28 February 2019
EMA/178275/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zynquista

International non-proprietary name: sotagliflozin

Procedure No. EMEA/H/C/004889/0000

Note

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

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List of abbreviations

A1C	haemoglobin A1C
AUC	area under the curve
BCS	Biopharmaceutics Classification system
bid	twice daily
CGM	continuous glucose monitoring
CHMP	Committee for Medicinal Products for Human use
CFU	Colony Forming Units
CPP	Critical process parameter
CQA	Critical Quality Attribute
CTD	Common technical document
CYP450	cytochrome P450
DBP	diastolic blood pressure
DEXA	dual-energy X-ray absorptiometry
DDI	drug-drug-interaction
DKA	diabetic ketoacidosis
DoE	Design of experiments
DSC	Differential Scanning Calorimetry
DTSQ	Diabetes Treatment Satisfaction Questionnaire
EC	European Commission
eGFR	estimated glomerular filtration rate
EU	European Union
FMEA	Failure mode effects analysis
FPG	fasting plasma glucose
fu	fraction unbound
GC	Gas Chromatography
GI	gastrointestinal
GLP-1	glucagon-like peptide 1
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
HI	hepatic impairment
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
IR	Infrared
ITT	intent-to-treat
KF	Karl Fischer titration
LTE	long-term extension
MA	Marketing Authorisation
MAG	mean absolute glucose
MAGE	mean amplitude of glucose excursion
MAR	missing at random
MNAR	missing not at random
MI	multiple imputation
mITT	modified Intention to Treat
MMRM	mixed model for repeated measures
MS	Mass Spectrometry

NMR	Nuclear Magnetic Resonance
NOR	Normal Operating Range
OGTT	oral glucose tolerance test
PAR	Proven Acceptable Range
PD	pharmacodynamic(s)
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic(s)
PMM	patten mixture model
PopPK	population PK analysis
PP	per protocol
PPG	postprandial glucose
PSDD	patient satiety daily diary
PSDD-NRS	patient satiety daily diary numeric rating scale
PVC/PCTFE/PVC-Al	polyvinyl chloride / polychlorotrifluoroethylene / polyvinyl chloride-aluminium
PYY	peptide YY
QbD	Quality by design
qd	once daily
QTPP	Quality target product profile
RI	renal impairment
SBP	systolic blood pressure
SGLT1	sodium glucose co-transporter 1
SGLT2	sodium glucose co-transporter 2
SH	severe hypoglycaemia
SMBG	self-monitoring of blood glucose
SmPC	Summary of Product Characteristics
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TAMC	Total Aerobic Microbial Count
TGA	Thermo-Gravimetric Analysis
TTC	Threshold of toxicological concern
TYMC	Total Combined Yeasts/Moulds Count
UGT	UDP-glucuronosyltransferase
USP	United States Pharmacopoeia
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant sanofi-aventis groupe submitted on 7 March 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Zynquista, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 July 2017.

The applicant applied for the following indication: Zynquista is indicated as an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0337/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0337/2017 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

New active Substance status

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

Scientific advice

The applicant received Scientific advice from the CHMP:

Scientific advice	date	Area
EMEA/H/SA/2417/1/1012/III	5 November 2012	non-clinical, clinical
EMEA/H/SA/2417/2/2014/III	24 July 2014	non-clinical, clinical

Scientific advice	date	Area
EMEA/H/SA/2417/2/FU/1/2015/II	19 November 2015	clinical
EMEA/H/SA/2417/3/2017/I	23 February 2017	quality

The Scientific Advice pertained to the following quality, non-clinical and clinical aspects of the dossier:

- Demonstration of Quality comparability of drug substance and drug product manufactured by different suppliers and adequacy of stability data plans
- Adequacy of non-clinical studies investigating bone safety, juvenile toxicity and potential toxicity of metabolites
- Appropriateness of planned clinical food-effect studies
- Appropriateness of a clinical phase 2b study design investigating adolescents and young adults with T1DM, in particular: definition of study population, sample size, treatment duration, efficacy endpoints, dose finding
- Appropriateness of the design of two proposed pivotal phase 3 clinical studies, in particular: definition of study population, screening and run-in periods, insulin-treatment management, dose and dose regimen, sample size, primary and secondary efficacy endpoints, safety database at the time of MAA, evaluation of severe hypoglycaemia risk and diabetic ketoacidosis: monitoring, risk evaluation and management
- Appropriateness of plans to assess cardiovascular safety

1.2. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: Bart Van der Schueren

The application was received by the EMA on	7 March 2018
The procedure started on	29 March 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	18 June 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	18 June 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	2 July 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	26 July 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	14 Sept 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	22 Oct 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 Oct 2018

The CHMP agreed on a 1st List of Outstanding Issues to be addressed in writing and/or in an oral explanation to be sent to the applicant on	15 Nov 2018
Ad Hoc Expert group was convened to address questions raised by the CHMP on The CHMP considered the views of the Ad Hoc Expert group as presented in the minutes of this meeting.	21 Nov 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	03 Jan 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	16 Jan 2019
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	29 Jan 2019
The CHMP agreed on a 2nd List of Outstanding Issues to be addressed in writing and/or in an oral explanation to be sent to the applicant on	31 Jan 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	05 Feb 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	13 Feb 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Zynquista on	28 Feb 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The indication proposed for Zynquista is:

"Zynquista is indicated as an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus with a Body Mass Index (BMI) ≥ 27 kg/m2, who have failed to achieve adequate glycaemic control despite optimal insulin therapy."

2.1.2. Epidemiology

The worldwide incidence of T1DM varies by at least 100-fold, being highest in Finland and Sardinia (~40 to 60/100 000) and lowest in Venezuela and China (<1/100 000). The incidence has been increasing worldwide at an annual rate of approximately 3% and T1DM currently affects approximately 30 million adults worldwide. On average, 40 000 people are diagnosed with T1DM each year in the United States.

2.1.3. Aetiology and pathogenesis

Type 1 diabetes mellitus is an autoimmune disease characterized by rapidly progressive pancreatic β-cell destruction leading to a state of absolute insulin deficiency. Exogenous insulin is required for survival and treatment in T1DM. Lack of insulin results in diabetic ketoacidosis (DKA), a condition which is potentially life-threatening. About 3% of patients with T1DM initially presents with DKA.

2.1.4. Management

Therapeutic options for type 1 diabetes are limited to intensive insulin or insulin analogue therapy delivered subcutaneously by MDI or insulin pump. The only non-insulin therapy indicated as adjunct to insulin treatment of T1DM is Symlin (pramlintide acetate injection), approved in 2005 in the US. Other non-insulin therapies for T1DM have been pursued over the past 2 decades, but no clear benefit has yet been shown. Segmental pancreatic and islet cell transplantation continues to be explored but to date are limited to very few patients.

Based largely on the results of the DCCT, current treatment guidelines recommend that patients with T1DM be treated to a goal HbA1c of <7.0% with intensive insulin therapy. Despite significant advances in insulin therapies, delivery methods and management, 70% of T1DM patients do not achieve optimal glycaemic control and are at increased risk of microvascular complications caused by chronic hyperglycaemia. Furthermore, some patients with T1DM experience wide fluctuation in their level of glucose control on currently available insulin regimens and high glucose variability may affect quality of life.

Intensive insulin therapy is associated with an increased risk of hypoglycaemia, which can be life-threatening and may prevent patients from achieving optimal glycaemic control. Furthermore, intensive insulin therapy is also associated with excessive weight gain and with peripheral insulin resistance, both being risk factors for hypertension, and CV disease. Approximately 60% of adults living with T1DM are overweight or obese, 60% have dyslipidaemia and 40% have hypertension, and are therefore at risk of developing macrovascular complications.

During insulin therapy, DKA may occur in situations where insulin administration is interrupted or when the insulin need is increased, e.g. with severe infections. In the literature, the incidence of DKA in T1DM

patients shows large variations with a range from 0-56 per 1000 person-years. The prevalence of DKA decreases with increasing age.

The fact that most patients fail to achieve glycaemic targets and are at risk of hypoglycaemia and excessive weight gain on current type 1 treatments constitute an unmet need that could potentially be addressed by a new treatment used as an adjunct to insulin.

About the product

Sotagliflozin is an orally delivered, small molecule dual inhibitor of SGLT1 and SGLT2. Sotagliflozin improves glycaemic and metabolic control through dual inhibition – local inhibition of SGLT1 in the gut and systemic SGLT2 inhibition in the proximal renal tubule. Inhibition of SGLT1 delays and reduces glucose absorption in the proximal intestine, resulting in a blunting and delay of postprandial hyperglycaemia. Inhibition of SGLT2 reduces renal glucose reabsorption and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.

Sotagliflozin is administered by the oral route. The proposed commercial formulation for sotagliflozin is a 200 mg immediate release film-coated tablet. The recommended dose is 200 mg sotagliflozin once daily (administered as 1 tablet of 200 mg). The dose may be increased to 400 mg once daily (administered as 2 tablets of 200 mg).

Type of Application and aspects on development

The development program has in all essential aspects followed the EMA Guideline “Clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus” (CHMP/EWP/1080/00 Rev. 1) and the scientific advice given (see sections 1.1 and 2.5.3 of this report).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 200 mg of sotagliflozin as active substance.

The other ingredients are: microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate, talc, a film-coating agent (polyvinyl alcohol, macrogol 4000, titanium dioxide (E171), talc, indigo carmine aluminium lake (E132)) and black ink (shellac, black iron oxide (E172), propylene glycol).

The product is available in polyvinyl chloride/polychlorotrifluoroethylene/ polyvinyl chloride/aluminium (PVC/PCTFE/PVC-Al) blisters as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of sotagliflozin is (5*S*)-Methyl 5-*C*-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-1-thio-β-L-xylopyranoside corresponding to the molecular formula $C_{21}H_{25}ClO_5S$. It has a relative molecular mass of 424.94 and the following structure:

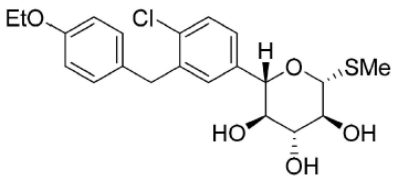


Figure 1: active substance structure

The active substance is a white to off-white non-hygroscopic solid that shows low aqueous solubility independent of pH.

The chemical structure of sotagliflozin was elucidated by a combination of spectroscopic methods [infrared spectroscopy (IR), nuclear magnetic resonance spectroscopy (NMR) (comprising 1D and 2D experiments, mass spectrometry (MS), ultraviolet absorption spectroscopy (UV)] and elemental analysis.

The solid state properties of the active substance were measured by X-ray powder diffraction (XRPD), Differential scanning calorimetry (DSC), Thermogravimetric analysis (TGA). A number of polymorphic forms of sotagliflozin have been identified. It has been conclusively demonstrated via XRPD pattern and DSC thermogram that the proposed manufacturing process consistently produces the same crystalline form of the active substance and that this form does not change upon storage.

Sotagliflozin exhibits stereoisomerism due to the presence of five chiral centres. The molecule contains five stereogenic centres and 32 stereoisomers are theoretically possible. However, sotagliflozin is produced via a highly stereoselective manufacturing process which has been demonstrated to consistently result in a single stereoisomer. The assigned absolute stereochemistry (2*S*,3*R*,4*R*,5*S*,6*R*) of sotagliflozin at its stereocentres has been confirmed by single crystal X-ray diffraction analysis.

Manufacture, characterisation and process controls

Sotagliflozin is synthesised in five main steps from two well defined starting materials with acceptable specifications.

The manufacturing process is operated by a traditional approach using target set points/normal operating ranges (NORs) for the applied process parameters. Process parameter studies on the manufacturing process are described and proven acceptable ranges (PARs) have been established for each process step based on univariate experiments but supportive data are not included in the documentation. This is considered acceptable as the PARs presented in the file constitute manufacturing process development knowledge and have not been included in the proposed manufacturing process for regulatory flexibility.

Based on the risk assessment and development work, no critical parameters (CPPs) have been identified at the different stages of the manufacturing process.

The proposed GMP starting materials are considered acceptable based on requirements of the ICH Q11 guideline and taking account of Scientific Advice provided by CHMP prior to submission of this MA application. Satisfactory information with regard to suppliers, route of synthesis, specifications, analytical methods and batch analysis has been provided for the starting materials. The specifications presented for the reagents, solvents and auxiliary materials used in the process are considered adequate.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented and are considered acceptable.

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

generated during each step and their fate through the process. Possible impurities originating from the starting materials and intermediates, and their fate and purge during the downstream process to the final active substance, have overall been satisfactorily discussed and documented based on spiking studies and batch analysis data. The proposed impurities specifications for the starting materials, intermediates and the final active substance are deemed justified through these investigations.

The stereochemical purity of sotagliflozin has been demonstrated and is assured by an appropriate control strategy.

Mutagenic impurities have been addressed in line with the requirements of the ICH M7 guideline. An appropriate control strategy for mutagenic impurities is in place. It is informed that no Class 1 organic solvents are used in the active substance manufacturing process. An appropriate control strategy for residual Class 2 and 3 solvents used in the active substance manufacturing process is in place.

No Class 1, 2 or 3 metals are used in the active substance manufacturing process. An appropriate control strategy for relevant metals is in place.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. The process development history is described in sufficient detail. Over time, changes have been made to the process in order to improve manufacturing efficiency while ensuring quality. These changes are related to the solvents and reagents used. The overall synthetic route has not changed. Satisfactory comparative analytical data for batches manufactured with the former and current process are provided. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance packaging complies with the EC directive EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, identification (IR, HPLC), assay (HPLC), related substances (HPLC), water content (KF), residual solvents (GC), sulfated ash (Ph. Eur.), polymorphic form (DSC), particle size distribution (Laser diffraction) and microbiological examination (Ph. Eur.).

All appropriate test parameters are included in the active substance specification and the corresponding acceptance limits are considered adequate and well justified. The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and related substances testing has been presented.

Batch analysis data of the active substance are provided covering the proposed commercial batch size range. The results are within the specifications and consistent from batch to batch. The provided batch analysis data confirm the consistency of the manufacturing process and the quality of the active substance.

Stability

Stability studies on three batches (two production and one pilot scale) of the active substance stored in the proposed commercial packaging for up to 36 months under long term conditions (25 °C/60% RH) and up to 12 months under accelerated conditions (40 ºC/75% RH) have been provided. The following relevant stability indicating parameters were tested*:* appearance, identity, assay, impurities, water content, particle size, crystal form and microbiological quality. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications and no meaningful changes or trends in any of the monitored parameters have been observed during the evaluated storage periods.

Photostability testing following the ICH guideline Q1B was performed on one batch. A slight change in appearance, without any quantifiable degradation, was observed in the photostability study. Based on these results, sotagliflozin is considered to be sensitive to light and must therefore be stored in a secondary container to provide adequate light protection.

A stress testing study has been conducted on sotagliflozin active substance in order to demonstrate the stability indicating nature of the HPLC assay/purity method and to study the degradation pathway. The active substance remained stable following subjection to the heat/humidity and photolytic stress conditions in the solid state while degradation was observed during the acidic, alkaline and oxidative stress conditions in the solution state. The degradation impurities that appeared during the stress testing in the solution state are separated from the sotagliflozin peak, demonstrating that the method is suitably stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 48 months without any specific storage condition when packaged in the proposed container as described in Section S.6.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is blue oval-shaped film-coated tablets printed with “2456” on one side in black ink (tablet length: 14.2 mm, tablet width: 8.7 mm) containing 200 mg of sotagliflozin.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

Tests for relevant functionality-related characteristics are included in the excipient specifications. A ready-to-use film-coating agent is used to allow ease of swallowing of the tablet and black ink is utilised for imprint. Purified water is used for the film-coating suspension and is removed in the manufacturing process.

Pharmaceutical Development

The finished product has been developed by a traditional approach according to ICH Q8 and no regulatory flexibility is applied for. The applicant has however made use of a mixture prior knowledge and quality by design (QbD) approaches during development. The quality target product profile (QTPP) was defined as summarised in Table 1.

Table 1 Quality target product profile for sotagliflozin 200 mg film-coated tablets

QTTP element	Target
Therapeutic indication	Adult patients with diabetes mellitus
Drug delivery requirement	Oral immediate release
Dosage form and strength	Film coated tablet 200 mg
Appearance of dosage form	Blue oval shaped, imprinted on one side
Dose regimen	Once a day

Primary packaging	Blister (for US & EU), HDPE bottles (for US)
Shelf-life and storage conditions	At least 36 months at 2-30°C

The formulation and manufacturing development have been evaluated through the use of prior knowledge, risk assessments and design of experiments to identify the critical product quality attributes and critical process parameters. A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies. The critical quality attributes (CQAs) and potential critical process parameters (CPPs) have been adequately investigated. The resulting formulation and manufacturing process are considered well justified.

Formulation development

Sotagliflozin is a white to off-white powder and its crystalline form is used for the film-coated tablets. The solubility of sotagliflozin in water is very low and the solubility is pH independent. Permeability studies have been conducted results of which suggest good permeability and the applicant classifies sotagliflozin as a BCS Class 2 compound (low solubility, good permeability).

The proposed particle size specification has been set on the basis of development data generated on a large number of active substance batches used for manufacture of clinical development product batches and by taking the possible impact on dissolution performance of the finished product as well as the analytical variability of the particle size test method into consideration. The formulation development has been described in detail.

For the commercial tablet, the critical quality attributes identified were assay and identity of sotagliflozin, uniformity of dosage units, dissolution, related substances, moisture and microbiological quality. A blue film-coating was chosen, and black imprinting on one side of the tablet was added. All (historic) changes made to the formulations have been described and accounted for in detail in the dossier.

The dissolution method development has been described in sufficient detail and the final selected method apparatus and parameters are considered justified. The proposed limit at release and during shelf-life has been derived from dissolution profiles obtained from clinical development and registration batches of the finished product. The same dissolution method has been utilised throughout development and the discriminatory power of the dissolution method has been adequately demonstrated by testing tablets manufactured with varied manufacturing parameters and excipient contents.

Manufacturing process development

The manufacturing process is a standard process comprising mixing, granulation, lubrication, compression, film-coating and printing. The process development has been described in detail.

An acceptable and justified control strategy has been presented. The process parameters and process controls have satisfactorily been derived from adequate prior knowledge and suitable design of experiments. The developed process is adequately reflected and described with normal operating ranges (NORs) and in-process controls (IPCs). The critical steps, process parameters and process controls are adequately described.

Packaging development

The primary packaging is white opaque standard polyvinyl chloride / polychlorotrifluoroethylene / polyvinyl chloride-aluminium (PVC/PCTFE/PVC-Al) blisters. The secondary package is a cardboard box.

The container closure system has been acceptably described and the control specifications for the packaging components are considered adequate. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of nine main steps: pre-blending, granulation, blending, final blending, compression, film-coating suspension, film-coating, printing and packaging. The process is considered to be a standard manufacturing process.

The manufacturing process has been sufficiently well described in a narrative and flow charts. The applicant has acquired substantial knowledge of the process during development. The process parameters and in-process controls have been adequately derived from the manufacturing process development and are adequate for this type of manufacturing process / pharmaceutical form.

The critical steps of the process have been identified. The proposed process parameters and in-process controls for the critical steps are well and are considered justified.

Bulk stability data, along with an evaluation of the transport conditions, have been provided for the coated tablets prior to packaging in the intended commercial packaging and the proposed maximum holding time of 12 months is acceptable. It has been confirmed that the finished product shelf-life is calculated in accordance with the guideline 'Note for guidance on start of shelf-life of the finished dosage form' (CPMP/QWP/072/96).

The process has been developed and scaled up at the proposed manufacturing site. The process has been studied in detail at pilot and commercial scale using the same type of equipment. A pre-qualification batch at production scale has also been manufactured. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The process will be formally validated with three consecutive production scale batches prior to marketing. An acceptable process validation scheme has been provided.

Product specification

The finished product specifications includes appropriate tests for this kind of dosage form; appearance, identification (HPLC, UV), assay (HPLC), degradation products (HPLC), dissolution (Ph. Eur.), uniformity of dosage units (Ph. Eur.), water content (KF) and microbiological examination (Ph. Eur.).

The finished product is released on the market based on the above release specifications, through traditional final product release testing. The specifications are considered justified based on batch analysis, stability data and regulatory guidelines / requirements. Based on the risk analysis and data presented for elemental impurities in the finished product as per the ICH Q3D guideline, it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification.

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

Batch analysis results are provided for a number of batches (10 in total) manufactured for Phase 3 clinical trials, for development studies, for primary stability studies and batches representing the commercial scale and manufacture. The results for all reported batches comply with the acceptance criteria confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three pilot scale batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The batches of finished product are representative of those proposed for marketing and were packed in in different primary container closure systems: blisters and HDPE bottles.
The stability studies of the primary batches are conducted according to a reduced matrix design with these different packages, which was considered acceptable.

The batches were tested for appearance, assay, degradation products, dissolution, water content and microbiological quality. The analytical procedures used were stability indicating. All results were within proposed specification limits and no trends or significant changes were seen.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No change in tablet assay, water content, dissolution or degradation was observed as a result of light exposure.

Based on available stability data, the proposed shelf-life of 30 months with no special storage conditions for the finished product packaged in opaque PVC/PCTFE/PVC-aluminium blisters as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients of human origin are used in the manufacture of the product. As regards animal origin, the only component of animal origin is shellac which is used in the printing ink. Shellac is obtained from the resinous secretion of insects. Insects are not a transmissible spongiform encephalopathy (TSE)-relevant animal species, as defined in the "Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3). The magnesium stearate is of vegetable origin.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Pharmacology

Primary pharmacodynamics

In vitro studies demonstrated sotagliflozin is an inhibitor of human SGLT2 (IC_{50} = 1.8 nM) and SGLT1 (IC_{50} = 36.3 nM). Sotagliflozin also inhibits SGLT2 and SGLT1 from non-human species (mouse, rat, dog and monkey). SGLT2 potency ranged from 0.5 - 1.4 nM, while SGLT1 potency ranged from 40.2 to 85.6 nM.

Through its activity at SGLT2 sotagliflozin enhanced glucose secretion in urine in mice, rats, dogs and monkeys. In diabetic and non-diabetic mice and in obese-prone non-diabetic rats, sotagliflozin improved glucose tolerance. In obese-prone non-diabetic rats, sotagliflozin lowered postprandial insulin. Through inhibition of SGLT1 in the intestine, sotagliflozin reduced glucose absorption. Postprandial levels of GLP-1 and PYY were increased. A study in SGLT1 knockout mice showed that the increase in GLP-1 was not dependent on SGLT1-inhibition. No increase in PYY was observed in the SGLT knockout mice. In non-obese diabetic (NOD) mice with T1DM, sotagliflozin significantly improved glycemic control in animals maintained on a low dose of insulin; fed blood glucose and A1C levels were comparable to mice treated with high-dose insulin only. The incidence of hypoglycaemia was much lower in the sotagliflozin-treated mice receiving low dose of insulin than in the mice receiving high-dose insulin only.

Secondary pharmacodynamics

No relevant off-target activity was observed in a general screen with 75 different receptors, enzymes and ion channels. In an assay with other members of the SGLT family, relevant activity was observed with hSGLT5 (IC_{50} = 54.1 nM) and hSGLT6 (IC_{50} = 27.3 nM).

Safety pharmacology

Sotagliflozin has an IC_{50} >23.5 µM in the human ether-a-go-go related gene (hERG) assay. A cardiac telemetry study in Beagle dogs showed that sotagliflozin had no significant effect on QT or QTc interval (corrected with the Fridericia method) at dose levels up to 500 mg/kg. Sotagliflozin at 500 mg/kg caused significantly higher heart rates (51% higher than controls) in Beagle dogs. Increased heart rate (+18%) was also noted for animals administered 100 mg/kg at two hr post-dose. Sotagliflozin at doses ≤100 mg/kg had no adverse effects on the CNS, respiratory, GI, and renal systems. As expected based on the mode of action, sotagliflozin had pharmacologic effects on the renal system. These changes were considered non-adverse at doses ≤100 mg/kg sotagliflozin.

2.3.2. Pharmacokinetics

Following single intravenous administration of sotagliflozin to mice, rats, dogs and monkeys, sotagliflozin exhibited a generally similar volume of distribution, whereas clearance appeared to be slightly greater in rodents than in the dog or monkey. Following administration of a single oral dose of sotagliflozin, good oral bioavailability (≥50%) was observed in the mouse, rat, and dog. In the monkey, oral bioavailability of sotagliflozin was lower (approximately 5%). In all species, exposure following oral administration of sotagliflozin increased as a function of the dose administered. In multiple dose studies, sex-related differences were observed with females exhibiting increased exposure when compared to the males. There was no evidence of significant sotagliflozin accumulation on repeated oral administration.

Sotagliflozin exhibited high plasma protein binding (>90%) in all species tested. Quantitative whole-body autoradiography (QWBA) studies in male rats administered ^{14}C-sotagliflozin by oral gavage, demonstrated that radioactivity was extensively distributed to tissues and organs. Tissues showing the highest peak concentrations of radioactivity were the liver, kidney medulla, kidney cortex, kidney,

adrenal gland, and pancreas. There was no significant accumulation of radioactivity in the central nervous system (CNS), and radioactivity was not selectively associated with the melanin-containing tissues or red blood cells. The placental transfer of sotagliflozin was assessed following administration of ^{14}C-sotagliflozin to timed pregnant rats. The results showed that ^{14}C-sotagliflozin-related radioactivity crossed the placenta at low levels.

Both *in vitro* and *in vivo* metabolism studies demonstrated that metabolic profiles are qualitatively similar among species, except dog where minimal metabolism was observed. Sotagliflozin was extensively metabolized in the in vivo human absorption, metabolism, and excretion study. Direct glucuronidation, forming sotagliflozin-3-O-glucuronide, was the major metabolic pathway, accounting for 94% of total radioactivity in plasma (0.25 to 48 hr AUC pool), and 33% of the dose in urine. The glucuronide of sotagliflozin was present in all species except dog. All other metabolites detected in human plasma each accounted for 2.5% or less of the total radioactivity.

2.3.3. Toxicology

Single dose toxicity

In a single dose toxicity study in rats, sotagliflozin was well tolerated at doses up to 1000 mg/kg.

Repeat dose toxicity

In the rat repeat dose toxicity studies, the expected pharmacologic effect of marked glucosuria was observed. The glucosuria predisposed for infection and inflammation of the urogenital system. In the 26-week repeat-dose study in rats, glucosuria-related changes were observed at ≥75 mg/kg/day males and 300 mg/kg/day females. Sotagliflozin-related targets included the prostate, trabecular bone of the sternum, renal pelvis (females), and urinary bladder (females). The applicant refers to other marketed SGLT2 inhibitors, where prostate inflammation was not observed. Based on an evaluation of available nonclinical and clinical data as well as published literature, the applicant is of the view that this observation is of limited relevance in humans. Sotagliflozin-related increase in trabecular bone (minimal to moderate) was noted within the sternum of males (≥30 mg/kg/day) and females (≥75 mg/kg/day) in the 26-week repeat-dose rat study and was characterized by a thickening of the trabecular bone adjacent to the growth plate. An assessment of bone turnover markers in the 26-week rat study showed that there was a decrease in bone turnover markers (osteocalcin, N-terminal propeptide of type 1 collagen, and Osteoclast-derived tartrate-resistant acid phosphate) and calciotropic hormones (1,25 Vit. D and PTH). The trend for a decrease in bone turnover markers at 30 mg/kg/day was generally marginal and not considered biologically significant.

In the dogs, adverse effects were observed at the highest dose (500/300 mg/kg) in the 4-weeek and 13-week studies. In the 39 week study no adverse effects were observed at the highest dose 200 mg/kg. All observations were considered related to the desired pharmacological effect. No changes in the bone turnover markers and calciotropic hormones were observed in the 39-week dog study.

Genotoxicity

A standard battery of genetic toxicology studies (*Salmonella-Escherichia coli*/mammalian-microsome reverse mutation assay (Ames assay); chromosomal aberration test in Chinese Hamster Ovary (CHO) cells; and the *in vivo* rat bone marrow micronucleus assay) determined that sotagliflozin was not mutagenic or clastogenic.

Carcinogenicity

The carcinogenic potential of sotagliflozin was assessed in transgenic (Tg.RasH2) mice and Sprague-Dawley rats. In the 26-week mouse study, no sotagliflozin-related effects on survival or

incidence of neoplasms were observed at doses up to 100 mg/kg/day, the highest dose evaluated. In the 104-week rat study, sotagliflozin-related proliferative changes (neoplasia and hyperplasia) were observed in the thyroid gland, and sotagliflozin-related non-neoplastic microscopic findings were noted in the kidney, urinary bladder, parathyroid, prostate, seminal vesicle, nonglandular and glandular stomach, tongue, sternum, and femur. An increase in the incidence of thyroid follicular cell carcinoma was observed for 75 mg/kg/day males. Sotagliflozin was not considered to cause carcinogenicity in rats at ≤30 mg/kg/day. In a mechanistic study it was shown that sotagliflozin significantly increased serum TSH. Sotagliflozin increased the average frequency of Ki67-postive staining (a marker for cell proliferation) in the thyroid. The applicant concludes that the thyroid carcinoma observed in the study were the result of the TSH increase, known to increase follicular cell tumour incidence in rats by a mechanism that is not relevant for humans.

Reproductive and developmental toxicity

Sotagliflozin did not impair fertility or alter early embryonic development in the rat at doses up to 300 mg/kg/day, the highest dose evaluated. Embryo-fetal development was evaluated in rats and rabbits. In rats, the NOAEL for embryo-fetal development was 100 mg/kg/day, with marked maternal and embryo-fetal toxicity at 350 mg/kg/day. In the rabbit, the embryo-fetal toxicity no-observed-effect level (NOEL) was 200 mg/kg/day, the highest dose evaluated. In a rat pre- and post-natal development study the NOAEL was 100 mg/kg/day, the highest dose administered. In a rat juvenile toxicity study, the NOAEL was considered to be 75 mg/kg/day, the highest dose evaluated.

Toxicokinetics

Exposure multiples in relation to clinical exposure at the maximal recommended human dose is summarized in the following table:

Study Type	Species	Sex	NOEL / NOAEL (mg / kg / day)	AUC_{0-24h} (ng*hr / mL)	MOE[a]
26-Week Repeat-dose	Rat	M	30	15 077	8x
		F	75	84 145	43x
39-Week Repeat-dose	Dog	M	200	158 334	80x
		F		143 795	73x
Carcinogenicity	Mouse	M	100	87 400	44x
		F		207 000	105x
	Rat	M	30	14 800	8x
		F		40 300	20x
Embryo-fetal toxicity	Rat	F	100	78 012	40x
	Rabbit	F	200[b]	18 145	9x
Juvenile toxicity	Rat	M	75	34 500	18x
		F		60 100	31x

Abbreviations: F=female; M=male; MOE=margin of exposure; MRHD=maximum recommended human dose; NOAEL= no-observed-adverse-effect level; NOEL=no-observed-effect level

[a] MOE = Margin of exposure. Compares exposure of sotagliflozin in animal plasma (AUC_{0-24h}) at the NOEL/NOAEL to the human AUC_{0-24h} at the maximum recommended human dose (MRHD) of 400 mg dose (1969.3 ng*hr/mL; Population PK study report LX4211-N101).

[b] NOEL value

Other toxicity

Process-related impurities were observed in sotagliflozin drug substance, however no individual impurities that exceeded the ICH identification threshold of 0.10% were observed in clinical batches.

A mutagenic risk assessment was performed on actual and potential mutagenic impurities of sotagliflozin according to the ICH M7 guideline.

No phototoxicity study has been performed since sotagliflozin does not absorb within the 300 to 800 nm range of the electromagnetic spectrum. While weak absorption was observed at 290 nm, its molar

extinction coefficient was below 1000 L $mol^{-1}cm^{-1}$ and is therefore not considered to be sufficiently photoreactive to result in direct phototoxicity.

2.3.4. Ecotoxicity / environmental risk assessment

The phase I default PEC_{SW} for sotagliflozin was calculated to 2.0 x 10^{-3}mg/L or 2.0µg/L, triggering a Phase II assessment. The log K_{OW} for sotagliflozin was reported as 2.98 but the study report provided (#LP-802034-01-014) was of insufficient quality. The CHMP requested the study reports and an updated ERA to be provided post-approval.

2.3.5. Discussion on non-clinical aspects

Pharmacology

The data on primary pharmacodynamics presented by the applicant suggest that sotagliflozin acts through inhibition of SGLT1 and SLT2 to improve glycemic role. The inhibition of SGLT2 is the most important mode of action. The contribution of SGLT1 inhibition was shown in the animal studies but it is difficult to extrapolate this to the human situation. The 20-fold lower activity at SGLT1 results in that inhibition of SGLT1 is likely to take place only locally in the intestine. In mice and rats, the activity at SGLT1 is even lower (84-fold in mouse, 202-foldl in rat), suggesting a lesser role for SGLT-1 in the rodent models. However, there are clear differences in the metabolism of sotagliflozin between species that makes the comparison difficult. An estimate of the relative role of SGLT2 vs SGLT1 inhibition must be made on clinical PD data.

No relevant off-target activity was observed in a general screen with 75 different receptors, enzymes and ion channels. In an assay with other members of the SGLT family, relevant activity was observed with hSGLT5 (IC_{50} = 54.1 nM) and hSGLT6 (IC_{50} = 27.3 nM). SGLT5 and SGLT6 act primarily in the kidney and CNS, respectively. The activity at these targets is similar to the activity at SGLT1. Since systemic inhibition of SGLT1 has not been observed, it unlikely that any inhibition of SGLT5 or SGLT6 will occur at clinically relevant exposures.

Although a few compound-related findings were noted in these safety pharmacology assessments, it is agreed that the dose levels associated with the findings were well in excess of those required to produce the desired pharmacologic effects.

Pharmacokinetics

The major human metabolite, sotagliflozin-3-O-glucuronide constitutes the dominant form in human plasma (94%). This metabolite is formed in the toxicity species, but to a much smaller extent. This is important to consider in the safety evaluation.

Toxicology

Repeat-dose toxicity studies were performed in rats and dogs. Carcinogenicity evaluation was performed in mice and rats. Embryofetal development studies were performed in rats and rabbits. All species are pharmacologically relevant. While no data on the activity of sotagliflozin on rabbit SGLT1 and SGLT2 were provided, maternal effects related to the expected pharmacology were observed. The main human metabolite sotagliflozin-3-O-glucuronide was formed in rats and mice at much lower levels than in humans and was not found in dog. Whereas this metabolite is not qualified in these animal studies it is not considered a safety concern, based on experience with other glucuronides. The choice of animal species for toxicity evaluation is endorsed.

Repeat dose toxicity

In the rat repeat dose toxicity studies, the expected pharmacologic effect of marked glucosuria was observed. The glucosuria predisposed for infection and inflammation of the urogenital system, including prostate, renal pelvis and urinary bladder. The applicant refers to other marketed SGLT2 inhibitors, where prostate inflammation was not observed. Based on an evaluation of available nonclinical and clinical data as well as published literature, the applicant is of the view that this observation is of limited relevance in humans. This conclusion is endorsed.

Sotagliflozin-related increase in trabecular bone (minimal to moderate) was noted within the sternum of males (≥30 mg/kg/day) and females (≥75 mg/kg/day) in the 26-week repeat-dose rat study. An assessment of bone turnover markers in the 26-week rat study showed that there was a decrease in bone turnover markers. Bone mineral density and bone resorption biomarkers were monitored in clinical studies. There were small changes observed in bone density versus placebo in a 52 week substudy, while the bone density values were still within the normal range. In view of these minor effects, it is agreed that the rat findings are of little clinical importance.

In all repeat-dose toxicity studies, NOAEL values did not consider the pharmacologic effect of glucosuria as adverse. While it is generally not acceptable to disregard an adverse effect that is related to primary pharmacology, and glucosuria would normally be considered an adverse effect, in this case such NOAEL determination would not be meaningful. Glucosuria is the desired effect in the clinical situation. The NOAEL values proposed by the applicant are endorsed.

Carcinogenicity

In the rat carcinogenicity state, an increase in the incidence of thyroid follicular cell carcinoma was observed for 75 mg/kg/day males. In a mechanistic study it was shown that sotagliflozin significantly increased serum TSH. It is agreed that these data support a mechanism where sotagliflozin causes an increase in thyroid hormone concentrations which in rat is associated with a carcinogenic risk. Such effect is considered not relevant in humans and it is therefore concluded that the rat findings do not suggest a carcinogenic potential in humans.

Reproductive and developmental toxicity

A standard package on reproductive and developmental toxicity was performed in rat and rabbit. It is agreed that these data do not suggest a risk for reproductive or developmental toxicity for sotagliflozin. Reversible renal changes (kidney weight; tubular dilatation) were observed in the rat juvenile toxicity study. Because glomerular development/nephrogenesis in humans is completed prenatally and the timing of nephrogenesis in the rat occurs postnatally, the findings in the juvenile rat toxicity study are relevant for exposure during the 2nd and 3rd trimester in humans. A recommendation against use during this period is included in the SmPC section 4.6

Metabolites

The main human metabolite, sotagliflozin-3-O-glucuronide,is formed in small levels in the toxicity species. The exposure levels in the animal studies have not been quantified, but they are unlikely to provide a formal qualification. However, glucuronides other than acyl glucuronides are considered of little safety concern and no further qualification studies are warranted. This was also the conclusion in a previous CHMP Scientific Advice.

RMP

In the view of the CHMP, there are no nonclinical findings, which have not already been covered by clinical safety data that should be raised as important potential risks in the RMP.

Environmental risk assessment

The CHMP requested the missing ERA files (phase II and log Kow study) to be provided post-approval.

2.3.6. Conclusion on non-clinical aspects

This application was considered approvable from a non-clinical point of view. Remaining information needed for finalising the Environmental Risk Assessment is requested post-approval.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- ***Tabular overview of clinical studies***

Table 2 Overview of studies included in the clinical pharmacology package of sotagliflozin

Description	Phase	Subject	n	Dose	Reference
SAD	1	HV	96	5, 15, 25, 50, 100, 200, 300, 500 mg 50, 100, 200, 300 od - 1 week	LX4211-1-101
MAD			32		
SAD - high doses	1	HV	24	800, 1200, 2000 mg	LX4211-1-106
MAD - high doses	1	HV	25	400, 800 mg od - 10 days	LX4211-1-110
QT	1	HV	58	800, 2000 mg	LX4211-1-109
F_{rel} tablet *vs* solution	1	T2DM	15	300 mg 6x50mg, 2x150 mg, 30 ml 10 mg/ml	LX4211-1-102
BE 2x200 mg *vs* 400 mg	1	HV	30	400 mg	LX4211-1-117
BE commercial *vs* development tablet	1	HV	76	200 mg	BEQ15271
Food effect	1	HV	14	400 mg	PKM15047
Mass balance	1	HV	8	400 mg 14C-sotagliflozin (100 µCi)	LX4211-1-108
Renal impairment	1	T2DM	16 (pk)	400 mg od - 1 week	LX4211-1-107
Renal impairment	1	RI	26	400 mg	LX4211-1-121
Hepatic impairment	1	HI	32	400 mg	LX4211-1-116
DDI - metformin	1	HV	30	400 mg	LX4211-1-103
DDI - COC	1	HV	30	400 mg - 1 week	LX4211-1-120
DDI - rifampicin	1	HV	16	400 mg	INT14936
DDI - mefenamic acid	1	HV	16	400 mg od for1 week	INT14937
DDI - digoxin	1	HV	24	400 mg od for 12 days	LX4211-1-114
DDI- rosuvastatin	1	HV	24	400 mg od for 13 days	LX4211-1-115
DDI - metoprolol midazolam	1				INT14972

Table 3 Overview of modelling and simulation reports included in the submission of sotagliflozin

Description	Reference
PopPK - healthy volunteers, CKD pats	POH0532
PopPK and HBA1c exposure-response - T1D2 pats	LX4211-N101
Pop exposure-response - T1D2 pats	LX4211-N103

Table 4 Phase 2 and 3 studies included in the clinical development program

Study Number CTD Location	Study Short Title / Design	Dosing Schema / Study Duration	Patient Population	Number of Patients Randomized to Treatment	Status
Phase 2 Studies					
LX4211.202 (Study 202)	Phase 2, Placebo-controlled, Dose-Ranging Study in Combination with Metformin in T2DM	Multiple oral doses of sotagliflozin (75 mg qd, 200 mg qd, 400 mg qd; 200 mg bid) or placebo administered for 12 weeks	T2DM with inadequate glycemic control on metformin monotherapy	299 total 59 in 75 mg qd; 60 in 200 mg qd; 60 in 400 mg qd; 60 in 200 mg bid; 60 in placebo qd.	Initiated: 15-Jun-2011 Completed: 15-May-2012
LX4211.203 (Study 203)	Phase 2, Placebo-controlled, Proof-of-Concept Study in T1DM	Sotagliflozin 400 mg or placebo administered qd for 29 days	Inadequately controlled T1DM	36 total 19 in 400 mg qd; 17 in placebo qd.	Initiated: 08-Feb-2013 Completed: 13-Jan-2014
LX4211.204 (Study 204)	Phase 2, Placebo-controlled Study in Young Adult Patients with T1DM and Elevated A1C	400 mg sotagliflozin or placebo administered qd for 12 weeks	18 to 30 year-old adult patients with T1DM with A1C ≥9%	87 total 43 in 400 mg qd; 44 in placebo qd.	Initiated: 20-April-2015 Completed: 23-Sep-2016
LX4211.206 (Study 206)	Phase 2, Placebo-controlled, Dose-Ranging Study in T1DM	75 mg, 200 mg, or 400 mg administered qd for 12 weeks	T1DM and inadequate glycemic control with insulin therapy	141 total 35 in 75 mg qd; 35 in 200 mg qd; 35 in 400 mg qd; 36 placebo qd.	Initiated: 10-Jul-2015 Completed: 26-Aug-2016
Phase 3 Studies					
LX4211.309[a] (Study 309)	Phase 3, Placebo-controlled Study in T1DM with Optimized Insulin Therapy	200 mg or 400 mg sotagliflozin or placebo qd for 52 weeks (24-week Core Treatment; 28-week Long Term Extension)	T1DM North America	793 total 263 in 200 mg qd; 262 in 400 mg qd; 268 in placebo qd	Initiated: 23-Mar-2015 Completed: 17-Feb-2017

Study Number CTD Location	Study Short Title / Design	Dosing Schema / Study Duration	Patient Population	Number of Patients Randomized to Treatment	Status
LX4211.310[a] (Study 310)	Phase 3, Placebo-controlled Study in T1DM with Optimized Insulin Therapy	200 mg or 400 mg sotagliflozin or placebo qd for 52 weeks (24-week Core Treatment; 28-week Long Term Extension)	T1DM Europe & Israel	782 total 261 in 200 mg qd; 263 in 400 mg qd; 258 in placebo qd.	Initiated: 21-May-2015 Completed: 23-Jun-2017
LX4211.312[b] (Study 312)	Phase 3, Placebo-controlled Study to Evaluate the Net Clinical Benefit[c] of Sotagliflozin as Adjunct to Insulin Therapy in T1DM	400 mg sotagliflozin or placebo qd for 24 weeks	T1DM Worldwide	1405 total 700 in 400 mg qd; 705 in placebo qd	Initiated: 18-Sep-2015 Completed: 18-Apr-2017

[a] For Studies 309 and 310, insulin therapy was optimized prior to randomization, as detailed in Section 1.3.4
[b] For Study 312, insulin was not optimized prior to randomization.
[c] Net benefit was defined as the proportion of patients with A1C <7.0% and no episode of SH and no episode of DKA from randomization to Week 24.

2.4.2. Pharmacokinetics

Bioanalysis

A HPLC-MS/MS method for simultaneous determination of sotagliflozin and M19 (sotagliflozin-3-O-glucuronide) in plasma has been developed, pre- and within study validated.

A HPLC-MS/MS bioanalytical assay for determination of sotagliflozin and M19 in the urine has been developed and pre-study qualified.

LC-MS/MS methods for determination of rifampicin, mefenamic acid, rosuvastatin, digoxin, metoprolol, midazolam, ethinylestradiol and norelgestromin were also developed and validated for the intended purposes.

Absorption

Sotagliflozin is characterized as a BCSII compound. At least 57% of the dose entered the systemic circulation as parent compound/or metabolites. Following both single and repeated dosing with sotagliflozin tablets, the C_{max} occurred at 1-4h but secondary peaks/shoulders were seen in the concentration-time profiles.

The increase in systemic exposure was dose-proportional in the therapeutic dose range. The accumulation index at steady state was *ca* 2.

Bioequivalence was demonstrated between the commercial 200-mg tablet and the 200-mg development tablet used in the clinical program including phase 3.

The exposure of sotagliflozin was increased when co-administered with food (high fat/high caloric), the C_{max} was *ca* 2.5-fold and total exposure *ca* 1.5-fold higher compared to under fasted condition.

Distribution

The f_u (unbound fraction) was determined *in vitro* to 2.7% and to 2.3% for sotagliflozin and M19, respectively, in the therapeutic concentration range.

Ex vivo protein binding of sotagliflozin in plasma from subjects diagnosed with renal and hepatic impairment did not show any differences in f_u compared to in healthy subjects.

Elimination

The terminal $t_{1/2}$ of sotagliflozin was calculated to about 24-30h and to about 24h for M19.

Fifty-seven percent of a 14C-sotagliflozin dose was excreted in the urine and 37% in faeces. Less than 1% of the dose was excreted unchanged compound in the urine and 23% of the dose was identified as sotagliflozin in faeces.

Metabolism

Sotagliflozin was extensively metabolised by UGT1A9 *in vitro* and UGT1A1 and 2B7 were also involved but to a lesser extent. UGT1A9 is characterized as a polymorphic enzyme and genotyping for UGT1A9*3 was performed in four phase-1 studies. One subject bearing the UGT1A9*3 allele was identified and exhibited increased exposure of sotagliflozin.

In vitro phenotyping showed that sotagliflozin was also metabolised by CYP3A4.

A total of 22 metabolites were characterised based on pooled plasma, urine and faeces samples. Twelve in the urine and 11 in faeces. Many of the metabolites were identified as glucuronides.

One major metabolite M19, a direct glucuronide (sotagliflozin-3-O-glucuronide) was identified, representing 94% of the total plasma radioactivity. M19 was characterized as a very poor inhibitor with IC50s of >10000 nM for both SGLT2 and SGLT1 transporters.

No active metabolites were identified.

Time-dependency

No signals of time-dependent PK of sotagliflozin have been seen following repeated dosing.

PK in the target population

The individual model predicted exposure of sotagliflozin at steady state following 200 mg od was C_{ave}=40 ng/ml with C_{max}=64 ng/ml and C_{min}=29 ng/ml. The estimated time to peak concentration varied considerably with a typical value of 2h *post* dose. The total exposure was AUCτ=968 ng/ml.h and the terminal $t_{1/2}$ *ca* 28h. The inter-individual variability was *ca* 47% (CV) and the intra-individual 9-32% and the intra-individual 9-32%.

