evaluation report for the submission for Steglatro). Furthermore, it is important to note that a FDC containing SGLT-2 inhibitor +DPP-4 inhibitor is already available in Australia (Glyxambi available in doses of 10 mg or 25 mg of empagliflozin with 5 mg of Linagliptin, to be taken once daily in the morning) with the added advantage that empagliflozin is also approved for prevention of CV death in T2DM patients with CV disease.

Overall, the benefit-risk profile of Steglujan (ertugliflozin+sitagliptin FDC) is not favourable for the following proposed indication: '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'. However, the benefit risk profile may become favourable if the changes recommended in section 10 are adopted.

9.4. First round recommendation regarding authorisation

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

> *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*.

However, approval could be granted for a slightly modified wording of the above 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).*

It is important to note that approval for above modified indication is also conditional to the following:

- Resolution of outstanding issues of the ertugliflozin submission (please refer to the evaluation report for the submission for Steglatro).
- Incorporation of suggested changes to proposed PI.
- Satisfactory response to Clinical questions below.

10. Clinical questions

10.1. Pharmacokinetics

10.1.1. Question 1

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

10.2. Pharmacodynamics

No questions.

10.3. Efficacy

The questions related to efficacy of ertugliflozin, the NCE in the proposed FDC should be addressed. Please refer to the evaluation report for the submission for Steglatro for questions regarding the ertugliflozin submission (see Attachment 2).

10.4. Safety

The questions related to safety of ertugliflozin, the NCE in the proposed FDC should be addressed. Please refer to the evaluation report for the submission for Steglatro for questions regarding the ertugliflozin submission.

11. Second round evaluation

11.1. Clinical Questions

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

11.1.1. Pharmacokinetics

11.1.1.1. Question 1

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

Sponsor's response

The sponsor confirms that the compositions of the proposed Steglujan and MSD-ertugliflozin-sitagliptin FDC tablets of matching dose strengths are identical.

Evaluator's comment

The evaluator is satisfied with the sponsor's response.

11.1.2. Efficacy

11.1.2.1. Question 3

The questions related to efficacy of ertugliflozin, the NCE in the proposed FDC should be addressed. Please refer to the evaluation report for the submission for Steglatro for questions regarding the ertugliflozin submission.

Sponsor's response

Please refer to the responses provided in the ertugliflozin monotherapy document.

Evaluator's comments

Please refer to evaluator's comments provided in the second round report for ertugliflozin. Overall, the sponsor's response was satisfactory (see Attachment 2 for further details).

11.1.3. Safety

11.1.3.1. Question 4

The questions related to safety of ertugliflozin, the NCE in the proposed FDC should be addressed. Please refer to the evaluation report for the submission for Steglatro for questions regarding the ertugliflozin submission.

Sponsor's response

Please refer to the responses provided in the ertugliflozin monotherapy document.

Evaluator's comments

Please refer to evaluator's comments provided in the second round report for ertugliflozin. Overall, the sponsor's response was satisfactory (see Attachment 2 for further details).

11.2. Second round benefit-risk assessment

11.2.1. Second round assessment of benefits

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

11.2.2. Second round assessment of risks

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

11.2.3. 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.

11.3. 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 (CVMA) of adjudicated, confirmed CV events from the Phase II/III studies and from the ongoing CV outcome study (Study P004/1021) upon completion.

12. References

American Association of Clinical Endocrinologists, American College of Endocrinology-2002. The American Association of Clinical Endocrinologists medical guidelines for the management of diabetes mellitus: The AACE system of intensive diabetes self-management -2002 update. *Endocrine Practice* 2002; 8(Suppl.1): 40-82.

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

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.

Seck, T, et al. 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.

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