26 May 2016
EMA/428168/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Qtern

International non-proprietary name: saxagliptin / dapagliflozin

Procedure No. EMEA/H/C/004057/0000

Note

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

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List of abbreviations

Abbreviation or special term	Explanation
5-OH	5-hydroxy
30-MSU	30-Month Safety Update
AACE	American Association of Clinical Endocrinologists
ADA	American Diabetes Association
AE	Adverse event
AEoSI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
API	Active Pharmaceutical Ingredient
AR	Assessment Report
AR	Adverse reaction
AS	Active Substance
ASM	Active Substance Manufacturer
AST	Aspartate aminotransferase
AUC	Area under the concentration vs. time curve
$AUC_{(0-T)}$	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration
$AUC_{(INF)}$	Area under the plasma concentration-time curve from time zero extrapolated to infinity
BE	Bioequivalence
BCS	Biopharmaceutics Classification System
BMI	Body mass index
BMS	Bristol-Myers Squibb Company
BMS-477118	Saxagliptin
BMS-510849	5-OH saxagliptin, major hydroxylated metabolite of saxagliptin (pharmacologically active)
BMS-512148	Dapagliflozin
BP	Blood pressure
CD3	Cluster of differentiation 3
CD26	Cluster of differentiation 26
CEP	Certificate of Suitability of the Ph.Eur.
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CK	Creatine kinase
CLTp	total plasma clearance
CNS	Central Nervous System
C_{max}	Maximum plasma concentration
CoA	Certificate of Analysis
CPMP	European Medicines Agency – Committee for Proprietary Medicinal Products (now known as CHMP)
CPPs	critical process parameters
CQAs	Critical quality attributes
CrCl	Creatinine clearance
CRS	Chemical Reference Substance (official standard)
CSP	Clinical study protocol
CSR	Clinical study report
CV	Cardiovascular

CYP	Cytochrome
DAE	Adverse event leading to study discontinuation
DCCT	Diabetes Control and Complications Trial Research Group
DDI	Drug-drug interaction
DoE	Design of Experiments
DPP4	Dipeptidyl peptidase 4
DPP8	Dipeptidyl peptidase 8
DPP9	Dipeptidyl peptidase 9
EASD	European Association for the Study of Diabetes
ECG	Electrocardiogram
ED50	Dose producing 50% effect
EEF	environmental equivalency factor
eGFR	Estimated glomerular filtration rate
EP	European Pharmacopoeia
ESRD	End stage renal disease
EU	European Union
fa/fa	Homozygous fatty mutation
FAP	Fibroblast activation protein-alpha
FDA	Food and Drug Administration (US Department of Health and Human Services)
FDC	Fixed-dose combination
FPG	Fasting plasma glucose
GC	Gas Chromatography
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic peptide
GLP-1	Glucagon-like peptide-1
GM	Geometric mean
GMP	Good Manufacturing Practice
HbA1c	Glycosylated haemoglobin
HDL-C	High density lipoprotein-cholesterol
HDPE	High Density Polyethylene
HPLC	High Pressure Liquid Chromatography
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation
IC50	Concentration required for 50% inhibition
IV	intravenous
IDF	International Diabetes Federation
IPC	In-process control
IR	Immediate release
IR (-ATR)	Infrared (Attenuated total reflection)
Ki	Inhibition constant
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LDL-C	Low density lipoprotein-cholesterol
LOD	(1) Limit of Detection, (2) Loss on Drying
LOQ	(1) Limit of Quantification, (2) List of Questions
LT	Long-term
MA	Marked abnormality
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MDRD	Modification in Diet and Renal Disease

MEB	Medicines and Evaluation Board
MI	Myocardial infarction
MOA	Mechanism of action
MPA	Medical Products Agency
MRHD	Maximum recommended human dose
MTT	Meal tolerance test
NF	USP National Formulary
NHANES	National Health and Nutrition Examination Survey
NYHA	New York Heart Association
NOAEL	no observed-adverse-effect level
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NORs	normal operating ranges
OAT	organic anion transporter
OCT	organic cation transporter
OATP	organic anion transporting polypeptide
OL	Open-label
ob/ob	Obese mouse
OGTT	Oral glucose tolerance test
PA/Alu/PVC-Alu	Polyamide/Aluminum/PVC-Aluminum
PARs	proven acceptable ranges
PEPT	peptide transporter
P-gp	P-glycoprotein
PD	Pharmacodynamics
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PPG	Postprandial glucose
PT	Preferred term
QbD	Quality by Design
QTPP	quality target product profile
RMP	Risk Management Plan
RH	Relative Humidity
RRT	Relative retention time
RSD	Relative standard deviation
RVG #	Marketing Authorisation number in NL
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SGLT2	Sodium-glucose cotransporter 2
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA Query
SOC	System Organ Class
ST	Short-term
STP	Sewage treatment plan
SU	Sulphonylurea
T2DM	Type 2 diabetes mellitus
TAMC	Total Aerobic Microbial Count
TB	Total bilirubin
TC	Total cholesterol
TG	Triglycerides

TGA	Thermo-Gravimetric Analysis
TYMC	Total Combined Yeast/Mould Count
TZD	Thiazolidinedione
UDU	Unit Dose Uniformity
UGT	Uridine diphosphate glucuronosyl transferase
UHPLC	Ultra High Performance Liquid Chromatography
UKPDS	United Kingdom Prospective Diabetes Study Group
ULN	Upper limit of normal
USP	United States Pharmacopoeia
UTI	Urinary tract infection
UV	Ultraviolet
Vss	steady-state volume of distribution
XR	Extended-release
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 20 April 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Qtern, 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 24 July 2014.

The applicant applied for the following indication:

Qtern is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control in combination with other oral glucose lowering medicinal products, when these alone, together with diet and exercise, do not provide adequate glycaemic control (see sections 4.2, 4.4, 4.5 and 5.1 for available data on combinations studied).

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC – relating to applications for new fixed combination products.

The application submitted is a new fixed combination medicinal product.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0322/2014 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

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

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Pieter de Graeff Co-Rapporteur: Bart Van der Schueren

- The application was received by the EMA on 20 April 2015.
- The procedure started on 28 May 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 17 August 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 August 2015.
- During the meeting on 24 September 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 15 December 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 1 February 2016.
- PRAC RMP assessment overview adopted by PRAC on 11 February 2016.
- During the CHMP meeting on 25 February 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 28 March 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 14 April 2016.
- During the CHMP meeting on 26 April 2016, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 28 April 2016, the CHMP agreed on a second list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 3 May 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to second the List of Outstanding Issues to all CHMP members on 11 May 2016.
- During the meeting on 26 May 2016, 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 Qtern.

2. Scientific discussion

2.1. Introduction

Problem statement

The Application concerns a fixed dose combination (FDC) of saxagliptin and dapagliflozin, intended for the treatment of Type 2 diabetes mellitus (T2DM). The invented name is Qtern. The individual components of the FDC are already licensed in EU via the Centralised Procedure. Saxagliptin is licensed as Onglyza (EMEA/H/C/001039) and dapagliflozin is licensed as Forxiga (EMEA/H/C/002322).

About the product

Qtern is a fixed dose combination (FDC) of two active substances saxagliptin and dapagliflozin (film coated tablets containing 5mg saxagliptin and 10mg dapagliflozin). The individual components of the fixed dose combination are already licensed in EU via the Centralised Procedure.

Saxagliptin (saxagliptin hydrochloride) is an inhibitor of DPP4, an enzyme responsible for the breakdown of incretin hormones. This results in a glucose-dependent increase in insulin secretion, thus reducing fasting and post-prandial blood glucose concentrations. Saxagliptin is marketed as 2.5 mg and 5 mg film-coated tablets by AstraZeneca AB since 1st October 2009 and 28th February 2011, respectively (EU/1/09/545/012, EU/1/09/545/006). Onglyza is indicated in adult patients aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as monotherapy or as dual therapy in combination with metformin, a sulphonylurea, or a thiazolidinedione. The recommended dose of Onglyza is 5 mg once daily.