Special population

Renal impairment

The total exposure of sotagliflozin, and its variability, increased with decreasing renal function but levelled off between moderate and severe RI. The exposure was about 1.7-, 2.7-fold, 0.8- and 1.5-fold higher in mild, moderate and RI and ESRD, respectively, compared to healthy subjects. M19 represented >95% of the total systemic exposure independently of degree of renal function.

No difference in the exposure of sotagliflozin was, however, seen between T2DM subjects diagnosed with moderate (eGFR ≥45 ml/min/1.73m^2) and severe (eGFR <45 ml/min/1.73m^2) RI following 400 mg od for one week. The exposure on Day 7 *i.e.* at steady state was *ca* 2.5-fold higher than after a single dose.

Hepatic impairment

The total exposure of sotagliflozin was comparable (slightly lower 0.7-fold) in subjects diagnosed with mild HI with compared healthy subjects in a dedicated HI study. About 3- and 5.6-fold higher exposure of sotagliflozin was seen in subjects with moderate and severe HI, respectively, compared to healthy

subjects following single oral dose of 400 mg. Comparable exposure of M19 was seen in mild and severe HI compared to healthy subjects, respectively.

Co-variates

Body weight was identified as a significant covariate for CL/F. The model predicted CL/F was about 3.5-fold higher in a heavy subject weighing 166 kg compared to a small subject weighing 46 kg. Any increase in exposure of sotagliflozin with age was probably not due to increased age but rather to a lower eGFR with increasing age. Gender and race were not identified as clinical relevant co-variates.

Interactions

The PK interaction potential of sotagliflozin has been evaluated in a number of *in vitro* and seven *in vivo* studies. Sotagliflozin was extensively metabolised to M19 (sotagliflozin-3-O-glucuronide) which was investigated in the DDI studies as well. The results are tabulated/summarized below.

In vitro

Signals were shown for clinical relevant

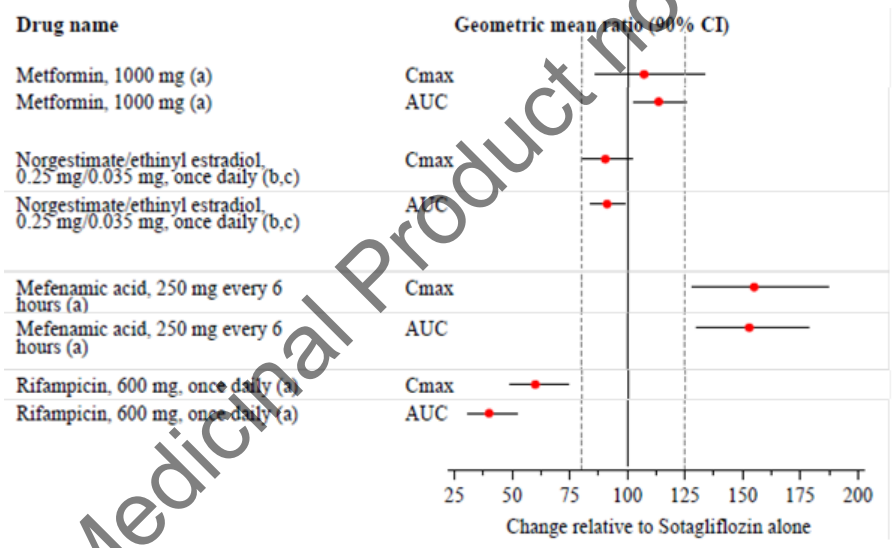
- inhibition of CYP2D6 and CYP3A4
- induction *in vivo* of CYP1A2, CYP2B6 and CYP3A4
- inhibition of Pgp, BCRP, OATP1B1 and OATP1B3

In vivo

Victim

Co-treatment with

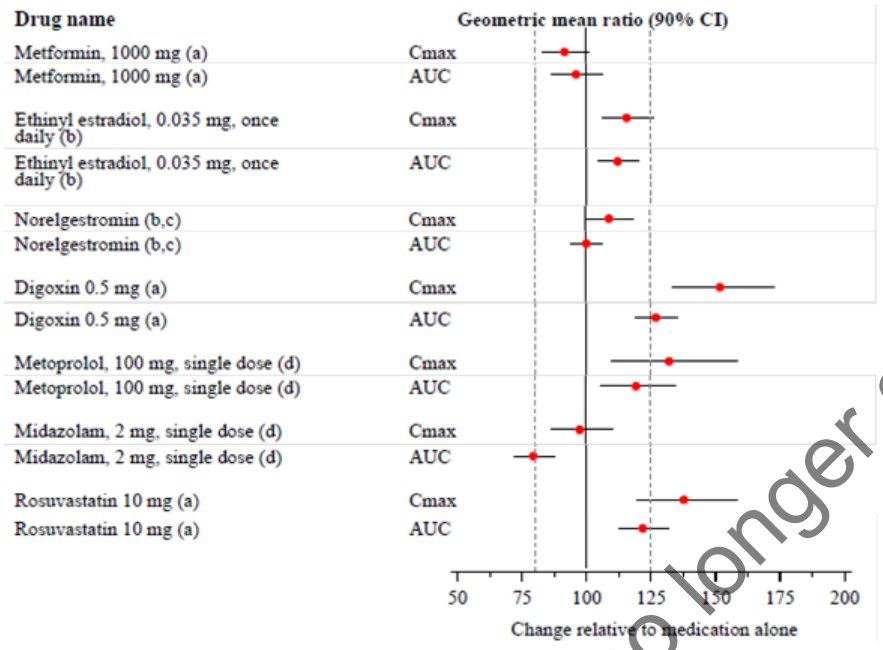
– rifampicin (strong inducer) - SmPC 4.5: frequent monitoring
– mefenamic acid (UGT inhibitor) - SmPC 4.5: no special dose recommendations
– metformin or combined oral contraceptive - no effect on the PK



Perpertrator

Co-treatment with sotaglflozin and

- digoxin (Pgp substrate) - SmPC 4.5: careful monitoring
- midazolam (CYP3A4 substrate) - SmPC 4.5: unclear mechanism, more data needed
- rosuvastatin (OATP, BCRP, OAT3 substrate) - SmPC 4.5: unclear
- metformin (OCT2 substrate), ethinyl estradiol (CYP3A4 substrate) and norgestimate (CYP3A4, UGT substrate) or metoprolol (CYP2D6 substrate) - no effect on their PK



2.4.3. Pharmacodynamics

Mechanism of action

Sotagliflozin is a dual SGLT1 and SGLT2 inhibitor. Based on anatomical location of SGLT, the half maximal inhibitory concentration and protein binding of sotagliflozin, the SGLT1 inhibition is limited to local in the GI tract, and the SGLT2 inhibition is systemic.

In normoglycaemic individuals, kidneys filter up to 180 g of glucose daily, 99% of which is reabsorbed into the circulation primarily by membrane-associated proteins of the SGLT family located in the proximal tubules of the nephron. This process results in little to no loss of glucose into the urine. When blood glucose (BG) concentrations exceed the renal threshold (approximately 150 to 200 mg/dL), which commonly occurs in diabetes, the maximum transport capability of SGLT2 is exceeded, resulting in incomplete glucose reabsorption and glucose loss into the urine. SGLT2 inhibition in the kidney has several consequences: 1) glucose is cleared from the circulation independently from insulin; 2) glucose clearance decreases with reduced levels of BG, which limits the risk of severe hypoglycaemia; 3) urinary glucose excretion (UGE) lowers blood pressure (BP) through mild diuresis; and 4) UGE leads to weight loss through caloric loss (2).

The primary transporter for absorption of glucose and galactose in the intestine is SGLT1. Inhibition of SGLT1 delays and reduces glucose absorption in the proximal intestine, resulting in blunting and delay of postprandial glucose (PPG) excursions, and decreased glycaemic variability. In addition, more glucose delivery distally triggers increased L-cell release of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY),

which is a natural peptide hormone response associated with enhanced glycaemic and appetite control. Thus inhibition of SGLT1 in the intestine may improve glucose control in several ways, namely: 1) reducing intestinal glucose absorption leading to reduced PPG; and 2) stimulation of GI peptides, such as GLP-1 and PYY, proteins that assist in glycaemic and appetite control, and are associated with reductions in BP and body weight (BW).

With sotagliflozin, the desirable effects of SGLT2 inhibition are complemented with SGLT1 inhibition in the GI tract to produce reductions in PPG while triggering lower UGE than the more selective SGLT2 inhibitors. The dual SGLT1 and SGLT2 inhibitory activity of sotagliflozin could potentially maintain efficacy in patients with renal impairment as well as reduce the side effects associated with high UGE, such as genitourinary tract infections.

Primary pharmacology

The PD of sotagliflozin has been studied in healthy subjects (LX4211.104, LX4211.111) and subjects with T2DM with/without concomitant sitagliptin (LX4211.105), at a single dose level of 400 mg (LX4211.105 and LX4211.111) or multiple dose regimens of 150 mg, 300 mg, or 400 mg qd (LX4211.201, LX4211.104). Main PD markers in these studies were PPG and UGE. In the glucose tracer study LX4211.111, the primary endpoint was RaO and was compared to canagliflozin. Among the further PD markers FPG, GLP-1 (total and active), and PYY were common across studies.

A Phase 2 study in the target population (LX4211.203) investigated a wide range of PD endpoints in T1DM patients with primary focus on the reduction in the bolus insulin doses under a dose regimen of 400 mg sotagliflozin qd or placebo over 4 weeks. PD data has further been provided from the dose-ranging study in T1DM (LX4211.206).

In addition limited PD data was provided from a study in patients with T2DM and renal impairment (LX4211.107).

Urinary glucose excretion

Urinary glucose excretion was increased in all populations tested, consistent with SGLT2 inhibition. After a single dose of 400 mg sotagliflozin in healthy volunteers, the amount of glucose excreted in urine over 24 hours after dosing ranged between 40 and 45 g glucose in LX4211.111, which was lower than what was seen after 300 mg of canagliflozin, a more selective SGLT2 inhibitor. After a single dose of 400 mg sotagliflozin given to patients with T2DM in LX4211.105, the 24-hour UGE was approximately 92 g, which constituted a change from Baseline of approximately 68 g.

Urinary glucose excretion was also assessed following multiple dosing of the liquid formulation in T2DM patients treated over 4 weeks at 2 dose levels vs. placebo (LX4211.201). The Baseline Day -1 values ranged from 13.8 to 16.6 g for the 3 dose groups. LS means of changes from baseline were around 46 and 66 g/day for the sotagliflozin 150 mg and 300 mg dose groups, respectively, on Day 1. This effect slightly decreased until Day 28. No change was observed in the placebo group. Patients with T2DM and moderate renal impairment have shown a slightly smaller change from baseline in 24-hour UGE of around 39 g/day on Day 7 of a multiple dosing regimen in study LX4211.107.

The change from baseline in 24-hour UGE in the target population of T1DM patients was investigated in the dose-ranging study LX4211.206. This study showed a dose-dependent mean increase in UGE from baseline at Week 12 in all of the sotagliflozin groups compared with placebo (Table 5).

Table 5 ANCOVA Analysis of Change from Baseline in Urinary Glucose Excretion at Week 12 – mITT Population, study LX4211.206

	Placebo (N = 36)	Sotagliflozin 75 mg (N = 35)	Sotagliflozin 200 mg (N = 35)	Sotagliflozin 400 mg (N = 35)
Urinary Glucose Excretion (g/day)				
Baseline				
N	28	30	26	29
Mean	6.9	15.8	6.6	10.0
Change from Baseline at Week 12				
N	23	24	23	24
LS Mean (SE)	0.26 (10.54)	42.0 (10.52)	58.0 (10.51)	70.7 (10.29)
95% CLs for Change from Baseline	(-20.7, 21.2)	(21.1, 62.9)	(37.1,78.9)	(50.3, 91.1)
p-value	0.98	<0.001	<0.001	<0.001
Summary of treatment comparison				
LS Mean Difference (SE) from Placebo	--	41.8 (15.0)	57.7 (14.8)	70.4 (14.7)
95% CLs for Difference	--	(12.0, 71.5)	(28.3, 87.2)	(41.3, 99.6)
p-value	--	0.006	<0.001	<0.001

Post Prandial Glucose

The 2-hour PPG for both 150 mg and 300 mg sotagliflozin groups in T2DM patients in study LX4211.201 showed a lower level compared to the placebo group as early as Day 1 ($p < 0.05$). At Day 28, the mean change from Baseline in 2-hour PPG was -50.6 and -57.6 mg/dL in the 150 and 300 mg dose groups, respectively, and were both statistically significant versus placebo ($p < 0.05$).

LX4211.201 also included an evaluation of PPG changes from Baseline by analysing the AUC over 4 hours after OGTT. In both the 150 mg and 300 mg dose groups, plasma glucose AUC_{0-4h} corrected for baseline and baseline-uncorrected AUC_{0-4h} were statistically significantly lower than in the placebo group ($p < 0.001$). Reduction of plasma glucose AUC0-4h was observed at Day 27 of dosing to be approximately 35% lower compared to baseline (Day -2).

In study LX4211.107 in patients with T2DM and moderate to severe renal impairment, the equivalent parameter of PPG, $AUC_{(predose-4)}$, confirmed a significant reduction from baseline with -176 mg*hr/dL on Day 7 of treatment with 400 mg sotagliflozin, which constituted a change from baseline of around -20%.

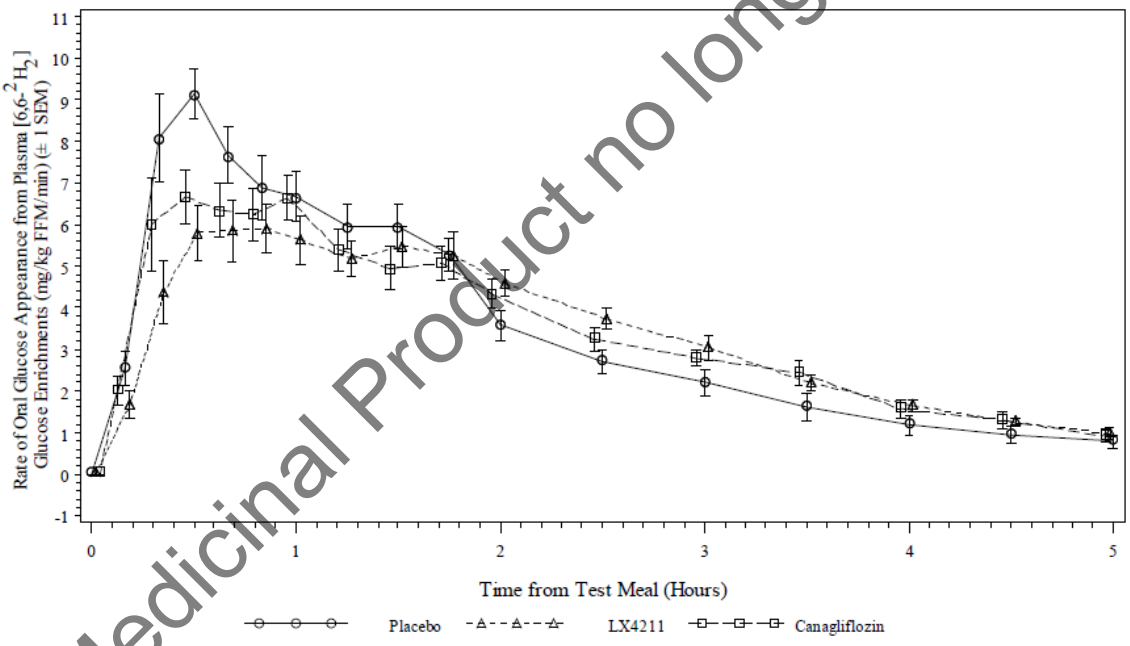
In the target population of T1DM patients, the lowering of the 2-hour PPG showed a linear trend for dose dependency in study LX4211.206 with the 400 mg qd dose level being statistically significantly different from placebo with a change from baseline of -49.5 mg/dL at Week 12. The dose levels of 75 mg and 200 mg qd reached changes from baseline -20.3 and -27.4 mg/dL, respectively (not significant). Of note, these values were observed while the patients (CSII group) had dose-dependently reduced their total

daily bolus insulin doses on average by -2.85, -1.32 and -6.97 IU/day for the 75, 200 and 400 mg qd dose levels, respectively.

In study LX4211.203, PPG was assessed by analysing the 3-hour post-breakfast glucose AUC (AUC_{0-3h}) in T1DM patients following a MMTT, performed on Days 1 and 29. In the sotagliflozin group (400 mg qd) the mean change was -250 ± 187 mg*hr/dL which constituted a nearly 30% reduction compared to baseline, compared with -200 ± 318 mg*hr/dL for the placebo group which was around 20% lower than baseline. The difference between treatment groups was statistically significant (p = 0.009). This occurred despite the reduction from Baseline in total daily bolus of insulin of 32.0 ± 18.1% in the sotagliflozin group, which was a significantly greater decrease than for the placebo group (6.36 ± 27.7%).

The triple glucose tracer study, LX4211.111 (healthy volunteers), enabled a more differentiated view on PPG by analysing oral and total glucose appearance after breakfast and lunch, as well as in comparison to canagliflozin, a more selective SGLT2 inhibitor. Both drugs given as single doses prior to breakfast reduced oral glucose appearance in the first 2 hours after a standard breakfast as compared to placebo, but the sotagliflozin effect remained visible also at lunch whereas under canagliflozin it was not present anymore at this time (Figure 2). On the other hand the oral glucose absorption after sotagliflozin was slightly higher than under placebo between 2 and 5 hours after start of the test meals. Overall, this resulted in a reduction in PPG excursions as also detected by CGM.

Figure 2 - Mean rate of oral glucose appearance from plasma [6,6-$^2H_2$] glucose enrichments vs. time from test meal by treatment (lunch meal test group: completers population)



Abbreviation: SEM: standard error of the mean

The differences of the PPG AUCs were evaluated in a multiple dosing study (104) over 12 days in healthy volunteers comparing on days 8 through 12 different dosing schedules relative to meal. In this study the PPG AUCs were compared over the 3 main meals of the day. The outcome favoured a dosing schedule immediately prior to breakfast, which was selected as the dosing schedule for the further Phase 2 and Phase 3 studies.

Fasting plasma glucose

Study LX4211.104 in healthy volunteers showed a decrease from Baseline in FPG with all sotagliflozin dose schedules, ranging from 5.17 mg/dL to 8.19 mg/dL, (p <0.001 for all dose groups).

After 4 weeks of treatment in the T1DM study LX4211.203, sotagliflozin was not significantly different from placebo in lowering fasting plasma glucose, but interpretation was limited by high variability of the data. In the dose ranging study in T1DM, LX4211.206, when the LS mean for each group was compared with the placebo group, the change in FPG from Baseline at Week 12 was not statistically significant at all sotagliflozin dose levels and no dose-dependent effect was observed. This study was, however, difficult to interpret due to group differences in the baseline FPG levels.

In the T2DM study LX4211.201, the decrease in mean FPG was observed starting on Day 7 in both sotagliflozin dose groups. The lowest mean FPG values were 123.0 mg/dL for the sotagliflozin 150 mg dose group and 120.3 mg/dL for the sotagliflozin 300 mg dose group on Day 29, after baseline values in the range from 175.3 to 192.4 mg/dL. The mean FPG levels for the placebo group were 179.3 to 201.3 mg/dL and remained relatively stable throughout the study. Both sotagliflozin dose groups had statistically significant lower FPG levels compared to that in the placebo group as early as Day 7 post-treatment through discharge on Day 29 ($p < 0.001$). A trend towards a greater reduction in the sotagliflozin 300 mg dose group was observed; however, the difference between the 2 sotagliflozin dose groups was not statistically significant for any day of evaluation.

Incretins and gut hormones (glucagon-like peptide-1, peptide YY)

In study LX4211.104 in healthy volunteers, increases in GLP-1 (active) $AUC_{0\text{-last}}$ were seen in all sotagliflozin dose schedules. In addition, all sotagliflozin dose schedules lead to increases from Baseline in LS mean $AUC_{0\text{-last}}$ values of PYY.

The Phase 2 study LX4211.203 in T1DM patients assessed GLP-1 and PYY on Day 1 and Day 29. The changes in active GLP-1 from Day 1 to Day 29 at 1-hour post-meal were 4.6 ± 4.0 pmol/L for the sotagliflozin group compared with 1.8 ± 2.0 pmol/L for the placebo group. The changes in total GLP-1 from Day 1 to Day 29 at 1-hour post-meal were 7.5 ± 4.9 pmol/L for the sotagliflozin group compared with 3.2 ± 2.3 pmol/L for the placebo group. Also, there were significant differences between the 2 treatment groups for the change in PYY. The changes from Day 1 to Day 29 at 1-hour post-meal were 9.8 ± 4.8 pmol/L for the sotagliflozin group compared with 4.5 ± 5.9 pmol/L for the placebo group (LS mean difference between groups 8.2 pmol/L, 95% CI: 4.5, 11.8; $p < 0.001$).

Secondary pharmacology

QT-study (LX4211.109)

Study LX4211.109 evaluated the ECG effects of a single dose of sotagliflozin 800 mg and 2000 mg compared with placebo and open-label moxifloxacin in 63 healthy subjects. The placebo-subtracted change of QTcI from Baseline for both doses of sotagliflozin showed only slight elevation, primarily in the first 6 hours post-dose, and all 1-sided 95% UCB were less than 10 msec compared to 10.76 msec for moxifloxacin at 2 hours post-dose. The maximal mean value of ΔΔQTcI for the sotagliflozin 2000 mg dose group was at 3-hours post-dose, where the ΔΔQTcI was 2.74 msec and the UCB was 4.50 msec. The sotagliflozin 800 mg dose group produced a maximal change at 2-hours post-dose of 1.93 msec and an UCB of 3.69 msec.

The steady state C_{max} and $AUC_{0\text{-}24h}$ in T1DM patients at the maximum recommended human dose of 400 mg is 130 ng/mL and 1969 ng*hr/mL, respectively. In study LX4211.109, the C_{max} and $AUC_{0\text{-last}}$ (last measurable concentration was the last sampling time point: 60 hr) for the 800 mg and 2000 mg dose were 139 ng/mL and 2257 ng*hr/mL; and 290 ng/mL and 4440 ng*hr/mL, respectively, indicating that adequate coverage was achieved.

Relationship between plasma concentration and effect

Pharmacokinetic/pharmacodynamic relationships related to efficacy

Population exposure-response (E-R) analyses were conducted to characterize the relationship between sotagliflozin exposure and A1C, BW and 2-hour PPG.

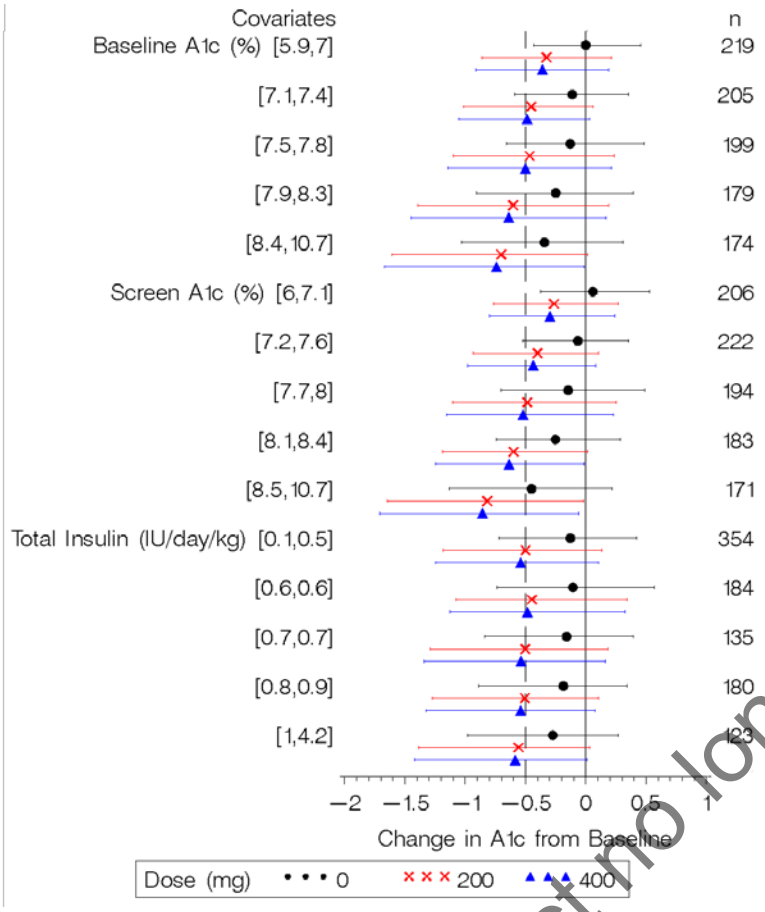
Exposure-response analysis on Haemoglobin A1C

The exposure-A1C analysis aimed to characterize the relationship between the exposure of sotagliflozin and A1C as a function of time. The covariates evaluated were: age, race/ethnicity, sex, BW, body mass index, eGFR, renal function category, baseline and screening A1C and mean total daily insulin.

The exposure-response model on A1C was best described by a sigmoid inhibitory maximum pharmacologic effect (I_{max}) model of time with a higher I_{max} (i.e. typical value of the effect on A1C response) for subjects with screening A1C values (>10%) and with higher I_{max} values as weekly AUC of sotagliflozin increases. Furthermore, the rate of increase in I_{max} related to drug exposure was found to be higher for mean total daily insulin doses less than 0.73 IU/day/kg and lower for mean total daily insulin dose greater than 0.73 IU/day/kg. The disease progression component of the model offsets the inhibition of A1C, as compared to the predicted A1C, for placebo and drug effect.

The response on A1C was shown to be best predicted by using weekly AUC (sum of $7AUC_{0\text{-}tau}$) of sotagliflozin as a marker for exposure. Model-predictions of the exposure-response relationships at week 24 showed that the effect was close to its maximum level at a weekly AUC of around 12000 ng*hr/mL. The mean weekly AUC is simulated to be approximately 6999 and 14081 ng*hr/mL for 200 and 400 mg qd doses of sotagliflozin, respectively. Furthermore, the model predicted that subjects treated with sotagliflozin and total daily insulin doses <0.5 IU/kg had a decrease of 0.50% in A1C as compared to a decrease of 0.59% for subjects with total daily insulin doses >1 IU/kg. Overall, the effect on A1C was shown to be markedly influenced by a placebo effect, a treatment effect (i.e. sotagliflozin exposures), baseline A1C and to a lesser extent by mean total daily insulin doses, as visualised in Figure 3. Of note, eGFR was not found to be a significant covariate in the model.

Figure 3 - LX4211-N101: Model-predicted Mean (90% Prediction Interval) of Change in A1C From Baseline at Week 24, Stratified by Statistically Significant Covariate



Abbreviations: AUC, area under the plasma concentration-time curve; n, number of subjects in each group.

Exposure-response analysis on body weight and on 2-hour postprandial glucose

This exposure-response analysis aimed to characterize the relationship between the exposure of sotagliflozin and BW or 2-hour PPG as a function of time. The covariates evaluated were: age, race, ethnicity, sex, BW, body mass index, eGFR, renal function category and mean total daily insulin.

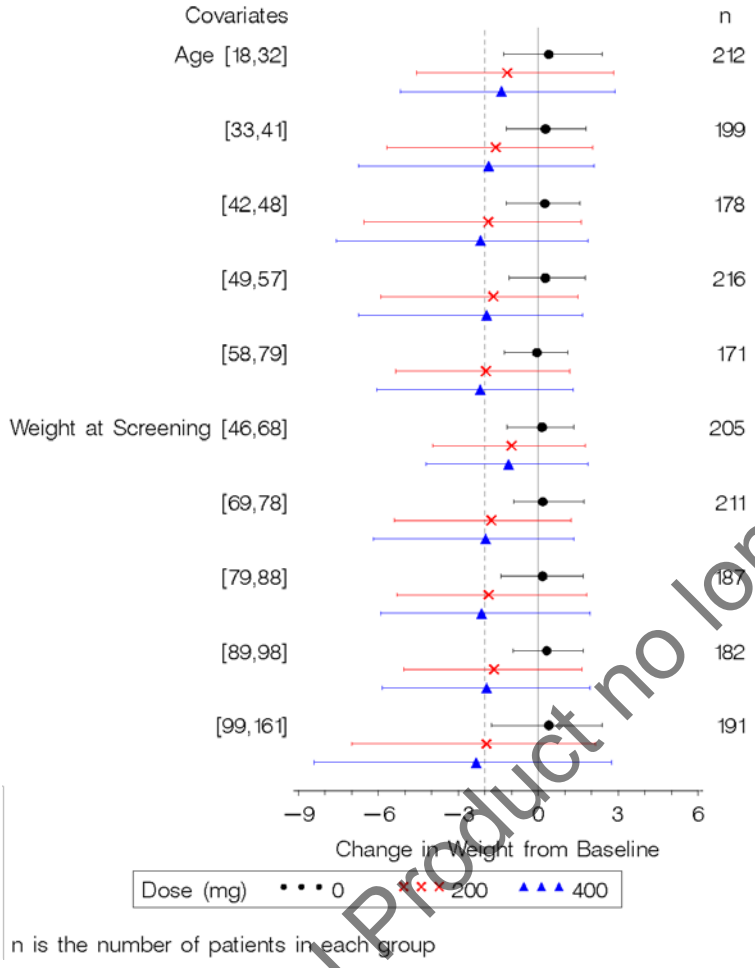
Exposure-response model on body weight

The exposure-response model on BW was described by 2 exponent of time functions: 1 for the placebo effect and 1 for the treatment effect. The placebo effect was well described using a shift power function of time with observed screening BW as the starting value and the exponent of the time function described as a power function of age. The exponent describing the treatment effect was best described with an E_{max} function of the weekly AUC. The decrease in BW was shown to begin plateauing at approximately 32 weeks postdose.

The exposure-response model, on average, resulted in an increase in BW of 0.24 kg for placebo by week 24 as compared to a decrease of 1.1 to 2.4 kg for active treatments with exposures as predicted for the subjects of the Phase 3 studies. The probability of having an average decrease in BW of 2.2 to 2.4 kg was predicted to be 7.3% for 200 mg and 43% for 400 mg of sotagliflozin. The model also predicted a decrease in BW of 0.05 kg in placebo subjects ≥58 years as compared to an increase of 0.40 kg for placebo subjects ≤32 years. In addition, the model predicted a higher decrease in BW in placebo subjects with screening BW ≥99 kg (0.40 kg) as compared to placebo subjects with screening BW ≤68 kg (0.15 kg). As a result, subjects treated with sotagliflozin were predicted to have an 86% higher decrease in BW

in the oldest (2.2 kg) as compared to the youngest (1.2 kg) and; a 133% higher decrease in BW for the heaviest (2.3 kg) as compared to the lightest (1.0 kg). The effects of baseline body weight and age on the change of body weight is visualised in Figure 4. Of note, eGFR was not found to be a significant covariate in the model.

Figure 4 - LX4211-N103: Means and 90% Prediction Intervals of the Change in Body Weight From Baseline After 24-weeks of Treatment, by Significant Covariate Groups and Dose Level



Abbreviations: AUC, area under the plasma concentration-time curve; n, number of patients.

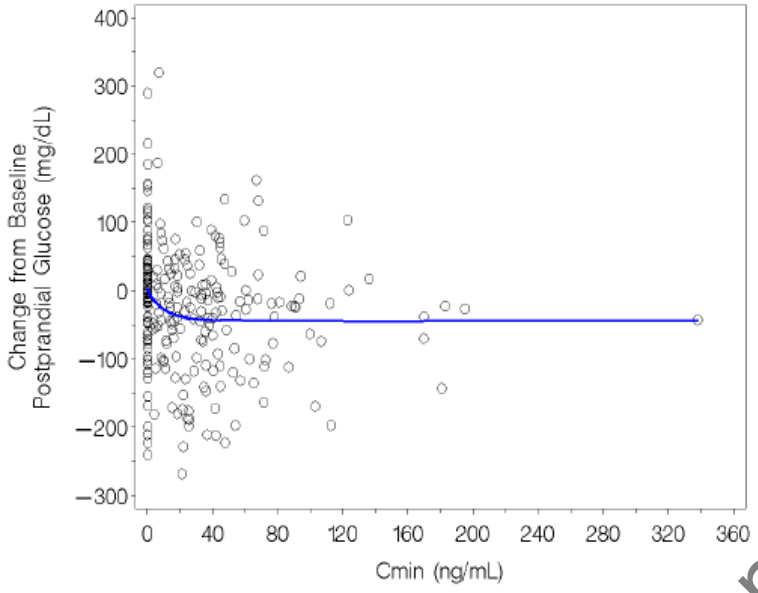
Exposure-response model on postprandial glucose

The exposure-response model on the change in 2-hour PPG from baseline was described by a decreasing exponential function of the model-predicted C_{min} on the day of the 2-hour PPG measurement. This model predicted the 2-hour PPG for placebo subjects to increase 3.6 mg/dL from baseline and predicted for patients on active treatment the maximum decrease in 2-hour PPG (as C_{min} approaches infinity) to be 44.7 mg/dL from baseline. Furthermore, 90% of the maximum decrease in 2-hour PPG from baseline was predicted to occur at a C_{min} value of approximately 20 ng/mL. Of note, eGFR was not found to be a significant covariate in the model.

The model-predicted decrease in 2-hour PPG from baseline was 42 and 45 mg/dL by Week 24 at the approximate median C_{min} values of 26 and 46 ng/mL for 200 mg and 400 mg sotagliflozin, respectively. The percentage of patients with predicted C_{min} >23 ng/mL was approximately 60% for 200 and 88% for 400 mg sotagliflozin. Thus, the probability of a patient experiencing a greater than 40 mg/dL decrease in 2-hour PPG from baseline is 47% higher for 400 mg, as compared to a 200 mg sotagliflozin. At C_{min} values

of 20 ng/mL, the model-predicted the effect to be close to its maximum level (Figure 5). Median C_{min} values for 200 and 400 dose of sotagliflozin is of 42 and 45 ng/mL, respectively.

Figure 5 - LX4211-N103: Model-predicted changes from baseline in 2-hour PPG versus C_{min} of sotagliflozin overlaid with observed data from studies LX4211.204 and LX4211.206 (at week 12), LX4211.309 and LX4211.310 (at week 24)



Abbreviations: C_{min}, drug concentration at 24 hours after a dose.
Note: The line represents the model predicted change from baseline

Overall, these results indicate a small difference between 200 and 400 mg dose of sotagliflozin on the average model-predicted effect for A1C, BW and 2-hour PPG. Active subjects in the 400 mg dose group had a higher probability of having a slightly larger decrease in A1C than subjects in the 200 mg dose group.

Pharmacokinetic/pharmacodynamic relationships related to safety

Safety analyses were conducted to describe the probability of occurrence of positively adjudicated DKA and severe hypoglycaemia as a function of sotagliflozin exposure. In these analyses, the influence of different markers of sotagliflozin exposure at steady state (i.e. $AUC_{0\text{-}tau}$, C_{min}, and C_{ave}) was evaluated.

Exploratory graphical analyses of the relationship between measures of steady-state sotagliflozin exposure and the occurrence of DKA and severe hypoglycaemia showed that median $AUC_{0\text{-}tau}$ for patients experiencing DKA is higher than in patients where DKA was not observed. Median $AUC_{0\text{-}tau}$ is similar in patients with or without severe hypoglycaemia.

The effect of each sotagliflozin exposure on the probability of DKA and severe hypoglycaemia was formally evaluated using linear logistic regression models. For DKA, $AUC_{0\text{-}tau}$ was found to be a significant predictor, but the validity of the model-predicted probabilities could not be determined. For adjudicated severe hypoglycaemia, no statistically significant exposure-response relationship was detected.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Following both single and repeated dosing with sotagliflozin tablets, the C_{max} occurred at 1-4h but secondary peaks/shoulders were seen in the concentration-time profiles, which might be an indication on enterohepatic circulation.

Sotagliflozin is characterized as a BCS II compound *i.e.* low solubility and good permeability. An oral solution was used in the early phase-1 studies and co-administration with food resulted in a lower exposure of sotagliflozin compared to in fasted state. This is expected when dissolution is not limiting but delayed motility due to the concomitant food intake. The food effect was the opposite when the development 200-mg tablet was administered together and without food, with a 1.5-fold higher exposure in fed state. *In vitro* solubility data show that the local concentration of sotagliflozin in the intestine will be well below concentrations inhibiting local transporter proteins.

All phase-1 studies have been performed in fasted state. In phase 3 sotagliflozin was administered before the first meal of the day which is also the dose recommendation in the SmPC. Thus the clinical pharmacology of sotagliflozin has been evaluated at lower concentrations (fasted condition) than in the pivotal clinical studies. The phase-1 studies have been performed with a single dose of 400 mg and not 200 mg which is the recommended standard dose, 400 mg od should be used just in case of insufficient response. The clinical pharmacology package is deemed satisfactory, considering the DDI profile for sotagliflozin with no potential of dramatic interactions.

The elimination of sotagliflozin has not been completely elucidated with only *ca* 35% characterized, 33% was excreted as M19 (direct glucuronide) and ca 1% excreted as parent compound in the urine. Thus 65% of the elimination pathways are unknown. Thirty-seven percent of an oral 14C-sotagliflozin dose was excreted in faeces with 23% as sotagliflozin. However, it is unknown if the excreted sotagliflozin is not absorbed sotagliflozin, sotagliflozin excreted *via* the bile or sotagliflozin formed as a degradation product from instable metabolites *eg* glucuronides. Biliary excretion seems as a potential elimination pathway. *In vitro* stability data show that sotagliflozin-glucuronides are completely hydrolysed to sotagliflozin in the presence of *E.coli* or bovine β-glucuronidase and M19 is characterized as a BCRP and MRP2 substrate, two transporters known to be involved in the biliary excretion. An alternative way to understand the elimination pathways is an *in vivo* DDI study with a known CYP3A4 inhibitor to characterize its importance *in vivo* as CYP3A4 was identified *in vitro* as an enzyme involved in the metabolism of sotagliflozin. But adding together small phase-1-metabolites, of which some was further conjugated, results in that *ca* 20% of the dose was excreted *via* that way.

UGT1A9 is characterized as one of the main enzymes involved in the metabolism of sotagliflozin. Genotyping for UGT1A9*3 allele was performed in four of the phase-1 studies, one subject bearing the heterozygous UGT1A9*3 variant was identified and exhibited increased exposure. The *in vivo* DDI study with co-administration of mefenamic acid (UGT inhibitor) resulted in a 1.5-fold higher exposure of sotagliflozin when dosed together compared to when administered alone. This 1.5-fold increase is not deemed clinical relevant resulting in any changes in the dose regimen. As sotagliflozin is an adjunct to insulin and subjects are monitored at start of treatment, no change in the proposed dosing is considered necessary for subjects bearing heterozygous UGT1A9*3 allele. Potential consequences (decreased exposure) of other alleles with higher prevalence and associated with increased expression of UGT1A9 is neither deemed clinical relevant with respect to changed dosing regimen as subjects are monitored at start of treatment.

Adequate methods have been used in the development and evaluation of the popPK analysis of phase 1-3 data in T1DM patients and healthy volunteers. The structural model described the data sufficiently well. The double peak behaviour seen in phase 1 data has not been captured, but is acceptable since it is not foreseen that this simplification will impact the covariate analysis or the exposure-response analysis. Only 4% of the subjects in the dataset were classified with moderate renal impairment which could make the influence of eGFR on CL/F for the lower range of the observed eGFR values less certain. Adequate methods were used in the development and evaluation of the popPK analysis in healthy volunteers and chronic kidney disease patients. The model described the data fairly well, although some bias was visible for low concentrations, however, the results of the analysis are in agreement with the basic analysis of the renal impairment studies and further refinement will not be pursued.

The PK of sotagliflozin in T1DM patients were characterised by PopPK analysis. The individual predicted exposure of sotagliflozin at steady state following 200 mg od was C_{ave}=40 ng/ml. The estimated time to C_{max} varied considerably with a typical value of 2h *post* dose. The inter-individual variability was *ca* 47% (CV) and the intra-individual to between 9-32%.

The total exposure of sotagliflozin, and its variability, increased with decreasing renal function and was about 1.7-, 2.7-, 0.8- and 1.5-fold higher in mild, moderate and severe RI and ESRD, respectively, than in subjects with normal renal function. The increase in exposure levelled off between moderate and severe RI. The renal excretion of unchanged compound was <1% following an oral 14C-sotagliflozin dose and the reason to the reported increase in systemic exposure in RI compared to in healthy subjects is unclear. The interplay of renal and biliary excretion of sotagliflozin glucuronides and their intestinal back-conversion to parent drug and enterohepatic circulation appears a reasonable explanation to the unexpected increase in exposure with decreasing renal function for a compound excreted <1% unchanged in the urine.

The PK interaction potential of sotagliflozin has been evaluated in a number of *in vitro* and seven *in vivo* studies. Signals of inhibition of both CYP isozymes (CYP2D6 and 3A4) and transporter proteins (Pgp, BCRP, OATP1B1 and OATP1B3) were shown *in vitro* for sotagliflozin or M19. M19 also showed *in vitro* signals for induction of CYP1A2, CYP2B6 and CYP3A4. No inhibition of UGT isoenzymes was seen *in vitro* at clinically relevant concentrations.

An increase in total exposure and C_{max} of rosuvastatin of ca 1.2- and 1.4-fold, respectively, was seen when co-administered with sotagliflozin. This is not deemed clinical relevant. However, the mechanism behind the small increase in exposure is unclear as sotagliflozin and M19 (sotagliflozin glucuronide) are characterized as BCRP inhibitors in vitro and M19 also as an inhibitor OATP1B3 and OAT3. Rosuvastatin is a known OATP, BCRP and OAT3 substrate. It cannot be ruled out that sotagliflozin may interact with other sensitive OATP- and/or BCRP-substrates resulting larger increases of exposure than seen for rosuvastatin.

A single-dose DDI study with metformin, a known OCT2 substrate, was performed. Comparable systemic exposure of metformin was seen when dosed together with sotagliflozin compared to when dosed alone. Thus sotagliflozin/M19 are not an OCT2 inhibitor at clinically relevant concentrations. However, metformin has dose-dependent PK and how representative the single-dose data are for the clinical situation is not clear. However, metformin has a relatively short $t_{1/2}$, ca 5h, and does not exhibit accumulation. Thus, a multiple dose administration of metformin is not expected to impact the PK of sotagliflozin in a significant different way compared to the single dose administration.

Sotagliflozin was a CYP3A4 inhibitor *in vitro*, with an IC50 of clinical relevance for a DDI in the GI tract. M19 is identified as an inducer. The current *in vivo* DDI results show a decrease in exposure of midazolam when co-administered with sotagliflozin of ca 0.8-fold compared to when dosed alone. Thus the net effect of CYP3A4 inhibition + induction is 0.8-fold which leaves the maximum induction potential unknown.

Pharmacodynamics

The mechanism of action for SGLT2-inhibitors is well known as sotagliflozin is the fifth product in this class. Sotagliflozin also exerts inhibition of SGLT1, predominantly expressed in the gut. This is predicted to provide reductions in PPG through less glucose absorption after a meal. Furthermore, GI peptides are stimulated which may further assist in glycaemic and appetite control. The applicant expect that the dual effect on SGLT2 and SGLT1 will result in a lower UGE (due to lower absorption of glucose in the gut) which in turn is expected to reduce side effects such as genitourinary infections and also will result in a measurable effect also in patients with renal impairment.

SGLT2 inhibitors trigger multiple mechanisms that could predispose to DKA. When they are combined with insulin, it is often necessary to decrease the insulin dose to avoid hypoglycaemia. The lower dose of

insulin may be insufficient to suppress lipolysis and ketogenesis. Furthermore, SGLT2 is expressed in pancreatic α-cells, and SGLT2 inhibitors promote glucagon secretion which stimulates lipolysis. Finally, phlorizin, a nonselective inhibitor of SGLT family transporters, decreases urinary excretion of ketone bodies. A decrease in the renal clearance of ketone bodies could also increase the plasma ketone body levels.

Primary pharmacology of sotagliflozin was investigated in healthy subjects (studies 104 and 111), patients with T2DM (studies 201 and 105) and patients with T1DM (study 203 and 206). One study included patients with impaired renal function (107). The PD markers considered of most importance and that were included as endpoints are UGE and PPG, considering sotagliflozin's mechanism of action. In addition the effect on FPG and incretins (GLP-1 (total and active) and PYY) were evaluated.

Studies 111 and 105 were single dose studies whereas the remaining studies investigated dosing over 2 to 4 weeks. In study 107, sotagliflozin was administered for 7 days.

Across the populations investigated, sotagliflozin resulted in an increase in UGE which appeared dose-dependent (study 201, T2DM and study 203, T1DM). The magnitude of the effect differed between populations as expected since the UGE is dependent on the blood glucose level, with the most prominent effect observed in T2DM patients.

In all populations investigated (healthy volunteers, T2DM and T1DM) a consistent decrease of PPG was observed with sotagliflozin treatment. As for UGE, the magnitude of the effect varied between populations but the effect was larger with higher doses. The post-meal plasma glucose AUC_{0-4h}/AUC_{0-3h} decreased with about 30% to 35% in both T1DM and T2DM patients with the higher dose.

When compared to canagliflozin, which also inhibit both SGLT2 and SGLT1 (study 111), the effect on PPG appeared to be sustained for a longer time with sotagliflozin than with canagliflozin. This may indicate a stronger SGLT1 inhibition with sotagliflozin. When compared to canagliflozin in healthy subjects, UGE was lower with sotagliflozin than with canagliflozin. The applicant proposes that this is due to a stronger effect on SGLT1 with sotagliflozin, which leads to less glucose being absorbed in the gut.

Concerns were raised that it could be more difficult to treat hypoglycaemia in patients under treatment with a SGLT1 inhibitor. However, as seen in Figure 2, glucose appearance is not affected by the SGLT1 inhibition although the maximal glucose concentration is somewhat lower than with placebo**.**

Different dosing schedules were investigated in healthy volunteers in study 104. PPG data from this study provide support for the recommendation to administer sotagliflozin immediately prior to breakfast.

Although a decrease in FPG was observed in all populations studied, statistical significance was not achieved for all sotagliflozin treated groups in the T1DM study due to a high variability of the data.

When measured in the studies, sotagliflozin resulted in increases in GLP-1 and PPY. These findings suggest that sotagliflozin may have additional effects apart from a reduced absorption of glucose from the gut and an increase in the excretion of glucose from the kidney. The relevance of these mechanisms of action, however, still remains uncertain.

In study 107, which included in total 31 T2DM patients with moderate or severe renal impairment, a statistically significant increase in UGE compared to placebo was observed. However the UGE was lower, with the 400 mg dose, than observed with the 300 mg dose when administered to patients with T2DM and normal renal function. Furthermore, only a 20% reduction in post-meal plasma glucose AUC_{0-4h} was observed compared to a 30-35% reduction in patients with normal renal function. These data indicate that the SGLT1 is not the only contributor to the effect on PPG. This raise concerns with regards to the use of sotagliflozin in patients with renal impairment.

The QT-study (Study 109) was of adequate design and showed that single oral doses of sotagliflozin 800 mg and 2000 mg did not cause prolongation of the QTcI interval in excess of the threshold of 10 msec. Thus the outcome is consistent with a negative QT study according to the ICH E14 guideline.

Pharmacodynamic interactions have not been specifically discussed by the applicant. The most important interaction is the interaction with insulin. The evaluation of this interaction is part of the objectives in the phase 3 studies, thus this is discussed in the efficacy part of this report.

Population exposure-response (E-R) analyses were conducted to characterize the relationship between sotagliflozin exposure and HbA1c, BW and 2-hour PPG. Adequate methods have been used in model development and evaluation in all presented exposure-response analyses. The data indicate that there is a large overlap in exposure for the two doses investigated and that the difference between the two doses is very small with regards to the effects on HbA1c and body weight. The data on PPG is difficult to interpret as inter-individual variability could not be assessed.

The population exposure-response related to safety, i.e. DKA and SH, was also assessed. There was a trend towards a higher risk of DKA with higher exposure, but the finding is uncertain due to the low number of events. No association between exposure and the risk of SH was observed.

2.4.5. Conclusions on clinical pharmacology

Overall the pharmacokinetics of sotagliflozin have been appropriately described.

The pharmacodynamic profile of sotagliflozin has been adequately characterised in the populations studied. There is however very limited pharmacodynamic data in patients with renal impairment. This is of concern, taking sotagliflozin's mechanism of action into account. The available data in T2DM patients with moderate renal impairment indicate an effect of sotagliflozin in patients with eGFR 45-60 mL/min/1.73 m^2.

2.5. Clinical efficacy

The clinical development program included seven studies (Table 4). Studies 202 and 206 were dose response studies. Study 203 was a proof-of concept study in T1DM patients; this study is discussed in the pharmacology section of this report and not further discussed in this section.

Three Phase 3 studies were included in the sotagliflozin T1DM program (studies 309, 310, and 312). Studies 309 and 310, which were conducted in North America and in Europe and Israel, respectively, included intensive insulin optimization, and evaluated 200 mg versus 400 mg versus placebo. The third Phase 3 study, Study 312, was conducted globally, without insulin optimization.

In the following all three studies are discussed in parallel to facilitate comparison between studies 309/310 to study 312. For a summary of the single studies, please refer to the summary of efficacy tables (Table 20, Table 21 and Table 22)

Data from a small supportive study (204) was also provided.

2.5.1. Dose response studies

Study 202 – T2DM

This was a Phase 2, placebo-controlled, dose-ranging study conducted to assess the safety, tolerability, and efficacy of 4 dosing regimens of sotagliflozin administered as add-on to metformin in patients with

T2DM. Patients were randomly assigned (1:1:1:1:1 ratio) to 1 of 5 dosing groups: sotagliflozin 75 mg qd, 200 mg qd, 400 mg qd (2 x 200-mg tablets), or 200 mg bid, or placebo tablets.

The study consisted of a 2-week (minimum) Screening Period, 12-week Treatment Period, and a 2-week Follow-up Period. The primary endpoint was the change from Baseline to Week 12 in A1C; the main secondary endpoints were the proportion of patients achieving an A1C value of <7.0% at Week 12 and changes from Baseline in FPG, 3-hour oral glucose tolerance test (OGTT), body weight, and blood pressure.

Eligible patients were adults, aged 18 to 75 years inclusive, with a confirmed diagnosis of T2DM, A1C 7.0% to 10.5%, on a stable dose of metformin monotherapy of ≥1500 mg/day for at least 8 weeks prior to Screening, and for the duration of the study.

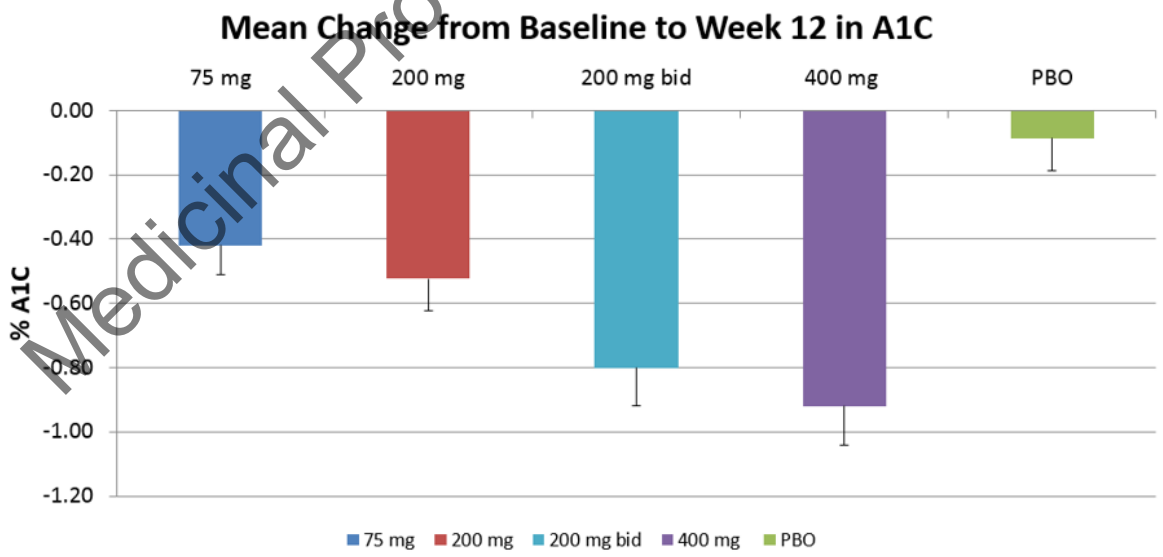
Patient disposition and demographics

A total of 299 patients were equally randomized at 52 sites in the US and were included in the intent-to-treat (ITT) Population, which consisted of all subjects randomized to receive study drug. Overall, 267 patients (89.3%) completed the study. The treatment groups were similar in terms of age, ethnicity, race, BMI, and physical characteristics at Baseline. The proportion of females was higher in the sotagliflozin 200 mg qd group (71.7%) and lower in the sotagliflozin 75 mg qd group (42.4%) compared to the overall proportion of females (54.8%). The mean age overall was 55.9 years. The overall proportion of white patients was 84.3% and the overall proportion of Hispanic or Latino patients was 27.4%. Baseline mean A1C ranged from 7.92 to 8.35%. The mean BMI overall was 33.08 kg/m².

Efficacy results

At Week 12, all sotagliflozin dose regimens showed a statistically significant reduction from Baseline compared with placebo for A1C, the primary efficacy endpoint (Figure 6). The least squares (LS) mean difference from placebo showed the greatest reduction for the 400 mg qd group (-0.79%; p <0.001), followed by the 200 mg bid group (-0.61%; p <0.001), the 200 mg qd group (-0.34%; p = 0.018), and the 75 mg qd group (-0.33%; p = 0.025).

Figure 6 - Study 202: Mean Change in A1C (%) from Baseline to Week 12



The proportion of patients who achieved an A1C <7.0% at Week 12 was highest in the 400 mg qd group (38.6%), and this proportion was significantly different from the placebo group (24.6%; p = 0.022). The difference from placebo was also statistically significant in the 200 mg bid group (29.8%; p = 0.036).

The 3 higher sotagliflozin dose regimens (200 mg, 200 mg BID and 400 mg) were statistically significant compared with placebo in reducing FPG, in reducing blood glucose area under the curve (AUC) during the 3-hour oral glucose tolerance test (all p ≤0.005) and in reducing body weight (all p ≤0.001).

Study 206

This was a Phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy and safety of several doses of sotagliflozin in patients with T1DM with inadequate glycaemic control. The study consisted of a 2-week Screening Period, 2-week Single-blind Placebo Run-in Period, 12-week Double-blind Treatment Period, and a 30-day (post last dose) follow-up phone call. During the 12-week Double-blind Treatment Period, the protocol stipulated that the patients' insulin dose should remain stable (within ±20% of the Baseline total insulin dose), unless an adjustment in insulin dose was required for recurrent hypoglycaemia. The primary efficacy endpoint was the change in A1C from Baseline to Week 12. The secondary efficacy endpoints included change from Baseline to Week 12 for each of the following: 2-hour PPG following a standardized Mixed Meal; body weight (absolute and percent change); UGE; and FPG.

Eligible patients were 18 years and older with confirmed diagnosis of T1DM made at least 1 year prior to informed consent, a screening A1C from 7.0% to 10.0% (inclusive), and a basal insulin that had not changed ≥20% for the 2 weeks prior to the Screening Visit. Patients were being treated with insulin(s) or insulin analogue(s) delivered via CSII or MDI; using the same method of insulin delivery for the 3 months prior to the Screening Visit. On Day 1, of the Double-blind Treatment Period, patients were randomly assigned (1:1:1:1 ratio) to sotagliflozin (75 mg, 200 mg, or 400 mg [given as 2 x 200-mg tablets]) or matching placebo, all given once daily before the first meal of the day as an adjunct to their insulin therapy.

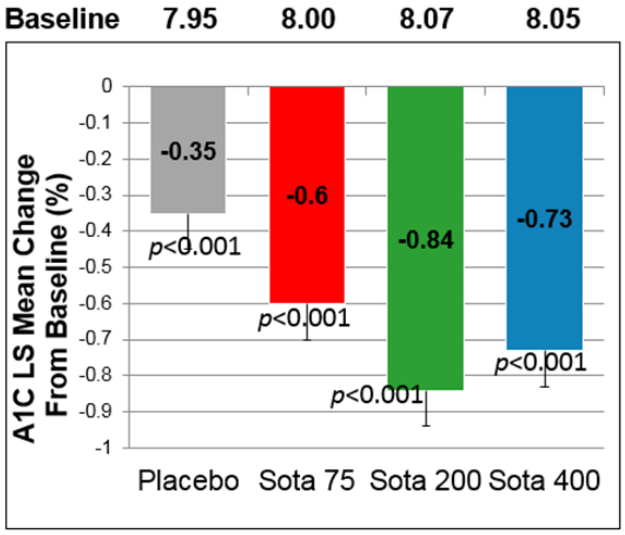
Patient disposition and demographics

A total of 141 patients were equally randomized at 17 study sites in the US, and included in the mITT population. By randomization stratum, there were a total of 73 (51.8%) patients who received insulin by CSII and 68 (48.2%) patients who received insulin by MDI. A total of 130 patients completed the study. At Baseline, the mean (SD) age was 45.6 (13.29) years. The majority of patients were white (131, 92.9%). Sex was acceptably distributed given the group size (male 48.2%; female 51.8%). The mean (SD) Baseline body weight was 85.48 (18.557) kg, and the mean (SD) BMI was 29.17 (5.569) kg/m^2. The mean A1C at Baseline was comparable across the sotagliflozin groups.

Efficacy results

The primary efficacy objective was met by observing a dose relationship from Baseline to Week 12 in A1C reduction across placebo and the 3 sotagliflozin treatment groups (p = 0.008) (Figure 7).

Figure 7 - Study 206: mean change in A1C from Baseline to Week 12



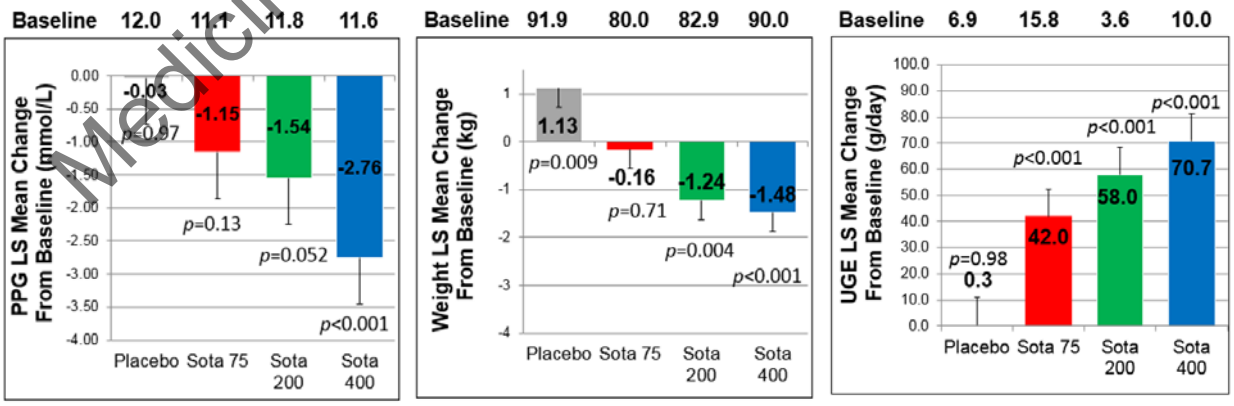
The outcome for the secondary endpoints (change from Baseline to Week 12 for 2-hour PPG; body weight and UGE) are shown in Figure 8.

A dose-dependent effect of sotagliflozin on mean reduction from Baseline in 2-hour PPG following a standardized mixed meal at Week 12 was observed (linear trend p = 0.008). The LS mean difference from placebo in change from Baseline in the 2-hour PPG at Week 12 was -20.3 mg/dL in the sotagliflozin 75 mg group (p = 0.27), -27.4 mg/dL in the sotagliflozin 200 mg group (p = 0.15), and -49.5 mg/dL in the sotagliflozin 400 mg group (p = 0.006).

There was a statistically significant mean decrease from Baseline to Week 12 in absolute body weight compared with placebo for all groups, with the greatest effect observed for sotagliflozin 200 mg and 400 mg groups (p <0.001). The LS mean difference from placebo in change from Baseline in absolute body weight was -2.37 kg in the sotagliflozin 200 mg group and -2.61 kg in the sotagliflozin 400 mg group.

The LS mean difference from placebo in change from Baseline in UGE at Week 12 was statistically significant for all sotagliflozin dose groups: 41.76 g/day in the sotagliflozin 75 mg group (p = 0.006), 57.73 g/day in the sotagliflozin 200 mg group (p <0.001), and 70.45 g/day in the sotagliflozin 400 mg group (p <0.001).

Figure 8 - Study 206: secondary and other efficacy endpoints



The LS mean difference from placebo in change from Baseline in FPG at Week 12 was -8.6 mg/dL in the sotagliflozin 75 mg group, -8.9 mg/dL in the sotagliflozin 200 mg group, and -21.4 mg/dL in the sotagliflozin 400 mg; none of these decreases were statistically significant compared with placebo.

2.5.2. Main studies

Methods

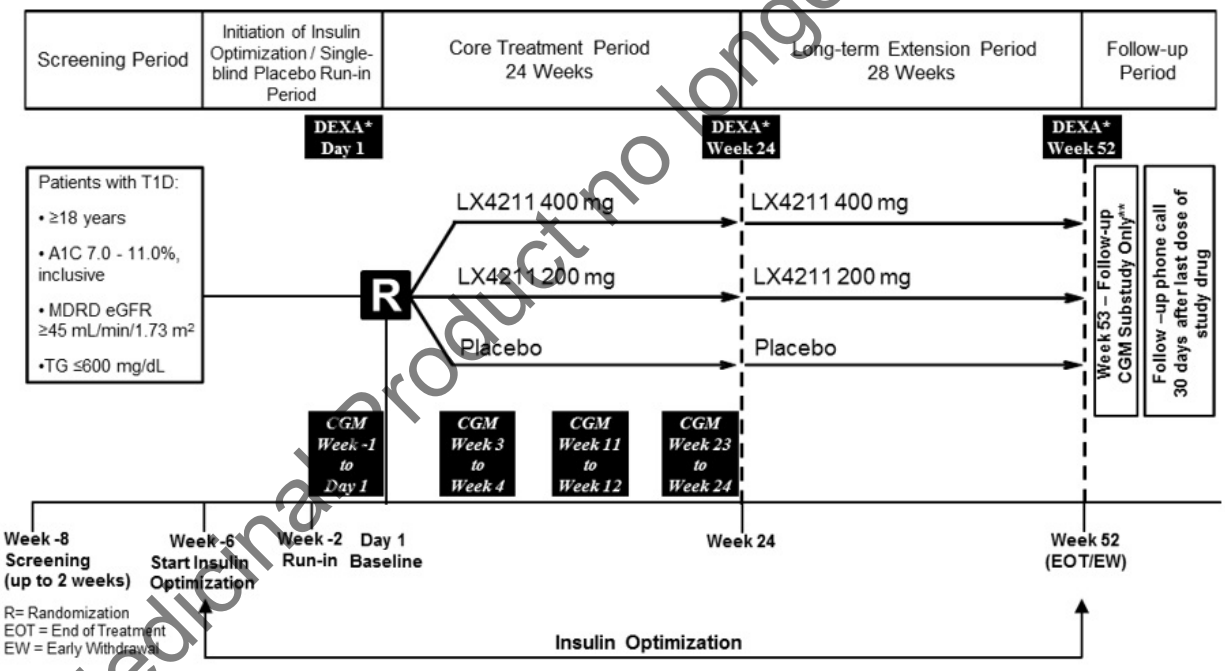
Studies 309 and 310

Studies 309 and 310 had the same design. Both studies were Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies to evaluate the efficacy, safety, and tolerability of sotagliflozin 200 mg and 400 mg versus placebo administered qd as an adjunct therapy in adults with T1DM who had inadequate glycaemic control with insulin therapy (delivered via continuous subcutaneous insulin infusion [CSII] or multiple daily injection [MDI]). For each study, the total duration of exposure to study drug was up to 52 weeks. A key design feature for studies 309 and 310 was insulin optimization.

The primary objective was to establish the superiority of sotagliflozin 200 mg and/or 400 mg administered before the first meal of the day compared with placebo, as measured by the change in A1C from Baseline to Week 24.

The total duration of study participation was up to 64 weeks. The study schema is presented in Figure 9.

Figure 9 - Studies 309 and 310: Study Schema



* Patients who participated in the optional DEXA substudy were to complete the Baseline DEXA -2weeks from the Day 1 visit. The visit window for DEXA after the Day 1 visit was to be ± 2 weeks

** Patients who participated in the optional CGM substudy, and all patients who were screened after IRB approval of Amendment 2, were to complete the Week 53 Follow-up visit

Two substudies were included in both 309 and 310: a CGM substudy, designed to obtain continuous data on blood glucose values and a dual-energy X-ray absorptiometry (DEXA) substudy, designed to evaluate fat mass and bone density. Patients could have participated in 1 or both substudies.

Patients eligible were 18 years and older with a diagnosis of T1DM made at least 1 year prior to informed consent, a Screening A1C of 7.0% to 11.0% (inclusive), an eGFR >45 mL/min/1.73 m^2, and a triglyceride value <600 mg/dL. Patients were being treated with insulin(s) or insulin analogue(s) delivered via CSII or

MDI; using the same method of insulin delivery for the 3 months prior to the Screening Visit. Antidiabetic treatments other than insulin were prohibited. Patients with a history of SH or DKA within 1 month prior to Screening were excluded.

All patients who completed the Core Treatment Period were eligible to participate in the LTE Period.

Patients could participate in 1 or both (CGM and DEXA) substudies. Patients selected for DEXA evaluation had to satisfy additional eligibility criteria: age 30 to 80 years old, inclusive and not on any medications that could affect bone density for at least 3 years.

Key design features related to Insulin Optimization in Studies 309 and 310

In order to evaluate the efficacy of sotagliflozin beyond what can be provided by insulin alone, all patients in Studies 309 and 310 entered a 6-week insulin optimization period prior to randomization, with the objective of improving glycaemic control using insulin alone. Patients were maintained on optimized insulin after being randomized to 1 of 2 doses of sotagliflozin (200 mg or 400 mg) or placebo. During insulin optimization, insulin adjustment was assessed by an insulin dose monitoring committee (IDMC) of independent experts from Week -5 to Week 24 (time of primary and secondary endpoint assessment). To be eligible for inclusion in both studies, the screening (pre-optimization) A1C was required to be ≥7.0%. This A1C inclusion criterion was not repeated after optimization, therefore the study population included approximately 20% patients with A1C <7.0% at Baseline.

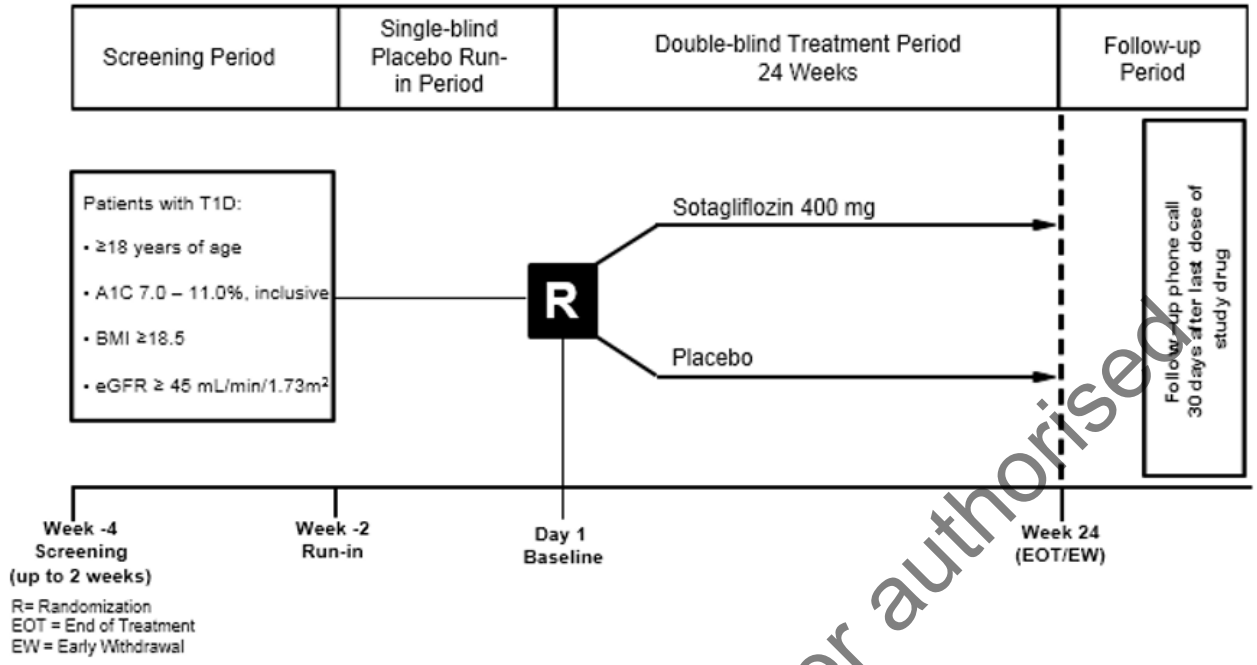
Study 312

Study 312 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the net benefit (defined as the proportion of patients with A1C <7.0% and no episode of SH and no episode of DKA from Randomization to Week 24) of sotagliflozin 400 mg versus placebo administered qd as an adjunct to insulin in patients with T1DM. This study did not utilize insulin optimization, and treatment was not confined to any specific insulin regimen.

The primary objective of this study was to demonstrate the superiority of sotagliflozin 400 mg qd administered before the first meal of the day compared with placebo in the proportion of patients with A1C <7.0% at Week 24 and no episode of SH and no episode of DKA after Randomization.

The total duration of study participation was up to 32 weeks. The study schema is presented in Figure 10.

Figure 10 - Study 312: Study Schema



Sotagliflozin 400 mg qd dosage was used in Study 312 to evaluate safety exposure at the higher dose. The total duration of exposure to study drug was up to 24 weeks.

Eligible patients were ≥18 years of age, with a BMI ≥18.5 kg/m^2, a confirmed diagnosis of T1DM made at least 1 year before Screening, and a Screening A1C of 7.0% to 11.0%, (inclusive), an eGFR >45 mL/min/1.73 m^2, and a triglyceride value <600 mg/dL. Use of any antidiabetic agent other than insulin or insulin analogue within 8 weeks prior to Screening was excluded. Patients using any background insulin regimen including CSII, MDI, intermediate acting, and pre-mixed insulins, were eligible to participate. Patients with a history of SH or DKA within 1 month prior to Screening were excluded.

Glycaemic goals and adjustment of insulin dose in studies 309, 310 and 312

The recommended target for fasting/preprandial glucose was 80-130 mg/dL (4.4 to 7.2 mmol/L). Recommended target for 1-2-hour postprandial glucose (PPG) by SMBG was <180 mg/dL (<10.0 mmol/L). Goals could have been adapted for individual patients based on investigator discretion.

For the first meal on Day 1, patients were to be instructed to decrease their calculated (or usual) mealtime carbohydrate bolus insulin by 30%. Subsequent adjustments in insulin dosing were to be made by the Investigator, based on SMBG trends. The mealtime insulin adjustment recommendations for Day 1 were based on results from Study 203. It was expected that the insulin-to-carbohydrate ratio would be decreased by approximately 30% with sotagliflozin treatment. It was also predicted that such an adjustment would convey appropriate margins of safety for both the treated and placebo groups. The insulin-to-carbohydrate was to be subsequently adjusted as frequently as required by the Investigator to meet glycaemic goals recommended for this study. No change in high blood glucose correction factor (sliding scale), basal (or nonbolus) insulin, or basal rate was to be recommended at initiation of study drug, although the Investigator was not to be prohibited from making any changes in any insulin dose consistent with meeting glycaemic goals recommended for this study.

Outcomes/endpoints

Table 6 - Main efficacy endpoints in phase 3 studies

	Studies 309 and 310	Study 312
Primary Endpoint	A1C change from Baseline at Week 24	Net benefit at Week 24[a]
Secondary Endpoints (in hierarchical order)	Net benefit at Week 24[0]	A1C change from Baseline at Week 24
	Body Weight change from Baseline at Week 24	Body Weight change from Baseline at Week 24
	Bolus insulin change from Baseline at Week 24	SBP change from Baseline at Week 16 (in patients with SBP ≥130 mm Hg at Baseline)
	FPG change from Baseline at Week 24	Bolus insulin change from Baseline at Week 24
	DTSQs score change from Baseline at Week 24	
	DDS2 score change from Baseline at Week 24	
Other Endpoints	SBP change from Baseline at Week 12 (in patients with SBP ≥130 mm Hg at Baseline)	FPG change from Baseline at Week 24
	Composite Endpoints evaluating benefit/risk: Other clinical benefits (achieving benefit, defined as A1C reduction, while having low risk in other parameters such as SH, DKA, body weight, and insulin dosing).	Composite Endpoints evaluating benefit/risk: Other clinical benefits (achieving benefit, defined as A1C reduction, while having low risk in other parameters such as SH, DKA, body weight, and insulin dosing).

Net benefit was defined as the proportion with A1C <7.0% at week 24 and no episode of SH and no episode of DKA after randomization.

In studies 309 and 310, SBP changes were evaluated at Week 12, consistent with the protocol design to keep antihypertensive medication doses stable until Week 12. Additionally, the mean change from Baseline in SBP was evaluated in a subset of patients with Baseline SBP ≥130 mm Hg at Weeks 12 and 24.

Table 7 CGM primary, key secondary and other endpoints (mITT CGM population)

	Pooled 309 and 310
Primary Endpoint	Percent time spent in target range (70 to 180 mg/dL)
Secondary Endpoints	% time spent outside the target range, AUC outside the target range (by hyperglycaemia and hypoglycaemia), % time and AUC in hyperglycaemia or hypoglycaemia by Sleep-Wake Time Blocks
	Average minutes/day in target, hyperglycaemia or hypoglycaemia range, number of hypoglycaemic events, MAGE, MAG, coefficient of variation, mean SD, mean daily glucose, and distance travelled (all endpoints Week 24)

Table 8 DEXA primary, key secondary and other endpoints (mITT DEXA population)

	Pooled 309 and 310
Primary Endpoint	Total fat mass (Week 24)
Secondary Endpoints	Total lean mass and % total fat (Week 24, 52)

Sample size

Studies 309 and 310

Separately for both Studies 309 and 310, the sample size estimate was based on satisfying design assumptions and statistical testing requirements for the primary efficacy endpoint. The final sample size was estimated as 250 randomized patients per treatment group (750 total) for each study. The two substudies, a CGM substudy and a DEXA substudy, will target approximately 70 patients per treatment group to satisfy their primary objectives.

Study 312

For Study 312, the sample size was based on satisfying assumptions made for the primary efficacy endpoint of net clinical benefit and to provide a suitable number of patients so that a reliable estimate of treatment group differences in SH could be made. Based on these considerations, 700 randomized patients were required per treatment group or 1400 total patients.

Randomisation

The desired balances were to be accomplished by use of randomly permuted blocks of fixed size. An Interactive Voice/Web Response System (IXRS) was to be used as a central mechanism to assign patients to study treatment. Patients who terminated the study early were not to be replaced in this study.

Studies 309 and 310

Patients were to be randomly assigned among 3 parallel treatment groups in a 1:1:1 manner. The treatment randomization schedule, was centralized and stratified by insulin delivery method (MDI or CSII) and Week -2 A1C (≤8.5%, >8.5%). Enrolment of patients using insulin via MDI was to be capped at 60%; no more than 150 patients on MDI were to be randomly assigned to each treatment arm. Upon reaching this threshold, patients were to have been randomly assigned to the treatment groups, being stratified only by Week -2 A1C (≤8.5%, >8.5%).

Study 312

Patients were to be randomly assigned between 2 treatment groups in a parallel, 1:1 manner. The treatment randomization schedule was centralized and stratified by BMI at Screening (<25 kg/m2, ≥25 kg/m2), Week 2 A1C (≤9.0%, >9.0%), and use of CSII at Screening (yes, no).

Blinding (masking)

In all the double-blind studies, the designated group and treatment assigned to each patient was not to have been revealed to the Investigator, site staff, the patient, or the Sponsor, or designee, until the decision was made to unblind the study. To maintain the double-blind design, A1C, FPG, and 2-hour PPG results (in the CGM substudy) were masked from the visit after Randomization to the visit before Week 24. In addition, because of the glycosuria effect of sotagliflozin, urine glucose values were to have been masked to all study staff.

Statistical methods

Studies 309 and 310

For summaries based on use of inferential statistics, all significance tests were 2-sided and used a 0.05 α-level. Confidence limits (CLs) were likewise 2-sided and used a 95% confidence coefficient.

All efficacy analyses were performed on the modified intent to treat (mITT) population. A supportive analysis of the primary endpoint was also performed on the per-protocol (PP) population. All safety analyses were performed on the Safety Population.

Randomized Population: All randomly assigned patients were included in the Randomized Population. Randomized patients were analysed according to their randomized treatment.

Safety Population: All randomly assigned patients treated with at least 1 dose of study drug were included in the Safety Population. Safety patients were analysed according to their actual treatment received on Day 1.

Modified Intent-to-treat Population: The mITT population consists of all randomly assigned patients who had taken at least 1 dose of study drug. Patients in the mITT population were analysed according to their randomized treatment.

Per-Protocol Population: The PP Population comprises all patients in the mITT population who completed treatment through the primary CT Period of 24 weeks, and did not have any significant protocol deviations during this time. Significant protocol deviations were defined as those deviations considered having a major effect on the collection or interpretation of the primary efficacy endpoint. In addition, a separate PP Population was defined for the CGM substudy for analysis of the change from Baseline to Week 24 in the 2-hour PPG following the standardized Mixed Meal.

The primary efficacy endpoint was the change from Baseline to Week 24 in A1C in either sotagliflozin dose (200 mg or 400 mg) compared with placebo. The primary analysis of the primary efficacy endpoint used mixed-effects MMRM statistics based on the restricted maximum likelihood method for estimation and to be performed using the mITT Population. The analysis model included fixed, categorical effects of treatment, randomization strata of insulin delivery method (MDI, CSII), randomization strata of Week -2 A1C (≤8.5%, >8.5%), time (study week), a treatment-by-time interaction, and Baseline A1C-by-time interaction as a covariate. An unstructured (co)variance structure was used to model the within-patient errors. The model adjusted mean (i.e. least squares [LS] mean) change in A1C from Baseline to Week 24 for each treatment group was estimated in the framework of this model, as well as the between group differences (comparing sotagliflozin to placebo) and the 95% CLs for the difference.

In addition, the primary efficacy endpoint was analysed for the PP Population using an analysis of covariance (ANCOVA) model fitted for the fixed, categorical effects of treatment, randomization strata of insulin delivery method, randomization strata of Week -2 A1C, and Baseline A1C as a covariate.

A key assumption for drawing valid conclusions using the MMRM analysis was that the reason for missing data was a function of the MAR mechanism. Since one could not be fully certain that other mechanisms might underlie the reason for missing data (e.g., MNAR), it was important to perform sensitivity analyses of the MMRM results. Under an assumption of MNAR, the PMM with control based pattern imputation was used in the sensitivity analysis for this study. The model's actual implementation dependent on the extent and pattern of missing data and, as such, it might not be used. For the analysis of binary efficacy endpoints, missing observations at Week 24 were imputed as nonresponse (i.e., nonresponder imputation).

The secondary efficacy endpoints were measured for either sotagliflozin dose compared with placebo for each of the following:

- Proportion of patients with A1C <7.0% (at Week 24) and no episode of severe hypoglycaemia, and no episode of DKA (severe hypoglycaemia and DKA occurrence over the cumulative randomized Double-blind 24-week CT Period)
- Change from Baseline in body weight at Week 24 (absolute and percent change)

- Change from Baseline in mean daily bolus insulin dose at Week 24
- Change from Baseline in FPG at Week 24
- Change from Baseline in Diabetes treatment satisfaction as measured by DTSQs scores at Week 24
- Change from Baseline in Diabetes Distress as measured by DDS2 scores at Week 24

For continuous secondary efficacy endpoints, an MMRM model, as specified for the primary efficacy variable was applied, with the corresponding endpoint and Baseline value-by-time covariate specific for that secondary endpoint used in the model. Since the continuous secondary efficacy endpoints are all changes (or percent changes, for some) from Baseline to Week 24, all post-Baseline observations collected during the CT Period, and following application of the visit window rules, were used as dependent variables in the MMRM.

For the binary secondary efficacy endpoint, a Cochran-Mantel-Haenszel (CMH) test stratified by the different levels of the randomization stratification factors of insulin delivery method (MDI, CSII) and Week -2 A1C (≤8.5%, >8.5%) was used.

Multiplicity in statistical testing of the efficacy variables occurred from 2 main sources: (a) testing of the primary endpoint and multiple secondary endpoints, and (b) testing of 2 sotagliflozin dose groups against placebo for each endpoint. These considerations yielded 14 hypotheses to be tested that can be grouped into 7 families: each family corresponded to the specific endpoint under test.

Family F1 consisted of the sotagliflozin 200 mg versus placebo and sotagliflozin 400 mg versus placebo comparisons for the primary endpoint. Family F2 included the same treatment group comparisons for the first listed secondary endpoint, F3 included the same comparisons for the second listed secondary endpoint, and so on. The 7 families were to be tested sequentially with the restriction that the test of each treatment group comparison required all prior tests of that particular comparison to meet statistical significance criteria. The primary endpoint hypotheses were to be tested by a Bonferroni procedure with $\alpha = 0.05$ (2-sided) and use of equal weights so that the per comparison error rate = 0.025 (2-sided). The raw p-value for each treatment contrast was compared with $\alpha = 0.025$ and if the raw p-value was less than or equal to 0.025, the comparison was declared statistically significant and testing for that contrast could proceed to the next listed endpoint. Consistent with testing the primary endpoint, the family-wise error rate (FWER) within each secondary endpoint family was 0.05 (2-sided), and with hypothesis weights of 0.5 assigned to each contrast within each testable family, the per comparison α-level = 0.025 (2-sided). Formal testing was to stop at that endpoint for which a raw p-value exceeded 0.025.

Progression in testing across the hypothesis families was to be carried out, in essence, using a tree gatekeeping test procedure so that the study-wise error rate across all primary and secondary hypotheses tested was strongly controlled at $\alpha = 0.05$.

CGM study: Due to recruitment of the CGM substudy not meeting the planned target, CGM data from the 309 study was to be pooled with data from Study LX4211.310. This eventuality was prespecified in the protocols for the respective studies prior to unblinding any CGM data.

Study 312

The primary efficacy endpoint was the proportion of patients with A1C <7.0% at Week 24 and no episode of severe hypoglycaemia and no episode of DKA from Randomization to Week 24. The analysis of this endpoint was based on the mITT population. The frequency and percentage of patients with A1C <7.0% at Week 24 and no episode of severe hypoglycaemia or episode of DKA from Randomization to Week 24 were presented by treatment group.

Analysis of the primary efficacy endpoint at Week 24 was performed using the CMH test and 95% CLs based on normal approximation methods with a continuity correction factor, stratified by the different levels of the randomization stratification factors of BMI at Screening (<25 kg/m2, ≥25 kg/m2), Week -2 A1C (≤9.0%, >9.0%), and use of CSII at Screening (yes, no). The treatment group comparisons were performed at Week 24 only. The individual components of the endpoint were summarized separately using descriptive methods.

Analysis of the secondary efficacy endpoints were based on the mITT population. The secondary efficacy endpoints were measured as change from Baseline in sotagliflozin 400 mg compared with placebo and were analysed using MMRM model using the restricted maximum likelihood method for estimation. The analysis mode included treatment, randomization strata of BMI at Screening (<25 kg/m2, ≥25 kg/m2), randomization strata of Week -2 A1C (≤9.0%, >9.0%), randomization strata of use of CSII at Screening (yes, no), time (study week), and a treatment-by-time interaction as fixed categorical effects, and baseline-dependent variable-by-time interaction as a covariate. For the endpoint of percent change from Baseline, the analysis model was not to include the interaction covariate. An unstructured (co)variance structure was used to model the within-patient errors.

The test for superiority of sotagliflozin versus placebo based on the primary efficacy endpoint was performed at the 2-sided 0.05 α-level. If this null hypothesis was rejected, analysis of the secondary endpoints at Week 24 were to occur in a sequential, prespecified hierarchy so that the overall type I error rate was strongly controlled at a 2-sided, 0.05 α-level across these endpoints. The order of testing for the secondary endpoints was 1) A1C change from Baseline at Week 24, 2) Body weight at Week 24 change from Baseline (absolute and percent change; the absolute change will be used in the sequence of analyses), 3) SBP change from Baseline at Week 16 in the subset of patients with Baseline SBP ≥130 mm Hg, 4) Percent change from Baseline in bolus insulin dose at Week 24.

Missing data was handled as described for studies 309 and 310.

Pool E1 and E2

Efficacy analyses from all Phase 3 studies were pooled into 2 groupings, ES1 and ES2. The ES1 pool included the 52-week Studies 309 and 310, both of which defined change from Baseline in A1C at Week 24 as their primary endpoint. The ES2 pool included placebo and the 400 mg sotagliflozin dose groups from all 3 Phase 3 studies. Both pools were designed to allow for analysis of efficacy endpoints across several subgroups of clinical interest. Another objective for the ES1 pool was to provide increased precision for the CGM and DEXA substudy assessments.

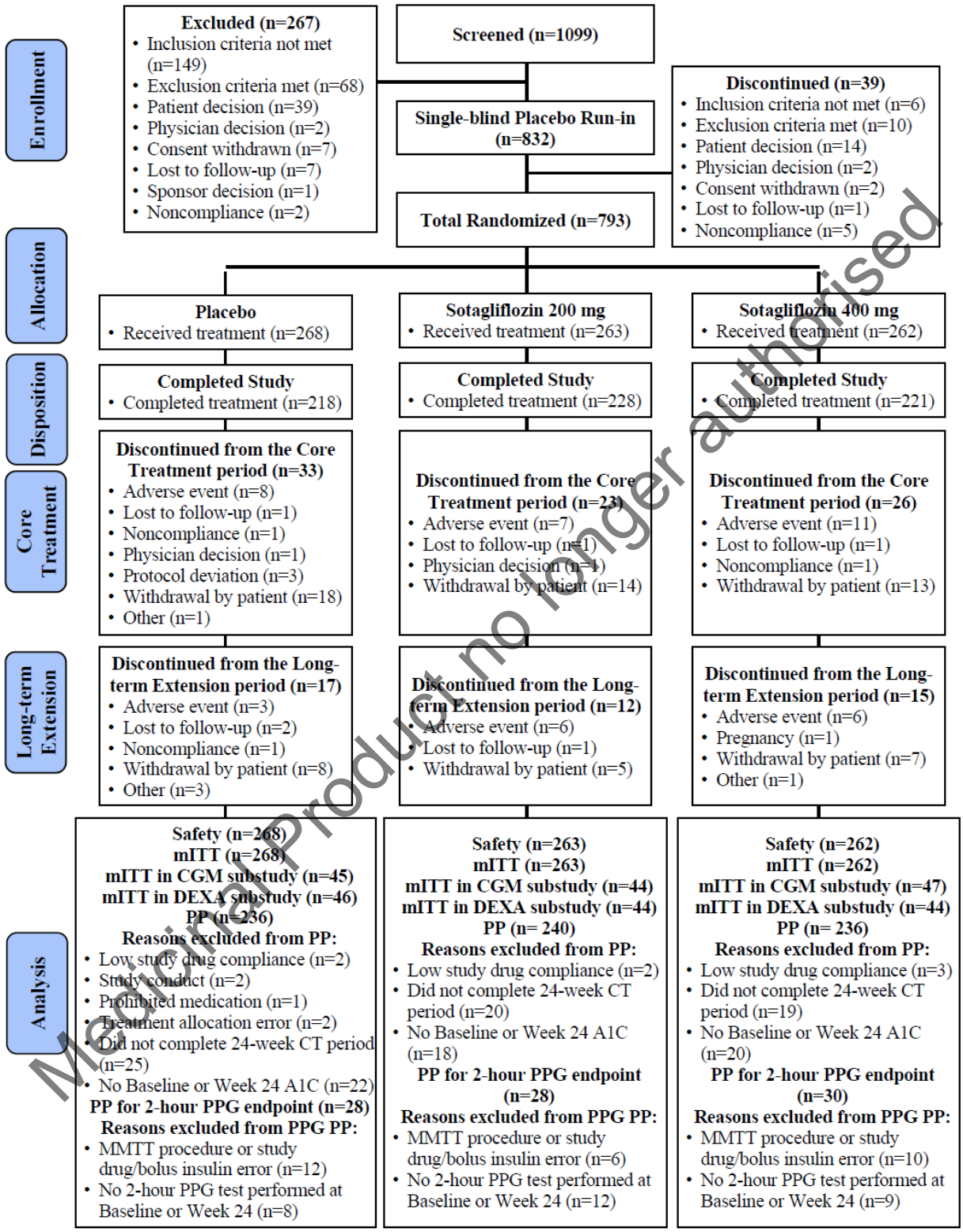
The pooled analyses of the primary and secondary endpoints followed the methods provided in the individual study SAPs. No multiple testing adjustments were performed for the pooled analyses.

Results

In the following, the results for studies 309, 310 and 312 are discussed in parallel. For the outcome of the studies one by one, please refer to the efficacy tables (Table 20, Table 21 and Table 22).

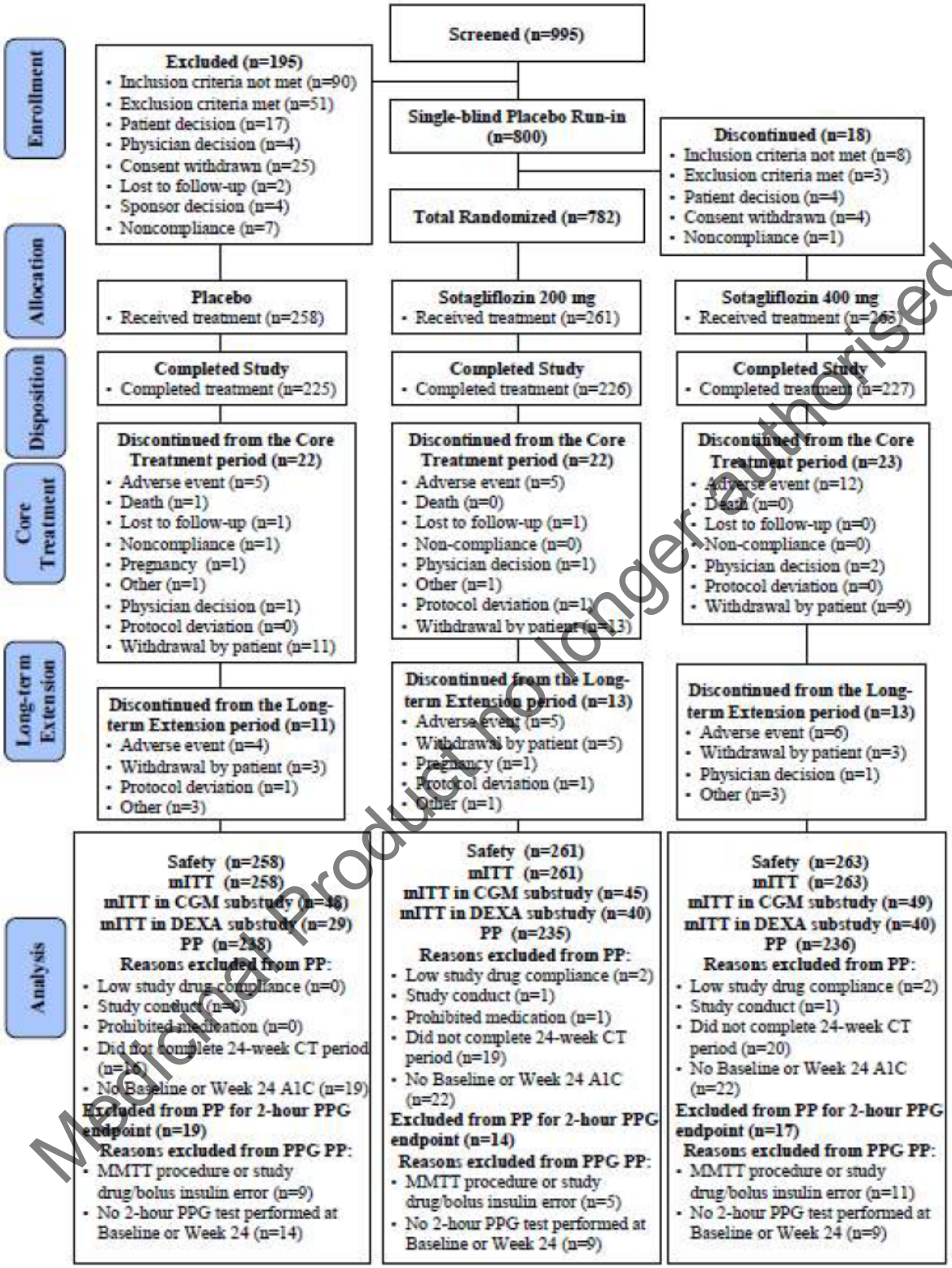
Participant flow

Figure 11 Study 309: Flow Diagram of the Study – All Patients Enrolled



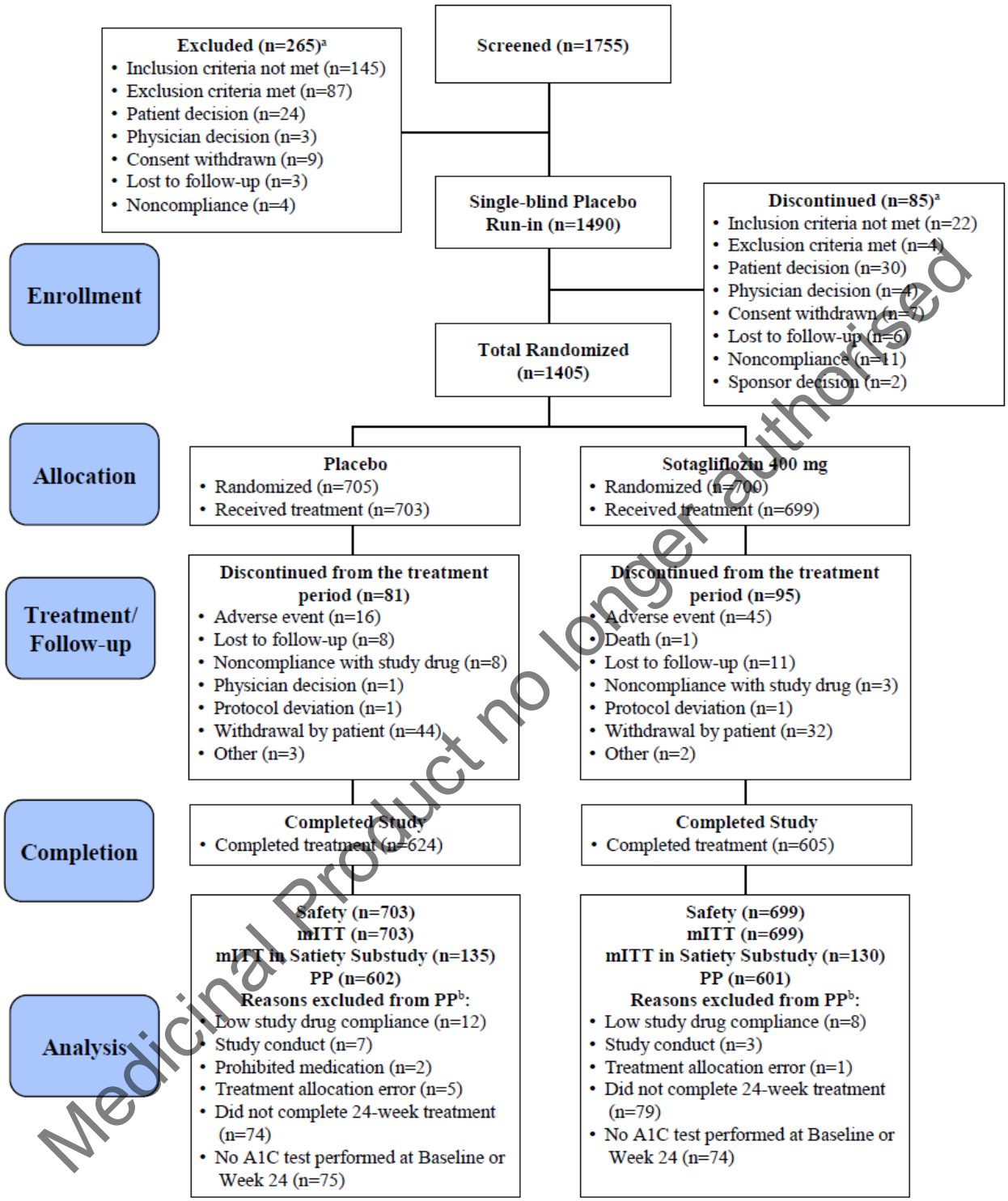
Abbreviations: A1C = haemoglobin A1C; CGM = continuous glucose monitoring; CT = Core Treatment; DEXA = dual-energy X-ray absorptiometry; mITT = modified intent-to-treat; MMTT = Mixed Meal tolerance test; n = number of patients; PP = per-protocol; PPG = postprandial glucose.
Note: Patients may have had more than 1 exclusionary event.