Dapagliflozin (dapagliflozin propanediol monohydrate) is an inhibitor of sodium-glucose co-transporter 2 (SGLT2). Dapagliflozin blocks reabsorption of filtered glucose from the S1 segment of the renal tubule, effectively lowering blood glucose in a glucose-dependent and insulin-independent manner. Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. Dapagliflozin is marketed as 5 mg and 10 mg film-coated tablets by AstraZeneca AB since 12 November, 2012 (EU/1/12/795/002, EU/1/12/795/007). Forxiga is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as monotherapy and as add-on combination therapy, including insulin. The recommended dose of Forxiga is 10 mg once daily. Worldwide, dapagliflozin is currently authorised for marketing in over 55 countries and may be co-administered with another oral diabetes treatment, such as metformin, a sulphonylurea, a thiazolidinedione, or a DPP4 inhibitor (with or without metformin), as an adjunct to diet and exercise to improve glycaemic control in patients with T2DM.

Qtern is thought to combine the complementary mechanisms of action of both monocomponents. The actions of both medicines are regulated by the plasma glucose level.

The requested therapeutic indication (at initial submission of the application) was:

Qtern is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control in combination with other oral glucose lowering medicinal products, when these alone, together with diet and exercise, do not provide adequate glycaemic control (see sections 4.2, 4.4, 4.5 and 5.1 for available data on combinations studied).

The approved indication is:

Qtern, fixed dose combination of saxagliptin and dapagliflozin, is indicated in adults aged 18 years and older with type 2 diabetes mellitus:

- to improve glycaemic control when metformin and/or sulphonylurea (SU) and one of the monocomponents of Qtern do not provide adequate glycaemic control,
- when already being treated with the free combination of dapagliflozin and saxagliptin.

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

The recommended dose is one 5 mg saxagliptin/10 mg dapagliflozin tablet once daily (see sections 4.5 and 4.8).

Type of Application and aspects on development

On 24 July 2014, Qtern was confirmed as eligible for submission of an application for a Union Marketing Authorisation under Article 3(1)- Annex (3) New active substance for mandatory indications of Regulation (EC) No.726/2004. The Marketing Authorisation Application (MAA) is submitted as per Article 10(b) of Directive 2001/83/EC as amended.

The saxagliptin/dapagliflozin FDC clinical development programme was designed in accordance with the CHMP Guideline on Clinical Development of Fixed Combination Medicinal Products (see CHMP/EWP/240/95, Rev. 1, 2009). Both the saxagliptin and dapagliflozin clinical development programmes were designed in accordance with the CHMP Guideline on Clinical Investigation of Medicinal Products in the Treatment or Prevention of Diabetes Mellitus (see CPMP/EWP/1080/00, 2002 and CPMP/EWP/1080/00, Rev 1, 2012). CV outcome studies were designed for each program. For the SAVOR trial (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus; D1680C00003) the CHMP opinion (EMEA/H/C/1039/0529/G) was established 24 July 2014. The data have been re-discussed in CHMP/PRAC regarding its effect on overall survival following a reanalysis of the data by FDA; a Type 2 variation has been finalised to implement results in section 5.1 of the saxagliptin SmPC. The Dapagliflozin Effect on Cardiovascular Events (DECLARE) study (D1693C00001) is an ongoing CV outcomes study projected to be completed by second-third quarter 2019.

The applicant did not seek Scientific Advice from the CHMP, but a Request for Scientific Advice was made to the Medical Products Agency (MPA, Sweden) and Medicines and Evaluation Board (MEB, the Netherlands) to discuss rationale and positioning of a FDC product of saxagliptin/dapagliflozin in Europe and to discuss the indication and clinical practicality aspects of the proposed product.

2.2. Quality aspects

2.2.1. Introduction

Qtern finished product is presented as film-coated tablets containing a fixed-dose combination containing 5 mg of saxagliptin (as hydrochloride) and 10 mg dapagliflozin (as dapagliflozin propanediol monohydrate) as the active substances.

Other ingredients of the tablet core are microcrystalline cellulose (E460i), croscarmellose sodium (E468), lactose anhydrous, magnesium stearate (E470b) and dental type silica (E551). The film coating is composed of polyvinyl alcohol (E1203), macrogol 3350, talc (E553b), titanium dioxide (E171), iron oxide yellow (E172) and iron oxide red (E172). The printing ink is made of shellac and indigo carmine aluminium lake (E132).

The product is available in PA/Alu/PVC-Alu blister packs.

2.2.2. Active Substance

Saxagliptin

General information

The chemical name of saxagliptin is(1*S*,3*S*,5*S*)-2-((2*S*)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl)-2-azabicyclo[3.1.0]hexane-3-carbonitrile hydrate corresponding to the molecular formula $C_{18}H_{25}N_3O_2 \cdot H_2O$ and a relative molecular mass of 333.43 g/mol (315.41 g/mol anhydrous). It has the following structure:

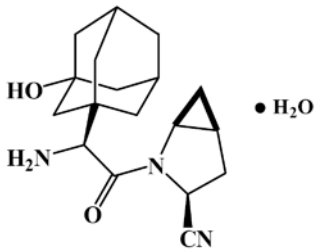

Figure 1. *Saxagliptin monohydrate structure*

The structure of the active substance (AS) has been confirmed by elemental analysis, UV-, IR-, NMR- (^1H, ^{13}C and ^{15}N) spectroscopy and mass spectrometry, all of which support the chemical structure. The structure is also supported by the synthetic route.

The substance is soluble in water, and very soluble at low pH showing a minimum solubility of 17.6 mg/ml over the pH range 1.2 to 9. The pKa value of saxagliptin was determined to be 7.3. The distribution coefficient octanol / water (Do/w) at pH 7.0 is 0.607.

It appears as a white to light to off white non-hygroscopic, crystalline powder that exists as a stable monohydrate. The molecule contains 4 chiral centres. A single crystal X-ray study confirmed the molecular structure and stereochemical assignment in which all centres have the *S*-configuration.

All stereocentres originate and are controlled in the starting materials. It has been shown that the stereochemical purity is maintained during manufacture and storage.

Only one crystalline form (free base monohydrate) has been observed to date. An anhydrous crystalline from of the free base has been characterised. No stable solvate forms have been observed.

Manufacture, characterisation and process controls

The synthesis of saxagliptin comprises a total of five chemical transformation steps involving two starting materials and two isolated intermediates. The manufacturing process of the substance is thoroughly described and sufficient information is given on the synthesis of the starting materials. The process is identical to that used in Onglyza.

The development approach for saxagliptin manufacturing process includes elements of Quality by Design. Critical quality attributes (CQAs) of the active substance were defined together with an associated control strategy which is considered satisfactory. Risk assessment for unit processes was performed to identify critical process parameters (CPPs). There are no CPPs in the manufacture of the first intermediate; the CPPs in the manufacture of the final intermediate and active substance were described. Process parameters influencing active substance quality were studied using Design of Experiments (DoE) to verify the acceptability of the proposed parameters and range thereof. Based on

this outcome, process parameters and associated proven acceptable ranges (PARs) and normal operating ranges (NORs) were established that ensure each isolated intermediate and saxagliptin are isolated in consistent yield and specified quality. Appropriate control measures were implemented for impurities in each step of the process based upon fate and tolerance studies. Finally, in-process monitoring and controls were established to ensure that a specific process end-point or condition has been achieved before progressing to the next operation or step, including development and implementation of appropriate analytical methods for in-process control (IPC) testing. The proposed re-working steps are also considered to be justified as no new solvents are introduced.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities, including any potential genotoxic ones, were well discussed with regards to their origin and characterised. No metal catalysts are used during manufacture.

The active substance is packaged in closed, double, antistatic-treated, low-density polyethylene (LDPE) bags within a HDPE drum with a secure fitting lid. The suitability is supported by stability results. The polyethylene bags comply with the Ph. Eur. requirements and with the relevant EC regulations for plastic materials and articles intended to come into contact with foodstuffs.

Specification

The active substance release specification includes appropriate tests and limits for: appearance and colour (visual inspection), identity (IR-ATR or Raman, HPLC), assay (HPLC), impurities /degradants (HPLC), and residual solvents (GC).

The specifications for saxagliptin have been appropriately justified and remain unchanged in comparison to the other approved saxagliptin products from the same applicant MAH. The suitability of the HPLC impurity method used for the control of active substance has been shown. The omission of routine testing for some parameters has been satisfactorily justified based on batch data and because they are also checked during the process as IPCs. Particle size is not relevant for the finished product performance and is therefore not included. No test for the enantiomer is needed as the chiral centres are sufficiently controlled during the process.

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 has been presented.

Batch analysis results of 8 representative commercial batches manufactured at the proposed site have been provided. Batch analysis results for 25 batches used during development were also provided. All batches complied with the specifications in force at the time of their manufacture confirming the robustness of the process and consistent quality.

Stability

The applicant submitted the same stability package as for Onglyza consisting of three pilot scale batches of active substance manufactured according to a previous (but representative) process and two pilot scale batches of saxagliptin manufactured according to current commercial process at the commercial site. All stability batches were packaged in the same primary packaging material intended for commercial use with some differences in the secondary packaging configuration.

Samples were stored for up to 37 months under long term conditions at 5 °C and up to 12 months under accelerated at 25 °C / 60 % RH according to the ICH guidelines. In addition, supportive data

were generated for 12 months at -20 °C and for 36 months at 5 °C testing without the secondary packaging.

The parameters tested during the stability studies were appearance, colour, assay, impurity content, total volatiles (residual solvents), water content and polymorphism. Method descriptions and where needed, validation information were given for the additional tests total volatiles, water content and polymorphism. Methods were shown to be stability indicating.

The results were in general within the specifications and any out of specification results were adequately investigated and justified. The first three commercial batches of saxagliptin produced at the proposed site and one batch annually will be placed into the post-approval stability program.

Photostability studies on two pilot scale batches as per the ICH Q1B conditions showed that the substance is not sensitive to light.

Based on presented stability data, the proposed retest period remains unchanged in comparison with the already authorised saxagliptin containing product of the same applicant.

Dapagliflozin propanediol

General information

The chemical name of dapagliflozin propanediol monohydrate is (2*S*,3*R*,4*R*,5*S*,6*R*)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro- 2*H*-pyran-3,4,5-triol, (2*S*)-propane-1,2-diol (1:1) monohydrate corresponding to the molecular formula $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$ and a relative molecular mass of 502.98 g/mol (408.87 g/mol for dapagliflozin). It has the following structure:

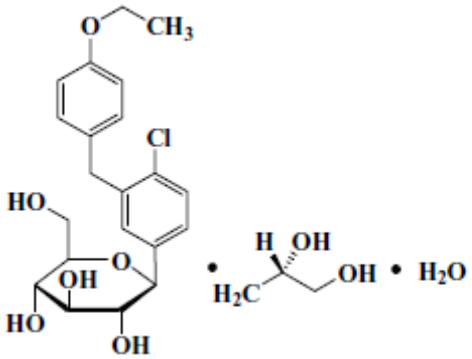

Figure 2. *Dapagliflozin propanediol monohydrate structure.*

The structure of the active substance has been confirmed by elemental analysis, IR & Raman spectroscopy, mass spectrometry, one- and two-dimensional ^{1}H and ^{13}C NMR spectroscopy, UV-vis spectroscopy and single crystal X-ray crystallography, all of which support the chemical structure. The structure is also supported by the synthetic route.

Dapaglifozin is a white to off-white, non-hygroscopic powder, soluble in many polar organic solvents. Water solubility at 24 ºC is 1.6 mg/ml. The aqueous solubility of dapagliflozin propanediol is not affected by changes in pH in the physiological range at 37 ºC.

It is not ionisable in the pH range between 2 and 11. Its partition coefficient in n-octanol/water is 2.45 at pH 7.4. Dapaglifozin is a chiral molecule with five stereogenic centres. The relative and absolute stereochemistry is defined by the process. Only one polymorphic form of dapagliflozin propanediol designated as form SC-3 has been observed. It is the thermodynamically stable form of dapagliflozin

propanediol and is consistently produced by the synthetic process. A number of different solvates and hydrates have been also identified but it has been shown that they are unlikely to form in the manufacturing process. The X-ray powder diffraction test method allows clear discrimination between the different solvates. The process controls implemented in the manufacturing process of dapagliflozin propanediol ensures the desired crystalline form of the active substance. In addition, environmental controlled storage and shipment are implemented to prevent temperature excursion and maintain the physical properties of dapagliflozin propanediol.

Manufacture, characterisation and process controls

The commercial manufacturing process for the synthesis of dapagliflozin propanediol is the same as for Forxiga and utilises two well defined starting materials and involves a sequence of five reaction steps with two isolated intermediates. A Quality by Design (QbD) approach was used during process development. Risk assessment, uni- and multivariate experiments and scientific knowledge were used to identify and understand process parameters and process steps that impact critical quality attributes (CQAs) and to develop a control strategy including proven acceptable ranges (PARs). No critical process parameters are identified. A design space is not claimed. The proposed specifications of the starting materials and intermediate are considered acceptable. The description of the manufacturing process is sufficient and the proposed PARs are justified. The yields and batch size are stated.

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, including any potential genotoxic ones, were well discussed with regards to their origin and characterised. No metal catalysts are used during manufacture.

The relative and absolute stereochemistry is ensured by the synthetic process. It has been shown that epimerization during the process or on storage is unlikely.

The active substance is packaged in closed, double, antistatic-treated, low-density polyethylene bags within a HDPE drum with a secure fitting lid. The suitability is supported by stability results. The polyethylene bags comply with the Ph. Eur. requirements and with the relevant EC regulations for plastic materials and articles intended to come into contact with foodstuffs.

Specification

The active substance release specification includes appropriate tests and limits for: appearance and colour (visual inspection), identity (IR-ATR or Raman, HPLC), assay (HPLC), impurities (HPLC), water content (Karl Fischer), propylene glycol (GC), residual solvents (GC) and particle size (laser light diffraction).

The proposed specification and limits have been satisfactorily justified. The omission of testing of some parameters is acceptable based on batch data and the applied IPCs during manufacture. The particle size specification derived from the phase 3 clinical batches and is appropriate to ensure good content uniformity of the tablets.

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 testing has been presented.

Batch analysis results from 30 batches used during development including 4 commercial scale process validation batches were provided. The batches were tested and evaluated against the specifications and test methods in force at the time of their manufacture. In addition, batch analysis data on three recent batches produced in accordance with the proposed maximum batch size were also provided. All

batches meet the proposed specification confirming the robustness of the process and the consistent quality delivered.

Stability

Stability data on three pilot scale batches of active substance manufactured by the commercial manufacturing process packaged in the proposed packaging and in addition, in a slightly different one (one batch only), were provided. Samples were stored for up to 36 months under long term conditions at 25 °C / 60% RH and 30 °C/ 65% RH, for up to 24 months at 5 °C, and for up to six months under accelerated conditions at 40 °C / 75 % RH according to the ICH guidelines. In addition, stress testing was performed on one of the above batches at -20 °C and 40 °C / 75% RH in an open bag. The parameters tested were appearance, colour, identity by HPLC, assay by HPLC, impurities by HPLC, polymorphic form by X-ray powder diffraction (annual), water content and propylene glycol content. The same analytical procedures as for the release analysis were used, which had been shown to be stability indicating. The X-ray powder diffraction method has been sufficiently described and validated. No changes in the different parameters tested under long term or accelerated conditions were observed.

A photostability study has been performed on one pilot batch as per the ICH Q1B guideline on photostability. Results showed that the substance is not sensitive to light.

A forced degradation study in aqueous solution under heat, oxidative conditions, acidic and basic conditions and UV/visible light and in solid state exposed to heat and humidity and UV/visible light was also performed in order to identify the degradation pathway of the active substance. The samples were analysed using HPLC with photodiode array and mass spectrometry detection for overall degradation. The applicant will complete all on-going long term stability studies up to 36 months and will place the first three commercial batches and one batch incorporating the maximum batch size and one batch annually into the post-approval stability program.

Based on the presented stability data, the proposed retest period is acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Qtern is an immediate release film-coated tablet containing saxagliptin 5 mg and dapagliflozin 10 mg in a fixed dose combination. The tablets are light brown to brown, biconvex, round, film-coated tablets with 5/10 printed on one side and 1122 printed on the other side in blue ink.

The formulation development was largely based on the development of the saxagliptin (Onglyza) and dapagliflozin (Forxiga) as well as saxagliptin/metformin (Komboglyze) film–coated tablets. Qtern is comprised of a formulated dapagliflozin core tablet (similar to Forxiga), with a three-layer film-coating containing saxagliptin (similar to Onglyza).

Dapagliflozin core tablet

From Forxiga development, environmental controls on storage and shipment of the AS have been established to ensure consistent quality of AS for finished product manufacture. In addition, the *in vitro* dissolution profiles and *in vivo* exposure from the heat-stressed and non-heat-stressed Forxiga tablets were found to be similar. Moreover, the impurity profile of heat stressed and the non-heat stressed tablets were essentially the same. These results show that the form of the dapagliflozin in the finished product has no impact on product performance and quality.