Figure 12 Study 310: Flow Diagram of the Study – All Patients Enrolled



Abbreviations: A1C = haemoglobin A1C; CGM = continuous glucose monitoring; CT = core treatment; DEXA = dual-energy X-ray absorptiometry; mITT = modified intent-to-treat; MMTT = mixed meal tolerance test; n = number of patients; PP=per-protocol; PPG = postprandial glucose.
Note: Patients may have had more than 1 exclusionary event.

Figure 13 Study 312: Flow Diagram of the Study – All Patients Enrolled



Abbreviations: A1C = haemoglobin A1C; mITT = modified Intent-to-Treat; n = number of patients; PP = per-protocol.
[a] Patients may have been excluded or discontinued for more than 1 reason.
[b] Patients may have been excluded for more than 1 reason.

Conduct of the studies

In study 310 there was 1 incident where ethical conduct of the study was compromised. Inspections have been performed by the Lithuanian health authority, which concluded that the safety of the subjects and integrity of their data were not compromised, as the initial IEC approvals had been obtained.

All patients in Study 310 were to have trough plasma levels of sotagliflozin and its main metabolite determined at Weeks 12 and 24. The Sponsor identified 42 of the 782 randomized patients who had plasma PK samples suggesting that they had received incorrect study drug or had failed to take study drug as required for some periods during the study. The Sponsor performed a root cause investigation. As a result of this investigation, the Sponsor believes that the issues were a consequence of specific site errors in dispensing and handling of investigational product, a laboratory sample handling error, as well as patient noncompliance, and affect only limited number of patients (42 patients), 5% of the total patients randomized in the 310 study. Because of these PK sample findings, additional analyses were performed to assess their potential impact on overall study results. Sensitivity analyses applying several statistical methods were performed on the safety and efficacy data to evaluate the potential impact of the anomalous findings on study outcomes. Results of these analyses showed no impact on the primary and secondary efficacy nor safety endpoints, nor on the benefit-risk profile of sotagliflozin as demonstrated in this study.

Baseline data

Table 9 Summary of demographics for Studies 309, 310, and 312 (mITT population)

	Study 309			Study 310			Study 312	
	Placebo (N = 268)	SOTA 200 mg (N = 263)	SOTA 400 mg (N = 262)	Placebo (N = 258)	SOTA 200 mg (N = 261)	SOTA 400 mg (N = 263)	Placebo (N = 703)	SOTA 400 mg (N = 699)
Mean (SD) age at study entry (years)	45.2 (12.72)	46.6 (13.48)	46.4 (13.12)	39.7 (13.42)	42.3 (13.59)	41.7 (13.23)	42.4 (14.04)	43.3 (14.17)
Age at study entry (years), n (%)								
≥18 to <26	20 (7.5)	21 (8.0)	19 (7.3)	43 (16.7)	39 (14.9)	39 (14.8)	98 (13.9)	90 (12.9)
≥26 to <50	140 (52.2)	128 (48.7)	132 (50.4)	151 (58.5)	138 (52.9)	149 (56.7)	378 (53.8)	371 (53.1)
≥50 to <65	89 (33.2)	91 (34.6)	89 (34.0)	50 (19.4)	75 (28.7)	65 (24.7)	181 (25.7)	183 (26.2)
≥65 to <75	18 (6.7)	20 (7.6)	21 (8.0)	13 (5.0)	8 (3.1)	8 (3.0)	45 (6.4)	50 (7.2)
≥75	1 (0.4)	3 (1.1)	1 (0.4)	1 (0.4)	1 (0.4)	2 (0.8)	1 (0.1)	5 (0.7)
Age at T1DM diagnosis (years)								
Mean (SD)	21.0 (12.88)	21.6 (13.37)	22.4 (13.14)	21.7 (12.59)	24.0 (12.88)	22.8 (12.54)	22.8 (13.51)	22.8 (13.65)
Age at T1DM diagnosis (years)								
<18	119 (44.4)	120 (45.6)	112 (42.7)	111 (43.0)	88 (33.7)	99 (37.6)	296 (42.1)	294 (42.1)
≥18	149 (55.6)	143 (54.4)	150 (57.3)	147 (57.0)	173 (66.3)	164 (62.4)	407 (57.9)	405 (57.9)
Sex								
Male	137 (51.1)	126 (47.9)	120 (45.8)	134 (51.9)	139 (53.3)	133 (50.6)	339 (48.2)	358 (51.2)
Female	131 (48.9)	137 (52.1)	142 (54.2)	124 (48.1)	122 (46.7)	130 (49.4)	364 (51.8)	341 (48.8)
Race								
White	244 (91.0)	241 (91.6)	246 (93.9)	250 (96.9)	252 (96.6)	250 (95.1)	621 (88.3)	619 (88.6)
Black	9 (3.4)	11 (4.2)	8 (3.1)	1 (0.4)	0	0	22 (3.1)	24 (3.4)
Weight (kg)								
Mean (SD)	87.30 (17.709)	86.96 (18.539)	86.50 (18.004)	81.08 (16.857)	81.93 (17.386)	81.97 (17.963)	81.55 (17.032)	82.40 (17.131)
BMI (kg/m^2)								
Mean (SD)	29.55 (5.188)	29.81 (5.686)	29.63 (5.297)	27.50 (5.170)	27.97 (5.275)	27.85 (4.921)	28.10 (5.183)	28.29 (5.128)
BMI (kg/m^2), category								
<18.5	0	0	0	0	3 (1.1)	2 (0.8)	1 (0.1)	3 (0.4)
≥18.5 to <25	53 (19.8)	60 (22.8)	51 (19.5)	88 (34.1)	79 (30.3)	74 (28.1)	205 (29.2)	201 (28.8)
≥25 to <30	101 (37.7)	82 (31.2)	97 (37.0)	98 (38.0)	95 (36.4)	109 (41.4)	279 (39.7)	259 (37.1)
≥30	114 (42.5)	121 (46.0)	114 (43.5)	72 (27.9)	84 (32.2)	78 (29.7)	218 (31.0)	236 (33.8)
Geographic Region								

	Study 309			Study 310			Study 312	
	Placebo (N = 268)	SOTA 200 mg (N = 263)	SOTA 400 mg (N = 262)	Placebo (N = 258)	SOTA 200 mg (N = 261)	SOTA 400 mg (N = 263)	Placebo (N = 703)	SOTA 400 mg (N = 699)
North America (US and Canada)	268 (100.0)	263 (100.0)	262 (100.0)	0	0	0	302 (43.0)	277 (39.6)
Outside North America	0	0	0	258 (100.0)	261 (100.0)	263 (100.0)	401 (57.0)	422 (60.4)
Duration of T1DM (years)								
<20	107 (39.9)	99 (37.6)	104 (39.7)	158 (61.2)	160 (61.3)	160 (60.8)	385 (54.8)	373 (53.4)
≥20 to <40	125 (46.6)	122 (46.4)	126 (48.1)	85 (32.9)	89 (34.1)	88 (33.5)	270 (38.4)	268 (38.3)
≥40	36 (13.4)	42 (16.0)	32 (12.2)	15 (5.8)	12 (4.6)	15 (5.7)	48 (6.8)	58 (8.3)
Insulin Delivery Method								
CSII	160 (59.7)	156 (59.3)	157 (59.9)	66 (25.6)	68 (26.1)	67 (25.5)	280 (39.8)	275 (39.3)
Non-CSII	108 (40.3)	107 (40.7)	105 (40.1)	192 (74.4)	193 (73.9)	196 (74.5)	423 (60.2)	424 (60.7)

Table 10 Summary of Baseline characteristics for Studies 309, 310, and 312 (mITT population)

	Study 309			Study 310			Study 312	
	Placebo (N = 268)	SOTA 200 mg (N = 263)	SOTA 400 mg (N = 262)	Placebo (N = 258)	SOTA 200 mg (N = 261)	SOTA 400 mg (N = 263)	Placebo (N = 703)	SOTA 400 mg (N = 699)
A1C (%) at Week -2, n (%)								
≤8.5%	228 (85.1)	226 (85.9)	227 (86.6)	202 (78.3)	205 (78.5)	208 (79.1)	417 (59.3)	423 (60.5)
>8.5%	40 (14.9)	37 (14.1)	35 (13.4)	56 (21.7)	56 (21.5)	55 (20.9)	284 (40.4)	276 (39.5)
Mean (SD) A1C (%)	7.54 (0.712)	7.61 (0.735)	7.56 (0.724)	7.79 (0.881)	7.74 (0.806)	7.71 (0.819)	8.21 (0.921)	8.26 (0.965)
Mean (SD) A1C (mmol/mol)	58.92 (7.805)	59.67 (7.984)	59.12 (7.911)	61.64 (9.627)	61.11 (8.774)	60.82 (8.945)	66.23 (10.073)	66.72 (10.521)
Baseline eGFR (ml/min/1.73m^2), n (%)								
<60	15 (5.6)	14 (5.3)	16 (6.1)	9 (3.5)	8 (3.1)	9 (3.4)	42 (6.0)	32 (4.6)
≥60 to <90	141 (52.6)	146 (55.5)	143 (54.6)	104 (40.3)	124 (47.5)	116 (44.1)	300 (42.7)	312 (44.6)
≥90	112 (41.8)	103 (39.2)	103 (39.3)	145 (56.2)	129 (49.4)	138 (52.5)	361 (51.4)	355 (50.8)
Mean (SD) FPG (mg/dL)	153.66 (64.534)	155.06 (68.710)	148.24 (62.949)	160.45 (65.356)	163.66 (74.482)	165.46 (71.059)	163.42 (69.083)	165.10 (71.603)
n[a]	42	42	45	39	43	45	NA	NA
Mean (SD) 2-hour PPG (mg/dL)	227.60 (91.627)	198.40 (91.819)	202.98 (69.113)	232.10 (107.304)	223.09 (103.539)	216.33 (99.922)	NA	NA
Mean (SD) Total Daily Insulin Dose (IU/kg)	0.74 (0.357)	0.72 (0.386)	0.72 (0.335)	0.75 (0.295)	0.73 (0.277)	0.74 (0.267)	0.71 (0.291)	0.69 (0.276)
Mean (SD) Total Daily Insulin Dose (IU/day)	66.79 (41.265)	65.11 (42.698)	64.15 (37.636)	61.85 (30.862)	60.30 (28.963)	61.38 (28.653)	58.35 (29.085)	56.88 (27.601)
Mean (SD) Ratio of Daily Bolus vs. Total Insulin Doses (IU/IU)	0.46 (0.128)	0.45 (0.138)	0.46 (0.129)	0.50 (0.132)	0.51 (0.134)	0.51 (0.125)	0.48 (0.151)	0.47 (0.152)
Mean (SD) Sitting SBP (mm Hg)	120.9 (13.47)	120.0 (14.84)	119.5 (14.73)	123.1 (15.53)	123.0 (15.08)	123.1 (13.69)	121.8 (14.82)	122.0 (15.25)
Baseline Sitting SBP (mm Hg), n (%)								
<130	204 (76.1)	203 (77.2)	202 (77.1)	173 (67.1)	175 (67.0)	183 (69.6)	499 (71.0)	496 (71.0)
≥130	64 (23.9)	60 (22.8)	60 (22.9)	85 (32.9)	86 (33.0)	80 (30.4)	203 (28.9)	203 (29.0)
<140	248 (92.5)	237 (90.1)	241 (92.0)	228 (88.4)	228 (87.4)	235 (89.4)	618 (87.9)	601 (86.0)
≥140	20 (7.5)	26 (9.9)	21 (8.0)	30 (11.6)	33 (12.6)	28 (10.6)	84 (11.9)	98 (14.0)
Baseline								
Mean (SD) Sitting DBP (mm Hg)	76.4 (8.24)	76.4 (9.28)	75.3 (9.17)	76.3 (8.48)	77.4 (9.83)	76.2 (8.37)	76.7 (9.06)	76.4 (8.77)
Baseline Pulse Rate (beats/minute)	73.5 (10.88)	74.3 (10.85)	72.4 (11.60)	75.5 (10.87)	74.6 (11.59)	74.3 (11.05)	75.2 (11.17)	74.9 (11.54)

	Study 309			Study 310			Study 312	
	Placebo (N = 268)	SOTA 200 mg (N = 263)	SOTA 400 mg (N = 262)	Placebo (N = 258)	SOTA 200 mg (N = 261)	SOTA 400 mg (N = 263)	Placebo (N = 703)	SOTA 400 mg (N = 699)

[a] 2hr-postprandial glucose was evaluated only in the CGM population in Studies 309 and 310.

Numbers analysed

Table 11 - Summary of patient disposition for Studies 309, 310, and 312 (randomized population)

	Study 309			Study 310			Study 312	
	Placebo (N = 268) n (%)	SOTA 200 mg (N = 263) n (%)	SOTA 400 mg (N = 262) n (%)	Placebo (N = 258) n (%)	SOTA 200 mg (N = 261) n (%)	SOTA 400 mg (N = 263) n (%)	Placebo (N = 705) n (%)	SOTA 400 mg (N = 700) n (%)
Randomized	268 (100.0)	263 (100.0)	262 (100.0)	258 (100.0)	261 (100.0)	263 (100.0)	705 (100.0)	700 (100.0)
mITT Population	268 (100.0)	263 (100.0)	262 (100.0)	258 (100.0)	261 (100.0)	263 (100.0)	703 (99.7)	699 (99.9)
Completed 24 Weeks	235 (87.7)	240 (91.3)	236 (90.1)	236 (91.5)	239 (91.6)	240 (91.3)	624 (88.5)	605 (86.4)
Completed 52 Weeks	218 (81.3)	228 (86.7)	221 (84.4)	225 (87.2)	226 (86.6)	227 (86.3)	NA	NA

Table 12 - Summary of patient disposition for the ES1 pool and the ES2 pool (randomized population)

	ES1 Pool				ES2 Pool[a]	
	Placebo (N = 526) n (%)	SOTA 200 mg (N = 524) n (%)	SOTA 400 mg (N = 525) n (%)	All SOTA (N = 1049) n (%)	Placebo (N = 1231) n (%)	SOTA 400 mg (N = 1225) n (%)
Randomized	526 (100.0)	524 (100.0)	525 (100.0)	1049 (100.0)	1231 (100.0)	1225 (100.0)
mITT Population	526 (100.0)	524 (100.0)	525 (100.0)	1049 (100.0)	1229 (99.8)	1224 (99.9)
Completed 24 Weeks	471 (89.5)	479 (91.4)	476 (90.7)	955 (91.0)	1095 (89.0)	1081 (88.2)
Completed 52 Weeks	443 (84.2)	454 (86.6)	448 (85.3)	902 (86.0)	NA	NA

[a.] Duration included in the analyses of ES2 pooled population is 24 weeks.

Outcomes and estimation

Primary efficacy endpoint: change from Baseline to Week 24 in A1C

Change from Baseline to Week 24 in A1C was the primary efficacy endpoint in Studies 309 and 310, while it was the first secondary efficacy endpoint in Study 312. In all studies and all pools, the change from Baseline in all active groups and the difference versus placebo were statistically significant ($p < 0.001$) (Table 13).

The change from Baseline to Week 24, and LS mean differences in A1C (%) for ES1 and ES2 (mITT population) was consistent with individual Phase 3 study results. In the ES1 pool, the LS mean change from Baseline was -0.41% and -0.43% for sotagliflozin 200 mg and 400 mg, the Week 24 placebo-subtracted LS mean A1C reduction was -0.36% and -0.38%, respectively, ($p < 0.001$ for both). Similar results were observed for the ES2 pool at Week 24 (-0.43% for sotagliflozin 400 mg; $p < 0.001$).

Table 13 - Analysis of change from Baseline to Week 24 in A1C (%) in the Phase 3 studies (mITT population)

	Study 309			Study 310			Study 312	
	Placebo (N = 268)	SOTA 200 mg (N = 263)	SOTA 400 mg (N =262)	Placebo (N = 258)	SOTA 200 mg (N = 261)	SOTA 400 mg (N = 263)	Placebo (N = 703)	SOTA 400 mg (N = 699)
Screening								
Mean (SD)	8.21 (0.853)	8.26 (0.864)	8.20 (0.847)	8.42 (0.936)	8.35 (0.922)	8.38 (0.937)	8.44 (0.956)	8.48 (0.944)
Change from Screening at Baseline								
Mean (SD)	-0.66 (0.567)	-0.65 (0.538)	-0.64 (0.552)	-0.64 (0.644)	-0.61 (0.666)	-0.67 (0.548)	-0.23 (0.470)	-0.22 (0.553)
Baseline								
Mean (SD)	7.54 (0.712)	7.61 (0.735)	7.56 (0.724)	7.79 (0.881)	7.74 (0.806)	7.71 (0.819)	8.21 (0.921)	8.26 (0.965)
Week 24								
Mean (SD)	7.50 (0.755)	7.17 (0.713)	7.08 (0.725)	7.79 (0.927)	7.36 (0.889)	7.35 (0.906)	7.88 (1.031)	7.41 (0.952)
Change from Baseline at Week 24								
Mean (SD)	-0.06 (0.519)	-0.42 (0.570)	-0.49 (0.566)	-0.01 (0.654)	-0.39 (0.702)	-0.39 (0.654)	-0.31 (0.775)	-0.81 (0.783)
MMRM Model Statistics								
LS Mean (SE)	-0.07 (0.036)	-0.43 (0.036)	-0.48 (0.036)	-0.02 (0.044)	-0.39 (0.044)	-0.37 (0.043)	-0.33 (0.031)	-0.79 (0.032)
95% CLs for change from Baseline	(-0.14, -0.00)	(-0.50, -0.36)	(-0.56, -0.41)	(-0.11, 0.07)	(-0.47, -0.30)	(-0.46, -0.29)	(-0.39, -0.27)	(-0.85. -0.73)
p-value	0.038	<0.001	<0.001	0.63	<0.001	<0.001	<0.001	<0.001
Summary of Treatment Comparison								
LS Mean Difference (SE) from Placebo	NA	-0.36 (0.047)	-0.41 (0.047)	NA	-0.37 (0.058)	-0.35 (0.058)	NA	-0.46 (0.042)
95% CLs for Difference	NA	(-0.45, -0.27)	(-0.50, -0.32)	NA	(-0.48, -0.25)	(-0.47, -0.24)	NA	(-0.54, -0.38)
p-value	NA	<0.001	<0.001	NA	<0.001	<0.001	NA	<0.001

Secondary efficacy endpoints

Net benefit

Net benefit (defined as the proportion of patients with A1C <7.0% and no episode of SH and no episode of DKA from Randomization to Week 24) was the primary endpoint in Study 312, and it was the first secondary efficacy endpoint in Studies 309 and 310.

The proportion of patients with A1C <7.0% at Week 24 is the main component of this composite endpoint. At Week 24, the difference versus placebo for the responders in net benefit was statistically significant in all studies and all groups (p <0.001). Table 14 summarizes the results for the Phase 3 studies.

In the ES1 pool, the absolute difference compared to placebo at Week 24 was 14.0% for sotagliflozin 200 mg and 19.5% for sotagliflozin 400 mg (p <0.001 for both). Similar results were observed for the ES2 pool at Week 24 (16.0% difference from placebo for sotagliflozin 400 mg; p <0.001).

Table 14 - Analysis of net benefit at Week 24 for the Phase 3 Studies (mITT population)

	Study 309			Study 310			Study 312	
	Placebo (N = 268)	SOTA 200 mg (N = 263)	SOTA 400 mg (N = 262)	Placebo (N = 258)	SOTA 200 mg (N = 261	SOTA 400 mg (N = 263)	Placebo (N = 703)	SOTA 400 mg (N = 699)
Components of Net Benefit								
A1C <7.0% at Baseline, n (%)	51 (19.0)	50 (19.0)	51 (19.5)	44 (17.1)	50 (19.2)	46 (17.5)	31 (4.4)	29 (4.1)
A1C <7.0% at Week 24, n (%)	61 (22.8)	97 (36.9)	123 (46.9)	39 (15.1)	87 (33.3)	89 (33.8)	111 (15.8)	207 (29.6)
A1C <7.0% at Week 24 and No SH, n (%)	58 (21.6)	89 (33.8)	117 (44.7)	39 (15.1)	83 (31.8)	85 (32.3)	107 (15.2)	202 (28.9)
A1C <7.0% at Week 24 and No DKA from randomization to Week 24, n (%)	61 (22.8)	96 (36.5)	120 (45.8)	39 (15.1)	86 (33.0)	89 (33.8)	111 (15.8)	204 (29.2)
Analysis of Net Benefit at Week 24								
A1C <7.0% at Week 24 and no SH and no DKA from randomization to Week 24								
Responders, n (%)	58 (21.6)	88 (33.5)	114 (43.5)	39 (15.1)	82 (31.4)	85 (32.3)	107 (15.2)	200 (28.6)
Net benefit difference versus placebo	NA	11.8	21.9	NA	16.3	17.2	NA	13.4
95% CI	NA	(4.28, 19.36)	(14.10, 29.64)	NA	(9.17, 23.43)	(10.06, 24.35)	NA	(9.12, 17.67)
p-value	NA	0.002	<0.001	NA	<0.001	<0.001	NA	<0.001

Postprandial glucose

Two-hour PPG after a standardized mixed meal was evaluated in patients participating in the CGM sub-study of Studies 309 and 310 and is primarily evaluated in the ES1 pool (Table 15).

Table 15 - Analysis of change from Baseline to Week 24 in 2-hour postprandial glucose (mg/dL) in the ES1 Pool (mITT CGM population)

	Placebo (N = 93)	SOTA 200 mg (N = 89)	SOTA 400 mg (N = 96)
Baseline			
Mean (SD)	229.8 (98.88)	211.5 (99.15)	209.7 (85.69)
Week 24			
Mean (SD)	215.1 (86.95)	181.8 (79.11)	171.3 (62.86)
Median (Min, Max)	225.0 (50, 409)	173.0 (58, 479)	170.0 (43, 339)
Change from Baseline at Week 24			
Mean (SD)	-9.7 (110.26)	-39.0 (87.38)	-35.0 (84.53)
ANCOVA Model; Statistics			
LS Mean (SE)	-7.9 (9.38)	-42.7 (9.66)	-48.8 (9.10)
95% CLs for Difference	(-26.4, 10.6)	(-61.7, -23.6)	(-66.8, -30.9)
p-value	0.40	<0.001	<0.001
Summary of Treatment Comparison			
LS Mean Difference (SE) from Placebo	NA	-34.8 (11.85)	-41.0 (11.50)
95% CLs for Difference	NA	(-58.1, -11.4)	(-63.6, -18.3)
p-value	NA	0.004	<0.001

Body weight

More than 70% of patients included in the Phase 3 studies were overweight or obese. Table 16 summarizes the change from Baseline to Week 24 in body weight in the Phase 3 studies.

Pooled analyses showed results consistent with the individual Phase 3 studies. In the ES1 pool, the LS mean change from Baseline at Week 24 was -1.70 kg and -2.55 kg for sotagliflozin 200 mg and 400 mg, respectively. The LS mean difference from placebo in body weight change at Week 24 was -2.17 for 200 mg and -3.02 kg for 400 mg respectively (p <0.001 for both). Similar results were observed for the ES2 pool at Week 24 (-2.99 kg LS mean difference from placebo for sotagliflozin 400 mg; p <0.001). In ES1, 18.70% (200 mg) and 23.81% (400 mg) of patients had a weight loss >5% at Week 24 compared to 4.18% with placebo (p <0.001 for both doses).

Table 16 - Analysis of change from Baseline to Week 24 in absolute body weight (kg) in Phase 3 Studies (mITT population)

	Study 309			Study 310			Study 312	
	Placebo (N = 268)	SOTA 200 mg (N = 263)	SOTA 400 mg (N = 262)	Placebo (N = 258)	SOTA 200 mg (N = 261)	SOTA 400 mg (N = 263)	Placebo (N = 703)	SOTA 400 mg (N = 699)
Screening								
Mean (SD)	86.39 (17.554)	86.01 (18.291)	85.76 (17.900)	80.46 (16.685)	81.25 (17.146)	81.28 (17.376)	81.07 (16.901)	82.11 (17.039)
Change from Screening at Baseline								
Mean (SD)	0.90 (1.894)	0.95 (2.190)	0.74 (1.904)	0.62 (1.925)	0.69 (1.867)	0.68 (2.072)	0.48 (1.546)	0.30 (1.530)
Baseline								
Mean (SD)	87.30 (17.709)	86.96 (18.539)	86.50 (18.004)	81.08 (16.857)	81.93 (17.386)	81.97 (17.963)	81.55 (17.032)	82.40 (17.131)
Week 24								
Mean (SD)	87.91 (17.665)	85.00 (18.494)	84.15 (17.680)	81.48 (16.978)	80.05 (17.384)	80.09 (17.919)	82.70 (17.513)	80.19 (17.017)
Change from Baseline at Week 24								
Mean (SD)	0.78 (2.745)	-1.68 (2.928)	-2.72 (2.863)	0.17 (2.684)	-1.88 (2.990)	-2.40 (3.373)	0.71 (2.924)	-2.33 (3.044)
MMRM Model Statistics								
LS mean (SE)	0.78 (0.187)	-1.57 (0.188)	-2.67 (0.188)	0.11 (0.201)	-1.88 (0.200))	-2.47 (0.199)	0.77 (0.122)	-2.21 (0.122)
95% CLs for change from Baseline	(0.41, 1.15)	(-1.94, -1.20)	(-3.04, -2.30)	(-0.29, 0.50)	(-2.27, -1.49)	(-2.86, -2.08)	(0.53, 1.01)	(-2.45, -1.97)
p-value	<0.001	<0.001	<0.001	0.60	<0.001	<0.001	<0.001	<0.001
Summary of treatment comparison								
LS mean difference (SE) from Placebo	NA	-2.35 (0.256)	-3.45 (0.256)	NA	-1.98 (0.276)	-2.58 (0.276)	NA	-2.98 (0.166)
95% CLs for difference	NA	(-2.85, -1.85)	(-3.95, -2.94)	NA	(-2.53, -1.44)	(-3.12, -2.04)	NA	(-3.31, -2.66)
p-value	NA	<0.001	<0.001	NA	<0.001	<0.001	NA	<0.001

Mean daily insulin dose

In Studies 309 and 310, the mean total daily insulin dose at Screening ranged between 58.7 and 64.0 IU/day. During the 6-week Run-in Period with insulin optimization, the mean Baseline total daily insulin dose increased up to 60.3 to 66.8 IU/day, with individual doses ranging between 11.9 and 290.0 IU/day.

In Study 312 (conducted without insulin optimization), the mean total daily insulin dose at Baseline was approximately 57 IU/day, with individual doses ranging between 6.5 and 253.0 IU/day.

Because of the high range of insulin dose expressed as IU/day at Baseline, the changes from Baseline in insulin doses are mainly expressed as percent change from Baseline. While change in bolus insulin dose at Week 24 was the secondary endpoint, results for basal and total insulin dose are also presented here for completeness.

Daily bolus insulin dose

In Studies 309 and 310, the mean Baseline bolus insulin dose after the 6-week Run-in Period with insulin optimization ranged between 30.3 and 32.1 IU/day. In the placebo groups, a further LS mean increase from Baseline of +3.9% and +5.9%, respectively was observed at Week 24. In the sotagliflozin groups, a LS mean decrease was observed, ranging between -1.8% and -10.5%, in parallel of an improvement in glucose control. In Studies 309 and 310, the LS mean difference from placebo was -5.7% (p = 0.12) and -12.9% (p <0.001) with sotagliflozin 200 mg; it was -12.7% and -16.4% (both p <0.001) with sotagliflozin 400 mg (Figure 14 and Figure 15).

Similar results were observed in Study 312, with an LS mean increase of +6.6% in the placebo group and a LS mean decrease of -5.7% in the sotagliflozin 400 mg group. The LS mean difference from placebo at Week 24 was -12.3% (p <0.001) (Figure 16).

Figure 14, Figure 15, and Figure 16 below provide mean percent change in Total, Basal, and Bolus insulin doses at Week 24 observed in Studies 309, 310, and 312, respectively.

Figure 14 - LS mean percent change in total, basal and bolus insulin doses at Week 24 in Study 309 (mITT population)

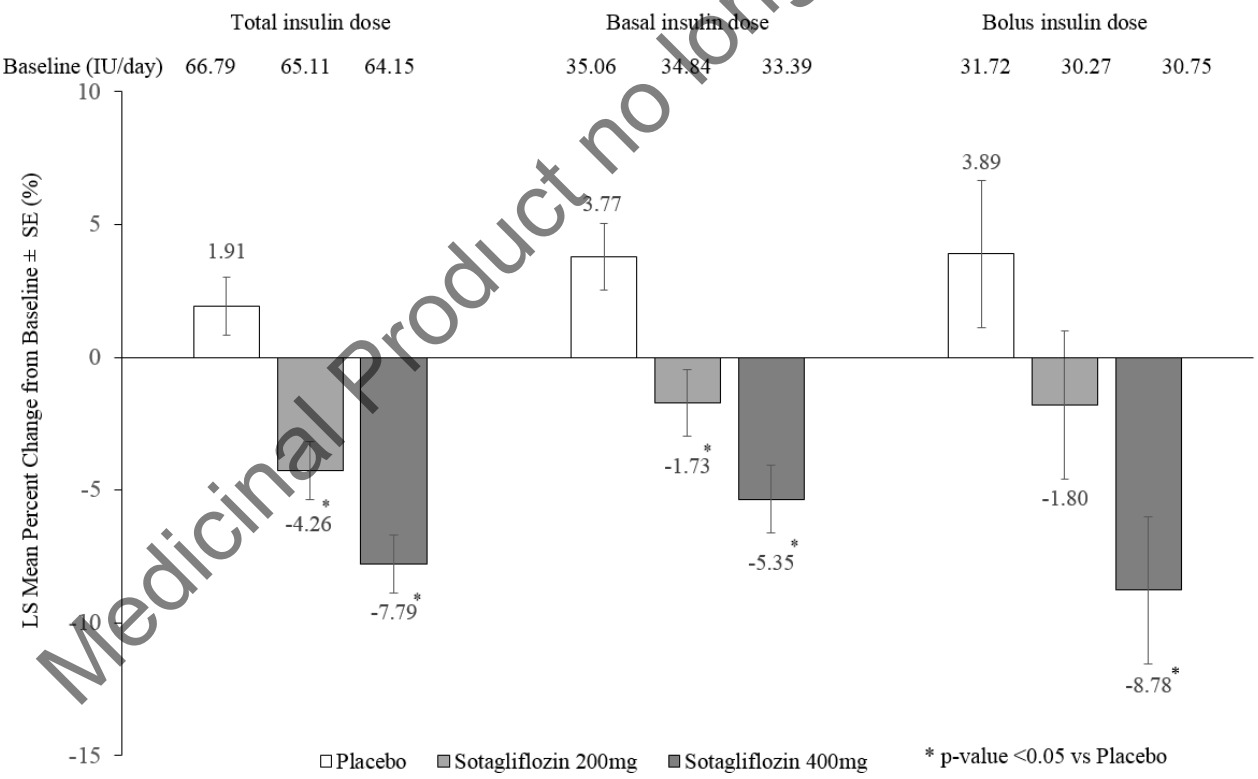


Figure 15 - LS mean percent change in total, basal and bolus insulin doses at Week 24 in Study 310 (mITT population)

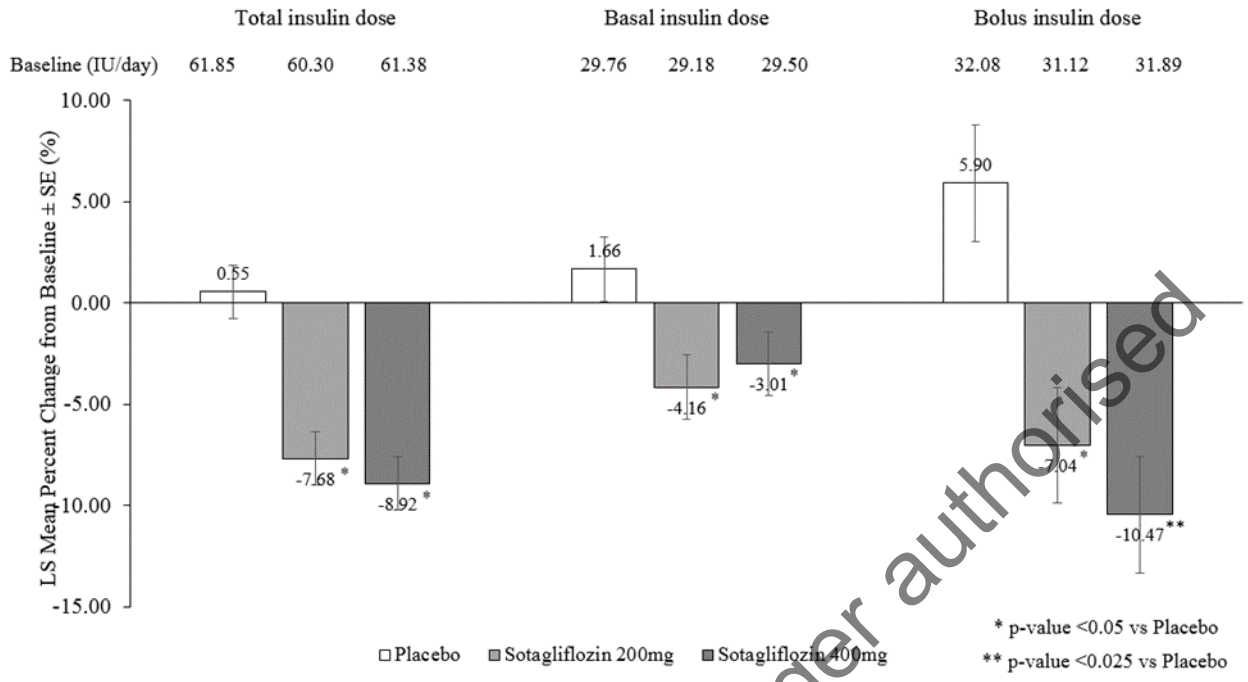
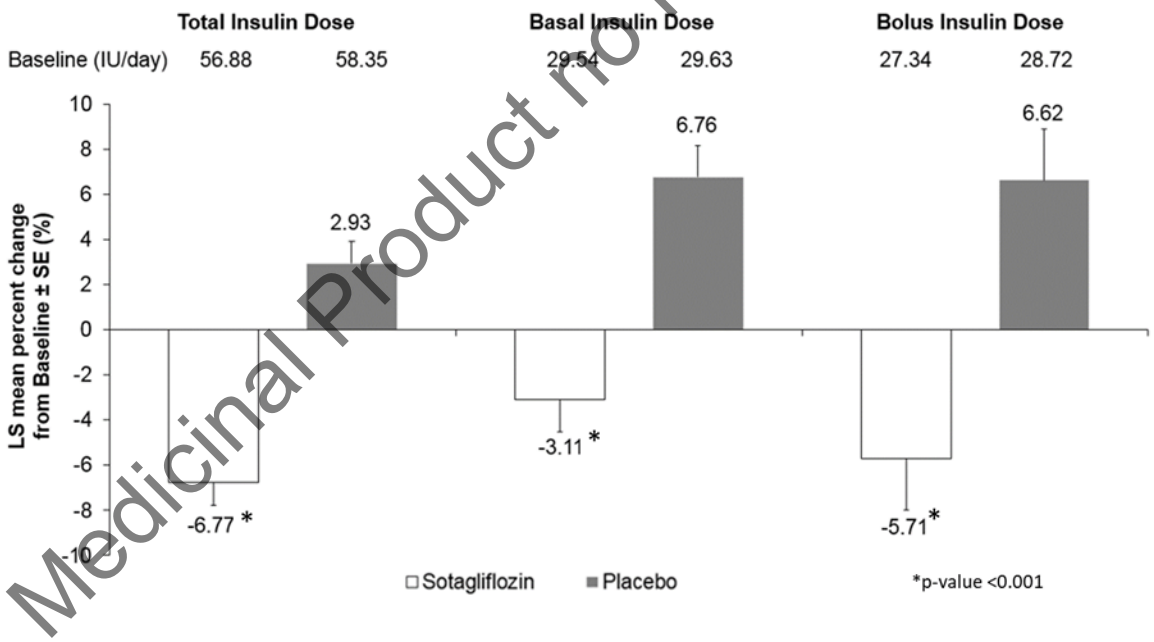


Figure 16 - LS mean percent change in total, basal and bolus insulin doses at Week 24 in Study 312 (mITT population)



The analysis of percent change from Baseline to Week 24 in mean daily bolus insulin dose in the ES1 and ES2 pools (mITT population) showed results consistent with the individual Phase 3 studies. In the ES1 pool, the Week 24 LS mean difference from placebo was -9.29% and -14.39% for sotagliflozin 200 mg and 400 mg ($p < 0.001$ for both). Similar results were observed for the ES2 pool at Week 24 (-13.27% LS mean difference from placebo for sotagliflozin 400 mg; $p < 0.001$).

Daily basal insulin dose

In Studies 309 and 310, the mean Baseline basal insulin dose after insulin optimization Run-in ranged between 29.2 and 35.1 IU/day. In the placebo groups, a further LS mean increase at Week 24 of +3.8%

and +1.7% from Baseline was observed, showing that insulin optimization was maintained during the study. In the sotagliflozin groups, a slight LS mean decrease was observed, ranging between -1.7% and -5.4%, in parallel with an improvement in glucose control. The LS mean difference from placebo with sotagliflozin ranged between -4.7% (p = 0.030) and -9.1% (p <0.001) (Figure 14 and Figure 15).

Similar results were observed in Study 312 with a LS mean increase of +6.8% in the placebo group and a decrease of -3.1% in the sotagliflozin 400 mg group. The LS mean difference from placebo at Week 24 was -9.9%; p <0.001 (Figure 16).

Consistent results were observed in the ES1 pool (Week 24 placebo-subtracted LS mean reduction of -5.7% and of -6.9% for the sotagliflozin 200 mg and 400 mg groups; p <0.001 for both) and for the ES2 pool at Week 24 (-8.6% LS mean difference from placebo for sotagliflozin 400 mg; p <0.001).

Total daily insulin dose

Overall, a slight but statistically significant decrease in the mean total insulin dose was observed, consistent across the Phase 3 program. In all 3 Phase 3 studies the pattern of total insulin dose reductions was just under 10% compared to placebo, with the percent reductions being somewhat greater for bolus than basal insulin (Figure 14, Figure 15 and Figure 16).

Consistent results were observed in the ES1 pool (Week 24 placebo-subtracted LS mean reduction -7.2% and -9.6% for the sotagliflozin 200 mg and 400 mg groups; p <0.001 for both) and for the ES2 pool at Week 24 (-9.7% LS mean difference from placebo for sotagliflozin 400 mg; p <0.001).

Fasting plasma glucose

At Baseline, the mean FPG was between 148.2 and 165.5 mg/dL in the 3 Phase 3 studies. At Week 24, the LS mean difference from placebo in FPG was statistically significant for all sotagliflozin groups, ranging from -9.8 to -25.7 mg/dL (p <0.001 for all groups with the exception of sotagliflozin 200 mg in Study 309 [p = 0.036]).

Results for the ES1 and ES2 pools were consistent with the Phase 3 study results. In the ES1 pool at Week 24, the LS mean difference from placebo was -15.7 mg/dL and -21.4 mg/dL for the sotagliflozin 200 mg and 400 mg (p <0.001 for both) and for the ES2 pool at Week 24, the LS mean difference from placebo was -22.3 mg/dL with sotagliflozin 400 mg (p <0.001).

Patient reported outcomes

Diabetes treatment satisfaction as measured by DTSQs

The change from Baseline to Week 24 in DTSQs scores was analysed in Studies 309 and 310. The DTSQs total scores range from 0 to 36, with higher scores indicating higher satisfaction. The LS mean difference compared to placebo ranged between +1.7 and +2.5 in all sotagliflozin groups (all p <0.001), indicating an improved satisfaction with sotagliflozin.

The DTSQs responder rate (defined as a change in score of 3 or more as threshold) for the 200 mg and 400 mg sotagliflozin groups were significantly higher (p <0.005) for both groups compared to placebo in both Studies 309 and 310. In Study 309, the responder rates for the 200 mg and 400 mg doses were 53.7% and 52.0%, respectively, compared with 27.9% for placebo. In Study 310, the responder rates for the 200 mg and 400 mg doses were 40.9% and 43.0%, respectively, compared with 28.8% in the placebo.

Diabetes distress as measured by 2-item DDS2 scores

The change from Baseline to Week 24 in DDS2 scores was analysed in Studies 309 and 310. The DDS2 is a validated 2-item diabetes distress screening instrument requesting respondents to rate, on a 6-point scale, the degree of their distress. A higher score indicates higher distress. At Week 24, the LS mean

difference compared to placebo ranged between -0.3 (p = 0.025) and -0.8 (p <0.001) in all sotagliflozin groups, indicating a lower distress with sotagliflozin.

Other efficacy endpoints

Systolic blood pressure

Changes in SBP were evaluated in Studies 309 and 310 at Week 12, consistent with protocol recommendation to keep doses of antihypertensive medications stable until Week 12 to allow for appropriate blood pressure assessment. For Study 312, the SBP evaluation was performed at Week 16 for similar reasons.

Modest reductions in SBP were observed at Week 12 for the overall population for both sotagliflozin doses compared to placebo in all Phase 3 studies as noted in Table 17. Reductions in SBP were maintained at Week 24 for both sotagliflozin doses in all Phase 3 studies.

Consistent results were observed for change in SBP in the overall population in the pooled ES1 population at Week 12, with a placebo-adjusted change in SBP of -2 mmHg (95%CI -3.2, -0.7) in the 200 mg group and -3.5 mmHg (95%CI -4.7, -2.3) in the 400 mg group. Reductions in SBP were maintained at Week 24 for both sotagliflozin doses.

Table 17 - Change from Baseline in systolic blood pressure (mm Hg) at Week 12 in the Studies 309 and 310 and at Week 16 in Study 312 in the overall population (mITT population)

	Study 309			Study 310			Study 312	
	Placebo (N = 268)	SOTA 200 mg (N = 263)	SOTA 400 mg (N = 262)	Placebo (N = 258)	SOTA 200 mg (N = 261)	SOTA 400 mg (N = 263)	Placebo (N = 703)	SOTA 400 mg (N = 699)
Baseline								
Mean (SD)	120.9 (13.47)	120.0 (14.84)	119.5 (14.73)	123.1 (15.53)	123.0 (15.08)	123.1 (13.69)	121.8 (14.82)	122.0 (15.25)
Week 12 (309 and 310) Week 16 (312)								
Mean (SD)	121.2 (13.25)	117.2 (13.89)	116.6 (12.99)	121.6 (14.74)	121.4 (14.50)	118.3 (13.54)	122.5 (14.83)	118.7 (14.47)
Change from Baseline at Week 12 for 309 and 310; at Week 16 for 312								
Mean (SD)	0.6 (10.89)	-2.6 (12.20)	-3.3 (10.27)	-1.8 (10.07)	-2.2 (11.59)	-4.8 (10.81)	0.5 (11.36)	-3.3 (11.31)
MMRM Model; Statistics								
LS Mean (SE)	1.0 (0.66)	-2.5 (0.67)	-3.2 (0.66)	-2.4 (0.68)	-2.8 (0.67)	-5.2 (0.67)	0.3 (0.43)	-3.5 (0.44)
95% CLs for change from Baseline	(-0.3, 2.3)	(-3.8, -1.2)	(-4.5, -1.9)	(-3.7, -1.1)	(-4.1, -1.5)	(-6.5, -3.9)	(-0.6, 1.1)	(-4.4, -2.7)
p-value	0.14	<0.001	<0.001	<0.001	<0.001	<0.001	0.53	<0.001
Summary of Treatment Comparisons								
LS Mean Difference from Placebo	NA	-3.5 (0.88)	-4.2 (0.88)	NA	-0.4 (0.89)	-2.8 (0.89)	NA	-3.8 (0.57)
95% CLs for difference	NA	(-5.2, -1.8)	(-5.9, -2.4)	NA	(-2.2, 1.3)	(-4.6, -1.1)	NA	(-4.9, -2.7)
p-value	NA	<0.001	<0.001	NA	0.64	0.001	NA	<0.001

SBP results in subset of patients with Baseline SBP ≥130 mm Hg:

Change from Baseline at Week 16 in SBP in the subset of patients with Baseline SBP ≥130 mm Hg was a secondary efficacy endpoint in Study 312. The LS mean difference from placebo at Week 16 was -3.5 mm Hg (p = 0.002). The statistically significant effect was maintained at Week 24 (LS mean difference -3.6 mm Hg; (p = 0.003). SBP was also evaluated in the subset of patients with Baseline SBP ≥140 mm Hg. There were 84 patients in the placebo group and 98 patients in the sotagliflozin 400 mg group for evaluation in this subset. Statistically significant reductions in SBP at Week 16 of -6.5 mm Hg (p <0.001) were observed for this subset of patients.