Dapagliflozin's poor flow properties and its susceptibility to oxidative degradation were addressed by the choice and design of the finished product manufacturing process, the excipients selected and the choice of appropriate primary packaging for the finished product.
Finally, to ensure dose uniformity for this low drug load formulation, the particle size of dapagliflozin is controlled in its specification. The established AS specifications, based on studies conducted during Forxiga development, are also adequate for the Qtern product.

The dapagliflozin core tablet formulation and manufacturing process is similar to that of the Forxiga products. The film-coating process was optimized to achieve satisfactory saxagliptin content uniformity using this core's shape, weight and size.

Saxagliptin active coating
Saxagliptin is prone to undergo an intramolecular cyclisation. The selection of excipients was based upon the results of excipient compatibility studies to minimize the formation of the cyclic amidine. During the coating process, saxagliptin free base is converted in situ into its hydrochloride salt. The outer layer is a distinctive colour coat. The manufacturing process is similar to that of Onglyza tablets.

Both ASs are classified as BCS class III substances. The excipients are well known pharmaceutical excipients and are the same as those used in the manufacture of the respective mono-component tablets (Forxiga and Onglyza), except for the disintegrant in the dapagliflozin core; croscarmellose sodium is used in the FDC tablet instead of crospovidone. Chemical compatibility between each active substance and the excipients included in their respective layers was established during development of the mono-component formulations.
Principles of Quality by Design (QbD) were applied during the development of Qtern. The strategy for formulation and process development was implemented by:

1) defining the quality target product profile (QTPP) to guide development ,
2) identifying potential critical quality attributes (CQAs) of the product ,
3) determining quality attributes of the substances or excipients that may impact product performance, and
4) leveraging prior knowledge

The manufacturing process development was directed towards manufacturing process parameters for the dapagliflozin core tablets and the saxagliptin film-coating process. The control strategy is acceptable.
A bioequivalence study was performed using the Qtern vs the Saxagliptin and Dapagliflozin mono-component products. The comparative dissolution profiles have been provided in three media (pH 1.2, pH 4.5 and pH 6.8). Dissolution of both substances from all products in all media was fast and hence the profiles can be considered similar. The dissolution method used has been described and validated.
The primary packaging of the finished product is PA/Alu/PVC-Alu blisters.

The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. The materials comply with Ph. Eur. and EC requirements.

Manufacture of the product and process controls

The manufacturing process is divided into the manufacture of the core tablets and the successive film-coating operations.

The dapagliflozin tablet manufacturing process comprises the following main steps: blending, milling, roller compaction, milling, final blending tablet compression and film-coating including the active layer film-coating and the colour-coating.

The manufacturing process has been described in sufficient detail. The IPCs are considered acceptable and are standard for both tabletting and film-coating operations. Experimental data regarding the impact of the coating parameters to the stability of the active substance in the product has been presented. This data shows that the proposed proven acceptable ranges applied during coating are suitable to ensure saxagiptin stability.

The process can be considered a non-standard process because of the unit dose content of 2% for saxagliptin and the specialised process. However, the applicant has provided a satisfactory justification for not providing validation data pre-approval in line with the process validation guideline (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1). The applicant has extensive experience with the manufacture of the mono-component products upon which the process of Qtern is based. The batch size for the manufacture of the core (dapagliflozin) tablets is defined and the proposed batch size is considered validated. With regard to the saxagliptin film coating process, the validity of process parameter ranges used for the mono-component tablets has been demonstrated for several batches and for one batch of Qtern, which showed compliance with IPCs and finished product specification. The commitment to validate the film coating process on three full-scale batches post-approval is considered acceptable. Based on the presented information, it considered that the manufacturing process is sufficiently validated and capable of producing the finished product of the intended quality in a reproducible manner.

Product specification

The finished product release and shelf life specifications include tests and limits for: description (visual), identification (UHPLC and UV), assay (UHPLC), impurities/degradants (UHPLC), uniformity of dosage units (Ph. Eur.), tablet disintegration, water content (Karl Fischer) and microbial quality (Ph. Eur.).

The absence of a test for dissolution and its replacement by a test for disintegration was justified in line with ICH Q6A decision tree 7, where in it is stated that if a relationship has been determined between disintegration and dissolution, the disintegration acceptance criteria with an upper limit are acceptable.

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 testing has been presented.

Batch analyses results from three commercial scale batches manufactured at the proposed site and of three pilot scale batches manufactured at a different site, and used for stability studies, were provided. All batches meet the specifications.

Stability of the product

Stability data on three pilot scale batches of the finished product manufactured at the development facility and packaged in the proposed packaging were provided. Samples were stored for up to 24 months under long term conditions at 5 °C, 25 °C / 60% RH and 30 °C / 75% RH, for up to 6 months under accelerated conditions at 40 °C / 75 % RH according to the ICH guidelines. The stability batches were packaged in the proposed bulk packaging container for two months before final packaging.

The parameters tested were appearance, assay (saxagliptin and dapagliflozin), impurity/degradants (saxagliptin and dapagliflozin), disintegration, water content, dissolution (saxagliptin and dapagliflozin), and hardness. Dissolution and hardness were performed for information purposes only. Microbial testing was performed at initial, 12, 24, and 36 month time points for tablets stored at 30°C / 75%RH. Since microbial testing is also performed at release, this is deemed sufficient. The

dissolution method used has been described and validated. All other analytical procedures used were the same as for release and were shown to be stability indicating.

After 24 months at 5 °C, 25 °C / 60% RH, or 30 °C / 75% RH, all parameters remained within the limits, no trends and no temperature effect was noticed. Under accelerated conditions (for 6 months), all parameters remained within the limits and no significant change was noted.

In addition one pilot batch was tested under the stressed condition of 25 °C / 60% RH in an open dish for 12 months. It was concluded from the results that the increase in moisture content is without quality impact and that tablets are stable after 12 months of exposure in open dishes.

Photostability studies on one pilot scale batch, as per ICH Q1B, showed no significant difference between exposed and protected samples. It is concluded that the tablets do not need to be protected from light.

Bulk stability studies
One batch packaged in in-process bulk containers was been tested after 12 months of storage at 30 °C / 65% RH. Results were presented for appearance, assay (saxagliptin and dapagliflozin), total impurities/degradants (saxagliptin and dapagliflozin), disintegration, water content, dissolution (saxagliptin and dapagliflozin) and hardness. All results complied with the specifications and there was no significant difference observed between the “re-closed” and “sealed” samples. The data support a 12 months hold period for the bulk tablets prior to final packaging.

Statistical analysis showed with 95% assurance that after 36 months, all analysed parameters will be within the proposed shelf life specification.

Finally the long-term studies will continue throughout the proposed shelf life; three production batches of each product strength/package presentation will be placed on stability at accelerated and long-term conditions, according to the presented and agreed protocol.

Based on the presented data, the proposed 3 years shelf life without any special storage conditions as stated in the SmPC is acceptable.

Adventitious agents

The anhydrous lactose is sourced from bovine milk. Satisfactory TSE/BSE safety statement were provided confirming that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner and has been sufficiently documented and justified. Qtern film coated tablets development was based on the two mono-component products which are currently authorised: Onglyza (saxagliptin) and Forxiga (dapagliflozin). Therefore some of the development information of those was not included in the current application. Sufficient process validation information regarding the finished product manufacture has been presented.

The results of tests carried out on the active substances and finished product indicate the 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 for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- to validate the saxagliptin film coating process on three full-scale batches prior to commercialisation of tablets produced at this batch size.

2.3. Non-clinical aspects

2.3.1. Introduction

Qtern combines the 2 oral antihyperglycaemic agents – saxagliptin (5 mg per tablet) and dapagliflozin (10 mg per tablet) - with complementary mechanisms of action to improve glycaemic control.

The pharmacological profiles of saxagliptin and dapagliflozin have been previously established in a comprehensive development programme that included studies of in-vitro and in-vivo pharmacodynamics including core safety pharmacology. Each individual compound is already licensed in EU via centralized procedure for the treatment of T2DM as monotherapy and in combination with metformin. Saxagliptin is approved as Onglyza tablets, 2.5 mg and 5 mg (EMEA/H/C/001039) and dapagliflozin is approved as Forxiga tablets, 5 mg and 10 mg (EMEA/H/C/002322).

2.3.2. Pharmacology

Primary pharmacodynamic studies

No studies on the primary pharmacodynamics of the saxagliptin/dapagliflozin fixed-dose combination have been performed, since there is sufficiently known about the primary pharmacodynamics of the individual compounds. Each compound contributes via a different mechanism of action to a normalisation of the glucose concentration in plasma.

Saxagliptin inhibits DPP4 enzyme activity leading via increased levels of incretin hormones to higher insulin concentrations in plasma. Dapagliflozin improves glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion acting independently of insulin secretion and insulin action. Based on the complementary mechanism of action of the individual components, exaggerated pharmacodynamic effects of the fixed-dose combination are not expected.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies were conducted with the saxagliptin/dapagliflozin fixed-dose combination. This is acceptable, since from the nonclinical studies performed as part of the marketing authorization application for Onglyza and Forxiga and from extensive clinical use of these products after registration there is sufficient knowledge about potential off-target effects of the individual compounds.

Safety pharmacology programme

Safety pharmacology studies with saxagliptin reported no significant findings. Non-clinical studies on cardiovascular safety of dapagliflozin did not identify any concern, but safety pharmacology studies assessing effects of dapagliflozin on the CNS or the respiratory system were not performed. Within a 3-month oral combination toxicity study in rats, co-administration of saxagliptin and dapagliflozin showed no relevant effects on these organ systems at Cmax exposures of 2x (males) and 5x (females) for saxagliptin, and 2x (males and females combined) for dapagliflozin of the maximum recommended human dose of 5 and 10 mg for fixed-dose combination.

Based on these data, no adverse effects on the cardiovascular, respiratory and central nervous system are anticipated for the saxagliptin/dapagliflozin fixed-dose combination in humans

Pharmacodynamic drug interactions

Both saxagliptin and dapagliflozin were approved as individual components for the treatment of T2DM as monotherapy and in combination with other oral T2DM therapy. Based upon the different mechanisms of action for saxagliptin and dapagliflozin and the available clinical data in patients with both drugs, no adverse pharmacologic interactions are anticipated with the fixed dose combination. Therefore no additional nonclinical pharmacology studies assessing pharmacodynamics/efficacy were conducted with the combination; this was considered acceptable.

2.3.3. Pharmacokinetics

Assessment of the pharmacokinetics and metabolism of saxagliptin and dapagliflozin were derived from a series of in vitro test systems and in vivo PK studies (i.e. mouse, rat, dog and monkey) conducted in the context of individual marketing authorisation submission through the centralised procedure. Saxagliptin is approved as Onglyza tablets, 2.5 mg and 5 mg (EMEA/H/C/001039) and dapagliflozin is approved as Forxiga tablets, 5 mg and 10 mg (EMEA/H/C/002322). Based on what is known about the pharmacokinetics of saxagliptin and dapagliflozin apart, pharmacokinetic studies on the saxagliptin/dapagliflozin fixed-dose combination are not required.

To support the combination MAA, toxicokinetics was assessed as a part of a 3-month oral combination toxicity study conducted in the rat with dapagliflozin at 0.4 mg/kg/day and saxagliptin at 2 mg/kg/day.

Saxagliptin

Absorption: Saxagliptin was rapidly absorbed, with maximum plasma concentrations of saxagliptin and its major metabolite BMS-510849 within 2 to 4 hours. The oral bioavailability was 70% in rats, 77% in dogs and 51% in monkeys. The intrinsic membrane permeability of saxagliptin is very low. Both saxagliptin and BMS-510849 were not prominent substrates for P-gp or for cellular uptake transporters.

Distribution: Saxagliptin was extensively distributed in tissues The highest concentrations of saxagliptin related material were the gastrointestinal tissues, liver, urinary bladder and kidney. Saxagliptin and BMS-510849 levels were lowest in the brain. Protein binding of saxagliptin was not observed in dog and human, and low in mouse (27%), rat (18%) and monkey (20%). Protein binding of BMS-510849 was very low (up to 10%). Saxagliptin-derived material crosses the placenta in rats

Metabolism:. Saxagliptin was rapidly and primarily excreted in human urine mainly as a mixture of saxagliptin and BMS-510849, whereas urine and feces were the primary routes of excretion in rats, dogs, and monkeys. Dapagliflozin is eliminated by multiple pathways including biliary, renal, and metabolic clearance, with metabolic clearance predominating. Primary biotransformation pathways include glucuronidation, oxidative dealkylation, and oxidation at various positions on the molecule.

Excretion: Saxagliptin-derived material is rapidly excreted in both urine and feces, with saxagliptin in urine accounting for ≥13.8% of the dose, indicating a role for renal clearance. Saxagliptin-derived material is excreted in milk of nursing rats.

Pharmacokinetic drug interactions: Interactions with other drugs are not expected. Saxagliptin and BMS-510849 are poorly bound to plasma proteins. Saxagliptin and BMS-510849 are neither inhibitors nor inducers of CYP enzymes.

Dapagliflozin

Absorption: Dapagliflozin is rapidly absorbed, with maximum plasma concentrations within 0.6 to 2 hours. The oral bioavailability was 84% in rats, 83% in dogs, and 25% in monkeys. Dapagliflozin is a weak substrate for P-gp. However, the membrane permeability of dapagliflozin was high and oral absorption was good in most species.

Distribution: Dapagliflozin exhibits a moderate volume of distribution. Tissues with the highest concentrations of dapagliflozin related material were the intestine, liver, and renal cortex. Brain penetration was low. Protein binding was high (>90 %). Dapagliflozin and/or its metabolites cross the placenta and are excreted in milk.

Metabolism: Dapagliflozin is mainly cleared via UGT1A9. Dapagliflozin was not an inducer or an inhibitor of CYP enzymes. However, there was a markedly different metabolism pattern in animals and humans. In animals, less than half of dapagliflozin was metabolized but the metabolites formed were much more heterogeneous than in humans. The main human metabolite was formed only in small amounts in animals, making toxicological qualification difficult. However, mere glucuronidation of a given compound is not expected to increase its toxicity. Therefore, this main human metabolite (dapagliflozin 3-O-glucuronide) is not considered to pose a toxicological concern.

Excretion: In animals, dapagliflozin excretion was proximally equally distributed between urine and faeces; in humans urine was the predominant route (around 75%). The difference in metabolism between humans and animals leads also to differences in its excretion since the main human metabolite dapagliflozin 3-O-glucuronide is mainly excreted via urine.

Pharmacokinetic drug interactions: Dapagliflozin has no meaningful potential to inhibit or induce CYP enzymes. Dapagliflozin is a substrate for various UGT enzymes (UGT1A9, UGT2B4, and UGT2B7). The high dependence on the formation of dapagliflozin 3-O-glucuronide suggests that dapagliflozin elimination could be affected by coadministration of inhibitors or inducers of UGT1A9.

Saxagliptin / dapagliflozin

The potential for saxagliptin and its metabolite BMS-510849 to act as a perpetrator of drug interactions with dapagliflozin through inhibition of UGT1A9 was evaluated in human liver microsomes. The results indicated that neither saxagliptin nor BMS-510849 inhibited the formation of dapaglifozin-3-O-glucuronide (IC50 values >50 µM). At measured Cmax values of 27.6 ng/ml (~87.5 nM) for saxagliptin and 59.ng/ml (~144.3 nM) for BMS-510849T in a human bioequivalence study (study nr CV181131), these results reveal no potential for drug interactions of the saxagliptin/dapagliflozin fixed-dose combination by inhibition of UGT1A9. Based on this information, nonclinical studies on drug interactions of the saxagliptin/dapagliflozin fixed-dose combination are not required.

2.3.4. Toxicology

Single dose toxicity

No single-dose toxicity studies were conducted with the saxagliptin/dapagliflozin fixed-dose combination. This is acceptable. The toxicological properties of saxagliptin and dapagliflozin are known from the results of the animal studies performed as part of the marketing authorization application for Onglyza and Forxiga and from extensive clinical use of these products after registration.

Repeat dose toxicity

Major toxicity findings of saxagliptin upon repeated administration were the gastrointestinal toxicity in dogs (bloody/mucoid faeces and enteropathy), reversible skin lesions (scabs, ulcerations and necrosis) in extremities (tail, digits, scrotum and/or nose) in cynomolgus monkeys and immune related findings (minimal, nonprogressive, lymphoid hyperplasia in spleen, lymph nodes and bone marrow) with no adverse sequelae in all species tested. The gastrointestinal toxicity in dogs started from 4 times the human exposure based, the immune related findings started in all species from 7 times the human exposure and the skin lesions in monkeys started at therapeutic exposures. Clinical correlates to these findings have not been observed thus far.