In studies 309 and 310, Change from Baseline in SBP in the subset of patients with Baseline SBP ≥130 mm Hg was also evaluated at Week 12 and at Week 24. To increase precision of the analysis in this subpopulation, results are presented for the ES1 pool. The LS mean difference from placebo in SBP at Week 12 for sotagliflozin 200 mg and sotagliflozin 400 mg was -3.6 mm Hg (p = 0.011) and -5.3 mm Hg (p <0.001). The LS mean difference from placebo was maintained at Week 24 with SBP reduction of -3.1 mm Hg (p = 0.031) for sotagliflozin 200 mg and -3.2 mm Hg (p = 0.026) for sotagliflozin 400 mg.

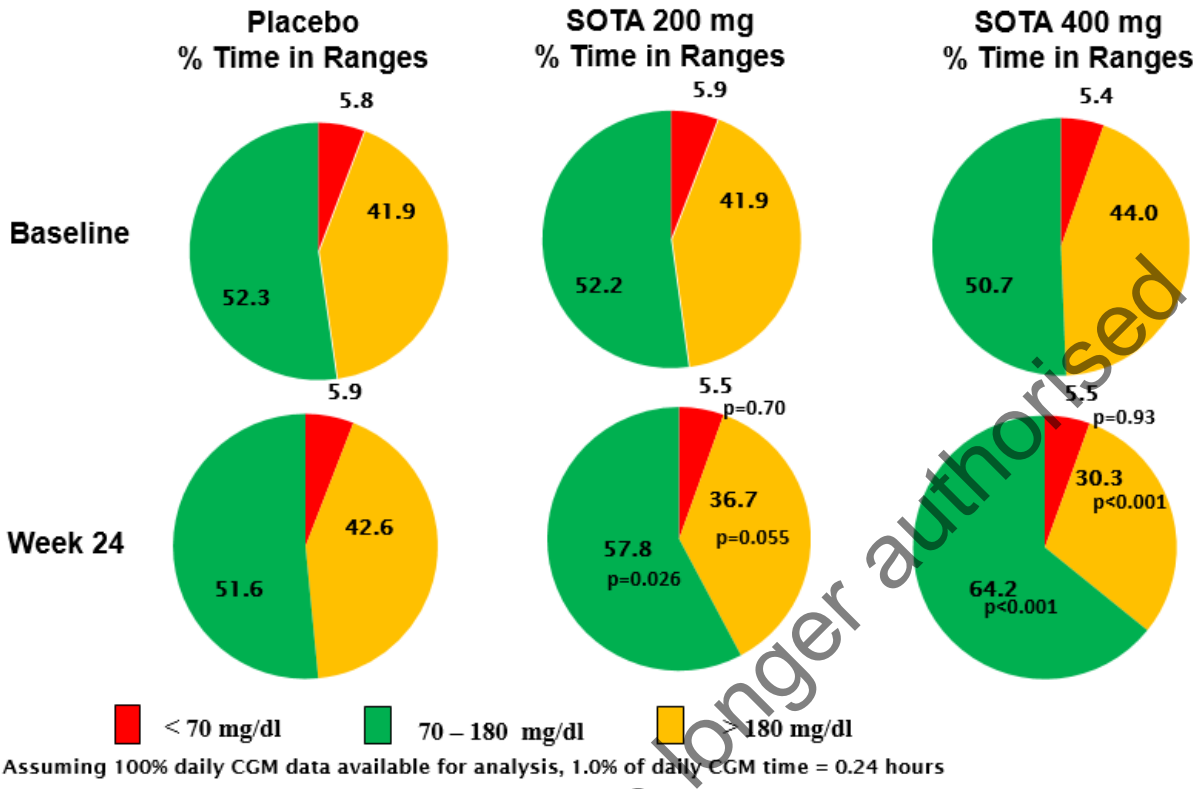
CGM sub-study

Pooled data from studies 309 and 310 was prespecified as the main evaluable dataset for the CGM substudy. A total of 278 patients were randomized, n = 93 placebo, n = 89 sotagliflozin 200 mg, n = 96 sotagliflozin 400 mg. Of the patients included, 49.2% were using CSII as their insulin delivery method.

Primary CGM efficacy endpoint: percent time spent inside target range (70-180 mg/dL)

The percent time spent inside the target range for CGM glucose (70-180 mg/dL) increased from 52.2% to 57.8% with sotagliflozin 200 mg and from 50.7% to 64.2% with sotagliflozin 400 mg from Baseline to Week 24, whereas no relevant change was observed for placebo. In both sotagliflozin dose groups, the increase in percent time in range was associated with a significant decrease in the percent time spent above 180 mg/dL, while the percent time spent below 70 mg/dL was not increased (Figure 17, Table 18). Assuming 100% daily CGM data is available for analysis, 1.0% of daily CGM time corresponds to approximately 15 minutes (0.24 hours).

Figure 17 - Percent time spent in range and outside range for CGM glucose in the pooled 309 and 310 studies (mITT CGM population)



p-values are for LS mean differences from placebo.

Secondary and other CGM endpoints

Secondary CGM endpoints confirmed that sotagliflozin 200 and 400 mg qd decreased the time spent in hyperglycaemia. Sotagliflozin therapy resulted in increased time in range with no increase in hypoglycaemia. The time spent in hypoglycaemia (<55 mg/dL or <70 mg/dL) was similar among treatment groups, although it was numerically lower with sotagliflozin.

Significant differences were also observed for various measures of glycaemic variability including mean daily glucose, SD and MAGE (Table 18).

Table 18 - CGM primary, key secondary and other endpoints (mITT CGM population)

	Pooled 309 and 310		
	Placebo (N = 93)	**SOTA 200 mg (N = 89)**	**SOTA 400 mg (N = 96)**
Percent Time of CGM Glucose 70-180 mg/dL			
Mean Baseline (SD)	52.301 (13.7950)	52.193 (15.2656)	50.656 (14.7623)
Mean Week 24 (SD)	51.577 (14.7206)	57.779 (15.8932)	64.172 (13.9760)
LS mean change from Baseline at Week 24 (SE)	-1.261 (1.8140)	4.088 (1.8017)	10.448 (1.6964)
95% CLs for change from Baseline	(-4.836, 2.314)	(0.537, 7.638)	(7.104, 13.791)
p-value	0.49	0.024	<0.001
LS mean difference (SE) from Placebo	NA	5.349 (2.3883)	11.709 (2.3159)
95% CLs for difference	NA	(0.639, 10.059)	(7.141, 16.276)
p-value	NA	0.026	<0.001

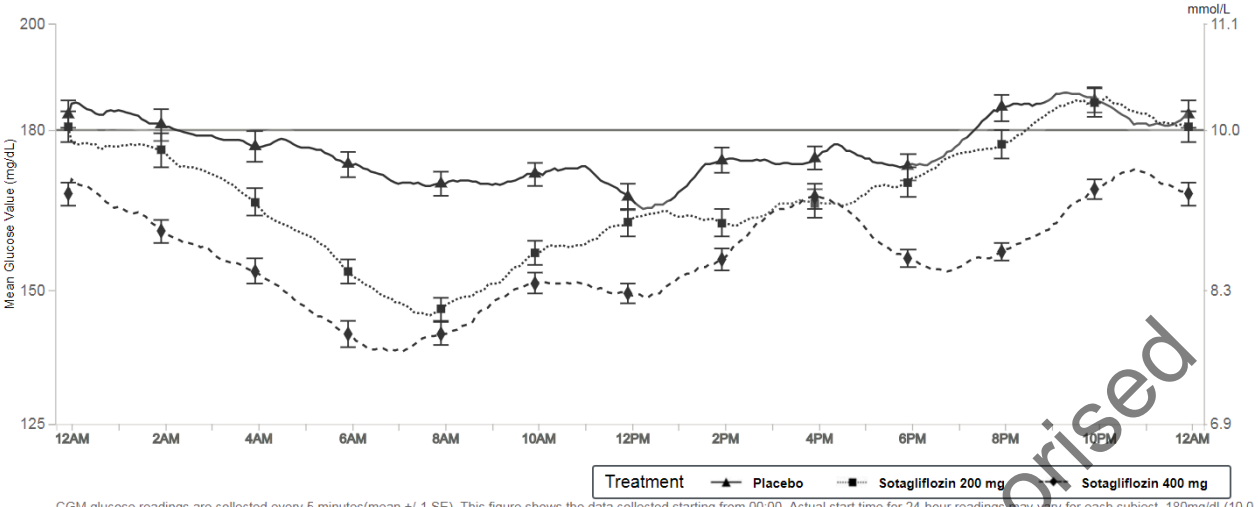
	Pooled 309 and 310		
	Placebo (N = 93)	**SOTA 200 mg (N = 89)**	**SOTA 400 mg (N = 96)**
Percent Time of CGM Glucose <55 mg/dL			
LS mean difference (SE) from Placebo	NA	-0.161 (0.4953)	-0.441 (0.4801)
95% CLs for difference	NA	(-1.137, 0.816)	(-1.388, 0.505)
p-value	NA	0.75	0.36
Percent Time of CGM Glucose <70 mg/dL			
LS mean difference (SE) from Placebo	NA	-0.330 (0.8618)	-0.068 (0.8375)
95% CLs for difference	NA	(-2.030, 1.369)	(-1.720, 1.583)
p-value	NA	0.70	0.93
Percent Time of CGM Glucose >180 mg/dL			
LS mean difference (SE) from Placebo	NA	-5.036 (2.6101)	-11.746 (2.5332)
95% CLs for difference	NA	(-10.183, 0.112)	(-16.742, -6.750)
p-value	NA	0.055	<0.001
Percent Time of CGM Glucose >250 mg/dL			
LS mean difference (SE) from Placebo	NA	-3.662 (1.8179)	-7.695 (1.7624)
95% CLs for difference	NA	(-7.248, -0.077)	(-11.171, -4.219)
p-value	NA	0.045	<0.001
Mean Daily Glucose (mg/dL)			
LS mean difference (SE) from Placebo	NA	-7.939 (4.7010)	-18.928 (4.5586)
95% CLs for difference	NA	(-17.210, 1.332)	(-27.918, -9.938)
p-value	NA	0.09	<0.001
MAGE			
LS mean difference (SE) from Placebo	NA	-12.702 (5.5164)	-22.111 (5.3718)
95% CLs for difference	NA	(-23.581, -1.822)	(-32.705, -11.517)
p-value	NA	0.022	<0.001
CGM Standard Deviation			
LS mean difference (SE) from Placebo	NA	-4.591 (2.2445)	-6.781 (2.1881)
95% CLs for difference	NA	(-9.017, -0.164)	(-11.097, -2.466)
p-value	NA	0.042	0.002

The CGM tracings of mean 24-hour glucose excursions

The CGM tracings of mean 24-hour glucose excursions (data collected from midnight [00:00]), consisting of interstitial glucose readings collected every 5 minutes from the week prior to the Week 24 visit are shown in Figure 18 below. Each line represents mean values from each treatment group (triangles = placebo [n=93]; squares = sotagliflozin 200 mg [n=89]; diamonds = sotagliflozin 400 mg [n=96]). Top of target CGM range = 10.0 mmol/L (180 mg/dL).

Compared with placebo the glycaemic curve is pulled down in both preprandial and postprandial periods. The decline in mean glucose value from 12 AM to 6 AM in sotagliflozin-treated patients was not associated with a significant increase in nocturnal hypoglycaemia.

Figure 18 - CGM tracings of mean 24-hour glucose excursions



CGM glucose readings are collected every 5 minutes(mean +/-1 SE). This figure shows the data collected starting from 00:00. Actual start time for 24-hour readings may vary for each subject. 180mg/dL(10.0 mmol/L) represents top of target CGM range.

DEXA sub-study

Pooled data from studies 309 and 310 were prespecified as the main evaluable dataset. The mITT population for the ES1 DEXA sub-study included 75 placebo patients, 84 sotagliflozin 200 mg patients, and 84 sotagliflozin 400 mg patients recruited from selected sites participating in the DEXA sub-study. Pooled fat mass and lean body mass data from the 309 and 310 DEXA substudies are provided below as the primary dataset for DEXA endpoints.

The primary objective for the pooled analysis was to compare the effect of sotagliflozin versus placebo on total fat mass at Week 24, and a decrease was noted for both sotagliflozin groups compared to an increase with placebo. The LS mean difference from placebo at Week 24 was -2188.12 g, p <0.001 for sotagliflozin 200 mg and -2515.95 g, p <0.001 for sotagliflozin 400 mg group. Similar results were observed expressing the data as percent total fat mass (LS mean difference -1.34%, p <0.001 for sotagliflozin 200 mg and -1.56%, p <0.001 for sotagliflozin 400 mg).

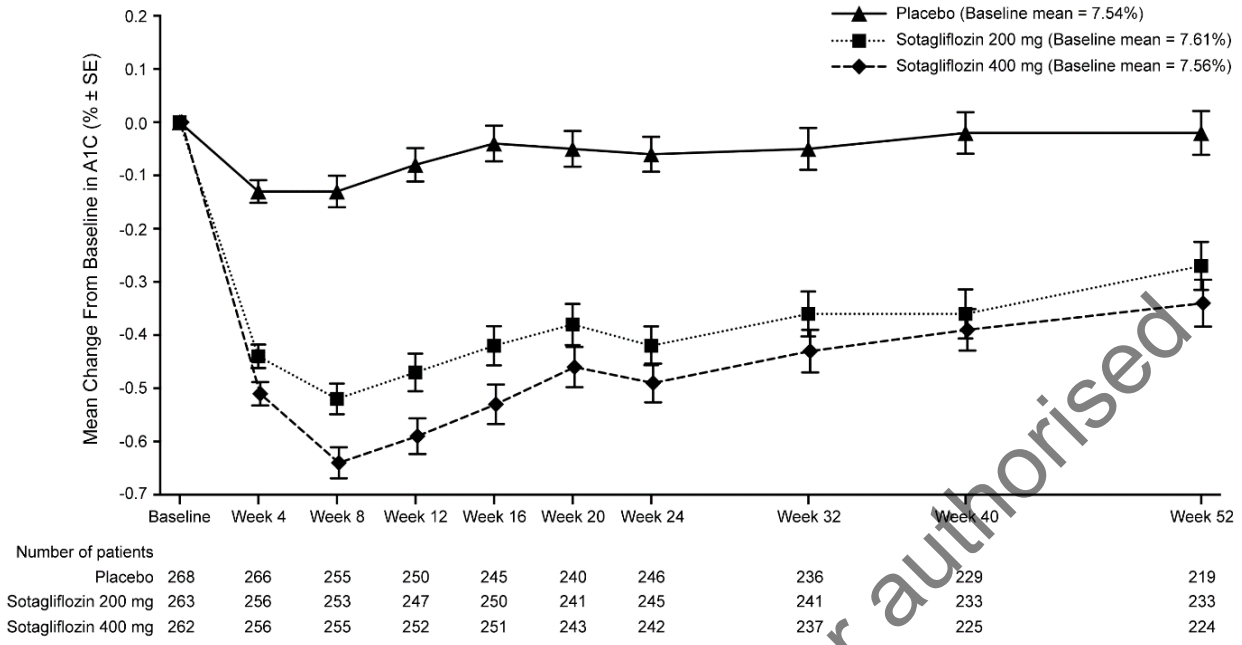
A modest but statistically significant decrease in total lean mass from Baseline to Week 24 was also noted for both sotagliflozin groups. The LS mean difference from placebo at Week 24 was -771.01 g, p = 0.015 for sotagliflozin 200 mg and -913.33 g, p = 0.003 for sotagliflozin 400 mg.

Ancillary analyses

Long-Term Effects on A1C

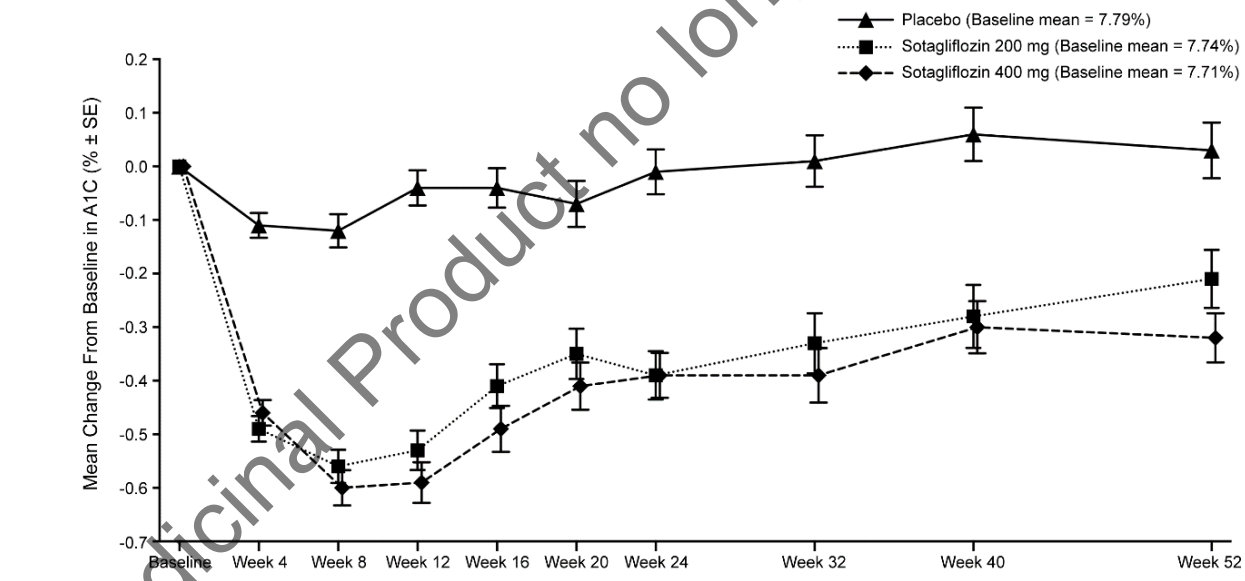
Figure 19 and Figure 20 show the kinetics of A1C during the course of Studies 309 and 310. Approximately 80% of the effect was observed during the first 4 weeks and the effect was maximum at Week 8 and Week 12. Although A1C then slightly increased in all groups, there was still a difference versus placebo at Week 52.

Figure 19 - Change in A1C from Baseline to Week 52 in Study 309 (mITT population)



Number of patients										
Placebo	268	266	255	250	245	240	246	236	229	219
Sotagliflozin 200 mg	263	256	253	247	250	241	245	241	233	233
Sotagliflozin 400 mg	262	256	255	252	251	243	242	237	225	224

Figure 20 - Change in A1C from Baseline to Week 52 in Study 310 (mITT population)



Number of patients										
Placebo	258	251	251	238	242	232	239	234	231	229
Sotagliflozin 200 mg	261	257	254	241	241	234	239	234	235	227
Sotagliflozin 400 mg	263	257	253	245	243	239	241	238	237	230

The LS mean difference from placebo remained statistically significant in all groups at Week 52, ranging between -0.21 to -0.32%. For the ES1 pool (mITT population), the LS mean difference from placebo was -0.23% for sotagliflozin 200 mg and -0.32% for sotagliflozin 400 mg (both p <0.001).

Long-Term Effects on Other Efficacy Parameters

Net benefit

The difference from placebo for the net benefit remained statistically significant in all groups in the Phase 3 Studies 309 and 310 at Week 52, ranging between 7.2 to 13.4% (Table 19). For the ES1 pool (mITT

population), the LS mean difference from placebo was 9.2% for sotagliflozin 200 mg and 12.8% for sotagliflozin 400 mg (both p <0.001).

Table 19 - Analysis of the components of net benefit and analysis of net benefit at Week 52 for Study 309 and Study 310 (mITT population)

	Study 309			Study 310		
	Placebo (N = 268)	**SOTA 200 mg (N = 263)**	**SOTA 400 mg (N = 262)**	**Placebo (N = 258)**	**SOTA 200 mg (N = 261)**	**SOTA 400 mg (N = 263)**
Components of Net Benefit						
Baseline						
A1C <7.0% at Baseline, n (%)	51 (19.0)	50 (19.0)	51 (19.5)	44 (17.1)	50 (19.2)	46 (17.5)
Week 52						
A1C <7.0% at Week 52, n (%)	56 (20.9)	79 (30.0)	93 (35.5)	40 (15.5)	71 (27.2)	73 (27.8)
A1C <7.0% at Week 52 and No SH from Baseline to Week 52, n (%)	51 (19.0)	72 (27.4)	87 (33.2)	37 (14.3)	67 (25.7)	70 (26.6)
A1C <7.0% at Week 52 and No DKA from Baseline to Week 52, n (%)	55 (20.5)	75 (28.5)	91 (34.7)	40 (15.5)	71 (27.2)	72 (27.4)
Analysis of Net Benefit at Week 52						
Patients with A1C <7.0% and no SH and no DKA						
Responders, n (%)	51 (19.0)	69 (26.2)	85 (32.4)	37 (14.3)	67 (25.7)	70 (26.6)
Treatment Comparison						
Net benefit difference in % responders versus placebo	NA	7.2	13.4	NA	11.3	12.3
95% CI	NA	(0.11, 14.30)	(6.05, 20.78)	NA	(4.52, 18.14)	(5.43, 19.12)
p-value	NA	0.049	<0.001	NA	0.001	<0.001

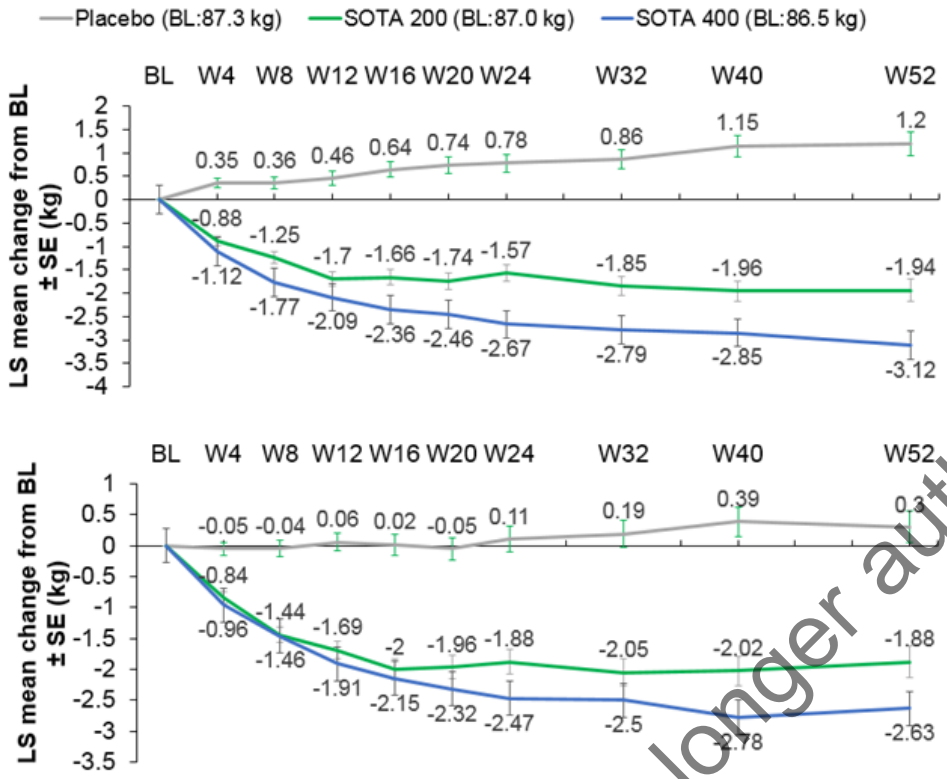
The subgroup analyses by demographics and Baseline factors at Week 52 confirmed that the LS mean difference from placebo at Week 52 was statistically significant at both doses in all subgroups of sufficient size.

Body weight

Figure 21 shows the kinetics of body weight reduction during the course of Studies 309 and 310. Weight reduction was progressive and sustained throughout the study. In Study 309, the Baseline mean body weight was 87.0 kg and 86.5 kg for patients on sotagliflozin 200 mg and 400 mg, respectively. Baseline mean body weight in Study 310 was 81.93 kg and 81.97 kg for sotagliflozin 200 mg and 400 mg, respectively. After Week 24, body weight continued to decrease or stabilized up to the end of the study.

The LS mean difference from placebo remained statistically significant in all groups at Week 52, ranging between -2.18 to -4.32 kg.

Figure 21 - Change from Baseline to Week 52 in absolute body weight (kg) in Study 309 (top with Baseline) and Study 310 (bottom) (mITT population)



For the ES1 pool (mITT population), the LS mean difference from placebo was -2.67 kg for sotagliflozin 200 mg and -3.64 kg for sotagliflozin 400 mg (both p <0.001). This corresponded to a -3.21% (200 mg) and -4.24% LS mean percent change from Baseline to Week 24 (both p <0.001).

Mean daily insulin dose

The LS mean difference from placebo in percent change in bolus insulin dose remained statistically significant in all groups in Study 309 and Study 310 at Week 52, ranging between -5.53 to -15.63%.

For the ES1 pool (mITT population), the LS mean difference from placebo in percent change in bolus insulin dose was -6.63% for sotagliflozin 200 mg (p = 0.037) and -13.73% for sotagliflozin 400 mg (p <0.001).

Similar results were observed for the mean daily basal insulin dose and for the mean daily total insulin dose, see Figure 22 and Figure 23.

Figure 22 - Percent change from Baseline to Week 52 in mean total daily insulin dose, basal insulin dose and bolus insulin dose (IU/day) in Study 309 (mITT population)

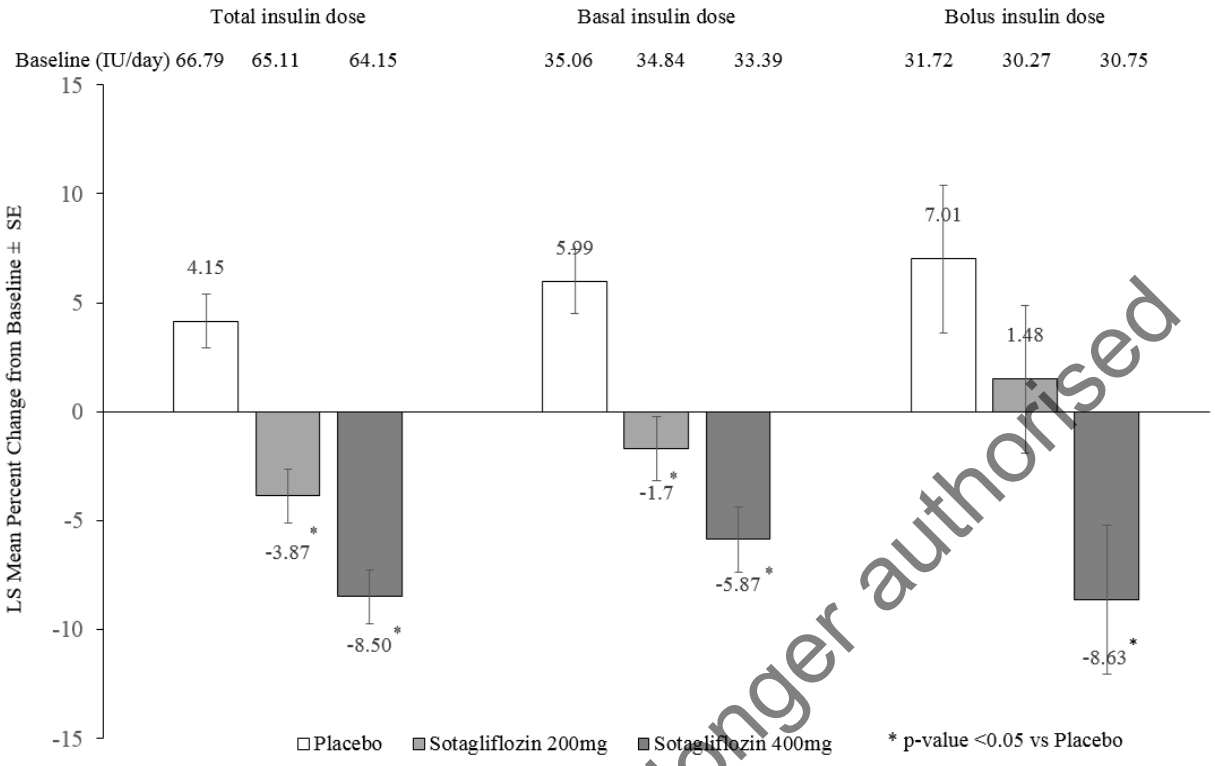
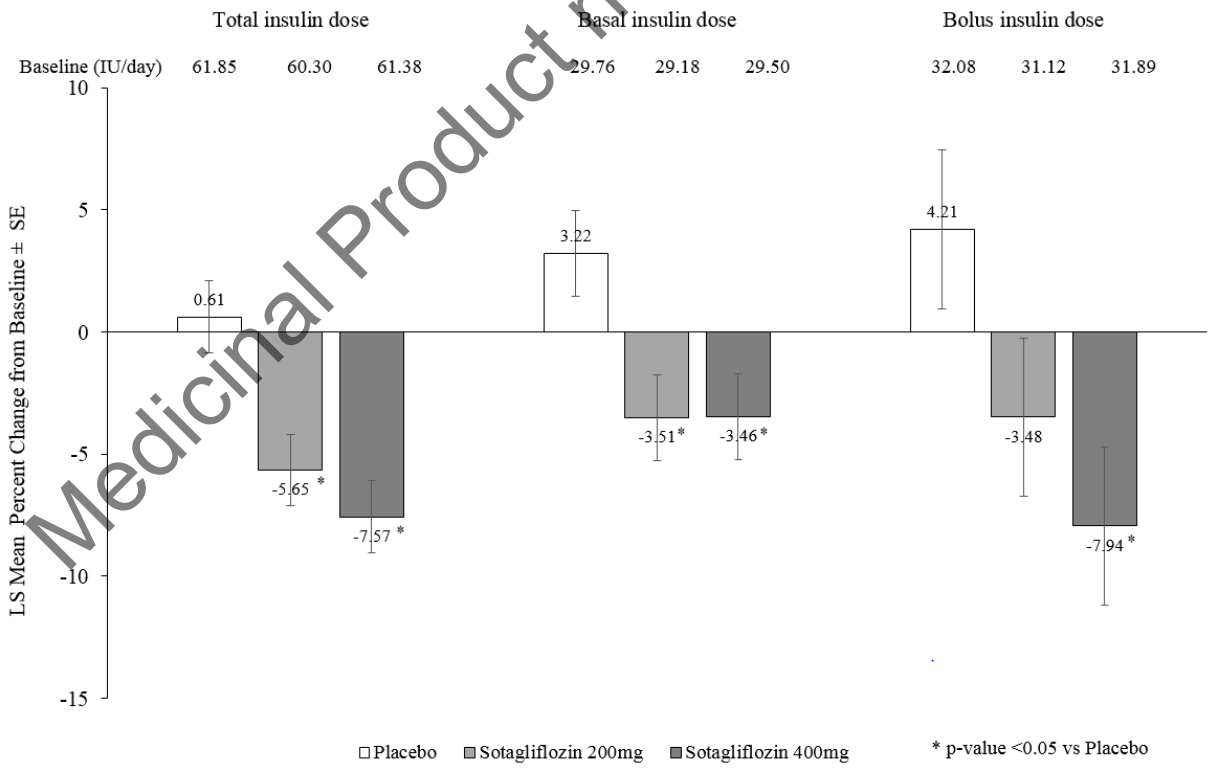


Figure 23 - Percent change from Baseline to Week 52 in mean total daily insulin dose, basal insulin dose, and bolus insulin dose (IU/day) in Study 310 (mITT population)



Fasting plasma glucose

Consistent with change from Baseline to Week 24, the LS mean difference from placebo remained statistically significant in most groups at Week 52 in Study 309 and Study 310, ranging between -4.9 to

-19.4 mg/dL. For the ES1 pool (mITT population), the LS mean difference from placebo was -8.7 mg/dL for sotagliflozin 200 mg (p = 0.032) and -17.7 mg/dL for sotagliflozin 400 mg (p <0.001).

Diabetes distress as measured by 2-item DDS2 scores

At Week 52, the LS mean difference in DDS2 scores compared to placebo remained statistically significant for sotagliflozin 400 mg in Study 310 and for the 2 doses in Study 309. For the ES1 pool (mITT population), the LS mean difference from placebo was statistically significant for sotagliflozin 200 mg (p = 0.003) and sotagliflozin 400 mg (p <0.001), which confirmed the persistence of the beneficial effect on patient distress.

Systolic blood pressure

Consistent with change from Baseline to Week 24, there was a modest but statistically significant decrease in the change from Baseline to Week 52 in SBP (mm Hg) in both sotagliflozin groups compared with placebo in Studies 309 and 310 and in the ES1 pool. In the ES1 pool, the LS mean difference from placebo at Week 52 was -2.9 mm Hg (p <0.001) for sotagliflozin 200 mg and -3.6 mm Hg (p <0.001) for sotagliflozin 400 mg.

DEXA substudy

The analysis of change from Baseline to Week 52 in DEXA total fat mass in the ES1 pool (mITT DEXA Population) demonstrated the continued persistence of efficacy of sotagliflozin. The LS mean difference (SE) from placebo at Week 52 was -1695.72 g (509.962), p = 0.001 for sotagliflozin 200 mg and -2123.19 g (499.843), p <0.001 for sotagliflozin 400 mg, confirming that the sustained beneficial effect on body weight was primarily due to a reduction in fat mass.

Summary of main efficacy results

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

Table 20 Summary of efficacy for trial 309

Title: A phase 3 randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety, efficacy, and tolerability of LX4211 as adjunct therapy in adult patients with type 1 diabetes mellitus who have inadequate glycemic control with insulin therapy			
Study identifier	LX4211.309		
Design	United States and Canada, randomized, double-blind, 3-arm, equal allocation, parallel-group		
	Duration of main treatment phase (Double-blind Core Treatment):		24 weeks
	Duration of run-in phase:		6 weeks
	Duration of long-term extension (Double-blind LTE):		24 weeks
	Total duration of treatment:		52 weeks
Hypothesis	Superiority		
Treatment groups 793 patients randomized	Placebo once daily		268 patients randomized
	Sotagliflozin 200 mg once daily		263 patients randomized
	Sotagliflozin 400 mg once daily		262 patients randomized
Endpoints and definitions	Primary endpoint	A1C (%)	Change from Baseline in A1C to Week 24

Title: A phase 3 randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety, efficacy, and tolerability of LX4211 as adjunct therapy in adult patients with type 1 diabetes mellitus who have inadequate glycemic control with insulin therapy					
Study identifier	LX4211.309				
	Key secondary endpoints	Net benefit	Proportion of patients with A1C <7.0% at Week 24 and no episode of severe hypoglycaemia or DKA during the main treatment phase		
		Body weight (kg)	Change from Baseline in body weight at Week 24		
		Bolus insulin dose (IU/day)	Change from Baseline in mean daily bolus insulin dose at Week 24		
		FPG (mg/dL)	Change from Baseline in FPG at Week 24		
Database lock	15 April 2017				
Results and Analysis					
Analysis description	**Primary and Key Secondary Analyses**				
Analysis population; time point description	mITT population (all randomized patients who took at least 1 dose of study drug); 24 weeks from Baseline (end of main treatment phase)				
Descriptive statistics and estimate variability	Treatment group		Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
	Number of patients		268	263	262
	A1C (%) change from Baseline: LSM (SE)		-0.07 (0.036) p = 0.038	-0.43 (0.036) p <0.001	-0.48 (0.036) p <0.001
	Net benefit (%)		21.6	33.5	43.5
	Body weight (kg) change from Baseline: LSM (SE)		0.78 (0.187) p <0.001	-1.57 (0.188) p <0.001	-2.67 (0.188) p <0.001
	Bolus insulin dose (IU/day) change from Baseline: LSM (SE)		-0.84 (0.688) p = 0.22	-2.33 (0.692) p <0.001	-4.13 (0.692) p <0.001
	FPG (mg/dL) change from Baseline: LSM (SE)		3.7 (3.45) p = 0.28	-6.1 (3.47) p = 0.08	-14.0 (3.48) p <0.001
Effect estimate per comparison			Comparison groups	Sotagliflozin 200 mg versus placebo	Sotagliflozin 400 mg versus placebo
	A1C (%) (primary endpoint)		LSM difference (SE)	-0.36 (0.047)	-0.41 (0.047)
			95% CI	-0.45, -0.27	-0.50, -0.32
			P-value	<0.001	<0.001
	Net benefit (%)		Difference	11.8	21.9
			95% CI	4.28, 19.36	14.10, 29.64
			P-value	0.002	<0.001
	Body weight (kg)		LSM difference (SE)	-2.35 (0.256)	-3.45 (0.256)
			95% CI	-2.85, -1.85	-3.95, -2.94
			P-value	<0.001	<0.001
	Bolus insulin dose (IU/day)		LSM difference (SE)	-1.50 (0.917)	-3.30 (0.916)
			95% CI	-3.30, 0.30	-5.09, -1.50

Title: A phase 3 randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety, efficacy, and tolerability of LX4211 as adjunct therapy in adult patients with type 1 diabetes mellitus who have inadequate glycemic control with insulin therapy				
Study identifier	LX4211.309			
		P-value	0.10	<0.001
	FPG (mg/dL)	LSM difference (SE)	-9.8 (4.67)	-17.8 (4.69)
		95% CI	-19.0, -0.7	-27.0, -8.6
		P-value	0.036	<0.001
Notes	The N for individual endpoints and time points may be less than the number randomized to the group. A1C = glycosylated hemoglobin (HbA1c); CI = confidence interval; FPG = fasting plasma glucose; IU = international unit; LSM = least squares mean; mITT = modified intent-to-treat; SE = standard error			

Table 21 Summary of efficacy for trial 310

Title: A phase 3 randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy, safety, and tolerability of LX4211 as adjunct therapy in adult patients with type 1 diabetes mellitus who have inadequate glycemic control with insulin therapy			
Study identifier	LX4211.310		
Design	Multinational, randomized, double-blind, 3-arm, equal allocation, parallel-group		
	Duration of main treatment phase (Double-blind Core Treatment):	24 weeks	
	Duration of run-in phase:	6 weeks	
	Duration of long-term extension (Double-blind LTE):	24 weeks	
	Total duration of treatment:	52 weeks	
Hypothesis	Superiority		
Treatment groups 782 patients randomized	Placebo once daily		258 patients randomized
	Sotagliflozin 200 mg once daily		261 patients randomized
	Sotagliflozin 400 mg once daily		263 patients randomized
Endpoints and definitions	Primary endpoint	A1C (%)	Change from Baseline in A1C to Week 24
	Key secondary endpoints	Net benefit	Proportion of patients with A1C <7.0% at Week 24 and no episode of severe hypoglycaemia or DKA during the main treatment phase
		Body weight (kg)	Change from Baseline in body weight at Week 24
		Bolus insulin dose (IU/day)	Change from Baseline in mean daily bolus insulin dose at Week 24
		FPG (mg/dL)	Change from Baseline in FPG at Week 24
Database lock	17 July 2017		
Results and Analysis			
Analysis description	**Primary and Key Secondary Analyses**		
Analysis population and time point description	mITT population (all randomized patients who took at least 1 dose of study drug); 24 weeks from Baseline (end of main treatment phase)		

Title: A phase 3 randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy, safety, and tolerability of LX4211 as adjunct therapy in adult patients with type 1 diabetes mellitus who have inadequate glycemic control with insulin therapy				
Study identifier	LX4211.310			
Descriptive statistics and estimate variability	Treatment group	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
	Number of patients	258	261	263
	A1C (%) change from Baseline: LSM (SE)	-0.02 (0.044) p = 0.63	-0.39 (0.044) p <0.001	-0.37 (0.043) p <0.001
	Net benefit (%)	15.1	31.4	32.3
	Body weight (kg) change from Baseline: LSM (SE)	0.11 (0.201) p = 0.60	-1.88 (0.200) p <0.001	-2.47 (0.199) p <0.001
	Bolus insulin dose (IU/day) change from Baseline: LSM (SE)	-1.19 (0.635) p = 0.06	-4.38 (0.636) p <0.001	-4.78 (0.634) p <0.001
	FPG (mg/dL) change from Baseline: LSM (SE)	8.8 (3.95) p = 0.026	-12.8 (3.97) p = 0.001	-16.9 (3.96) p <0.001
Effect estimate per comparison		Comparison groups	Sotagliflozin 200 mg versus placebo	Sotagliflozin 400 mg versus placebo
	A1C (%) (primary endpoint)	LSM difference (SE)	-0.37 (0.058)	-0.35 (0.058)
		95% CI	-0.48, -0.25	-0.47, -0.24
		P-value	<0.001	<0.001
	Net benefit (%)	Difference	16.3	17.2
		95% CI	9.17, 23.43	10.06, 24.35
		P-value	<0.001	<0.001
	Body weight (kg)	LSM difference (SE)	-1.98 (0.276)	-2.58 (0.276)
		95% CI	-2.53, -1.44	-3.12, -2.04
		P-value	<0.001	<0.001
	Bolus insulin dose (IU/day)	LSM difference (SE)	-3.20 (0.847)	-3.59 (0.845)
		95% CI	-4.86, -1.53	-5.25, -1.93
		P-value	<0.001	<0.001
	FPG (mg/dL)	LSM difference (SE)	-21.6 (5.38)	-25.7 (5.37)
		95% CI	-32.2, -11.0	-36.2, -15.1
		P-value	<0.001	<0.001
Notes	The N for individual endpoints and time points may be less than the number randomized to the group. A1C = glycosylated hemoglobin (HbA1c); CI = confidence interval; FPG = fasting plasma glucose; IU = international unit; LSM = least squares mean; mITT = modified intent-to-treat; SE = standard error			

Table 22 Summary of efficacy for trial 312

Title: A phase 3 randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the net clinical benefit of sotagliflozin as adjunct to insulin therapy in type 1 diabetes			
Study identifier	LX4211.312		
Design	Multinational, randomized, double-blind, 2-arm, equal allocation, parallel-group		
	Duration of main treatment phase (Double-blind):		24 weeks
	Duration of run-in phase:		2 weeks
	Total duration of treatment:		24 weeks
Hypothesis	Superiority		
Treatments groups 1405 patients randomized	Placebo once daily		705 patients randomized
	Sotagliflozin 400 mg once daily		700 patients randomized
Endpoints and definitions	Primary endpoint	Net benefit	Proportion of patients with A1C <7.0% at Week 24 and no episode of severe hypoglycaemia or DKA during the main treatment phase
	Key secondary endpoints	A1C (%)	Change from Baseline in A1C at Week 24
		Body weight (kg)	Change from Baseline in body weight at Week 24
		SBP (mm Hg)	Change from Baseline in SBP at Week 16 in subset of patients with Baseline SBP ≥130 mm Hg
		Bolus insulin dose (IU)	Change from Baseline in in mean daily bolus insulin dose at Week 24
Database lock	12 May 2017		
Results and Analysis			
Analysis description	**Primary and Key Secondary Analyses**		
Analysis population and time point description	mITT population (all randomized patients who took at least 1 dose of study drug); 24 weeks from Baseline (end of main treatment phase)		
Descriptive statistics and estimate variability	Treatment group	Placebo	Sotagliflozin 400 mg
	Number of patients	703	699
	Net benefit (%)	15.2	28.6
	A1C (%) change from Baseline: LSM difference (SE)	-0.33 (0.031) p <0.001	-0.79 (0.032) p <0.001
	Body weight (kg) change from Baseline: LSM difference (SE)	0.77 (0.122) p <0.001	-2.21 (0.122) p <0.001
	SBP (mm Hg) change from Baseline: LSM difference(SE)	Subset N=203 -5.7 (0.90) p <0.001	Subset N=203 -9.2 (0.92) p <0.001
	Bolus insulin dose (IU/day) change from Baseline: LSM difference (SE)	-1.09 (0.465) p = 0.020	-3.93 (0.470) p <0.001
Effect estimate per comparison		Comparison group	Sotagliflozin 400 mg versus placebo
	Net benefit (%) (primary endpoint)	Difference	13.4
		95% CI	8.97, 17.81

Title: A phase 3 randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the net clinical benefit of sotagliflozin as adjunct to insulin therapy in type 1 diabetes			
Study identifier	LX4211.312		
		P-value	<0.001
	A1C (%)	LSM difference (SE)	-0.46 (0.042)
		95% CI	-0.54, -0.38
		P-value	<0.001
	Body weight (kg)	LSM difference (SE)	-2.98 (0.166)
		95% CI	-3.31, -2.66
		P-value	<0.001
	SBP (mm Hg)	LSM difference (SE)	-3.5 (1.11)
		95% CI	-5.7, -1.3
		P-value	0.002
	Bolus insulin dose (IU/day)	LSM difference (SE)	-2.84 (0.614)
		95% CI	-4.05, -1.64
		P-value	<0.001
Notes	The N for individual endpoints and time points may be less than the number randomized to the group. A1C = glycosylated hemoglobin (HbA1c); CI = confidence interval; IU = international unit; LSM = least squares mean; mITT = modified intent-to-treat; SBP = systolic blood pressure; SE = standard error		

Clinical studies in special populations

No specific clinical studies have been conducted in special populations.

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	247 / 3574	18 / 3574	0 / 3574
Non Controlled trials	N/A	N/A	N/A

Analysis performed across trials (pooled analyses)

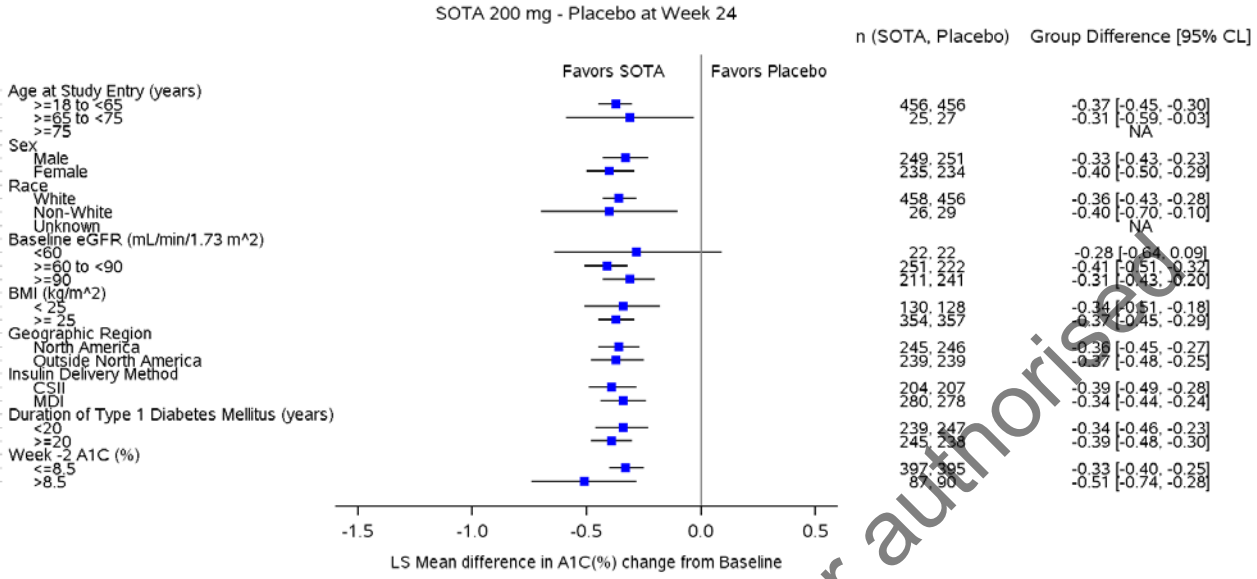
Subgroup analyses

In order to increase the precision of subgroup analyses on a larger dataset, a pooled analysis (ES1 and ES2) of A1C was planned.

A1C change by demographics and Baseline characteristics

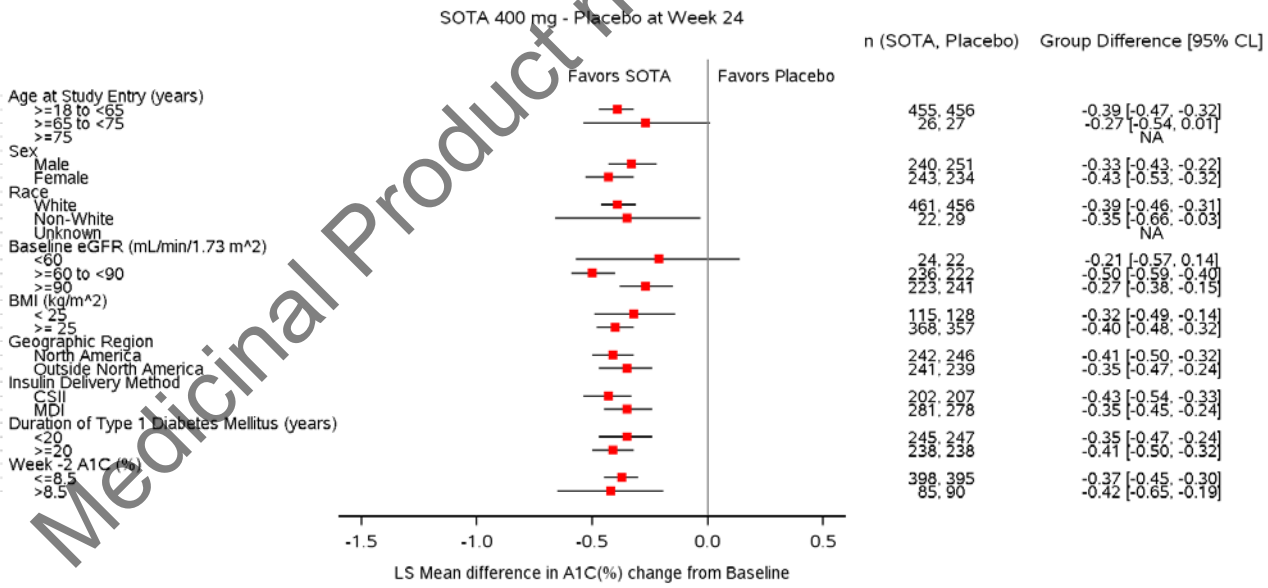
Overall, treatment effect was statistically significant in favour of sotagliflozin compared to placebo for each subgroup category in both the ES1 and ES2 pools. Figure 24 and Figure 25 summarize the analysis of the primary endpoint by demographic and Baseline characteristic subgroups for the ES1 pool (mITT population) for sotagliflozin 200 mg and 400 mg, respectively.

Figure 24 - Forest plot of difference in the LS mean change from Baseline to Week 24 in A1C (%) of sotagliflozin 200 mg compared to placebo by subgroups for ES1 pool (mITT population)



Note: The difference between the mean change from Baseline in A1C (%) and 95% CL estimated from MMRM models are plotted.

Figure 25 - Forest plot of difference in the LS mean change from Baseline to Week 24 in A1C (%) of sotagliflozin 400 mg compared to placebo by subgroups for ES1 pool (mITT population)



The effect of sotagliflozin on HbA1c was analysed by BMI <27 kg/m² and ≥27 kg/m² in the pooled 309/310 study dataset, a similar pattern was observed as when analysed by BMI <25 kg/m² and ≥25 kg/m².

Supportive study

Study 204

This was a Phase 2, multicenter, randomized double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of sotagliflozin 400 mg once daily before the first meal of the day in young-adult patients with T1DM who had poor glycaemic control on their current insulin regimen. Patients were randomly assigned (1:1 ratio) to receive sotagliflozin 400 mg (2 x 200-mg tablets) or placebo orally once daily for 12 weeks. Study drug was given in addition to the patient's insulin regimen. The randomization was stratified by insulin delivery method (CSII or MDI) and Week -4 A1C (≤10.0%, >10.0%). The primary efficacy endpoint was the change from Baseline to Week 12 in A1C for sotagliflozin 400 mg versus placebo. Eligible patients were young adults 18 to 30 years of age, with a confirmed diagnosis of T1DM at least 1 year prior to informed consent, and A1C ≥9.0%.

Patient disposition and demographics

A total of 87 patients were randomized to the study at 14 sites in the US: 44 patients to the placebo group and 43 patients to the sotagliflozin 400 mg group. Overall, 75 patients (35 on placebo and 40 on sotagliflozin) completed the study. Of the 85 patients in the mITT population, 45 (52.9%) were female and 40 (47.1%) male. The mean (SD) age at study entry was 22.3 (3.81) years. Of all patients in the mITT population, 46 (54.1%) received insulin via CSII and 39 (45.9%) received insulin via MDI; 37 (43.5%) had Week -4 A1C ≤10% and 48 (56.5%) had Week -4 A1C >10%. The mean (SD) age at T1DM diagnosis was 10.4 (5.84) years. Approximately 90% of all patients were diagnosed with T1DM before 18 years of age. Mean Baseline A1C values were 9.73% for the placebo group and 9.93% for the sotagliflozin group.

Efficacy results

For the primary endpoint, change from Baseline in A1C at Week 12, both the placebo group and the sotagliflozin 400 mg group showed a statistically significant LS mean reduction in A1C of -0.99% and -1.33%, respectively (both p <0.001). While the placebo-subtracted A1C reduction in the sotagliflozin 400 mg group reached statistical significance at Weeks 3, 6, and 9, the difference at Week 12 (-0.35%) did not achieve statistical significance. In the 2 subgroups of patients using CSII at Screening and patients with Screening (Week -4) A1C ≤10%, sotagliflozin 400 mg demonstrated larger, placebo-subtracted mean reductions in A1C of -0.60% and -0.75%, respectively.

Sotagliflozin demonstrated a change from Baseline at Week 12 in 2-hour PPG following a standardized Mixed Meal. The LS mean difference in 2-hour PPG between the placebo and sotagliflozin groups was -56.6 mg/dL (p = 0.001).

Patients in the sotagliflozin group showed numerically greater mean reductions in bolus, basal, and total insulin doses at Week 12 compared with placebo.

The change from Baseline at Week 12 for various CGM measures of glycaemic measures including percent time spent in the target blood glucose range was assessed. Patients treated with sotagliflozin achieved an increase from 33.1% at Baseline to 43.6% at Week 12 in the mean percent time spent in the target blood glucose range of 70-180 mg/dL as compared with a slight reduction from 33.5% to 32.9% for patients treated with placebo.

A difference was seen between sotagliflozin and placebo for the change from Baseline to Week 12 in body weight. The LS mean change from Baseline in body weight to Week 12 was 1.75 kg in the placebo group (p <0.001) and -0.62 kg in the sotagliflozin group (p = 0.12). The LS mean difference between the placebo and sotagliflozin groups in change from Baseline to Week 12 in absolute body weight was -2.37 kg (p <0.001).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Three phase 3 studies (studies 309, 310 and 312) provide the main support for the application. In addition, two dose response studies (studies 202 and 206) were submitted as well as a small supportive study (204).

Scientific Advice regarding the clinical development in T1DM was provided by the CHMP at several occasions. The advice given has in all essential aspects been followed except for the recommendation to specifically study patients with impaired renal function.

Most recommendations received were incorporated into the sotagliflozin Phase 3 T1DM studies:

1. A dose-ranging study (Study 206) was conducted to assess the safety and efficacy of qd dosing of 75 mg, 200 mg, or 400 mg versus placebo in T1DM.

2. The 309 and 310 studies included a 400 mg dose and the lower dose of 200 mg to include more than 1 dose in the Phase 3 clinical studies.

3. An insulin optimization period beginning 6-weeks prior to randomization in the 309 and 310 Phase 3 studies, which continued through the Core treatment period (Week 24) was included. Appropriateness of titration was assessed by an independent Insulin Dose Monitoring Committee (IDMC) in a blinded fashion. Insulin adjustment algorithms for pump and Multiple Daily Injections (MDI) (basal-bolus) regimen were provided to the Investigators as part of the site manual. These could be adapted per Investigator discretion.

4. Studies 309 and 310 were designed to evaluate the maintenance of efficacy over 12 months.

5. A plan to assess CV safety in the program was developed.

6. Events of Special Interest (EOSI) were included in the final protocols (adjudication of drug-induced liver injury [DILI], CV events, SH, and DKA [adjudication of DKA was expanded to include adjudication of metabolic acidosis]).

7. Assessment of effects on markers of bone metabolism and bone density were included.

8. Stratification according to baseline HbA1c was performed.

9. The exclusion criteria for DKA and SH were revised to be less restrictive.

10. A third Phase 3 study (Study 312) was conducted to increase safety exposure to sotagliflozin and meet ICH E1 guidelines requirements and to study the drug in a more real world setting.

A Follow-up CHMP Scientific Advice (EMEA/H/SA/2417/2/FU/1/2015) was requested in August 2015 to obtain agreement on the acceptability of the revised T1DM clinical development plan for sotagliflozin. The revised program was considered generally adequate by the CHMP and Phase 3 study designs and proposal for DKA monitoring were generally endorsed.

Overall, the recommendations from these meetings have been implemented in the program or were appropriately discussed in the dossier by the applicant. The CHMP Guideline (CPMP/EXP/1080/00 rev.1) “Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus” was also taken into account.

Study 202 was conducted in patients with T2DM on concomitant metformin treatment. Four different doses/dosing schedules were evaluated (75 mg, 200 mg, 200 mg BID and 400 mg). There was a clear dose response effect with regards to reduction in HbA1c and notably there was a numerically larger treatment effect with the 400 mg dose compared to the 200 mg BID dosing. The dose-response effect was not as prominent for other endpoints. While this study was conducted in patients with T2DM, the data formed the basis for the selection of the 200 mg qd and 400 mg qd doses to be further evaluated in the Phase 3 T1DM studies.

Study 206 investigated the effect of 3 different doses (75 mg, 200 mg and 400 mg) of sotagliflozin in patients with T1DM. This study was conducted in parallel with the phase 3 studies, in accordance with advice given, and thus did not inform on the doses to be selected in the phase 3 program. Although a dose-response relationship was observed for most of the selected endpoints, e.g. UGE, PPG and body weight, it is noted that the dose-response with regards to HbA1c was less clear than in T2DM patients. The data from study 206 however support the choice of doses since the 75 mg dose only provided borderline effects on HbA1c and body weight. Thus the doses selected appear adequate.

The phase 3 studies in the sotagliflozin T1DM program included Studies 309, 310, and 312. Studies 309 and 310 were conducted in North America and in Europe and Israel, respectively. The third phase 3 study, Study 312, was conducted globally.

Studies 309 and 310 were of similar design and were of adequate size and duration (24+28 weeks) with the endpoints assessed at week 24. The studies compared two doses of sotagliflozin (200 mg and 400 mg) with placebo on a background medication of optimised insulin treatment. Since no other treatment than insulin currently is available in the EU, the choice of placebo as comparator is adequate. The insulin treatment was optimised for six weeks before randomisation. Optimised insulin treatment was to be continued throughout the study duration. From the start of the insulin optimising period and throughout the course of the study, the patients SMBG was closely monitored and insulin doses adjusted. An IDMC reviewed the SMBG and insulin dosing data on an ongoing basis up to week 24 of the study. The measures taken to ensure optimised insulin treatment appear adequate.

Study 312 was a study of 24 weeks duration and did not include insulin optimisation. In this study, only the higher sotagliflozin dose, 400 mg, was compared to placebo. Insulin adjustment algorithms were provided, but there was no IDMC to assess the insulin optimisation. The aim was to provide data from a setting more close to a “real world” setting as opposed to studies 309/310.

Glycaemic goals and insulin adjustment algorithms were in place for all three studies. For the first meal on Day 1, patients were instructed to decrease the calculated (or usual) mealtime carbohydrate bolus dose by 30%. This recommendation was based on data from the phase 2 studies. After the first meal taken after study drug had been administered on Day 1, insulin doses in all study groups were adapted based on individual patients' needs and the initial reduction in bolus insulin dose was not expected to destabilise patients in the insulin only (i.e. placebo) arm.

Studies 309 and 310 also included two substudies, CGM and DEXA, for which it was prespecified that the analyses should be made on pooled data due to the small number of subject included.

All studies included TIDM patients >18 years of age and with inadequate metabolic control (HbA1c 7.0% to 11.0 at screening). There was no upper limit for age or BMI. Patients with eGFR>45 could be included. Patients with a recent history of severe hypoglycaemia or DKA during the last month before screening were not eligible. The inclusion and exclusion criteria are considered adequate. Inclusion and exclusion criteria were essentially similar in study 312 compared to studies 309 and 310, with the exception that no restrictions were made with regards to the type of insulin regimen.

Double-blinded treatment with placebo, sotagliflozin 200 mg (studies 309 and 310) and 400 mg was provided throughout the entire study duration. HbA1c and FPG data (and PPG data in the CGM study) was

masked to the sites, although at week 16 the HbA1c results were unmasked if they exceeded 11%. Adequate measure were taken to maintain the blind during the studies although it is questioned whether masking of FPG values would be efficient considering that patients and sites had access to SMBG values.

The primary objective of studies 309 and 310 was to show that sotagliflozin 200 mg and/or 400 mg was superior to placebo in reducing HbA1c whereas the primary objective of study 312 was to show that sotagliflozin 400 mg was superior to placebo in the proportion of patients with A1C <7.0% at Week 24 and no episode of SH and no episode of DKA after Randomization (net benefit). Although the same endpoints were included in both studies 309/310 and similarly in study 312, the primary endpoint and the hierarchical order of the secondary endpoints differed. The CGM substudy compared the effect on percent time spent inside and outside the target glucose ranges and the DEXA substudy compared the effect on total fat mass. The objectives and endpoints were adequate.

The applicant pooled data from studies 309 and 310, the ES1 pool. Considering the similarities between studies 309 and 310, this pool is considered adequate.

A second pool (ES2) was made by pooling data for all placebo treated patients and all patients treated with sotagliflozin 400 mg. This pool is of less interest considering that optimisation of the insulin treatment differed between studies 309/310 and study 312, which may influence the outcome and make interpretation difficult.

In summary, the sample size, treatment allocation procedure and statistical methodology for the main studies are generally considered acceptable.

The primary endpoint in studies 309 and 310 is change of HbA1c after 24 weeks analysed using a mixed model for repeated measures analysis (MMRM) and targeting a treatment effect as if patients adhered to treatment until week 24.

The primary efficacy analysis is based on a missing at random (MAR) assumption and it is not possible to know if this assumption is applicable. Other methods, such as placebo based imputation, may be considered giving more adequate estimates of efficacy. Analyses using placebo-based imputation were performed as a sensitivity analyses and results show very similar point estimates to the primary efficacy analyses.

For the net benefit endpoint in study 312 an approach imputing “failure” for data missing at week 24 was used. This is a sufficiently conservative method for handling missing data.

Control of the type I error is reasonable using an alpha-split (between active treatment groups) and sequential testing (of endpoints) in studies 309 and 310, and only sequential testing (of endpoints) in study 312.

Missing data was a minor problem for the studies 309 and 310 with less than 10% missing values in the primary endpoint, while missing values in study 312 were interpreted as non-response (ie non-missing). The primary efficacy analyses of studies 309 and 310 were based on the MAR assumption and it is not possible to know if this assumption is applicable. However, under the MNAR assumption and placebo based imputation analysis in studies 309, 310 the point estimates show similar results to the primary efficacy analysis, which can be regarded as a confirmation of the acceptability of the MAR assumption. In study 312, the primary analysis was performed in observed cases under an MNAR assumption imputing missing values as non-responders. Therefore, the primary analysis uses assumptions for missing values which are acceptable or confirmed by analyses with acceptable assumptions.

While the primary efficacy target of estimation, or estimand, and type of analysis has been common standard in studies for antidiabetic drugs in recent years, current discussions could suggest that other targets of estimation could be preferable. The actual adherence to treatment should be reflected in the target of estimation. Specifically, since patients are not expected to benefit once treatment is

discontinued (e.g. due to adverse events) the treatment effect should be estimated based on observed or modelled data reflecting adherence to treatment as observed in the study. Other important intercurrent events to consider are the changes to, or introduction of, other medication that will influence HbA1c values, including use of protocol-defined rescue medication. In T1DM studies the insulin treatment is adjusted to provide adequate treatment instead of other rescue treatments, and this is not considered an issue in these studies. Modelling based on data obtained in the placebo group is considered an acceptable approach to reflect discontinuation from treatment.

The sensitivity analysis provided used observed data as far as available and an imputation method for missing data imputing data on based observations in the placebo treatment group. Following the ICH E9 (R1, Step 2b) Addendum (EMA/CHMP/ICH/436221/2017), the primary estimand was based on a modified ITT approach for effect estimation, which can be regarded as a treatment policy estimand. However, as stated in the addendum, this estimand requires that data is collected after intercurrent events, ideally for all subjects and visits. Missing data after intercurrent events may compromise the interpretation of the results as treatment policy estimands. Therefore, the sponsor was asked to provide information 1) whether the degree of missing data before and after intercurrent events was similar, and 2) to what degree missing data after intercurrent events may compromise the interpretation of the results. The sponsor addressed these questions especially in relation to the applied missing-at-random assumption of the primary analysis model using a MMRM.

The studies were generally well conducted. The amendments made to the study protocols are not considered to affect the outcome or interpretation of the data in any of the studies. In general, protocol deviations were few and balanced between groups in all three studies. There was one incident where ethical conduct of study 310 was compromised. The incident did not impact the safety and well-being of the subjects, nor the integrity or conduct of the trial. This issue was adequately handled.

Further to this, it was discovered when analysing PK samples in study 310 that in 42 of the 782 randomised patients the plasma PK samples suggested that they had received incorrect study drug. The errors were distributed over 22 sites in 13 out of 17 countries participating in the trial. The issue was adequately investigated and handled by the applicant. Sensitivity analyses were performed, excluding all affected sites. The applicant concludes that the results of these analyses showed no impact on the primary and secondary efficacy or safety endpoints. This conclusion is endorsed.

Efficacy data and additional analyses

The three phase 3 studies included in total 2 980 patients, 1 231 on placebo, 263 on sotagliflozin 200 mg and 962 on sotagliflozin 400 mg. In all three studies, completion rate was high (about 90%) and drop-outs were balanced between groups. In study 312, more patients dropped out due to adverse events in the sotagliflozin treated group (45) compared to the placebo treated group (16). In studies 309/310, no patients were excluded from the mITT population and three patients were excluded from the mITT population in study 312.

Baseline demographic characteristics were balanced within each study. In study 309, which took place in the US, patients were somewhat older than in studies 310 and 312. A large proportion of subjects (>70%) included in the studies were overweight. Overweight was more common in study 309 conducted in the US, than in study 310 conducted in the EU/Israel. Although less common in the European T1DM population, overweight still is a problem associated with intensive insulin treatment also in this population and the population included in the study is therefore considered relevant. A higher proportion of patients in study 309 were using CSII (60%) as their insulin delivery method compared to study 310 (25%) and study 312 (40%). Baseline characteristics were balanced between treatment groups and comparable between studies with the exception of HbA1c which was somewhat higher in study 312 (about 8.2%)

compared to studies 309/310 (7.6% and 7.7% respectively). Both in study 309 and 310, all treatment groups showed a similar decrease in HbA1c of about 0.65% after the initial insulin optimising period.

The primary objective for studies 309 and 310 was met as the change from baseline in HbA1c was statistically significantly larger for both the sotagliflozin 200 mg and 400 mg dose. The treatment difference was comparable for both dose levels and of moderate magnitude (about -0.4%, p<0.001). As expected, pooling of data from these studies did not change the outcome. In both studies, there was virtually no change from baseline HbA1c in the placebo treated groups at week 24. The sensitivity analysis of the change from Baseline in A1C (%) at Week 24 using the PMM method with control (placebo) based imputation confirmed the results of the primary analysis. In study 312, change in HbA1c from baseline was a secondary endpoint. In this study, where insulin treatment was not optimised before the start of study treatment, the change in HbA1c was larger in both the sotagliflozin and the placebo groups compared to studies 309/310. The treatment difference was however comparable (-0.46%).

The proportion of patients achieving HbA1c <7.0% with no SH or DKA (net benefit) was the primary endpoint in study 312. The study met its primary endpoint as the net benefit difference vs placebo was 13.4% which was statistically significant. The main contributing factor was the change in HbA1c. In studies 309 and 310 a similar pattern was observed, although more patients had HbA1c <7.0% at baseline than in study 312. A dose-response was observed in study 309 (12% and 22% for the 200 mg and 400 mg dose respectively), whereas no apparent difference was observed between doses in study 310 (16% and 17% for the 200 mg and 400 mg dose respectively). The treatment differences were statistically significant for all comparisons. In the ES1 pool, the corresponding outcome was 14.0% for sotagliflozin 200 mg and 19.5% for sotagliflozin 400 mg. When the net benefit was analysed by its components (HbA1c < 7.0% without SH or DKA), the findings were consistently in favour of sotagliflozin treatment. Generally higher proportions were observed with the higher dose. All outcomes were statistically significant.

PPG was only evaluated in the CGM substudy and pooling of data for this analysis was predefined due to the low number of subjects participating. The data show that both doses of sotagliflozin resulted in a statistically significant decrease in PPG, the treatment difference being somewhat larger for the higher dose (-35 mg/dL and -41 mg/dL for the 200 mg and 400 mg dose respectively). The findings were consistent with the data from the phase 2 program.

Across the studies, a statistically significantly larger reduction in FPG was observed with sotagliflozin treatment compared to placebo although the decrease was modest ranging from 9.8 to 25.7 mg/dL.

As already stated, a large proportion of subjects (>70%) included in the studies were overweight. In all studies, the initial insulin optimising/run-in period was associated with a weight increase in all treatment groups. Across the three studies, sotagliflozin treatment resulted in consistent weight decrease of -1.7 to -1.9 kg with the 200 mg dose and -2.3 to -2.7 kg with the 400 mg dose. In the placebo treated groups a weight gain of +0.2 to +0.8 kg was observed. The treatment difference versus placebo was statistically significant for all comparisons. The DEXA substudy showed that the decrease in body weight was largely due to a loss of fat. This is in line with findings for other SGLT2-inhibitors.

Change in bolus insulin dose was a secondary endpoint in all three studies. In all studies the bolus insulin dose increased in the placebo treated groups (+3.9 to +6.6%) whereas a decrease was observed in the sotagliflozin treated groups which was larger in the higher dose groups. The change from baseline in the sotagliflozin treated groups ranged from -2.6 to -10.4% with a LS mean difference from placebo ranging from -5.7 to -16.4%. The change in basal insulin dose and total insulin dose was also assessed in all three studies. The pattern for the basal insulin dose was similar to that observed for the bolus doses but the percent changes were smaller. In the placebo groups, a LS mean increase in the total insulin dose at week 24 ranging from +0.6 to +2.9% was observed whereas the LS mean decrease in total insulin dose observed in the sotagliflozin treated groups ranged from – 4.3 to -8.9%.

The insulin dose adjustments were closely monitored by the IDMC in studies 309/310. For the vast majority of visits reviewed, the management of dose adjustments were considered to meet standards of care. This is supported by the data on HbA1c and insulin doses which show that insulin doses slowly increased in the placebo treated groups for the total study duration and that HbA1c remained stable in these groups.

Sotagliflozin treatment resulted in a modest placebo-adjusted decrease in SBP. There was no apparent difference in the treatment effect in the overall population compared to patients with SBP ≥130 mmHg whereas a slightly larger reduction was observed in patients with SBP ≥140 mmHg.

The aim of the CGM substudy was to investigate the effect of sotagliflozin on blood glucose variability. The data showed a statistically significant increase in the time spent in the desired blood glucose range (70-180 mg/dL). This was explained by a decrease in the time spent in the hyperglycaemic blood glucose range; whereas the time spent in the hypoglycaemic blood glucose range remained unchanged. CSII has been shown to reduce blood glucose variability per se. Of the patients included, 49.2% were using CSII as their insulin delivery method. Data from a subgroup analysis by administration method (CSII or MDI) however showed comparable results for both groups, thus the outcome does not appear to have been driven by the method of insulin administration.

A graph showing the 24-hour pattern of CGM measurements for placebo, sotagliflozin 200 mg and 400 mg respectively, was provided. Surprisingly, the most profound glucose-lowering effect of sotagliflozin in combination with insulin compared to insulin alone was found to occur during the early morning hours. It can only be speculated that sotagliflozin counteracts what is called the dawn phenomenon by increasing urinary glucose excretion in response to rising blood glucose levels. Another possible explanation could be that renal glucose excretion continues during the night. As no food intake compensates for this glucose loss, blood glucose steadily decreases. The applicant states that the decline in blood glucose values from 12 AM to 6 AM was not associated with a significant increase in hypoglycaemia.

During the rest of the day, blood glucose levels were generally lower with sotagliflozin 400 mg compared to placebo, whereas the difference between sotagliflozin 200 mg and placebo was less pronounced.

Patient related outcomes were assessed using the DTSQs and DDS2 scores. The DTSQs scores (range 0 to 36) indicated a higher satisfaction with sotagliflozin compared to placebo as reflected by a statistically significant increase in the score (+1.7 and +2.5 for sotagliflozin 200 mg and 400 mg respectively) as well as a higher proportion of patients reporting a change in score of 3 or more (54% and 52 % for sotagliflozin vs 28% for placebo). The DDS2 scores (range 0 to 6) indicated less distress with sotagliflozin treatment (-0.3 to -0.8, difference from placebo). These data may reflect the benefits of less variable blood glucose and weight loss observed with sotagliflozin treatment.

No direct comparison between the doses investigated in studies 309 and 310 (200 mg and 400 mg) was made; instead both doses were compared to placebo. Numerically there was no consistent treatment difference between the two doses with regards to HbA1c, neither in the overall population nor in the subgroups analysed. The only exception was patients with BMI >30 kg/m^2, where the 400 mg dose resulted in a larger HbA1c reduction. The higher dose consistently showed a higher risk of DKA except in patients with BMI >30 kg/m^2. Based on these data the use of the higher dose is questioned. However, as shown by the applicant in the responses to the LoOIs, there was a wide variability in the response with regards to HbA1c. The difference in treatment effect with regards to reduction in body weight was about 1 kg and the CIs do not overlap. There is a trend towards a better effect on time in range and SBP with the 400 mg dose and the reduction of SH was more pronounced with the 400 mg dose. Taking the individual response into account, a dose increase could be beneficial in some patients, especially in overweight patients in need of improved glycaemic control, thus the 400 mg dose is considered justified.

One-year exploratory efficacy data was provided from studies 309 and 310. The data show that HbA1c increased somewhat after week 24, the time point at which the IDMC did no longer review the insulin dose adjustments. This possibly illustrates the difficulties in maintaining a very tight metabolic control in T1DM. There was still a modest but statistically significant treatment difference between placebo and sotagliflozin of about -0.25% for the 200 mg dose and -0.3% for the 400 mg dose. Net benefit had decreased somewhat at week 52, now ranging from 7.2 to 13.4% as compared to 12 to 22% at week 24. This was mainly due to a lower proportion of patients achieving HbA1c <7.0%. The body weight slightly increased up to week 52 in the placebo treated groups, whereas body weight remained stable and reduced in all sotagliflozin treated groups after week 24 and up to week 52. No apparent change in the effect on total fat mass was observed. The insulin doses remained essentially unchanged after week 24 with the exception of study 309, where an increase in bolus dose was observed with the 200 mg dose. Patient reported outcomes measuring diabetes distress remained in favour of sotagliflozin.

No specific clinical studies have been conducted in special populations. The number of older subjects included in the studies was low, with only 18 subjects aged 75 to 85 years included. Additional analyses provided with the responses to the LoQ, gave no indication of a different effect due to age per se. Furthermore, the clinical data in patients with impaired renal function is scarce. It should be noted that the CHMP recommended that the applicant should consider investigating this population in a dedicated study. Subgroup analyses by renal function showed no attenuation of the effect in subjects with eGFR ≥60 to <90 mL/min/1.73 m^2 compared to patients with eGFR >90 mL/min/1.73 m^2. Subjects with eGFR <60 mL/min/1.73 m^2 were few, resulting in very wide CIs although the point estimates remained in favour of sotagliflozin treatment.

Pooled subgroup analyses from studies 309/310 were provided for the two doses, 200 mg and 400 mg (ES1 pool) as well as for the ES2 pool (all patients treated with sotagliflozin 400 mg). The analyses showed consistent findings for all demographic and baseline characteristics tested with regards to the change from baseline in HbA1c, except for patients with eGFR <60 where the 95%CI included zero in all three analyses. The number of patients were few, thus the 95%CI were wide. Notably, no patients aged 75 years or above were included in these analyses.

A small supportive study (study 204) was also submitted which included 85 young adults (18-30 years old) with T1DM and a high mean HbA1c of almost 10%, treated with either placebo or sotagliflozin 400 mg. The findings were in line with the outcome of the phase 3 studies.

Additional expert consultations

CHMP requested an ad hoc expert meeting to obtain the opinion of experts in the field of diabetes, as well as from patient representatives, on the benefits of the use of sotagliflozin in T1DM and the risk of diabetic ketoacidosis (see section 2.6.1. Discussion on clinical safety).

2.5.4. Conclusions on clinical efficacy

Three well conducted clinical studies of adequate design have been submitted to support the use of sotagliflozin, a dual SGLT2 and SGLT1 inhibitor in the treatment of T1DM. Treatment with sotagliflozin when added to optimised insulin treatment resulted in a modest decrease of HbA1c of about 0.4% after 24 weeks. This effect was attenuated after 52 weeks of treatment. A comparable effect was observed when sotagliflozin was added to a less strictly controlled insulin treatment. There was no apparent difference between doses with regards to reduction in HbA1c. Beneficial effects were also observed on PPG, body weight and blood glucose variability. In addition, a higher treatment satisfaction was observed with sotagliflozin treatment. The data in the elderly (>75 years of age) and in patients with moderate renal impairment (eGFR <60 mL/min/1.73 m^2) is very limited and does not allow any firm conclusions.

2.6. Clinical safety

The safety of sotagliflozin was evaluated in a total of 30 clinical studies, including 22 phase 1, 5 phase 2 and 3 phase 3 studies. The phase 2 and 3 studies included subjects with T1DM (3 phase 2 and 3 phase 3 studies) and T2DM (2 phase 2 studies).

Overall, during phase 2 and 3 studies of sotagliflozin in subjects with T1DM, 1,915 subjects were treated with sotagliflozin of which 35 with sotagliflozin 75 mg, 559 with sotagliflozin 200 mg and 1,321 with sotagliflozin 400 mg.

For the integrated summary of safety, data was pooled (Table 23):

The SAF-1 pool includes pooled safety data from 2 placebo-controlled phase 3 studies (309 and 310) in subjects with T1DM with similar study design (insulin optimization and committee oversight of insulin dosing) for 52 weeks of treatment.

The SAF-3 pool includes pooled safety data from 6 placebo-controlled studies in subjects with T1DM; 3 phase 2 studies (203, 204 and 206) and 3 phase 3 studies (309, 310 and 312). Study 312 was conducted in subjects with any insulin regimen, less frequent visits and no committee oversight of insulin dosing. Moreover, study 312 did not include sotagliflozin at the 200 mg dose and had only 24 weeks of treatment. However, SAF-3 represents the largest pool of data from T1DM subjects.

The SAF-4 pool includes pooled safety data from T1DM and T2DM subjects from 8 placebo-controlled studies; the 6 studies in T1DM subjects included in SAF-3 (203, 204, 206, 309, 310 and 312) and 2 phase 2 studies in T2DM subjects (201 and 202).

Table 23 Safety pools for clinical study data

Study Pool	Description of the studies	Number of patients randomized to treatment
SAF-1 (309, 310)	**T1DM** **Phase 3 studies** Placebo-controlled, randomized, double-blind **52 weeks** (24 w+ 28 w)	**Sotagliflozin; n=1,049** (200 mg; n=524, 400 mg; n= 525) **Placebo; n=526**
SAF-3 (203, 204, 206, 309, 310, 312)	**T1DM** **Phase 2 and 3 studies** Placebo-controlled, randomized, double-blind	**Sotagliflozin; n=1,915** (75 mg; n=35 200 mg; n=559 400 mg; n=1,321) **Placebo; n=1,324**
SAF-4 (201, 202, 203, 204, 206, 309, 310, 312)	**T1DM + T2DM** **Phase 2 and 3 studies** Placebo-controlled, randomized, double-blind	**Sotagliflozin; n=2,175** (75 mg; n=92 200 mg; n=631 400 mg; n=1,452) **Placebo; n=1,396**

Patient exposure

In total, 1,915 T1DM subjects in phase 2 and 3 studies were treated with sotagliflozin with 1,444 patients (75%) treated for at least 24 weeks and 668 patients (64%) treated for at least 52 weeks. A total of 260

patients with T2DM were exposed to sotagliflozin in the phase 2 and 3 clinical trials. An overview of exposure in the safety data pools SAF-1, SAF-3 and SAF-4 in Table 24.

Table 24 Overview of treatment exposure for SAF-1, SAF-3 and SAF-4

Safety Pool	sotagliflozin 200 mg		Sotagliflozin 400 mg		All sotagliflozin		Placebo	
	Tot subj	Mean exposure (Median exposure) Patient-years (PY)	Tot subj	Mean exposure (Median exposure) Patient-years (PY)	Tot subj	Mean exposure (Median exposure) Patient-years (PY)	Tot subj	Mean exposure (Median exposure) Patient-years (PY)
SAF-1 **T1DM** Phase 3 studies	524	334.6 days (364.0 days) **480 PY**	525	331.9 days (364.0 days) **477 PY**	1,049	333.3 days (364.0 days) **957 PY**	526	329.3 days (364 days) **474 PY**
SAF-3 *) **T1DM** Phase 2 and 3 studies	559	319.0 days (364.0 days) **488 PY**	1,321	219.7 days (170.0 days) **795 PY**	1,915	246.1 days (190.0 days) **1,290 PY**	1,324	219.7 days (169.0 days) **796 PY**
SAF-4 **) **T1DM + T2DM** Phase 2 and 3 studies	631	290.7.0 days (364.0 days) **502 PY**	1,452	206.6 days (169.0 days) **821 PY**	2,175	225.6 days (172.0 days) **1,343 PY**	1,396	211.9 days (169.0 days) **810 PY**

*) SAF-3; Included also exposure to 75 mg sotagliflozin (n=35, mean exposure=76.8 days (median expos.=85.0 days);7.36 PY

**) SAF-4; Included also exposure to 75 mg sotagliflozin (n=92, mean exposure=77.5 days (median expos.=84.0 days);19.53 PY

Adverse events

An overall summary of adverse events for SAF-1 through 52 weeks of treatment is presented in Table 25.

In SAF-1, about 75% of the subjects reported AEs. The frequency of SAEs was about 10% for sotagliflozin and 7% for placebo. The discontinuation rates due to adverse events were slightly higher for sotagliflozin (4-7%) compared to placebo (4%).

Table 25 Overall summary of TEAEs (treatment-emergent adverse events) through 52 weeks of treatment in SAF-1

Patients with TEAEs	Placebo N =526 n (%)	Sotagliflozin 200 mg N = 524 n (%)	Sotagliflozin 400 mg N =525 n (%)	All sotagliflozin N = 1,049 n (%)
Patients with any TEAE	374 (71.1)	393 (75.0)	390 (74.3)	783 (74.6)
Patients with treatment-related TEAEs	106 (20.2)	167 (31.9)	193 (36.8)	360 (34.3)
Patients with severe TEAEs	37 (7.0)	50 (9.5)	48 (9.1)	98 (9.3)
Patients with severe treatment-related TEAEs	11 (2.1)	19 (3.6)	22 (4.2)	41 (3.9)
Patients with treatment-emergent SAEs	37 (7.0)	53 (10.1)	50 (9.5)	103 (9.8)
Patients with treatment-emergent treatment-related SAEs	10 (1.9)	18 (3.4)	23 (4.4)	41 (3.9)
Patients with TEAEs leading to study drug discontinuation	20 (3.8)	23 (4.4)	35 (6.7)	58 (5.5)
Patients with treatment-related TEAEs leading to study drug discontinuation	12 (2.3)	19 (3.6)	31 (5.9)	50 (4.8)
Patients with any TEAEs leading to death	3 (0.6)	0	0	0

Most frequently reported adverse events

In SAF-1, the most frequently reported adverse events for sotagliflozin 200 mg and 400 mg versus placebo were *viral upper respiratory tract infection* (15% and 14% vs. 13%), *diarrhoea* (6.5% and 9.3% vs. 5.5%), *diabetic ketoacidosis* (4.0% and 5.7% vs. 1.0%), *blood ketone body increased* (4.0% and 5.1% vs. 0.6%), *urinary tract infections* (6.1% and 3.8% vs. 4.9%), *genital infection fungal* (3.4% and 4.0% vs. 0.2%) and *vulvovaginal mycotic infection* (2.9% and 5.1% vs. 1.9%), Table 26.

Table 26 Most common TEAEs (reported by ≥2% of patients in either sotagliflozin group and more frequently than placebo) through 52 weeks of treatment in SAF-1

System organ class Preferred term	Placebo (N = 526) n (%)	Sotagliflozin 200 mg (N = 524) n (%)	Sotagliflozin 400 mg (N = 525) n (%)	All sotagliflozin (N = 1,049) n (%)
Patients with any common TEAE	374 (71.1)	393 (75.0)	390 (74.3)	783 (74.6)
Ear and labyrinth disorders	**3 (0.6)**	**6 (1.1)**	**11 (2.1)**	**17 (1.6)**
Eye disorders	**19 (3.6)**	**22 (4.2)**	**20 (3.8)**	**42 (4.0)**
Gastrointestinal Disorders	97 (18.4)	106 (20.2)	122 (23.2)	228 (21.7)
Diarrhoea	29 (5.5)	34 (6.5)	49 (9.3)	83 (7.9)
Vomiting	15 (2.9)	16 (3.1)	11 (2.1)	27 (2.6)
Constipation	9 (1.7)	17 (3.2)	6 (1.1)	23 (2.2)
Flatulence	0	5 (1.0)	14 (2.7)	19 (1.8)
Abdominal pain	3 (0.6)	3 (0.6)	11 (2.1)	14 (1.3)
General Disorders and Administration Site Conditions	40 (7.6)	47 (9.0)	48 (9.1)	95 (9.1)
Pyrexia	10 (1.9)	10 (1.9)	13 (2.5)	23 (2.2)
Fatigue	10 (1.9)	8 (1.5)	11 (2.1)	19 (1.8)
Infections and Infestations	233 (44.3)	241 (46.0)	243 (46.3)	484 (46.1)
Viral upper respiratory tract infection	69 (13.1)	78 (14.9)	74 (14.1)	152 (14.5)
Urinary tract infection	26 (4.9)	32 (6.1)	20 (3.8)	52 (5.0)
Vulvovaginal mycotic infection	10 (1.9)	15 (2.9)	27 (5.1)	42 (4.0)
Genital infection fungal	1 (0.2)	18 (3.4)	21 (4.0)	39 (3.7)
Gastroenteritis	12 (2.3)	15 (2.9)	17 (3.2)	32 (3.1)
Sinusitis	16 (3.0)	15 (2.9)	16 (3.0)	31 (3.0)
Gastroenteritis viral	7 (1.3)	16 (3.1)	8 (1.5)	24 (2.3)
Investigations	47 (8.9)	64 (12.2)	66 (12.6)	130 (12.4)
Blood ketone body increased	3 (0.6)	21 (4.0)	27 (5.1)	48 (4.6)

System organ class Preferred term	Placebo (N = 526) n (%)	Sotagliflozin 200 mg (N = 524) n (%)	Sotagliflozin 400 mg (N = 525) n (%)	All sotagliflozin (N = 1,049) n (%)
Metabolism and Nutrition Disorders	41 (7.8)	64 (12.2)	82 (15.6)	146 (13.9)
Diabetic ketoacidosis	5 (1.0)	21 (4.0)	30 (5.7)	51 (4.9)
Hypoglycaemia	12 (2.3)	12 (2.3)	9 (1.7)	21 (2.0)
Ketosis	3 (0.6)	4 (0.8)	17 (3.2)	21 (2.0)
Vitamin D deficiency	5 (1.0)	10 (1.9)	11 (2.1)	21 (2.0)
Musculoskeletal and Connective Tissue Disorders	74 (14.1)	75 (14.3)	82 (15.6)	157 (15.0)
Back pain	11 (2.1)	14 (2.7)	20 (3.8)	34 (3.2)
Arthralgia	9 (1.7)	16 (3.1)	11 (2.1)	27 (2.6)
Neoplasms benign, malignant and unspecified	**8 (1.5)**	**10 (1.9)**	**13 (2.5)**	**23 (2.2)**
Nervous system disorders	66 (12.5)	58 (11.1)	56 (10.7)	114 (10.9)
Headache	19 (3.6)	15 (2.9)	20 (3.8)	35 (3.3)
Dizziness	9 (1.7)	13 (2.5)	9 (1.7)	22 (2.1)
Renal and Urinary Disorders	22 (4.2)	37 (7.1)	35 (6.7)	72 (6.9)
Pollakiuria	7 (1.3)	16 (3.1)	10 (1.9)	26 (2.5)
Reproductive system and breast disorders	**13 (2.5)**	**19 (3.6)**	**25 (4.8)**	**44 (4.2)**
Respiratory, Thoracic, and Mediastinal Disorders	59 (11.2)	35 (6.7)	56 (10.7)	91 (8.7)
Cough	12 (2.3)	12 (2.3)	25 (4.8)	37 (3.5)
Oropharyngeal pain	14 (2.7)	4 (0.8)	17 (3.2)	21 (2.0)

Adverse events of special interest

Diabetic ketoacidosis

During every visit, Investigators were trained to review patient reported signs or symptoms that might be suspicious for diabetic ketoacidosis (DKA). In addition, patients were instructed by the Investigator to measure blood or urine ketones or blood BHB level. If the urine ketones were positive or blood BHB level was >0.6 mmol/L, the patient was asked to contact the investigative site immediately. Under these circumstances, the patient was asked to increase hydration and administer additional rapid acting insulin with oral carbohydrate frequently, as often as every 2 hours until normalization of urine ketones or blood BHB level.

In SAF-1, there was a dose-dependent increase in the incidence of positively adjudicated DKA for sotagliflozin (2.9% and 3.8% for sotagliflozin 200 mg and 400 mg, respectively) compared to placebo (0.2%). The exposure-adjusted incidence rate (EAIR) was 3.12, 4.19 and 0.21 subjects per 100 PY for sotagliflozin 200 mg, sotagliflozin 400 mg and placebo, respectively. In total, 37 events of DKA in 36 subjects were received (of which 26 events of DKA for sotagliflozin). One subject, in the sotagliflozin group 200 mg, experienced more than one event of DKA. All events of DKA were serious. The overall incidence of events of DKA leading to study discontinuation was 33%[27% (4/15) for sotagliflozin 200 mg, 40% for sotagliflozin 400 mg (8/20) and 0% (0/1) for placebo] and the overall incidence resulting in study interruption was 56% [67% (10/15) for sotagliflozin 200 mg, 45% for sotagliflozin 400 mg (9/20) and 100% for placebo (1/1)] (Table 27). In SAF-1, 43% (15/35) of the cases experienced DKA with glucose values in the euglycaemic range (<14 mmol/L).

Table 27 Summary of treatment-emergent Investigator-reported and positively adjudicated acidosis-related events in SAF-1

	Placebo (N = 526) n (%) m	Sotagliflozin 200 mg (N = 524) n (%) m	Sotagliflozin 400 mg (N = 525) n (%) m	All sotagliflozin (N = 1,049) n (%) m
Total subject-years	**474.20 PY**	**480.02 PY**	**477.13 PY**	**957.15 PY**
Investigator-reported DKA/metabolic acidosis events				
All events	7 (1.3) 7	30 (5.7) 32	39 (7.4) 39	69 (6.6) 71
Positively adjudicated metabolic acidosis events				
All events	3 (0.6) 3	18 (3.4) 19	22 (4.2) 22	40 (3.8) 41
Positively adjudicated DKA events				
All events	1 (0.2) 1	15 (2.9) 16	20 (3.8) 20	35 (3.3) 36
Events per patient per year	0.002	0.033	0.042	0.038
EAIR per 1000 patient years (95% CL)	2.11 (0.00,6.24)	31.25 (15.43,47.06)	41.92 (23.55,60.29)	36.57 (24.45,48.68)
Severe events	0	11 (2.1) 12	15 (2.9) 15	26 (2.5) 27
Serious events	1 (0.2) 1	15 (2.9) 16	20 (3.8) 20	35 (3.3) 36
Events leading to study drug interruption	1 (0.2) 1	10 (1.9) 10	9 (1.7) 9	19 (1.8) 19
Events leading to study drug discontinuation	0	4 (0.8) 4	8 (1.5) 8	12 (1.1) 12

m = number of events, EAIR=Exposure-adjusted incidence rate Source: modified from 5.3.5.3 ISS Part 2 Table 1.10.3.1

In SAF-3 (excluding study 203), the exposure-adjusted incidence rate was higher in the sotagliflozin groups (3.07 and 5.29 subjects per 100 PY for sotagliflozin 200 mg and 400 mg, respectively) compared to placebo (0.76 subject per 100 PY), also in a dose-dependent manner. In total, 64 events of DKA in 63 subjects were received (of which 58 events of DKA for sotagliflozin). One subject, in the sotagliflozin group 200 mg, experienced more than one event of DKA. All but 3 positively adjudicated DKA were serious and all but 5 DKA led to hospitalization. Overall, the incidence of events of DKA leading to study discontinuation and study interruption was 38% and 46%, respectively.