Major toxicity findings of dapagliflozin were considered to be secondary to the pharmacologically mediated increase in urinary glucose and included decreases in body weights and/or body-weight gains, increases in urine volume and increases in urinary electrolytes. In rats, kidney and bone were identified as target organs. Kidney findings were reactive hyperplasia of collecting duct epithelium, dilation of cortical and/or medullary tubules, mineralisation of the collection ducts and exacerbation of chronic progressive neuropathy. The mineralisation and bone changes were related to increases in serum calcium. Mechanistic studies suggest that these effects were related to off-target effects on SGLT1 in the gut, and it maybe expected that those effects will not occur in humans at clinical doses. However, since type 2 diabetes is commonly associated with renal defects, the safety of dapagliflozin in patients with renal impairment should be addressed clinically (see discussion under Clinical aspects –Special populations).

A 3-month combination toxicity study was conducted to determine whether an interaction would occur when dapagliflozin and saxagliptin were co-administered orally to rats (BMS DN12107). The results showed no unique or synergistic toxicity outcomes relative to those dosed with the individual agents up to 5 times human exposures at the recommended dose of the fixed-dose combination. The increased kidney weights were specific to dapagliflozin as the result of secondary pharmacology of this compound. There was no effect of co-administration of saxagliptin on the severity of this change. Increases in water consumption (38 to 89%) were observed in males receiving dapagliflozin alone or in combination with saxagliptin, when compared to controls. These increases were considered secondary to dapagliflozin pharmacology (increased urinary glucose and resulting osmotic diuresis). There were no noteworthy effects on water consumption for male animals administered saxagliptin alone at 2 mg/kg/day or for female animals administered dapagliflozin or saxagliptin alone or in combination.

Genotoxicity

No genotoxicity studies were conducted with the saxagliptin/dapagliflozin fixed-dose combination. Individually, neither saxagliptin nor dapagliflozin was shown to be genotoxic. In addition, the major metabolite of saxagliptin, BMS-510849, showed no mutagenic potential. Therefore, additional genotoxicity studies were not requested.

Carcinogenicity

No carcinogenicity studies were conducted with the saxagliptin/dapagliflozin fixed-dose combination, and this was considered acceptable. Individually, neither saxagliptin nor dapagliflozin was shown to be carcinogenic in rodents. There is sufficiently known about the mechanisms of action and the potential off-target effects of these compounds and there is no evidence to suggest a greater carcinogenicity risk when using the saxagliptin/dapagliflozin fixed-dose combination.

Reproduction Toxicity

No reproductive and developmental toxicity studies have been performed with the saxagliptin/dapagliflozin fixed-dose combination. The reproductive and developmental toxicity of the two substances are well known. Studies with dapagliflozin in rats have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy. Studies in animals of saxagliptin have shown reproductive toxicity at high doses, including reduced ossification of the renal pelvis and decreased foetal body weight in rats and skeletal variations in rats. In the absence of human data, the use of Qtern is not recommended during the second and third trimesters of pregnancy. When pregnancy is detected, treatment with Qtern should be discontinued.

It is unknown whether saxagliptin and dapagliflozin and/or its metabolites are excreted in human milk. Pharmacokinetic data in rats have shown that saxagliptin, dapagliflozin and metabolites from these compounds are excreted in milk. Therefore, the saxagliptin/dapagliflozin fixed-dose combination should not be used while breast–feeding.

These findings have been adequately reflected in Section 4.6 of the Qtern SmPC and the package leaflet.

Toxicokinetic data

Toxicokinetic parameters of the saxagliptin/dapagliflozin fixed-dose combination were obtained in the 3-month repeated dose toxicity in rats. These data showed that, following repeated dosing alone or in combination, there were no differences in mean systemic exposures for dapagliflozin or saxagliptin, there were no sex differences in dapagliflozin exposures whereas mean saxagliptin values in males were lower (0.4 to 0.6×) than in females when administered alone or in combination. These findings are consistent with previous studies in the saxagliptin program.

With respect to the major pharmacologically active metabolite of 5-OH saxagliptin (BMS-510849), the exposure levels in the human bioequivalence study (CV181131), 59.5 ng/ml (Cmax) and 336 ng▪h/ml (AUCinf), were not reached. Nevertheless, synergistic toxicology effects of dapagliflozin and the 5-OH saxagliptin are unlikely. In the 3-month repeated dose toxicity in rats, the exposure to 5-OH saxagliptin was adequate in females, which was at least 50% of the levels in human based on Cmax and AUC values. These exposures in female rats satisfy the criteria ICH M3 Questions & Answers (R2) Document of March 2012. These levels were not reached in male rats, where the exposure to 5-OH saxagliptin was 0.4 to 0.6×of that in females. In human, the exposure to 5-OH saxagliptin in males was 0.8×of that in females, but there was no difference between the sexes in the ratio of 5-OH saxagliptin and saxagliptin. In addition, there was no clinically significant accumulation and there was no evidence of saxagliptin inducing or inhibiting its own metabolism. The difference in exposure to 5-

OH saxagliptin between males and females is most likely due to differences in distribution of saxagliptin, and most likely related to differences in body weight.

Local Tolerance

No non-clinical local tolerance studies were performed with the saxagliptin/dapagliflozin fixed-dose combination, due to the route of administration and the existing clinical experience. This is acceptable.

No specific lesions of the stomach were found in the repeat toxicity studies conducted with saxagliptin or dapagliflozin in rats. As mentioned in the SmPC of Onglyza, saxagliptin produced gastrointestinal toxicity in dog, including bloody/mucoid faeces and enteropathy at higher doses with a NOEL 4 and 2 times the human exposure for saxagliptin and the major metabolite of saxagliptin, BMS-510849, respectively, at the recommended human dose of 5 mg/day; this has been reflected also in the Qtern SmPC section 5.3. Clinical correlates to these findings have not been observed thus far.

Other toxicity studies

There is sufficient knowledge about saxagliptin or dapagliflozin when used separately. No concerns regarding their potential immunotoxicity, antigenicity, or drug dependence have been identified during their clinical use.

The combination of saxagliptin and dapagliflozin into a single tablet has not been associated with new impurities or degradation products. For this reason, no additional studies on impurities were conducted.

2.3.5. Ecotoxicity / environmental risk assessment

Saxagliptin

The Environmental Risk Assessment (ERA) for saxagliptin was based on the earlier assessment of the compound in the procedure EMEA/H/C/001039 (Onglyza).

No risk is identified for the STP, surface water, groundwater and sediment compartments. The used refined Fpen based on global estimated prevalence data has been accepted as it was considered to represent a worst-case.

Table 1 Saxagliptin - summary of main study results

Substance (INN / Invented Name): saxagliptin			
CAS-number (if available): 945667-22-1 (saxagliptin hydrate)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log D_{ow} = -1.74 at pH 4; log D_{ow} = 0.114 at pH 8.2; log D_{ow} = 0.169 at pH 9	Potential PBT: No
PBT-statement :	Saxagliptin is considered not PBT, nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default and refined	0.025 (default) 0.070 (refined)	µg/L	> 0.01 threshold YES Refined PEC accepted for Phase II
Other concerns (e.g. chemical class)			No

Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	$K_{oc\ soil}$ 992; 525; 915; 209; 857 L/kg $K_{oc\ sludge}$ 71.6 L/kg			
Ready Biodegradability Test	OECD 310	Not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	**Table 1.** Aerobic: $DT_{50,\ water}$ 23, 20 d (r/l) **Table 2.** $DT_{50,\ system}$ 30, 20 d (r/l) Anaerobic: $DT_{50,\ water}$ 23, 18 d (r/l) $DT_{50,\ system}$ 32, 22 d (r/l) Significant sediment shifting at day ≥14.			r = river; l = lake; All values determined at 20°C; Significant shifting to sediment observed.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchnella subcapitata*	OECD 201	NOEC	21	mg/ L	growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	35	mg/ L	survival, reproduction, length
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC	≥9.5	mg/ L	growth
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	821	mg/ L	respiration
Phase IIb Studies					
Sediment dwelling organism/ *Chironomus riparius*	OECD 218	NOEC	35.6	mg/ kg	survival, reproduction, growth; normalised to 10% o.c.

Dapagliflozin

The dosing (10 mg patient^{-1} d^{-1}) and indication remained the same in the current fixed combination product compared to the original submission (EMEA/H/C/002322, Forxiga) for which an ERA was performed and assessed in 2012, with the conclusion that dapagliflozin is considered unlikely to present a risk to the environment and is not a PBT substance. An increase in use of the active ingredient is not expected, and therefore a new ERA does not need to be performed.

Table 2 Dapagliflozin - summary of main study results

Substance (INN/Invented Name): dapagliflozin			
CAS-number (if available): 960404-48-2 (dapagliflozin propanediol)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	2.34 at pH 7	Potential PBT: No
PBT-statement :	Dapagliflozin is considered not PBT, nor vPvB		
Phase I			

Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default and refined	0.05 (default) 0.00915 (refined)	µg/L	> 0.01 threshold YES Refined PEC accepted for Phase II
Other concerns (e.g. chemical class)			No
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OPPTS 835.1110	K_{oc} = *138* K_d = 51	
Ready Biodegradability Test	OECD 301F	Not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = 13/ 7.2 d (h/l) $DT_{50,\ sediment}$ = 127/94 d (h/l) $DT_{50,\ total\ system}$ = 136/66 d (h/l) Significant sediment shifting at day ≥14	h = high organic matter; l = low organic matter; All values determined at 20°C; Dapagliflozin is persistent in sediments.
Phase IIa Effect studies			
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchnella subcapitata*	OECD 201	NOEC	37	mg/ L	growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	10	mg/ L	reproduction, length
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC	1.0	mg/ L	hatch, survival, standard length, and dry weight
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	107.6	mg/ L	respiration
Phase IIb Studies					
Sediment dwelling organism/ *Chironomus riparius*	OECD 218	NOEC	150	mg/ kg	emergence, development rate, sex ratio

2.3.6. Discussion on non-clinical aspects

The non-clinical profiles of saxagliptin and dapagliflozin are well documented in the nonclinical studies performed as part of the development for Onglyza and Forxiga to address the pharmacodynamic, pharmacokinetic and toxicology of these substances.

In support of the fixed-dose combination product, an in-vitro drug interaction study in human liver microsomes and a safety pharmacology, toxicity, and toxicokinetic assessments as a part of a 3-month oral toxicity in rats were conducted.

There were no differences in safety pharmacology (CNS and respiratory), toxicokinetic, or unique or synergistic toxicity outcomes in rats dosed with the combination relative to those dosed with the individual agents at AUC multiples at AUC multiples ranging from 2 to 5 and 4 to 5 times the exposure at the maximum human recommended dose for saxagliptin and dapagliflozin, respectively.

The Applicant has provided individual environmental risk assessments for saxagliptin and dapagliflozin. The introduction of this fixed-dose combination product is not expected to result in an increase in environmental exposure.

2.3.7. Conclusion on the non-clinical aspects

From a non-clinical point of view, there are no nonclinical findings that preclude the safe administration of saxagliptin in combination with dapagliflozin at the proposed daily doses of up to 5 mg and 10 mg, respectively.

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

An overview of the clinical studies supporting the saxagliptin / dapagliflozin FDC program is given in table below.

Table 3: Phase 1 and Phase 3 studies supporting the saxagliptin / dapagliflozin FDC programme

Study identifier	Type of study	Phase	Objective(s) of the study	No. of subjects
CV181341	BE study	1	BE, PK, Food effect, Safety	72
CV181191	DDI study	1	PK, Safety	42
CV181169	Dual Add-on to MET	3	Safety and efficacy	534
CV181168	Sequential Add-on to MET	3	Safety and efficacy	315
MB102129	Sequential Add-on to MET	3	Safety and efficacy	320

2.4.2. Pharmacokinetics

Qtern film coated tablet is a fixed dose combination tablet with two orally active glucose lowering agents for the treatment of patients with type 2 diabetes. Qtern contains 5 mg saxagliptin (BMS-477118), which is a reversible and competitive dipeptidyl peptidase 4 (DPP4) inhibitor and 10 mg dapagliflozin (BMS-512148) a competitive, reversible, highly selective inhibitor of the human sodium-glucose co-transporter 2 (SGLT2), the major transporter responsible for the renal glucose reabsorption.

To support this application the applicant has submitted two pharmacokinetic studies for the application of the FDC saxagliptin/dapagliflozin (see **Error! Reference source not found.**); these are discussed

in detail. The pharmacokinetics of saxagliptin and dapagliflozin have been extensively characterized in healthy subjects and patients with type 2 diabetes in procedures EMEA/H/C/001 039 and EMEA/H/C/002322. During the clinical development of saxagliptin the pharmacokinetics of saxagliptin has been investigated in 30 PK studies with 497 subjects exposed to saxagliptin doses up to 400 mg. The clinical pharmacology programme for dapagliflozin included 28 studies conducted in 688 subjects (635 of these subjects were exposed to dapagliflozin). In this report the results and conclusions of the pharmacokinetic studies submitted in these procedures are shortly summarised.

Table 4 Phase 1 studies supporting the saxagliptin / dapagliflozin FDC programme

Type of study	Study identifier	Objective(s) of the study	Study design and type of control	Test products, dosage regimen, route of administration	No. of subjects rand/ completed	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
BE study	CV181341	BE, PK, Food effect, Safety	Open label, randomised, 3-treatment, 3-period crossover study	Saxa 2.5 mg/dapa 5 mg FDC Saxa 5 mg/dapa 10 mg FDC Tablets, PO	72/72	Fed and fasted	Single dose	CSR Complete
DDI study	CV181191	PK, Safety	Open label, randomised, 3-treatment, 3-period, crossover study	Saxa 5 mg Dapa 10 mg Saxa 5 mg + dapa 10 mg Tablets, PO	42/41	Healthy subjects	Single dose	CSR Complete

BE Bioequivalence; CSR Clinical Study Report; Dapa:Dapagliflozin; DDI Drug-drug interaction; FDC Fixed dose combination; PK Pharmacokinetics; PO Orally; Saxa:Saxaglitpin.

The Applicant has provided the regulatory inspection reports for the clinical and bioanalytical study sites. No critical findings or significant observations were noted during inspections.

Bioanalytical methods

After oral administration saxagliptin and dapagliflozin are both well absorbed with a t_{max} of 2 - 4 hours and 1 hour respectively. Saxagliptin has a high bioavailability of approximately 75% and dapagliflozin has an absolute bioavailability of 78%.

Absorption and bioavailability

After oral administration saxagliptin and dapagliflozin are both well absorbed with a t_{max} of 2 - 4 hours and 1 hour respectively. Saxagliptin has a high bioavailability of approximately 75% and dapagliflozin has an absolute bioavailability of 78%.

Bioequivalence

The bioavailability of the fixed dose combination saxagliptin/10 mg dapagliflozin FDC tablets has been characterised and compared to the individual components in study CV181341. In study CV181341 was shown that 5-mg saxagliptin/10-mg dapagliflozin FDC tablet is bioequivalent to 5-mg saxagliptin + forxiga 10-mg (dapagliflozin) tablets under fasted conditions. The plasma dapagliflozin and saxagliptin GM ratios of C_{max}, AUC_{0-t}, and AUC_{INF} were close to 1.00 and the 90% confidence intervals (CIs) of the GM ratios were contained within the criterion interval of (0.80, 1.25) when Test and Reference treatment were compared (Table 11). However in the majority of subjects in this study the dapagliflozin C_{max} has been observed in at least one of the three periods as being the first point. The Applicant also provided an additional bioequivalence assessment for C_{max} of dapagliflozin not considering the data for the affected subjects, the data of 15 subjects could be used in the recalculation of the Ratio E/D (Table 12). The recalculated 90% CI's (without first time point C_{max} concentration-time profiles) for C_{max} and AUC_{0-t} are 0.908 (0.797-1.035) and 1.026 (0.993-1.061) respectively. Thus recalculated AUC was within the BE acceptance limits and recalculated C_{max} was outside the BE acceptance limits.

Further a justification was submitted to support that the 0.5 h time point is representative of early individual C_{max} values, in this justification the following data were discussed:

- The applicant has provided an assessment of the earliest time points observed for t_{max} across the dapagliflozin dossier. In two studies (study MB102001 and study MB102062) blood samples were collected at time points earlier than 0.5 h, namely 0.25 h. The earliest t_{max} observed in these studies was consistently 0.5h, demonstrating that there would have been no particular benefit in adding a time point at 0.25h for the characterization of C_{max} in these studies.

- The applicant has also presented the results of a further PK study with the saxagliptin/dapagliflozin FDC tablet. In this study no t_{max} earlier than 0.5 hours has been observed.