The incidence of positively adjudicated DKA increased over time for sotagliflozin as compared to placebo in a clearly dose-dependent manner. In SAF-1, the cumulative incidence of DKA at week 52 was approximately 2.8% and 4.1% for sotagliflozin 200 mg and 400 mg sotagliflozin compared to 0.2% for placebo (Figure 26). The Kaplan Meier plot of the cumulative incidence of adjudicated DKA in SAF-3 showed a more pronounced differentiation between the 200 mg and 400 mg dose of sotagliflozin, with earlier TTO with 400 mg compared to the SAF-1 plot. This may reflect the data from study 312 where no insulin optimization occurred prior to randomization (Figure 27).

In SAF-1, mean and median time to onset of DKA was shorter in sotagliflozin 400 mg (159 and 134 days) than in sotagliflozin 200 mg (208 and 214 days); although SD standard deviation was broad the differences suggests a shorter TTO with the sotagliflozin 400 mg compared to sotagliflozin 200 mg.

Figure 26 Kaplan-Meier plot of the cumulative incidence of positively adjudicated diabetic ketoacidosis over time by treatment group SAF-1

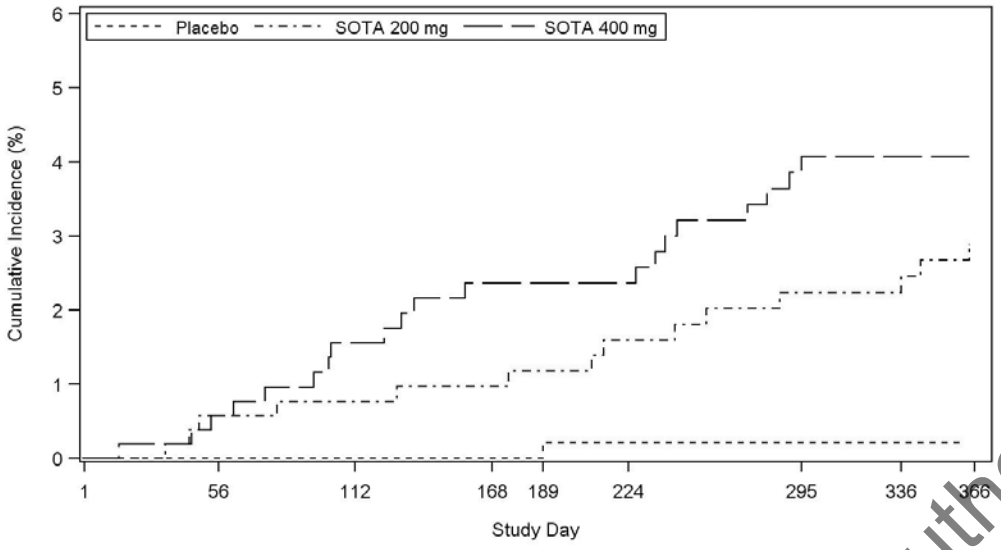
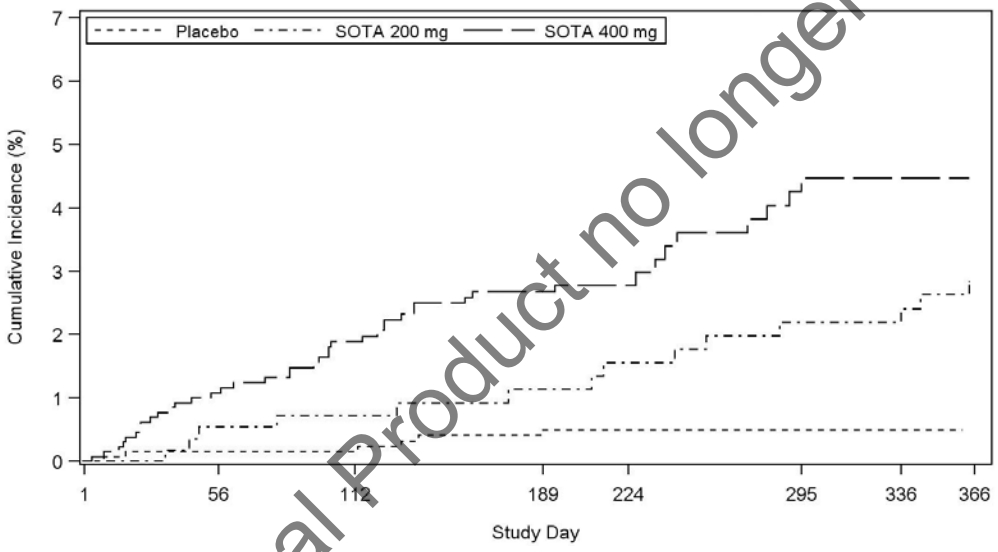


Figure 27 Kaplan-Meier plot of the cumulative incidence of positively adjudicated diabetic ketoacidosis over time by treatment group SAF-3



Possible risk factors/contributing factors associated with an event of a positively adjudicated DKA were analysed. However, the analyses of potential risk factors of DKA were associated with uncertainties due to low number of events. However, the subgroup analyses indicated that subjects with previous DKA, subjects with high BHB levels at baseline or greater increase in BHB levels, subjects who had their insulin dose decreased with more than 20% and subjects who were CSII-users, were at higher risk to develop DKA. This has been reflected in the proposed product information.

The applicant has proposed risk minimisation measures in order to mitigate the risk of DKA which includes education of health care professionals and patients about self-monitoring of ketones, situations at-risk to allow for early diagnosis of ketonaemia or ketonuria and how to manage potential ketosis and maintenance of optimal insulin therapy. Detailed recommendations are provided in the SmPC and in the proposed educational materials. These recommendations are considered adequate in order to mitigate the risk, based on the knowledge on DKA in general and on the experience from the clinical trials.

Hypoglycaemia

In SAF-1, the incidence of documented hypoglycaemia was high across all treatment groups (>98%). The event rate per patient-year was similar in the sotagliflozin groups (81 and 84 events per PY for sotagliflozin 200 mg and 400 mg, respectively) and slightly lower compared to placebo (96 events per PY), Table 28. The incidence of recurrent documented hypoglycaemia events was similar across treatment groups in subjects having 1-5, 6-9 or >10 events.

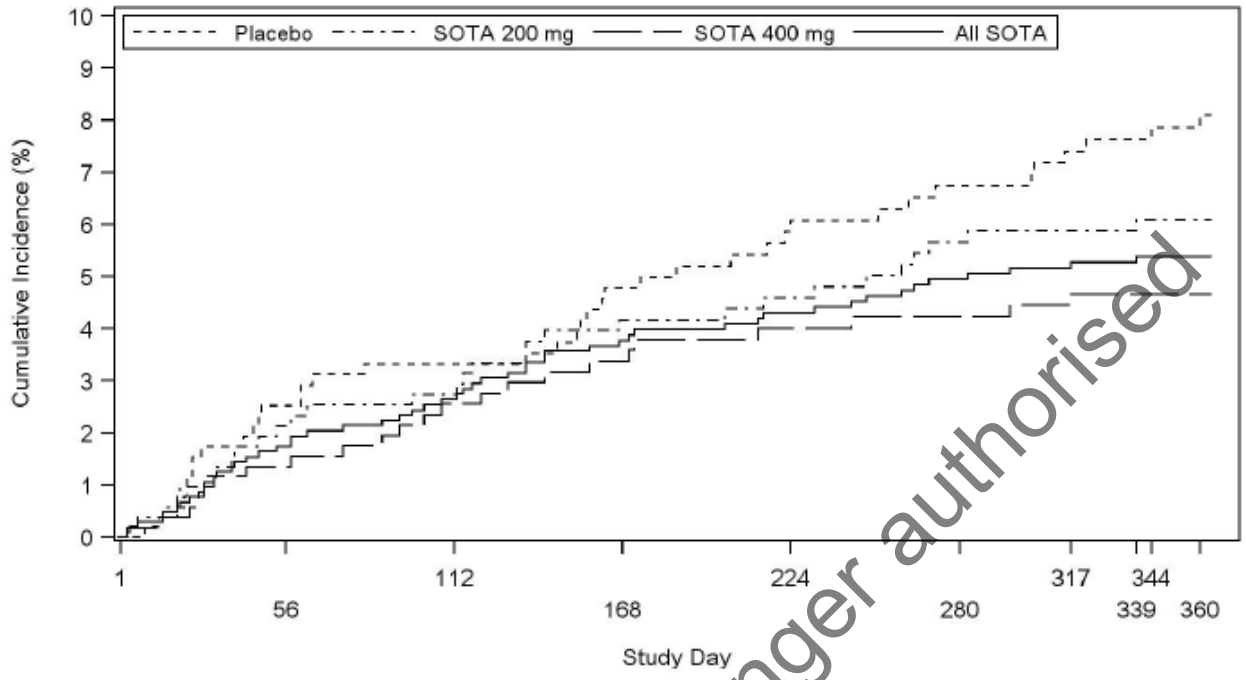
The incidence of events of positively adjudicated severe hypoglycaemia was slightly higher for sotagliflozin 200 mg (5.7%) compared to sotagliflozin 400 mg (4.4%) but was even higher for placebo (7.4%). The event rate was higher for sotagliflozin 200 mg (142 events per 1000 PY) compared to sotagliflozin 400 mg (69 events per 1000 PY) and placebo (105 events per 1000 PY). The majority of patients had one or two events of severe hypoglycaemia; however, subjects having ≥3 events of SH occurred in 30% (10/30) of the subjects in the sotagliflozin 200 mg group. In the Kaplan-Meier plot of the cumulative incidence of severe hypoglycaemia, the sotagliflozin curves became less steep over time and provided a separation from placebo after about 24 weeks of treatment (Figure 28).

Overall, 7 subjects discontinued due to events of severe hypoglycaemia in the phase 2 and phase 3 pooled studies; 1 subject in the sotagliflozin 75 mg group, 1 subject in the sotagliflozin 200 mg, 2 subjects in the sotagliflozin 400 mg and 3 subjects in the placebo group.

Table 28 Summary of events of documented hypoglycaemia and events of positively adjudicated severe hypoglycaemia through 52 weeks of treatment in SAF-1

	Placebo (N = 526)	**Sotagliflozin 200 mg (N = 524)**	**Sotagliflozin 400 mg (N = 525)**	**All sotagliflozin (N = 1,049)**
Total patient-year	474.20	480.02	477.13	957.15
Incidence of documented hypoglycaemia				
Number of events of documented hypoglycaemia	45,327	39,015	39,937	78,952
Patients with at least 1 event, n (%)	518 (98.5)	515 (98.3)	518 (98.7)	1,033 (98.5)
EAIR per 1,000 patient-years	1092.37	1072.87	1085.65	1079.24
Events per patient per year	95.587	81.278	83.702	82.486
Number of nocturnal events	5,771	5,286	5,313	10,599
Number of diurnal events	39,766	33,889	34,796	68,685
Incidence of positively adjudicated severe hypoglycaemia				
Number of events of positively adjudicated events of severe hypoglycaemia	50	68	33	101
Patients with at least 1 event, n (%)	39 (7.4)	30 (5.7)	23 (4.4)	53 (5.1)
EAIR per 1000 patient-years	82.24	62.50	48.20	55.37
Events per patient per year	0.11	0.14	0.07	0.11
Number of events nocturnal by time of day	13	20	6	26
Number of events nocturnal by sleep status	17	24	15	39
Number of events diurnal by time of day	36	48	29	77

Figure 28 Kaplan-Meier plot of the cumulative incidence of positively adjudicated severe hypoglycaemia over time by treatment group SAF-1 (52-week Phase 3 Studies) - Safety population



Volume depletion

Due to the mechanism of action, sotagliflozin induces an osmotic diuresis, which may lead to adverse events related to volume depletion. In the SAF-3 Pool, the incidence rate of events of volume depletion was higher in sotagliflozin-treated subjects (29 and 26 subjects per 1000 PY for sotagliflozin 200 mg and 400 mg, respectively) compared to placebo-treated subjects (10 subjects per 1000 PY).

In SAF-1, the incidence of osmotic diuresis-related adverse events ('urine output increased', 'polydipsia', 'micturition urgency', 'nocturia', 'pollakiuria', 'polyuria') was increased for sotagliflozin relative to placebo. The incidence of volume depletion events ('dehydration', 'hypovolaemia', 'postural dizziness', 'orthostatic hypotension', 'hypotension', 'syncope', 'presyncope') was 2.7%, 1.1% and 1.0% for sotagliflozin 200 mg, sotagliflozin 400 mg and placebo. Increased urination and volume depletion have been reflected in the proposed SmPC.

In the subgroup analyses in the SAF-3 Pool, subjects ≥65 years of age (n=209) had a higher incidence of events of volume depletion for sotagliflozin 200 mg and 400 mg relative to placebo. Subjects with eGFR <60 mL/min/1.73 m^2 (n=146) had a higher incidence of events of volume depletion for sotagliflozin 400 mg versus placebo. However, the total number of subjects in each analysis was small.

Genital mycotic infections

In SAF-1, the incidence of genital infections was higher in patients treated with sotagliflozin compared to placebo patients, and the increase was dose-related in both male and female patients.

In SAF-1, the incidence of genital infections in female subjects was 15%, 17% and 4.7% in sotagliflozin 200 mg, sotagliflozin 400 mg group and placebo. Most of the events were mild or moderate and no serious case was reported. Discontinuation due to genital mycotic infections occurred in 1.2%, 1.1% and 0.8% of subjects treated with sotagliflozin 200 mg, sotagliflozin 400 mg and placebo, respectively. Eighty-seven (87) female subjects experienced 130 events of genital infections. Recurrent events of genital infections were reported in 27% (35/130) of the female subjects in the sotagliflozin group in SAF-3.

In SAF-1, the incidence of male genital infections was 3.0%, 6.3% and 1.1% in sotagliflozin 200 mg, sotagliflozin 400 mg group and placebo. All events were mild or moderate in intensity and no serious cases. Discontinuation due to genital mycotic infections occurred in 0%, 0.4% and 0.4% of subjects treated with sotagliflozin 200 mg, sotagliflozin 400 mg and placebo, respectively. Twenty-four (24) male subjects experienced 29 events of genital infections. Recurrent events of genital infections were reported in 13% (4/31) of the male subjects in the sotagliflozin group in SAF-3.

Urinary tract infections

In SAF-1, the overall frequency of urinary tract infections reported were slightly higher for sotagliflozin 200 mg (7.1%) compared to sotagliflozin 400 mg (5.5%) and placebo (6.1%). The incidence of UTI in female subjects was highly increased and similar in subjects treated with sotagliflozin 200 mg (12%) and placebo (11%) compared to sotagliflozin 400 mg (7.0%); however, the incidence of UTI in male subjects was dose-dependently increased in the sotagliflozin 200 mg and 400 mg group (2.3% and 4.0%, respectively) as compared to placebo (1.8%). In SAF-3, all UTI events were mild or moderate in intensity except for one severe case (male subject in the sotagliflozin 400 mg group). Two cases (2 cases of cystitis) were serious; both occurred in male subjects in the sotagliflozin 400 mg group. Information regarding urinary tract infections has been reflected in the proposed SmPC.

Diarrhoea

In SAF-1, the incidence of diarrhoea was increased in the sotagliflozin 200 mg and 400 mg group (6.5% and 8.8%, respectively) as compared to placebo (5.1%). In SAF-3, all events were mild or moderate in intensity except for one severe case in the sotagliflozin 200 mg group. No serious cases and few subjects (<1%) in all groups) had diarrhoea events that lead do discontinuation.

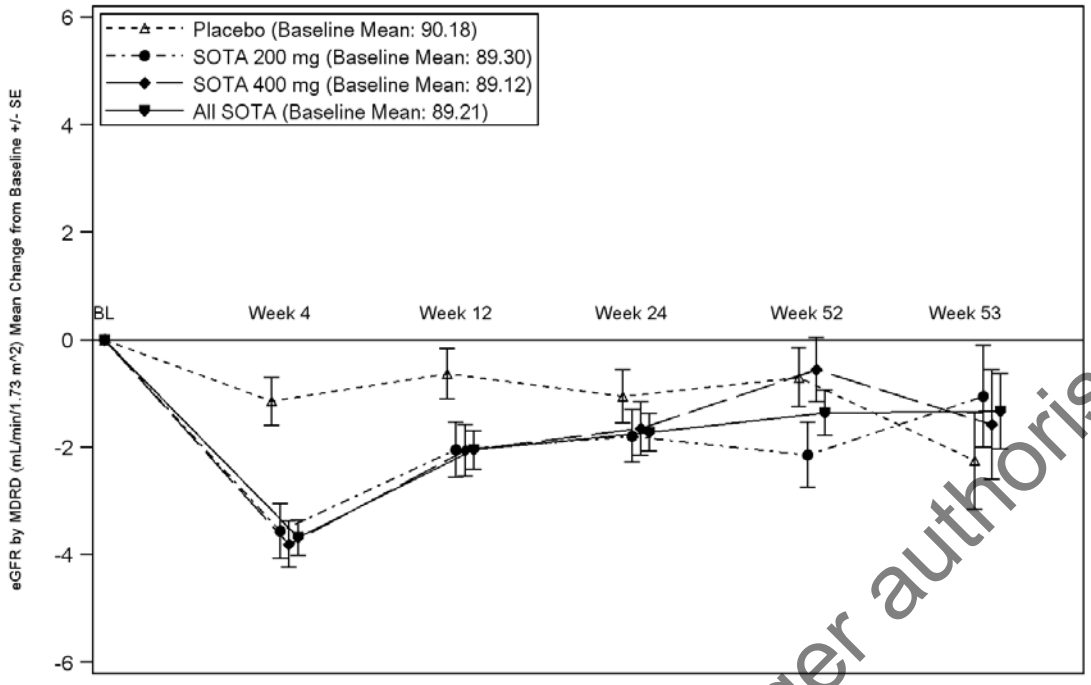
Renal events

In SAF-1, treatment with sotagliflozin was associated with a small decrease in eGFR; -3.6 and -3.8 mL/min/1.73 m^2 (-4.0% and -4.3%) in sotagliflozin 200 mg and sotagliflozin 400 mg vs. -1.15 mL/min/1.73 m^2 (-1.3%) in the placebo group that that did return towards baseline at week 52 and week 53 (1 week after discontinuation of study drug), Figure 29. Also in subjects with moderate and mild renal impairment, the eGFR returned towards baseline at week 52. However, subjects with eGFR <60 mL/min/1.73 m^2 made up for a small number in SAF-1 (n=71), wherefore difficult to draw any firm conclusions in this subgroup. Mean increases in serum creatinine from baseline to week 4 was 3.0, 3.2 and 1.0 umol/L (4.0%, 4.3% and 1.3%) for sotagliflozin 200 mg, sotagliflozin 400 mg and placebo, respectively. The changes in eGFR and serum creatinine have been reflected in the proposed SmPC.

The incidence of renal-related events was low and similar across the sotagliflozin groups and placebo in both SAF-1 (1.5%, 1.3% and 1.5%) and SAF-3 (16, 16 and 15 subjects per 1000 PY). One patient each in the placebo group, sotagliflozin 200 mg group, and sotagliflozin 400 mg group experienced a serious renal event.

In the subgroup analysis in the SAF-3 Pool, subjects with eGFR ≥90 mL/min/1.73 m^2 had a higher incidence of renal events for sotagliflozin (9.3 and 16 subjects per 1000 PY for sotagliflozin 200 mg and 400 mg, respectively) relative to placebo (7.5 subjects per 1000 PY). In subjects with eGFR 60 to <90 mL/min/1.73 m^2, the incidence of subjects with renal events was higher for sotagliflozin 200 mg (20 subjects per 1000 PY) compared to placebo (14 subjects per 1000 PY) and sotagliflozin 400 mg (11 subjects per 1000 PY). Subjects with eGFR <60 mL/min/1.73 m^2 (n=146) had a higher incidence of renal events in in the placebo group (103 subjects per 1000 PY) compared to sotagliflozin 200 mg and 400 mg (45 and 84 subjects per 1000 PY); however the total number of subjects was small.

Figure 29 Mean Change (+/-SE) in Estimated Glomerular Filtration Rate (eGFR) mL/min/1.73 m^2) From Baseline Over Time, 52 Weeks of Treatment SAF-1



Hepatic events

In the phase 2 and 3 studies in T1DM and T2DM subjects (SAF-4), the incidence of positively adjudicated drug-induced liver damage (DILI) was low; 1 event in the placebo group and 2 events in the sotagliflozin 400 mg group. No case met the definition for Hy's law case.

Pancreatitis

One case of pancreatitis was identified in a patient randomized to sotagliflozin 400 mg. The event of pancreatitis resolved one week after onset. The pancreatitis was during a case of DKA.

Venous thrombotic events

One patient randomized to sotagliflozin 400 mg, with a history of thrombophlebitis, was reported to have experienced 2 events of VTE (pulmonary embolism and deep vein thrombosis).

Hypersensitivity reactions

In the phase 2 and 3 studies in T1DM and T2DM subjects (SAF-4), sotagliflozin treatment did not result in a higher incidence of potential severe hypersensitivity reactions relative to placebo. The incidence of potential severe events of hypersensitivity reactions was low and similar in the sotagliflozin 200 mg and 400 mg groups (0.5% respectively) and the placebo group (0.7%).

Bone safety

In sub-studies of studies 309 and 310, DEXA assessments of bone density were performed at baseline and week 52. A total of 243 patients were randomized in the pooled DEXA sub-study, and 215 patients completed the DEXA sub-study; 75 patients in the placebo group, 84 patients in the sotagliflozin group 200 mg and 84 subjects in the sotagliflozin 400 mg.

The incidence of fractures through 52 weeks of treatment was low and similar across the groups: 2.9%, 1.9% and 3.4% for sotagliflozin 200 mg, sotagliflozin 400 mg and placebo. Additional studies to characterize the risk of bone fractures for sotagliflozin are ongoing in T2DM subjects; data should be provided when available.

The change from baseline to week 52 in BMD was nominally statistically significant in the 'lumbar spine' for sotagliflozin 200 mg [LS Mean difference from placebo -1.27% (-2.51%, -0.03%), p=0.044] and sotagliflozin 400 mg [LS Mean difference from placebo -2.53% (-3.79%, -1.28%), p<0.001] and in the 'total hip' for sotagliflozin 400 mg [LS Mean difference from placebo -1.18% (-2.07%, -1.28%), p=0.009].

At week 52, a decrease in *1.25-dihydroxyvitamin D* (-16% and -19% vs. -3.0%) and an increase in *25-hydroxyvitamin D* (40% and 41% vs. 34%) was observed for sotagliflozin 200 mg and 400 mg vs. placebo. A slight increase in *phosphate* for sotagliflozin 200 mg (8.7%) and sotagliflozin 400 mg (1.5%) vs. placebo (-2.5%) and a slight and similar increase in *PTH* for sotagliflozin 400 mg (4.2%) and placebo (3.3%) vs. sotagliflozin 200 mg (-0.83%) and no meaningful change in *calcium* (0.81% and -0.51% vs. -0.28%) was noted for sotagliflozin 200 mg and 400 mg vs. placebo. However, all changes in mean concentrations were within the reference range at baseline through week 52.

There was a dose-dependent increase from baseline to week 52 in the bone resorption marker CTX for sotagliflozin 200 mg and 400 mg (18% and 32%) relative to placebo (1.2%) and a non-dose-dependent increase in P1NP (8.7% and 3.4% vs. -4.9% for sotagliflozin 200 mg and 400 mg vs. placebo). There are plausible theories which indicate that treatment with SGLT2-inhibitors could induce decreases in BMD and increases in bone turnover caused by weight reduction. Long-term clinical relevance of the increase in CTX with regards to safety is unknown. 'Bone fractures' is included as an important potential risk in the RMP and will be closely monitored in ongoing clinical trials.

Cardiovascular risk

In the phase 2 and 3 studies in T1DM and T2DM subjects (SAF-4), the incidence rate of positively adjudicated MACE was higher for sotagliflozin 200 mg (9.97 subjects per 1000 PY) than for sotagliflozin 400 mg (4.95 subjects per 1000 PY) and placebo (8.65 subjects per 1000 PY); however, the incidence of MACE was lower in the 'all sotagliflozin' group (6.88 subjects per 1000 PY) compared to placebo. The estimated hazard ratio for positively adjudicated MACE in the 'all sotagliflozin' group relative to placebo was 0.68 and the upper CI 1.82. There was no notable difference in restricted mean survival time values between the all sotagliflozin group and placebo. Considering the known mechanism of action and experience from other products in the class, the provided data is reassuring although no firm conclusions could be drawn.

Malignancies

The incidence of malignancies 'of special interest' was low and similar across the groups (0.1-0.3%). When using the SMQ Malignant or unspecified tumours, there was no imbalance in the incidence of malignancies (0.4-0.6%). Further analysis, to identify subjects reporting a malignancy with onset greater than 6 months after the first dose of study medication, did also show low and similar incidence of malignancies across the groups (0.1-0.3%). Malignancy reported in more than one subject in the sotagliflozin groups was breast cancer (1 intraductal proliferative breast lesion and 1 invasive breast carcinoma). No trend could be observed, although, the risk for developing malignancies cannot be fully explored from controlled data in the clinical trial program covering rather short observation periods (mean duration less than a year).

Lower limb amputations

In total, there were two events of toe amputations (of which one transmetatarsal) in the sotagliflozin 200 mg and 400 mg group, respectively. Both cases had medical histories of multiple toe amputation. In accordance to the finalised CHMP/PRAC Referral procedure, a class warning regarding the increased risk of limb amputations has been included in the proposed SmPC.

Serious adverse events and deaths

Deaths

A total of 4 deaths occurred in the clinical studies, of which 3 in the placebo group and 1 in the sotagliflozin group (completed suicide).

Non-fatal serious adverse events

Non-fatal SAEs were most frequently reported in the SOC Metabolism and nutrition disorders, of which DKA was the most commonly reported event (3.6%, 5.0% and 0.6% for sotagliflozin 200 mg, sotagliflozin 400 mg and placebo).

Laboratory findings

Haematology

A slight increase from baseline to week 52 in haematocrit concentration was observed for sotagliflozin (2%) compared to placebo (0%). The proportion of subjects that met the PCI criteria (haematocrit >50%) were higher in the sotagliflozin 200 mg and 400 mg groups (6.7% and 8.2%, respectively) compared to the placebo group (2.7%). The observed increase in haematocrit is considered related to volume depletion associated with diuretic effect of sotagliflozin, as for other SGLT2 inhibitors. Increased haematocrit has been reflected in the proposed SmPC.

Serum lipids

Mean percent changes from baseline for sotagliflozin 200 mg and 400 mg versus placebo were: HDL-C 3.3% and 4.2% vs. 0.5%; LDL-C 5.0% and 6.1% vs. 3.3%; triglycerides 5.7% and 5.4% vs. 2.7%. Serum lipid changes have been reflected in the proposed SmPC.

Beta hydroxybutyrate (BHB)

BHB values that met the PCI criteria of ≥0.6 mmol/L were higher in the sotagliflozin 200 mg and 400 mg groups (47% and 46%, respectively) compared to the placebo group (20%) and BHB values that met the PCI criteria of ≥1.0 mmol/L were 20%, 18% and 6.8% for sotagliflozin 200 mg, sotagliflozin 400 mg and placebo, respectively.

Liver function tests

The percentages of subjects with increases in ALT and AST that met PCI criteria >3x ULN were similar across the groups or slightly higher in the placebo group; with increases in ALT (0.8%, 1.3% and 1.5%) and AST (1.3%, 1.3% and 1.5%) for sotagliflozin 200 mg, sotagliflozin 400 mg and placebo, respectively. The portion of subjects with increases in ALT or AST that met PCI criteria >5x ULN were low (0.4% increases in ALT across all groups and 0.4-0.6% increases in AST for sotagliflozin and 0% for placebo). No subjects had liver function test values that met Hy's Law criteria.

Blood pressure / pulse rate

Slight changes in in SBP and DBP were observed with sotagliflozin vs. placebo (mean changes of -1.6, -2.2 and 0.9 mmHg in SBP and -1.4, -1.0 and 0.1 mmHg in DBP for sotagliflozin 200 mg, sotagliflozin 400 mg and placebo). No clinically relevant mean change from baseline in pulse rate was observed.

Safety in special populations

Elderly

Overall in the clinical studies, there is rather limited data in subjects ≥65 years (n=265) and very limited data in subjects ≥75 years (n=18). Initiation of sotagliflozin in subjects above 75 years of age is not recommended. 'Use in subjects ≥75 years' has been included as missing information in the proposed RMP.

Gender

In SAF-1, adverse events were in general slightly more common in females (75-78%) than in males (68-73%) across the groups.

Race/Ethnicity

In SAF-1, adverse events were in general more common in non-whites (72-97%) than in whites (69-75%) across the groups; however, there is rather limited data for non-whites (n=92).

Baseline (week-2) A1C

The overall incidences of AEs were similar or slightly higher across the groups in subjects with baseline A1C ≤8.5% compared to subjects with baseline A1C >8.5%. The overall incidences of SAEs were higher across the groups in subjects with baseline A1C ≤8.5% (8-11%) compared to subjects with baseline A1C >8.5% (3-8%).

Body mass index

In SAF-1, the overall incidences of AEs and SAEs were similar or slightly higher across the groups in subjects with a BMI <25 kg/m^2 compared to subjects with a BMI ≥ 25 kg/m^2.

Subjects with renal impairment

In SAF-1, the subgroup of patients with eGFR <60 mL/min/1.73 m^2 made up for a small amount of subjects (n=71) wherefore difficult to draw any conclusions. In subjects with eGFR ≥60 to <90 mL/min/1.73 m^2 (n=774), the incidence of AEs and SAEs were similar across the groups; however, the incidence of volume depletion was slightly higher in the sotagliflozin groups (2.6% and 1.2% in sotagliflozin 200 mg and 400 mg, respectively) compared to placebo (0.8%). In subjects with eGFR ≥90 mL/min/1.73 m^2 (n=730), the overall incidence of AEs and SAEs were higher in sotagliflozin 200 mg (72% and 9.9%) and sotagliflozin 400 mg (75% and 8.3%) compared to placebo (68.9% and 4.7%).

In subgroup analyses in the SAF-3 Pool, subjects with eGFR <60 mL/min/1.73 m^2 (n=146) had a higher incidence of events of volume depletion for sotagliflozin 400 mg versus placebo; however the total number of subjects was small.

Subjects with hepatic impairment

Safety has not been established in subjects with moderate or severe hepatic impairment.

Immunological events

N/A

Safety related to drug-drug interactions and other interactions

Several phase 1 clinical pharmacology studies were conducted in healthy subjects to evaluate potential interaction between sotagliflozin and drugs commonly used in the T1DM population. No safety signal was identified in these studies.

Sotagliflozin is intended to be prescribed with insulin, and its impact on insulin dosing has been well characterized in phase 2 and 3 studies.

Discontinuation due to AEs

In SAF-1, the discontinuation rates due to AEs were higher in the sotagliflozin groups (4.4% and 6.7% for sotagliflozin 200 mg and 400 mg, respectively) than in the placebo group (3.8%). The most frequently reported AEs leading to study drug discontinuation was in the SOC Metabolism and nutrition disorders, of which DKA was the most commonly reported event (0.8%, 1.9% and 0% for sotagliflozin 200 mg, sotagliflozin 400 mg and placebo).

2.6.1. Discussion on clinical safety

The database is in general considered sufficient since a substantial number of subjects have been included. In total, 1,915 T1DM subjects were treated with sotagliflozin for a total exposure of 1,290 PY with 1,444 subjects (75%) treated for at least 24 weeks and 668 subjects (64%) treated for at least 52 weeks.

The approach for integrating and presenting safety data is acceptable. The primary safety pool (SAF-1) included two 52 weeks phase 3 studies in T1DM subjects. SAF-1 allows for comparison between placebo- and sotagliflozin-treated groups (200 mg and 400 mg). The two studies were conducted in subjects treated in the same way, i.e. with insulin optimization and committee oversight of insulin dosing. The broad safety pool (SAF-3) included T1DM subjects from both phase 2 and 3 studies (the two 52 weeks studies in SAF-1 and a world-wide 24 weeks study of sotagliflozin 400 mg vs placebo in T1DM subjects with insulin therapy that was not optimized). SAF-3 represents the largest pool of data from T1DM subjects.

Overall, the safety database is considered to be representative of a broad general population of adults with T1DM and includes a sufficient number of subjects with long duration of disease. However, there is rather limited data in subjects ≥65 years (n=265) and very limited data in subjects ≥75 years (n=18).

Discontinuation rates were similar across the treatment groups in SAF-1 (about 15%). The most common reason for discontinuation from study drug was withdrawal by subject and discontinuation due to adverse events.

In SAF-1, about 75% of the subjects reported AEs. The most frequently reported AEs for sotagliflozin 200 mg and sotagliflozin 400 mg versus placebo were viral upper respiratory tract infection (15% and 14% vs. 13%), diarrhoea (6.5% and 9.3% vs. 5.5%), diabetic ketoacidosis (4.0% and 5.7% vs. 1.0%), blood ketone body increased (4.0% and 5.1% vs. 0.6%), urinary tract infections (6.1% and 3.8% vs. 4.9%), genital infection fungal (3.4% and 4.0% vs. 0.2%) and vulvovaginal mycotic infection (2.9% and 5.1% vs. 1.9%).

Diabetic ketoacidosis

In SAF-1, there was a dose-dependent increase in the incidence of positively adjudicated DKA for sotagliflozin (2.9% and 3.8% for sotagliflozin 200 mg and 400 mg, respectively) compared to placebo (0.2%). The exposure-adjusted incidence rate was 3.12, 4.19 and 0.21 subjects per 100 PY for sotagliflozin 200 mg, sotagliflozin 400 mg and placebo, respectively. In total, 37 events of DKA in 36

subjects were received (of which 26 events of DKA for sotagliflozin). One subject (in the sotagliflozin group) experienced more than one event of DKA. All events of DKA were serious. The overall incidence of events of DKA leading to study discontinuation and study interruption was 33% and 56%, respectively.

In SAF-3 (excluding study 203), the exposure-adjusted incidence rate for positively adjudicated DKA was higher in the sotagliflozin groups (3.07 and 5.29 per 100 PY for sotagliflozin 200 mg and 400 mg, respectively) compared to placebo (0.76 per 100 PY), also in a dose-dependent manner. In total, 64 events of DKA in 63 subjects were received (of which 58 events of DKA for sotagliflozin).

The incidence of positively adjudicated DKA increased over time for sotagliflozin as compared to placebo in a clearly dose-dependent manner. In SAF-1, the cumulative incidence of DKA at week 52 was approximately 2.8% and 4.1% for sotagliflozin 200 mg and 400 mg sotagliflozin compared to 0.2% for placebo. The Kaplan Meier plot of the cumulative incidence of adjudicated DKA in SAF-3 showed a more pronounced differentiation between the 200 mg and 400 mg dose of sotagliflozin, with earlier TTO with 400 mg compared to the SAF-1 plot. This may reflect the data from study 312 where no insulin optimization occurred prior to randomization.

Mean time to onset of DKA was shorter in sotagliflozin 400 mg (159 days) than in sotagliflozin 200 mg (208 days); although SD standard deviation was broad the difference suggests a shorter TTO with the sotagliflozin 400 mg compared to sotagliflozin 200 mg.

Possible risk factors/contributing factors associated with an event of a positively adjudicated DKA was analysed. However, the analyses of potential risk factors of DKA were associated with uncertainties due to low number of events. However, the subgroup analyses indicated that subjects with previous DKA, subjects with high BHB levels at baseline or greater increase in BHB levels, subjects who had their insulin dose decreased with more than 20% and subjects who were CSII-users, were at higher risk to develop DKA. This has been reflected in the proposed product information. In 19% (7/35) of the cases, no cause (no contributing factor/ risk factor) to the DKA event could be identified.

The applicant has proposed risk minimisation measures in order to mitigate the risk of DKA which includes education of health care professionals and patients about self-monitoring of ketones, situations at-risk to allow for early diagnosis of ketonaemia or ketonuria and how to manage potential ketosis and maintenance of optimal insulin therapy. Detailed recommendations are provided in the SmPC and in the proposed educational materials. These recommendations are considered adequate in order to mitigate the risk, based on the knowledge on DKA in general and on the experience from the clinical trials.

Hypoglycaemia

In SAF-1, the incidence of documented hypoglycaemia was high across all treatment groups (≥98%). and the event rate was similar in the sotagliflozin groups (81 and 84 events per PY, respectively) and higher in the placebo group (96 events per PY). The incidence of recurrent documented hypoglycaemia events was similar across treatment groups in subjects having 1-5, 6-9 or >10 events.

The incidence of events of positively adjudicated severe hypoglycaemia was slightly higher for sotagliflozin 200 mg (5.7%) compared to sotagliflozin 400 mg (4.4%) but was even higher for placebo (7.4%). In the Kaplan-Meier plot of the cumulative incidence of severe hypoglycaemia, the sotagliflozin curves became less steep over time and provided a separation from placebo after about 24 weeks of treatment.

Volume depletion

In SAF-1, the incidence of volume depletion was 2.7%, 1.1% and 1.0% in sotagliflozin 200 mg, sotagliflozin 400 mg and placebo.

In the subgroup analyses in the SAF-3 Pool, subjects ≥65 years of age (n=209) had a higher incidence of events of volume depletion for sotagliflozin 200 mg and 400 mg relative to placebo. Subjects with eGFR <60 mL/min/1.73 m^2 (n=146) had a higher incidence of events of volume depletion for sotagliflozin 400 mg versus placebo. However, the total number of subjects in each analysis was small.

Genital mycotic infections

There was an increased risk of genital infections in sotagliflozin-treated subjects relative to placebo. Both female (15% and 17% vs 4.7%) and male (3.0% and 6.3% vs 1.1%) genital infections were highly increased compared to placebo. Most of the events were mild to moderate in intensity.

Urinary tract infections

The overall frequency of urinary tract infections was slightly higher for sotagliflozin 200 mg (7.1%) compared to sotagliflozin 400 mg (5.5%) and placebo (6.1%). The incidence of UTI in female subjects was highly increased and similar in subjects treated with sotagliflozin 200 mg (12%) and placebo (11%) compared to sotagliflozin 400 mg (7.0%); however, the incidence of UTI in male subjects was dose-dependently increased in the sotagliflozin 200 mg and 400 mg group (2.3% and 4.0%, respectively) as compared to placebo (1.8%).

Diarrhoea

The incidence of diarrhoea was increased in the sotagliflozin 200 mg and 400 mg group (6.5% and 8.8%, respectively) as compared to placebo (5.1%).

Renal events

Treatment with sotagliflozin was associated with a small decrease in eGFR in the sotagliflozin 200 mg and 400 mg groups (-4.0% and -4.3%) compared to placebo (-1.3%) that did return towards baseline at week 52. Also in subjects with moderate and mild renal impairment, the eGFR returned towards baseline at week 52. However, subjects with eGFR <60 mL/min/1.73 m^2 made up for a small number (n=71) in SAF-1, wherefore difficult to draw any firm conclusions in this subgroup.

The incidence of renal-related events was low and similar across the sotagliflozin groups (1.5% and 1.3%) and placebo (1.5%).

In the subgroup analysis in the SAF-3 Pool, subjects with eGFR 60 to <90 mL/min/1.73 m^2 had a higher incidence of renal events in sotagliflozin 200 mg (20 subjects per 1000 PY) compared to placebo (14 subjects per 1000 PY) and sotagliflozin 400 mg (11 subjects per 1000 PY). Subjects with eGFR <60 mL/min/1.73 m^2 (n=146) had a higher incidence of renal events in in the placebo group (103 subjects per 1000 PY) compared to sotagliflozin 200 mg and 400 mg (45 and 84 subjects per 1000 PY); however the total number of subjects was small to draw any firm conclusions.

Bone safety

The incidence of fractures through 52 weeks of treatment in study 309 and 310 was low and similar across the groups: 2.9%, 1.9% and 3.4% for sotagliflozin 200 mg, sotagliflozin 400 mg and placebo. Additional studies to characterize the risk of bone fractures for sotagliflozin are ongoing in T2DM subjects and data should be provided when available.

The change from baseline to week 52 in BMD was nominally statistically significant in the 'lumbar spine' for sotagliflozin 200 mg [LS Mean difference from placebo -1.27 (-2.51, -0.03), p=0.044] and sotagliflozin 400 mg [LS Mean difference from placebo -2.53 (-3.79, -1.28), p<0.001] and in the 'total hip' for sotagliflozin 400 mg [LS Mean difference from placebo -1.18 (-2.07, -1.28), p=0.009].

An increase in phosphate and 25-hydroxyvitamin D, a decrease in 1.25-dihydroxyvitamin D and no meaningful change in calcium were observed for sotagliflozin relative placebo. A slight and similar

increase in PTH for sotagliflozin 400 mg (4.2%) and placebo (3.3%) vs. sotagliflozin 200 mg (-0.83%) was noted. However, all changes in mean concentrations were within the reference range at baseline through week 52.

There was a dose-dependent increase from baseline to week 52 in the bone resorption marker, CTX, for sotagliflozin 200 mg and 400 mg (18% and 32%) relative to placebo (1.2%) and a non-dose-dependent increase in the bone formation marker, P1NP (8.7% and 3.4% vs. -4.9% for sotagliflozin 200 mg and 400 mg vs. placebo). Long-term clinical relevance of clinical relevance of the increase in CTX with regards to safety is unknown. 'Bone fractures' is included as an important potential risk in the RMP and will be closely monitored in ongoing clinical trials.

Cardiovascular risk

The estimated hazard ratio for positively adjudicated MACE in the all sotagliflozin group relative to placebo was 0.68 and the upper CI 1.82. There was no notable difference in restricted mean survival time values between the all sotagliflozin group and placebo. Considering the known mechanism of action and experience from other products in the class, the provided data are reassuring although no firm conclusions could be drawn.

Malignancies

There was no imbalance in the incidence of malignancies (0.4-0.6%). Further analysis, to identify subjects reporting a malignancy with onset greater than 6 months after the first dose of study medication, did also show low and similar incidence of malignancies across the groups (0.1-0.3%). Malignancy reported in more than one subject in the sotagliflozin groups was breast cancer (1 intraductal proliferative breast lesion and 1 invasive breast carcinoma). No trend could be observed, although, the risk for developing malignancies cannot be fully explored from controlled data in the clinical trial program covering rather short observation periods (mean duration less than a year).

Lower limb amputations

In total, there were two events of toe amputations (of which one transmetatarsal) in the sotagliflozin 200 mg and 400 mg group, respectively. Both cases had medical histories of multiple toe amputation.

Laboratory findings

Slight increases from baseline to week 52 in hematocrit (1.9% and 2.0% vs. 0%) and in serum lipids (HDL-C: 3.3% and 4.2% versus 0.5%; LDL-C: 5.0% and 6.1% versus 3.3%; triglycerides: 5.7% and 5.4% versus 2.7%) were noted for sotagliflozin 200 mg and 400 mg versus placebo.

Subgroups

In subgroup analyses in the SAF-3 Pool, there was rather limited data for subjects ≥65 years of age and subjects with eGFR <60 mL/min/1.73 m^2 to draw any firm conclusions.

In subjects ≥65 years of age (n=209), there was an increased risk of events related to volume depletion for sotagliflozin (102 and 38 EAIR per 1000 PY for sotagliflozin 200 mg and 400 mg, respectively) compared to placebo (zero events).

In subjects with eGFR 60 to <90mL/min/1.73 m^2 (n=1,492), the incidence of events of volume depletion was higher for sotagliflozin (28 and 24 subjects per 1000 PY for sotagliflozin 200 mg and 400 mg) compared to placebo (8.3 subjects per 1000 PY). In subjects with eGFR <60 mL/min/1.73 m^2 (n=146), the incidence of volume depletion was 111 subjects per 1000 PY for sotagliflozin 400 mg and 0 events for sotagliflozin 200 mg and placebo, respectively. Sotagliflozin should not be initiated in subjects with moderate renal impairment (eGFR <60 mL/min).

Overall in the clinical studies, there is rather limited data in subjects ≥65 years (n=265) and very limited data in subjects ≥75 years (n=18). Initiation of sotagliflozin treatment in subjects above 75 years of age is not recommended. 'Use in subjects ≥75 years' has been included as missing information in the proposed RMP.

Additional expert consultations

CHMP requested an ad hoc expert meeting to obtain the opinion of experts in the field of diabetes, as well as from patient representatives, on the benefits of the use of sotagliflozin in T1DM and the risk of diabetic ketoacidosis. Questions were addressed to the ad hoc expert group. The corresponding answers are presented below:

Question 1

What is the AHEG opinion on the clinical relevance of the treatment effects observed with sotagliflozin, esp. with regard to reduction of HbA1c, insulin doses, body weight and glucose variability?

Efficacy outcomes from studies 309, 310 and 312 were presented to the experts. With regard to individual aspects they had the following view:

The absolute reductions of HbA1c in the treatment groups (by 0.39 to 0.49 % (mean absolute change from baseline) in studies 309 and 310) were seen as positive and by several experts also as clinical relevant. Some experts with unrestricted participation agreed with the latter while others considered the reduction only of borderline clinical relevance.

The experts did not see an obvious benefit in the observed reduction of the average insulin doses (both basal and post prandial); one expert pointed out that insulin treatment in patients with type 1 diabetes mellitus (T1DM) is a hormone replacement therapy, therefore, conceptually, a lowering of the insulin dose may not be a goal at all (at least in non-overweight patients).

The reduction of body weight (by 1.68 to 2.72 kg (mean absolute change from baseline) in studies 309 and 310) was considered of minor benefit, but nevertheless was considered to be beneficial for some patients, according to some of the experts.

The studies also demonstrated a reduction of the variability of plasma glucose. This was seen by the experts in general as a relevant goal, in particular as it did not result in an increase of hypoglycaemic events. The AHEG noted that results from 2 questionnaires (DTSQ and DDS2) did demonstrate patients' preference for this treatment option and therefore could be supportive of the benefit of reduced glucose variability seen in the study. The experts found it, however, difficult to judge the clinical relevance of such patient reported outcomes. A benefit, mentioned by the patients participating in the expert meeting, is that such an improvement helps to simplify insulin dose calculations. An additional benefit noted was the lowering of blood pressure, although this was deemed relevant only by some of the experts.

The AHEG had a split view whether the totality of the efficacy outcomes demonstrated in studies would represent a clinically important benefit overall for patients with T1DM. Also among the experts with unrestricted participation some considered this to be clinically important while others as being of borderline clinical relevance.

Considering this to be a potentially lifelong treatment for T1DM, and the lack of data for sotagliflozin in T2DM (though available for already approved SGLT-2 inhibitors), experts and patients saw a need for the generation of more data with long-term treatment, including renal outcomes, and safety outcomes in general.

Question 2

The risk of DKA was considerably higher in the sotagliflozin treated groups compared to placebo despite careful information to patients and monitoring including measurements of ketones.

a. Please discuss the acceptability of this risk in clinical practice

All experts agreed that DKA represents a substantial and important risk. The experts also noted that the incidence of DKA in the real world is considerably higher than the incidence seen in the control group of the studies, presumably due to the highly selected patient population and study sites, as well as measures implemented during the trial to mitigate this risk. Nevertheless, the experts noted that cases of DKA where reported with similar frequency at all time points during the studies.

The experts stated that education and awareness of the problem, including the occurrence of DKA with only slightly elevated plasma glucose levels, is of foremost importance to reduce the risk.

The experts acknowledged the focused approach by the applicant to mitigate the risk, and thought measures such as 1-2 weeks intensified training prior to start of medication as beneficial.

The AHEG had split views on the acceptability of this risk. A majority of experts considered that the risk might be manageable in a restricted subpopulation (in particular in patients well trained and well-educated in treatment of T1DM). Some experts with unrestricted participation agreed with the latter while others were of the opinion that the expected extent of DKA could constitute an unacceptable risk in clinical practice.

The risk of DKA with the use of sotagliflozin maybe different in different health care systems as, according to experts, once available, the product could be expected to be prescribed also by less well-trained generalists in some member states.

b. Risk minimisation measures such as a guide for health care professionals and patients, as well as a Patient Alert Card have been proposed in order to mitigate the risks. What is the AHEG view on the appropriateness and effectiveness of the proposed measures in clinical practice?

The experts, including the 2 patients, raised some concerns that the proposed monitoring and precautionary activities may put quite a high burden on health care professionals and responsibility on patients.

The AHEG noted that the proposed minimisation of the risk of DKA relies heavily on the measurement of ketones, both before initiating therapy with sotagliflozin and in particular in case of signs or symptoms of DKA as well as circumstances perceived as posing an increased risk of DKA. It was acknowledged that ketone measurements by patients, as outlined by the applicant, represent an important contribution to the safe use of the product. It was pointed out, however, that this was not easily available in some member states, and even if this was the case, whether this was practical to measure on a frequent base and would achieve high acceptance by patients was questioned. Also, experience with this seems to indicate that slight increases for various causes (e.g. diet) may cause frequent follow-ups by health care professionals. From the patients' perspective the acceptance of another frequently to be self-measured laboratory parameter beyond glucose was questioned.

c. Please discuss any additional potential measures that could be introduced to decrease the risk of DKA.

The AHEG emphasized that general awareness and education of DKA (in particular also euglycaemic DKA), both with patients and health care professionals, is of high importance to reduce the risk. There

was also the unanimous view that to mitigate the risk treatment and prescription of this therapy should be exclusively by specialists.

The experts had no further proposals for risk mitigation.

Question 3

Please discuss which patients, if any, with T1DM could relevantly benefit from treatment with sotagliflozin, i.e. what could be a potential target population in clinical practice? Could restrictions with respect to BMI and insulin requirements be of relevance?

According to the applicant, the population should be selective, e.g. to include only patients who are compliant, who are willing and able to perform the foreseen ketone testing scheme, who do not have high alcohol consumption, who do not intend to get pregnant etc. The experts found any benefit in patients with T1DM could be expected to be most relevant in patients who are overweight, who are well educated and trained in T1DM, and who have large glucose variability. While it was acknowledged that the risk of DKA seemingly is higher in patients treated with insulin pump therapy, it was also said that those patients may particularly benefit as often suffering from high glucose variability in the first place, and in any case represent an increasing and important proportion of the T1DM population.

The experts were asked to discuss possible parameters indicative of an improved benefit/risk ratio. The total daily insulin dose as one possible parameter was discussed. While it was acknowledged that patients with low insulin requirements may be of somewhat increased risk of DKA, the experts were sceptical of the daily insulin dose as a possible parameter, as under some circumstances even patients with low insulin requirements may benefit and because insulin requirements may be the consequence of other underlying circumstances which should be taken into account. The experts thought that a low HbA1c value should not constitute an exclusion criterion per se, but that highly elevated HbA1c should, also considering that the latter may reflect a low degree of patient compliance. The experts also thought that body weight could be a relevant parameter, as the safety profile would improve with a higher BMI. One expert emphasized the importance of C-peptide levels, as an important marker of residual beta-cell function relevant for definition of the most appropriate target population to define an indication.

The experts agreed that the general T1DM population is in any case a too broad target population. They further agreed that proper patient education and compliance is very essential and, if approved for T1DM, the product should exclusively be prescribed in specialist centres, or at least by specialists, i.e. diabetologists or endocrinologists.

2.6.2. Conclusions on clinical safety

The safety profile for sotagliflozin is in general expected and most consistent with other SGLT2 inhibitors regarding the increased risk of volume depletion, genital infections and UTI. Inhibition of SGLT1 by sotagliflozin delays and reduces glucose absorption in the proximal intestine, which can lead to diarrhoea.

Initiation of sotagliflozin treatment in subjects above 75 years of age is not recommended. Sotagliflozin should not be initiated in subjects with moderate renal impairment (eGFR <60 mL/min).

The major safety concern of sotagliflozin is the increased and dose-dependent risk of DKA when used in T1DM patients. The increased risk is of concern considering that DKA is a condition which is potentially life-threatening that require hospitalisation. The incidence rate of DKA in T1DM patients is estimated to be about 3% (Hamdy and Khardori 2014) up to 7% (Weinstock et al 2013, Maahs et al 2015).

Analyses of potential risk factors of DKA were associated with uncertainties due to low number of events. However, the subgroup analyses showed that subjects with previous DKA, subjects with high BHB levels at baseline or greater increase in BHB levels, subjects who had their insulin dose decreased with more

than 20% and subjects who were CSII-users, were at higher risk to develop DKA. This has been reflected in the proposed product information.

The applicant has proposed risk minimisation measures in order to mitigate the risk of DKA which includes education of health care professionals and patients about self-monitoring of ketones, situations at-risk to allow for early diagnosis of ketonaemia or ketonuria and how to manage potential ketosis and maintenance of optimal insulin therapy. Detailed recommendations are provided in the SmPC and in the proposed educational materials. These recommendations are considered adequate in order to mitigate the risk, based on the knowledge on DKA in general and on the experience from the clinical trials.

2.7. Risk Management Plan

Safety concerns

Important identified risk	Diabetic ketoacidosis (DKA)
Important potential risks	Lower limb amputation Malignancies Pancreatitis Bone fractures
Missing information	Use of sotagliflozin in pregnant and lactating women Use of sotagliflozin in patients ≥75 years Long-term cardiovascular safety

DKA: Diabetic Ketoacidosis.

Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Risk of DKA in T1DM in patients treated with sotagliflozin as an adjunct to insulin versus insulin alone Planned Category 1	To evaluate the incidence of DKA with sotagliflozin treated patients as compared to non SGLTi treated patients to determine effectiveness of additional risk minimization measures for DKA in the post approval setting	DKA	Protocol submission	2 months after approval
			Registration in the EU PAS register	2 months after approval
			Interim report	Jul-2021; Dec-2021; Jul-2022; Dec-2022; Jul-2023; Dec-2023; Jul-2024 (To be adjusted based on launch plans)
			Final report	Dec-2024 (To be adjusted based on launch plans)

DKA: Diabetic Ketoacidosis; EU: European Union; PAS: Post-Authorization Study; SGLTi: Sodium–Glucose Co-transporter inhibitors; T1DM: Type 1 Diabetes Mellitus.

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
A randomized double-blind, placebo-controlled, parallel-group, multicenter study to demonstrate the effects of sotagliflozin on cardiovascular and renal events in patients with type 2 diabetes, cardiovascular risk factors and moderately impaired renal function Ongoing Category 3	The safety database of this study will provide safety information.	Lower limb amputation Pancreatitis Malignancies Bone fractures Long-term cardiovascular safety Patients ≥75 years	CSR	Q3 2022
A 26-week randomized, double-blind, placebo-controlled, parallel-group, multicenter, phase 3 study with a 78-week extension period to evaluate the efficacy and safety of sotagliflozin in patients 55 years and older with T2DM and inadequate glycemic control Ongoing Category 3	The safety database of this study will provide information on bone safety.	Bone fractures	First Step Analysis CSR (6-month data) Second Step Analysis CSR (24-month data)	Q2 2020 Q4 2021
Use of Sotagliflozin and Risk of Malignancies in Adult Patients with Type 1 Diabetes Mellitus Planned Category 3	To examine if there is an association between sotagliflozin use and the risk of bladder, renal, breast, Leydig cell, pancreatic, thyroid, and prostate cancers	Malignancies	Study protocol First interim report Second interim report Third interim report Fourth interim report Final study report	3 months following the drug approval and prior to study start 36 months post-launch 60 months post-launch 84 months post-launch 108 months post-launch 132 months post-launch

CSR: Clinical Study Report; DKA: Diabetic Ketoacidosis; EU: European Union; HCP: Healthcare Professional; PAS: Post-Authorization Study; Q: Quarter; T1DM: Type 1 Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus.

Risk minimisation measures

Safety concern	Risk minimization measures
Diabetic ketoacidosis (DKA)	**Routine risk minimization measures:** SmPC: Sections 4.1, 4.2, 4.4 and 4.8 PL: Sections 2 and 4 Prescription only medicine Legal status: Therapy with ZYNQUISTA should be under the supervision of a physician experienced in the management of T1DM **Additional risk minimization measures:** •HCP guide (including prescriber checklist) •Patient/carer's guide •Patient alert card
Lower limb amputation	**Routine risk minimization measures:** SmPC: Section 4.4 PL: Section 2 Prescription only medicine Legal status: Therapy with ZYNQUISTA should be under the supervision of a physician experienced in the management of T1DM **Additional risk minimization measures:** None
Malignancies	**Routine risk minimization measures:** SmPC: Section 5.3 PL: None Prescription only medicine Legal status: Therapy with ZYNQUISTA should be under the supervision of a physician experienced in the management of T1DM **Additional risk minimization measures:** None
Pancreatitis	**Routine risk minimization measures:** SmPC: None PL: None Prescription only medicine Legal status: Therapy with ZYNQUISTA should be under the supervision of a physician experienced in the management of T1DM **Additional risk minimization measures:** None
Bone fractures	**Routine risk minimization measures:** SmPC: None PL: None Prescription only medicine Legal status: Therapy with ZYNQUISTA should be under the supervision of a physician experienced in the management of T1DM **Additional risk minimization measures:** None
Use of sotagliflozin in pregnant and lactating women	**Routine risk minimization measures:** SmPC: Section 4.6 PL: Section 2 Prescription only medicine Legal status: Therapy with ZYNQUISTA should be under the supervision of a

	physician experienced in the management of T1DM **Additional risk minimization measures:** None
Use of sotagliflozin in patients ≥75 years	**Routine risk minimization measures:** SmPC: Sections 4.2, 4.4 and 5.2 PL: None Prescription only medicine Legal status: Therapy with ZYNQUISTA should be under the supervision of a physician experienced in the management of T1DM **Additional risk minimization measures:** None
Long-term cardiovascular safety	**Routine risk minimization measures:** SmPC: None PL: None Prescription only medicine Legal status: Therapy with ZYNQUISTA should be under the supervision of a physician experienced in the management of T1DM **Additional risk minimization measures:** None

AE: Adverse Event; DKA: Diabetic Ketoacidosis; HCP: Healthcare Professional; PASS: Post Authorization Safety Study; PL: Package Leaflet; RMP: Risk Management Plan; SGLTi: Sodium-Glucose Co-Transporter Inhibitor; SmPC: Summary of Product Characteristics; T1DM: Type 1 Diabetes Mellitus.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of sotagliflozin with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers sotagliflozin to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Quick Response (QR) code

A request to include a QR code in the labelling and package leaflet for the purpose of providing the patient alert card and educational material (Carer's guide) has been submitted by the applicant and has been found acceptable.

2.10.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Zynquista (sotagliflozin) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The indication proposed for Zynquista is:

"*Zynquista is indicated as an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus with a Body Mass Index (BMI) ≥ 27 kg/m^2, who have failed to achieve adequate glycaemic control despite optimal insulin therapy.*"

Type 1 diabetes mellitus is an autoimmune disease characterized by rapidly progressive pancreatic β-cell destruction leading to a state of absolute insulin deficiency. The aim of insulin treatment is to substitute for the lack of endogenous insulin.

3.1.2. Available therapies and unmet medical need

Therapeutic options for type 1 diabetes are limited to intensive insulin or insulin analogue therapy delivered subcutaneously by MDI or insulin pump. Based largely on the results of the Diabetes Control and Complications Trial (DCCT), current treatment guidelines recommend that patients with T1DM be treated to a goal HbA1c of <7.0% with intensive insulin therapy. Despite significant advances in insulin therapies, delivery methods and management, 70% of T1DM patients do not achieve optimal glycaemic control and are at increased risk of microvascular complications caused by chronic hyperglycaemia. Furthermore, some patients with T1DM experience wide fluctuation in their level of glucose control on currently

available insulin regimens. Intensive insulin therapy is also associated with an increased risk of hypoglycaemia, which can be life-threatening and may prevent patients from achieving optimal glycaemic control. Furthermore, intensive insulin therapy is associated with excessive weight gain and with peripheral insulin resistance, both being risk factors for hypertension, and CV disease. Approximately 60% of adults living with T1DM are overweight or obese, 60% have dyslipidaemia and 40% have hypertension, and are therefore at risk of developing macrovascular complications.

During insulin therapy, DKA may occur in situations where insulin administration is interrupted or when the insulin need is increased, e.g. with severe infections. In the literature, the incidence of DKA in T1DM patients shows large variations with a range from 0-56 per 1000 person-years. The prevalence of DKA decreases with increasing age.

For patients with T1DM no other treatment than insulin is authorized in the EU. The fact that most patients fail to achieve glycaemic targets and are at risk of hypoglycaemia and excessive weight gain on current type 1 treatments constitute an unmet need that could potentially be addressed by a new treatment used as an adjunct to insulin.

3.1.3. Main clinical studies

Three Phase 3 studies were included in the sotagliflozin T1DM program (studies 309, 310, and 312).

Studies 309 and 310 had the same design. Both studies were multicenter, randomized, double-blind, placebo-controlled, parallel-group studies to evaluate the efficacy, safety, and tolerability of sotagliflozin 200 mg and 400 mg versus placebo administered qd as an adjunct therapy in adults with T1DM who had inadequate glycaemic control with insulin therapy. For each study, the total duration of exposure to study drug was up to 52 weeks. A key design feature for studies 309 and 310 was insulin optimization prior to initiation of treatment with sotagliflozin. Study 309 included 793 patients and study 310 included 782 patients.

Study 312 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the net benefit (defined as the proportion of patients with A1C <7.0% and no episode of SH and no episode of DKA from randomization to Week 24) of sotagliflozin 400 mg versus placebo administered qd as an adjunct to insulin in patients with T1DM. This study did not utilize insulin optimization, and treatment was not confined to any specific insulin regimen. The total duration of study participation was up to 32 weeks. The study included 1405 patients.

3.2. Favourable effects

The primary objective for studies 309 and 310 was met as sotagliflozin was shown to be superior to placebo with regards to the primary endpoint - change in HbA1c from baseline. The treatment difference for sotagliflozin 200 mg vs placebo was -0.36% and -0.37% ($p<0.001$) and -0.41% and -0.35% ($p<0.001$) for the 400 mg dose in studies 309 and 310 respectively. Pooling of data from these studies did not change the outcome (-0.41% and -0.43% for 200 mg and 400 mg respectively). In both studies, there was virtually no change from baseline HbA1c in the placebo treated groups at week 24. In study 312, where change in HbA1c was a secondary endpoint and insulin treatment was not optimised, the change in HbA1c was larger in both the sotagliflozin and the placebo groups compared to studies 309/310. The treatment difference vs placebo was however comparable (-0.46%; $p<0.001$).

The proportion of patients achieving HbA1c <7.0% with no SH or DKA (net benefit) was the primary endpoint in study 312. The study met its primary endpoint as the net benefit difference vs placebo was 13.4% (95% CI 9.12, 17.67) which was statistically significant. The main contributing component was the proportion of patients achieving HbA1c <7.0% (29.6% vs 15.8% for 400 mg and placebo, respectively). In studies 309 and 310, the net benefit difference vs placebo was 12% (95% CI 4.28, 19.36) and 16%

(95% CI 9.17, 23.43) for sotagliflozin 200 mg and 22% (95% CI 14.10, 29.64) and 17% (95% CI 10.06, 24.35) for sotagliflozin 400 mg. Again the main contributing component was the proportion of patients achieving HbA1c <7.0% (36.9% and 33.3% in the 200 mg group, 46.9% and 33.8% in the 400 mg group vs 22.8% and 15.1% placebo, study 309 and 310 respectively).

When the net benefit was analysed by its components (HbA1c < 7.0% without SH or DKA), the findings were consistently in favour of sotagliflozin treatment. Generally higher proportions were observed with the higher dose. All outcomes were statistically significant.

PPG was only evaluated in the CGM substudy which included 278 patients from studies 309 and 310. Both doses of sotagliflozin resulted in a decrease in PPG. The treatment difference vs placebo was statistically significant: -35 mg/dL (95%CI -58.1, -11.4) for the 200 mg dose and -41 mg/dL (95%CI -63.6, -18.3) for the 400 mg dose. The findings were consistent with the data from the phase 2 program.

At Week 24, across the three studies, the LS mean difference from placebo in FPG was statistically significant for all sotagliflozin groups, ranging from -9.8 to -25.7 mg/dL (p <0.001 for all groups with the exception of sotagliflozin 200 mg in study 309 [p = 0.036]).

A large proportion of subjects (>70%) included in the studies were overweight. In all studies, the initial insulin optimising/run-in period was associated with a weight increase in all treatment groups, ranging from 0.3 kg to 0.95 kg with the largest increase observed in studies 309 and 310. At week 24, the treatment difference versus placebo was -2.35 (study 309) and -1.98 kg (study 310) with sotagliflozin 200 mg; it was -3.45 (study 309) and -2.58 kg (study 310) with sotagliflozin 400 mg (all p <0.001). In study 312, the treatment difference vs placebo was -2.98 kg (p <0.001). The DEXA substudy showed that the decrease in body weight was largely due to a loss of fat. This is in line with findings for other SGLT2-inhibitors.

Change in bolus insulin dose was a secondary endpoint in all three studies. In all studies the bolus insulin dose increased in the placebo treated groups (+3.9 to +6.6%). The change from baseline in the sotagliflozin treated groups ranged from -2.6 to -10.4% with a LS mean difference from placebo ranging from -5.7 to -16.4%. All comparisons vs placebo, except for the 200 mg group in study 309, were statistically significant (p<0.001). The change in basal insulin dose and total insulin dose was also assessed in all three studies. The pattern for the basal insulin dose was similar to that observed for the bolus doses but the percent changes were smaller than for the bolus doses. In the placebo groups, a LS mean increase in the total insulin dose at week 24 ranging from +0.6 to +2.9% was observed whereas the LS mean decrease in total insulin dose observed in the sotagliflozin treated groups ranged from – 4.3 to -8.9%.

Sotagliflozin treatment resulted in a modest placebo-adjusted decrease in SBP of -2 mmHg (95%CI -3.2, -0.7) in the 200 mg group and -3.5 mmHg (95%CI -4.7, -2.3) in the 400 mg group, pooled data. There was no apparent difference in the treatment effect in the overall population compared to patients with SBP ≥130 mmHg whereas a slightly larger reduction was observed in patients with SBP ≥140 mmHg.

The aim of the CGM substudy was to investigate the effect of sotagliflozin on blood glucose variability. The data showed an increase in the time spent in the desired blood glucose range (70-180 mg/dL) from 52.2% to 57.8% with sotagliflozin 200 mg and from 50.7% to 64.2% with sotagliflozin 400 mg, whereas no relevant change was observed for placebo. The difference vs placebo was statistically significant for the 200 mg group (5.3%, 95%CI 0.64, 10.06) and the 400 mg group (11.7%, 95%CI 7.14, 16.28). The difference was explained by a decrease in the time spent in the hyperglycaemic blood glucose range; whereas the time spent in the hypoglycaemic blood glucose range remained unchanged.

Patient related outcomes were assessed using the DTSQs and DDS2 scores. The DTSQs scores (range 0 to 36) indicated a higher satisfaction with sotagliflozin compared to placebo as reflected by a statistically significant increase in the score (+1.7 and +2.5 for sotagliflozin 200 mg and 400 mg respectively, all p

<0.001) as well as a higher proportion of patients reporting a change in score of 3 or more (54% and 52 % for sotagliflozin vs 28% for placebo). The DDS2 scores (range 0 to 6) indicated less distress with sotagliflozin treatment compared to placebo with a treatment difference vs placebo ranging from -0.3 (p = 0.025) to -0.8 (p <0.001) across the sotagliflozin groups.

One-year exploratory efficacy data was provided from studies 309 and 310. At 52 weeks there was still a modest but statistically significant treatment difference between placebo and sotagliflozin of about -0.25% for the 200 mg dose and -0.3% for the 400 mg dose. Net benefit had decreased somewhat at week 52, now ranging from 7.2 to 13.4% as compared to 12 to 22% at week 24. This was mainly due to a lower proportion of patients achieving HbA1c <7.0%. The body weight slightly increased up to week 52 in the placebo treated groups, whereas body weight remained stable and reduced in all sotagliflozin treated groups after week 24 and up to week 52. No apparent change in the effect on total fat mass was observed. The insulin doses remained essentially unchanged after week 24. Patient reported outcomes measuring diabetes distress remained in favour of sotagliflozin.

Pooled subgroup analyses from studies 309/310 were provided for the two doses 200 mg and 400 mg (ES1 pool) as well as for the ES2 pool (all patients treated with sotagliflozin 400 mg). The analyses showed consistent findings for all demographic and baseline characteristics tested with regards to the change from baseline in HbA1c, except for patients with eGFR <60 where the 95%CI included zero in all three analyses. The number of patients were few, thus the 95%CI were wide. The subgroup analysis indicates that the effect on HbA1c is attenuated in patients with eGFR <60 mL/min/1.73 m^2 (-0.28% for the 200 mg dose and -0.21% for the 400 mg dose) but the data is uncertain due to the low number of subjects (47) included in the analysis. The SmPC recommends that treatment should not be initiated in patients with eGFR <60 mL/min/1.73 m^2, although treatment may be maintained until eGFR falls to 45 mL/min/1.73 m^2.

Notably, no patients aged 75 years or above were included in the subgroup analyses.

No direct comparison between the doses investigated in studies 309 and 310 (200 mg and 400 mg) was made; instead both doses were compared to placebo. Numerically there was a consistent treatment difference between the two doses in favour of the 400 mg dose although the treatment difference with regards to HbA1c was very small. Taking the individual response into account, a dose increase could be beneficial in some patients, especially in overweight patients without increased ketosis and in need of further intensification of treatment.

3.3. Uncertainties and limitations about favourable effects

The outcome of the three Phase 3 studies showed consistent results in spite of the differences in study design between studies 309/310 and study 312. Thus there are no important uncertainties with regards to the favourable effects in the overall population.

No specific clinical studies have been conducted in special populations. The number of older subjects included in the studies was low. The SmPC includes recommendations not to initiate treatment in patients above the age of 75 which is considered adequate and sufficient.

The clinical data in patients with impaired renal function is scarce. It is postulated that effect is maintained also in renally impaired patients due to the combined effect of the SGLT1 and SGLT2 inhibition. The data provided is however not sufficient to clarify how much of the effect is mediated by the SGLT1 inhibition.

Data from the DCCT trial has shown that a decrease in HbA1c is correlated with a decrease in mortality in patients with T1DM. However the long-term effect of stabilised blood glucose levels is less well documented, thus the clinical significance of the decrease in the glucose variability observed in the studies is uncertain.

3.4. Unfavourable effects

For the safety evaluation, results of the phase 2 and 3 studies from T1DM subjects were pooled. The primary safety pool (SAF-1) includes two 52 weeks phase 3 studies conducted in T1DM subjects treated in the same way, i.e. with insulin optimization and committee oversight of insulin dosing. The broad safety pool (SAF-3) includes T1DM subjects from both phase 2 and 3 studies (the two 52 weeks studies in SAF-1 and a world-wide 24 weeks phase 3 study of sotagliflozin 400 mg vs placebo in T1DM subjects with insulin therapy that was not optimized). SAF-3 represents the largest pool of data from T1DM subjects.

In total, 1,915 T1DM subjects (1,290 PY) were treated with sotagliflozin with 1,444 subjects (75%) treated for at least 24 weeks and 668 subjects (64%) treated for at least 52 weeks.

The incidence of *diabetic ketoacidosis* was dose-dependently increased for sotagliflozin. In SAF-1, the exposure-adjusted incidence rate (EAIR) was 3.12, 4.19 and 0.21 subjects per 100 PY (2.9%, 3.8% and 0.2%) for sotagliflozin 200 mg, sotagliflozin 400 mg and placebo. In SAF-3, the EAIR was 3.07 and 5.29 per 100 PY for sotagliflozin 200 mg and 400 mg, respectively, compared to 0.76 per 100 PY for placebo. The incidence of DKA increased over time for sotagliflozin as compared to placebo in a clearly dose-dependent manner. In SAF-1, the cumulative incidence of DKA at week 52 was approximately 2.8% and 4.1% for sotagliflozin 200 mg and 400 mg sotagliflozin compared to 0.2% for placebo. The Kaplan Meier plot of the cumulative incidence of adjudicated DKA in SAF-3 showed a more pronounced differentiation between the 200 mg and 400 mg dose of sotagliflozin, with earlier TTO with 400 mg compared to the SAF-1 plot. This may reflect the data from study 312 where no insulin optimization occurred prior to randomization. Mean time to onset of DKA was shorter in sotagliflozin 400 mg (159 days) than in sotagliflozin 200 mg (208 days); although SD standard deviation was broad the difference suggests a shorter TTO with sotagliflozin 400 mg compared to sotagliflozin 200 mg.

The incidence of documented *hypoglycaemia* was ≥98% in all treatment groups. The event rate was 81, 84 and 96 events per PY and the incidence of severe hypoglycaemia was 5.7%, 4.4% and 7.4%, respectively, for sotagliflozin 200 mg, sotagliflozin 400 mg and placebo. In the Kaplan-Meier plot of the cumulative incidence of severe hypoglycaemia, the sotagliflozin curves became less steep over time and provided a separation from placebo after about 24 weeks of treatment.

Events of *volume depletion* were reported more frequently with sotagliflozin (200 mg: 2.7%; 400 mg: 1.1%) than with placebo (1.0%). In SAF-3, subjects ≥65 years of age (n=209) had a higher incidence of volume depletion for sotagliflozin 200 mg and 400 mg relative to placebo and subjects with eGFR <60 mL/min/1.73 m^2 (n=146) had a higher incidence of volume depletion for sotagliflozin 400 mg versus placebo.

There was an increased risk of *genital infections* in sotagliflozin-treated subjects relative placebo. Both female (15% and 17% vs 4.7%) and male (3.0% and 6.3% vs 1.1%) genital infections were increased compared to placebo. Most of the events were mild to moderate in intensity.

The incidence of *urinary tract infections* in female subjects was increased and similar in subjects treated with sotagliflozin 200 mg (12%) and placebo (11%) compared to sotagliflozin 400 mg (7.0%); however, the incidence of UTI in male subjects was dose-dependently increased in the sotagliflozin 200 mg and 400 mg group (2.3% and 4.0%, respectively) as compared to placebo (1.8%).

The incidence of *diarrhoea* was increased in the sotagliflozin 200 mg and 400 mg group (6.5% and 8.8%, respectively) as compared to placebo (5.1%). Most of the events were mild or moderate in intensity.

Treatment with sotagliflozin was associated with a *decrease in eGFR* in the sotagliflozin 200 mg and 400 mg groups (-4.0% and -4.3%) compared to placebo (-1.3%) that that did return towards baseline at week 52. Also in subjects with moderate and mild renal impairment, the eGFR returned towards baseline

at week 52, however; subjects with eGFR <60 mL/min/1.73 m^2 made up for a small number in SAF-1 (n=71), wherefore difficult to draw any firm conclusions in this subgroup. The incidence of renal-related events was similar across the sotagliflozin groups (1.5% and 1.3%) and placebo (1.5%).

The incidence of *fractures* through 52 weeks of treatment was similar across the groups: 2.9%, 1.9% and 3.4% for sotagliflozin 200 mg, sotagliflozin 400 mg and placebo. A statistically significant reduction in 'lumbar spine' bone mineral density was observed at week 52 for sotagliflozin 200 mg [LS Mean difference from placebo -1.27% (-2.51%, -0.03%), p=0.044] and sotagliflozin 400 mg [LS Mean difference from placebo -2.53% (-3.79%, -1.28%), p<0.001] and in 'total hip' BMD for sotagliflozin 400 mg [LS Mean difference from placebo -1.18% (-2.07%, -1.28%), p=0.009]. There was a dose-dependent increase from baseline to week 52 in the bone resorption marker, CTX, for sotagliflozin 200 mg and 400 mg (18% and 32%) relative to placebo (1.2%) and a non-dose-dependent increase in the bone formation marker, P1NP (8.7% and 3.4% vs. -4.9% for sotagliflozin 200 mg and 400 mg vs. placebo).

Subgroups

In subgroup analyses in the SAF-3 pool, there was rather limited data for subjects ≥65 years of age and subjects with eGFR <60 mL/min/1.73 m^2 to draw any firm conclusions.

In subjects ≥65 years of age (n=209), there was an increased risk of events related to volume depletion for sotagliflozin (102 and 38 EAIR per 1000 PY for sotagliflozin 200 mg and 400 mg, respectively) compared to placebo (zero events).

In subjects with eGFR 60 to <90mL/min/1.73 m^2 (n=1,492), the incidence of events of volume depletion was higher for sotagliflozin (28 and 24 subjects per 1000 PY for sotagliflozin 200 mg and 400 mg) compared to placebo (8.3 subjects per 1000 PY). In subjects with eGFR <60 mL/min/1.73 m^2 (n=146), the incidence of volume depletion was 111 subjects per 1000 PY for sotagliflozin 400 mg and 0 events for sotagliflozin 200 mg and placebo, respectively.. Sotagliflozin should not be initiated in subjects with moderate renal impairment (eGFR <60 mL/min), as advised in the SmPC.

3.5. Uncertainties and limitations about unfavourable effects

Overall, there is rather limited data from the clinical studies in subjects ≥65 years (n=265) and very limited data in subjects ≥75 years (n=18). Accordingly, the SmPC advises that initiation of sotagliflozin treatment in patients above 75 years of age is not recommended.

The major safety concern of sotagliflozin is the increased and dose-dependent risk of DKA. The incidence of DKA increased over time for sotagliflozin as compared to placebo in a clearly dose-dependent manner. In SAF-1, the cumulative incidence of DKA at week 52 was approximately 2.8% and 4.1% for sotagliflozin 200 mg and 400 mg sotagliflozin compared to 0.2% for placebo.

Possible risk factors/contributing factors associated with an event of a positively adjudicated DKA were analysed. However, the analyses of potential risk factors of DKA were associated with uncertainties due to low number of events. However, the subgroup analyses indicated that subjects with previous DKA, subjects with high BHB levels at baseline or greater increase in BHB levels, subjects who had their insulin dose decreased by more than 20% and subjects who were CSII-users, were at higher risk to develop DKA. This has been reflected in the proposed product information. In 19% (7/35) of the cases, no cause (no contributing factor/ risk factor) for the DKA event could be identified.

The applicant has proposed risk minimisation measures in order to mitigate the risk of DKA which includes education of health care professionals and patients about self-monitoring of ketones, situations at-risk to allow for early diagnosis of ketonaemia or ketonuria and how to manage potential ketosis and maintenance of optimal insulin therapy. Detailed recommendations are provided in the SmPC and in the

proposed educational materials. These recommendations are considered adequate in order to mitigate the risk, based on the knowledge on DKA in general and on the experience from the clinical trials.

3.6. Effects Table

Table 29 Effects Table for Zynquista in the treatment of T1DM.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
HbA1c	Change from baseline at week 24	%	200 mg -0.43 -0.39 400 mg -0.48 -0.37 400 mg -0.79	Placebo -0.07 -0.02 -0.33	Difference (95%CI) -0.36 (-0.45, -0.27) -0.37 (-0.48, -0.25) -0.41 (-0.50, -0.32) -0.35 (-0.47, -0.24) -0.46 (-0.54, -0.38)	Study 309 and 310 Study 312
Net benefit	Proportion of patients with A1C <7.0% and no SH and no DKA at week 24	%	200 mg 33.5 31.4 400 mg 43.5 32.3 400 mg 28.6	Placebo 21.6 15.1 15.2	Difference (95%CI) 11.8 (4.28, 19.36) 16.3 (9.17, 23.43) 21.9 (14.10, 29.64) 17.2 (10.06, 24.35) 13.4 (9.12, 17.67)	Study 309 and 310 Study 312
Bolus insulin dose	Change from baseline at week 24	%	200 mg -1.8 -7.0 400 mg -8.8 -10.5 400 mg -5.7	Placebo +3.9 +5.9 +6.6	Difference (95%CI) -5.7 (-12.82, 1.42) -12.9 (-20.50, -5.38) -12.7 (-19.79, -5.55) -16.4 (-23.90, -8.83) -12.3 (-18.17, -6.48)	Study 309 and 310 Study 312
Body weight	Change from baseline at week 24	kg	200 mg -1.57 -1.88 400 mg -2.67 -2.47 400 mg -2.21	Placebo +0.78 +0.17 +0.77	Difference (95%CI) -2.35 (-2.85, -1.85) -1.98 (-2.53, -1.44) -3.45 (-3.95, -2.94) -2.58 (-3.12, -2.04) -2.98 (-3.31, -2.66)	Study 309 and 310 Study 312

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Glucose variability	Percent time spent inside target range (70-180 mg/dL)	%	200 mg 57.8 400 mg 64.2	Placebo 51.6	Difference (95%CI) 5.3 (0.64, 10.06) P = 0.026 11.7 (7.14, 16.28) p <0.001	CGM sub-study
Systolic blood pressure	Changes from baseline at week 12	mmHg	200 mg -2.6 -2.2 400 mg -3.3 -4.8 400 mg -2.21	Placebo +0.6 -1.8 +0.5	Difference (95%CI) -3.5 (-5.2, -1.8) -0.4 (-2.2, 1.3) -4.2 (-5.9, -2.4) -2.8 (-4.6, -1.1) -3.8 (-4.9, -2.7)	Study 309 and 310 Study 312
DTSQs, responder	Change in score of 3 or more	%	200 mg 54, 41 400 mg 52, 43	Placebo 28, 29	p <0.005, all comparisons	Study 309 and 310
Unfavourable Effects						
Diabetic keto-acidosis	Number of subjects with definite DKA	n (%)	200 mg: 15 (2.9%) 400 mg: 20 (3.8%)	1 (0.2%)		SAF-1
Diabetic keto-acidosis	Exposure-adjusted incidence rate (subjects per 100 patient-years)	EAIR (n/100 PY)	200 mg: 3.12 subjects per 100 PY 400 mg: 4.19 subjects per 100 PY	0.21 subjects per 100 PY	Rate of DKA in T1DM reported in the literature to be 2 subjects per 100 PY (or 3%)	SAF-1
Diabetic keto-acidosis	Number of subjects with definite DKA	n	200 mg: 15 400 mg: 42	6		SAF-3
Diabetic keto-acidosis	Exposure-adjusted incidence rate (subjects per 100 patient-years)	EAIR (n/100 PY)	200 mg: 3.07 subjects per 100 PY 400 mg: 5.29 subjects per 100 PY	0.76 subjects per 100 PY	Rate of DKA in T1DM reported in the literature to be 2 subjects per 100 PY (or 3%)	SAF-3

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Severe hypo-glycaemia	Subjects with at least 1 event	n (%)	200 mg: 30 (5.7%) 400 mg: 23 (4.4%)	39 (7.4%)		SAF-1
Volume depletion	Incidence of volume depletion	%	200 mg: 2.7% 400 mg: 1.1%	1.0%		SAF-1
Urinary tract infections	Incidence of urinary tract infections	%	200 mg: 7.1% 400 mg: 5.5%	6.1%		SAF-1
Genital mycotic infections	Incidence of genital mycotic infections	%	*Female genital infections* 200 mg: 15% 400 mg: 17% *Male genital infections* 200 mg: 3.0% 400 mg: 6.3%	*Female genital infections* 4.7% *Male genital infections* 1.1%		SAF-1

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

T1DM is characterised by insulin deficiency due to destruction of the insulin-producing cells. Insulin treatment aims at normalising blood glucose levels in order to avoid acute symptoms of hyperglycaemia and to minimise the risk of long-term microvascular and macrovascular complications. Optimal treatment requires that the patient monitors blood glucose levels and makes insulin dose adjustments on a daily basis. Thus, the management of T1DM has a large impact on the patient's daily life. Currently only insulin is approved for the treatment of T1DM in the EU. In spite of improvements in insulins, methods of administration and monitoring of blood glucose, normalisation of glucose levels is difficult, and the treatment is associated with hypo- and hyperglycaemia as well as weight increase. Thus, there is a need for new therapies as an adjunct to insulin therapy, in order to alleviate the negative effects of insulin treatment in order to reach treatment targets. In addition, treatment of patients with T1DM carries an inherent risk of DKA since interruption of treatment or an excessive increase in insulin need will result in the development of DKA.

The data provided with this application show that sotagliflozin, when added to insulin, consistently reduced HbA1c by about 0.4% from a relatively low baseline HbA1c of 7.6-7.7%. This was achieved with a reduction of the risk of severe hypoglycaemia compared to placebo. Sotagliflozin was also shown to reduce glucose variability as indicated by a significant increase in time spent in the desired blood glucose

range. Although the clinical significance of time spent in range is not strongly established, the applicant refers to a recent analysis of DCCT data which shows that there is an association between time in range and the development of microvascular complications. Sotagliflozin also had consistent and clinically relevant effects on the CV risk factors body weight and SBP. In addition, patients treated with sotagliflozin reported a significant improvement in treatment satisfaction and distress due to the disease. Notably, these patient-related outcomes were observed in spite of the increased ketone monitoring used in the trials in order to reduce the risk of DKA. Thus, the effect of sotagliflozin is considered to be of clear clinical relevance.

The effect in different subgroups was comparable to that of the total population. The unmet need in patients with overweight/obesity is however very different compared to patients with normal weight considering that the alternative treatment, i.e. increase of insulin dose, will lead to additional weight gain which subsequently may increase the risk of cardiovascular disease. Therefore, the expected benefit in clinical practice is higher in overweight/obese patients compared to the total T1DM population.

There were no apparent differences between the two doses investigated with regards to the effect on glycaemic control; however, a more pronounced effect on body weight was observed with the higher dose, especially in obese subjects. There is a trend towards a better effect on time in range and blood pressure and the reduction of severe hypoglycaemias was more pronounced with the 400 mg dose. Taking the individual response into account, a dose increase could be beneficial in some patients and the higher dose is therefore considered justified.

The safety profile of sotagliflozin is in general as expected and consistent with other SGLT2 inhibitors regarding the increased risk of volume depletion, genital infections and UTI. Inhibition of SGLT1 by sotagliflozin delays and reduces glucose absorption in the proximal intestine, which can lead to diarrhoea.

There are limitations in both safety and efficacy data in elderly patients (>75 years of age) and patients with moderate renal impairment (eGFR <60 mL/min/1.73 m^2). Initiation of sotagliflozin treatment in subjects above 75 years of age is not recommended. Sotagliflozin should not be initiated in subjects with moderate renal impairment (eGFR <60 mL/min).

In 2015, an Art 20 referral procedure on SGLT2-inhibitors and DKA (EMA/PRAC/50218/2016) was initiated due to an increased reporting of DKA in T2DM patients. The data available at the time of the procedure was not sufficient to conclude whether SGLT2-inhibitors increased the risk of DKA. However, based on the knowledge about the pharmacodynamic effect of SGLT2-inhibition, it is plausible that treatment with SGLT2-inhibitors could promote DKA development.

The data presented with this application indeed show that, in spite of the precautionary measures taken, there was a considerable increase in the risk of DKA compared to placebo in T1DM patients. This lends support to a direct promoting effect of sotagliflozin on the development of DKA. The increased risk is of concern, considering that DKA is a condition which is potentially life-threatening that require hospitalisation.

Possible risk factors/contributing factors associated with an event of a positively adjudicated DKA was analysed. However, the analyses of potential risk factors of DKA are associated with uncertainties due to low number of events. However, the subgroup analyses indicated that subjects with previous DKA, subjects with high BHB levels at baseline or greater increase in BHB levels, subjects who had their insulin dose decreased with more than 20% and subjects who were CSII-users, were at higher risk to develop DKA. This has been reflected in the proposed product information.

The applicant has proposed risk minimisation measures in order to mitigate the risk of DKA which include education of health care professionals and patients about self-monitoring of ketones, situations at-risk to allow for early diagnosis of ketonaemia or ketonuria and how to manage potential ketosis and maintenance of optimal insulin therapy. Detailed recommendations are provided in the SmPC and in the

proposed educational materials. These recommendations are considered adequate in order to mitigate the risk, based on the knowledge on DKA in general and on the experience from the clinical trials.

However, as the risk of DKA may not be totally abolished, the benefit risk balance in the initially proposed target population, i.e. all patients with T1DM, is considered negative.

However, overweight patients (BMI ≥27 kg/m^2) with T1DM and inadequate glycaemic control is a population with an unmet medical need since currently the only treatment option is intensified insulin treatment, known to result in further increases in body weight. In addition to the blood glucose lowering effect, the weight reduction and the reduction of SBP are of greatest importance in patients with high BMI. Furthermore, patients with higher BMI have a higher insulin need and as indicated by the data, higher insulin doses decrease the risk of DKA. Therefore, the benefits are considered to outweigh the risks in patients with BMI ≥27 kg/m^2 who have failed to achieve desired glycaemic control despite optimal insulin therapy.

3.7.2. Balance of benefits and risks

The target population is restricted to patients with a BMI ≥27 kg/m^2. In this population the benefit risk balance is positive.

3.7.3. Additional considerations on the benefit-risk balance

An AHEG meeting was held 21 November 2018, see section 2.6.1. (Discussion on clinical safety).

A PASS study (category 1) is planned. This is a non-interventional study to evaluate the risk of DKA of sotagliflozin in patients with type 1 diabetes mellitus (T1DM) in a real-world setting. The objective is to evaluate the incidence of DKA with sotagliflozin treated patients in real life as compared to non-SGLTi treated patients to determine effectiveness of additional risk-minimisation measures for DKA in the post approval setting.

3.8. Conclusions

The overall B/R of Zynquista is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Zynquista is favourable in the following indication:

Zynquista is indicated as an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus with a Body Mass Index (BMI) ⩾ 27 kg/m2, who have failed to achieve adequate glycaemic control despite optimal insulin therapy.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription .

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch of Zynquista (sotagliflozin), as an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus with a Body Mass Index (BMI) ≥ 27 kg/m^2, who have failed to achieve adequate glycaemic control despite optimal insulin therapy, in each Member State, the Marketing Authorisation Holder (MAH) must agree the content and format of educational materials for sotagliflozin, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational materials are aimed at providing guidance on how to manage risk of diabetic ketoacidosis (DKA) in patients with type 1 diabetes.

The MAH shall ensure that in each Member State where sotagliflozin is marketed, all healthcare professionals and patients/carers who are expected to prescribe, dispense or use the product have access to:

- Guide for Health Care Professionals including a prescriber's checklist
- Patient's/Carer's Guide
- Patient Alert Card

The guide for healthcare professionals including the prescriber's checklist should contain the following key elements:

- Sotagliflozin is not a substitute for insulin (and does not alter insulin-sensitivity).
- The risk of DKA is increased with sotagliflozin treatment.
- If treated with sotagliflozin, glucose levels will not adequately reflect insulin needs, and DKA may occur in patients treated with sotagliflozin even if blood glucose levels are below 14 mmol/l (250 mg/dl). Therefore, glucose monitoring must be supplemented by ketone monitoring.
- Patients with euglycaemic DKA may need glucose in addition to standard of care for DKA and sotagliflozin should be discontinued if DKA occurs.
- Guidance to the physician for assessing whether the patient is eligible for sotagliflozin prescription, e.g. patient selection criteria including adherence to insulin treatment and insulin thresholds, patient's beta-hydroxybutyrate (BHB) < 0.6 mmol/L or urine ketones < 1+, BMI ≥ 27 kg/m^2, absence of DKA risk factors.
- Guidance to the physician for assessing whether the patient is prepared and engaged to perform self-ketone testing before and during therapy.
- Summary of the recommendations for patients, particularly regarding blood ketone measurement and managing sick days.
- For pump users: restrict sotagliflozin prescription to patients experienced in pump use, common trouble-shooting strategies when interruptions of insulin delivery via pump occur in case of pump failure.
- Counsel the patient and evaluate their adherence to ketone monitoring while establishing their baseline ketone level 1 to 2 weeks before treatment initiation and ensure the patient
  - Has received education/training in ketone testing and interpreting/acting upon test results
  - Is willing/able to perform ketone testing as prescribed
  - Is adequately informed about managing sick days
- Ensure the patient is on optimal insulin therapy prior to initiation of sotagliflozin treatment.
- Sotagliflozin treatment should be temporarily stopped before surgical procedures or in case of hospitalisation for acute serious illness.
- If addition of sotagliflozin leads to marked reduction of insulin need, discontinuation of sotagliflozin should be considered to avoid high risk of DKA.

The patient's/carer's guide should contain the following key elements:

- Sotagliflozin is not a substitute for insulin.
- DKA may occur in patients treated with sotagliflozin even if blood glucose levels are below 14 mmol/l (250 mg/dl), i.e. an explanation of the concept of euglycaemic DKA.
- Signs/symptoms of DKA - if not adequately managed DKA can be severe and fatal.
- How to measure ketones, how to interpret the results and what to do in case of hyperketonaemia/DKA (contact HCP immediately if BHB > 0.6 mmol/L with symptoms or if BHB > 1.5 mmol/L with or without symptoms).
- Insulin dose reduction during treatment should only be done when needed to prevent hypoglycaemia and should be done cautiously to avoid ketosis and DKA.
- Do not start caloric restriction or carbohydrate restriction while treated with sotagliflozin.

The patient alert card should contain the following key elements:

- The patient alert card should be presented to any HCP consulted.
- DKA may occur in patients treated with sotagliflozin even if blood glucose levels are below 14 mmol/l (250 mg/dl).
- Signs/symptoms of DKA.
- Patients with euglycaemic DKA should receive glucose, insulin and fluids for DKA, sotagliflozin should be discontinued.
- Sotagliflozin should be temporarily stopped before surgical procedures or hospitalisation for acute serious illness.
- Contact details of the sotagliflozin prescriber' and 'Name of patient'.

Obligation to conduct post-authorisation measures:

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date

Description	Due date
Non-interventional PASS: In order to estimate the incidence of DKA in T1DM sotagliflozin treated patients to assess the effectiveness of the risk minimisation measures implemented in Europe, the MAH should conduct and submit the results from an observational cohort study using existing data sources in European countries where sotagliflozin will be launched for T1DM.	31/12/2024

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that sotagliflozin is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.