Table 5 Dapagliflozin, saxagliptin and 5-OH saxagliptin pharmacokinetic parameters after administration of Saxagliptin 5mg/Dapagliflozin 10mg as separate tablets and as FDC tablet under fasting conditions CV181341

	Dapagliflozin		Saxagliptin		5-OH Saxagliptin	
Parameter statistic	Reference	Test	Reference	Test	Reference	Test
Cmax (ng/mL) GM [n] (CV)	150 [35] (38)	141 [35] (40)	26.1 [35] (38)	27.6 [35] (32)	53.9 [35] (33)	59.5 [35] (28)
GM Ratio T/R (90% CI)	0.946 (0.878, 1.019)		1.059 (0.993, 1.129)			
tmax (h) median [n] (min - max)	0.550 [35] (0.50 – 4.00)	1.00 [35] (0.50 – 3.00)	0.750 [35] (0.25 – 3.00)	0.600 [35] (0.25 – 1.50)	1.50 [35] (0.75 – 4.00)	1.50 [35] (1.00 – 3.02)
AUC0-t (ng·h/mL) GM [n] (CV)	580 [35] (23)	601 [35] (21)	95.6 [35] (23)	96.4 [35] (23)	316 [35] (21)	330 [35] (18)
GM Ratio T/R (90% CI)	1.036 (1.010, 1.062)		1.007 (0.973, 1.042)			
AUCINF (ng·h/mL) GM [n] (CV)	598 [35] (23)	620 [35] (21)	97.2 [35] (23)	97.5 [35] (23)	323 [35] (21)	336 [35] (18)
GM Ratio T/R (90% CI)	1.035 (1.008, 1.063)		1.003 (0.969, 1.038)			
t1/2 (h) mean [n] (SD)	15.0 [35] (4.72)	15.6 [35] (5.54)	7.20 [35] (4.66)	5.37 [35] (2.94)	16.3 [35] (3.95)	16.0 [35] (3.15)

Reference : 5-mg saxagliptin + forxiga 10-mg (dapagliflozin) tablets under fasted conditions.
Test: 5-mg saxagliptin/10-mg dapagliflozin FDC tablet under fasted conditions.
AUC: Area under the curve; AUC0-t :AUC from time 0 to last quantifiable concentration; AUCINF :AUC from time 0 extrapolated to infinity; Cmax :Maximum plasma concentration; CV : coefficient of variation; GM: geometric mean; h: hour; Max: Maximum; Min: Minimum; n: number of subjects; t1/2 :half life; tmax :Time to maximum concentration

Table 6 Dapagliflozin C_{max} after administration of Saxagliptin 5mg and Dapagliflozin 10mg as separate tablets and as FDC tablet under fasting conditions CV181341 with (Original Analysis) and without first time point C_{max} concentration-time profiles

Treatment	Original Analysis (all data)		Analysis Excluding First Time-Point Cmax	
	Adjusted geometric mean [n]	90% CI	Adjusted geometric mean [n]	90% CI
Reference	149 [35]	(134, 166)	135.449 [17]	(117.633, 155.965)
Test	141 [35]	(125, 158)	123.052 [24]	(108.765, 139.216)
Ratio Test/Reference (90% CI)	0.946	(0.878, 1.019)	0.908	(0.797, 1.035)

Reference: 5-mg saxagliptin + 10-mg dapagliflozin tablets under fasted conditions.
Test: 5-mg saxagliptin/10-mg dapagliflozin FDC tablet under fasted conditions.
Cmax Maximum plasma concentration; CI Confidence interval.

The influence of food

The absorption of saxagliptin is not affected by food. Administration of dapagliflozin with a high-fat meal reduced the rate but not the extent of absorption resulting in a 1 h delay of t_{max} and a 30-45% decrease in C_{max} but no change in AUC.

In study CV181341 the effect of food on the FDC tablets was characterized as well, the food effect on dapagliflozin was similar to that for the monotherapy product. There was no food effect observed for saxagliptin. For Dapagliflozin recalculated C_{max} values (without first time point C_{max} concentration-time profiles) were provided as well.

Table 7 Dapagliflozin, saxagliptin and 5-OH Saxagliptin pharmacokinetic parameters after administration of Saxagliptin 5mg/Dapagliflozin 10mg as separate tablets and as a FDC tablet under fed and fasted conditions CV181341

	Dapagliflozin		Saxagliptin		5-OH Saxagliptin	
Parameter statistic	Fasted	Fed	Fasted	Fed	Fasted	Fed
Cmax (ng/mL) GM [n] (CV)	141 [35] (40)	91.3 [36] (43)	27.6 [35] (32)	25.6 [36] (36)	59.5 [35] (28)	48.3 [36] (22)
GM Ratio T/R (90% CI)	0.648 (0.565, 0.743)		0.925 (0.837, 1.022)			
tmax (h) median [n] (min - max)	1.00 [35] (0.50 – 3.00)	2.50 [36] (0.50 – 8.08)	0.600 [35] (0.25 – 1.50)	1.00 [36] (0.50 – 4.00)	1.50 [35] (1.00 – 3.02)	3.00 [36] (1.00 – 6.00)
AUC0-t (ng·h/mL) GM [n] (CV)	601 [35] (21)	557 [36] (21)	96.4 [35] (23)	111 [36] (20)	330 [35] (18)	324 [36] (19)
GM Ratio T/R (90% CI)	0.931 (0.908, 0.955)		1.155 (1.117, 1.194)			
AUCINF (ng·h/mL) M [n] (CV)	620 [35] (21)	582 [36] (21)	97.5 [35] (23)	113 [36] (20)	336 [35] (18)	331 [36] (19)
GM Ratio T/R (90% CI)	0.943 (0.919, 0.968)		1.155 (1.118, 1.194)			
t1/2 (h) mean [n] (SD)	15.6 [35] (5.54)	16.4 [36] (5.53)	5.37 [35] (2.94)	7.28 [36] (4.31)	16.0 [35] (3.15)	16.8 [36] (2.49)

Reference : 5-mg saxagliptin/10-mg dapagliflozin FDC tablet under fasted conditions.
Test: 5-mg saxagliptin/10-mg dapagliflozin FDC tablet under fed conditions.
AUC Area under the curve; AUC_{0-t} AUC from time 0 to last quantifiable concentration; AUC_{INF} AUC from time 0 extrapolated to infinity; C_{max} Maximum plaxma concentration; CV coefficient of variation; GM geometric mean; h hour; Max Maximum; Min Minimum; n number of subjects; $t_{1/2}$ half life; t_{max} Time to maximum concentration.

Table 8 Dapagliflozin C_{max} after administration of Saxagliptin 5mg/Dapagliflozin FDC tablet under fasting and fed conditions CV181341 with (Original Analysis) and without first time point C_{max} concentration-time profiles

Treatment and comparison	Original Analysis (all data)		Analysis Excluding First Time-Point Cmax	
	Adjusted geometric mean [n]	90% CI	Adjusted geometric mean [n]	90% CI
FDC fasted	141 [35]	(125, 158)	123.052 [24]	(108.765, 139.216)
FDC fed	91.3 [36]	(81.1, 103)	91.175 [35]	(80.647, 103.077)
Ratio Fed/Fasted (90% CI)	0.648	(0.565, 0.743)	0.741	(0.630, 0.871)

FDC fasted: 5-mg saxagliptin/10-mg dapagliflozin FDC tablet under fasted conditions.
FDC fed: 5-mg saxagliptin/10-mg dapagliflozin FDC tablet under fed conditions.
C_{max} Maximum plasma concentration; CI Confidence interval.

Distribution

Saxagliptin and its major metabolite BMS-510849 do not bind to plasma proteins and plasma protein binding of dapagliflozin was 91%. Population PK analyses suggest that the apparent volume of distribution of saxagliptin is much higher than that of BMS-510849 (205 L versus 9 L, respectively). The mean V_{ss} for dapagliflozin following intravenous administration was 118L. No additional studies with the FDC were conducted, but as no displacement interactions are expected this is considered acceptable.

Metabolism and elimination

Saxagliptin is metabolised to an active metabolite 5-OH-Saxagliptin, primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). This metabolite contributes substantially to the pharmacological effect of saxagliptin. Saxagliptin and its metabolite are excreted by renal elimination (75%) and faecal elimination 22% with a half life of 2.5-3 hours, however its mean $t_{1/2}$ for DPP inhibition was 26.9 hours.

Dapagliflozin is extensively metabolized by UGT1A9 to inactive metabolites and mainly excreted by renal elimination, 73.7% of the dose being recovered as metabolites (72.0 and 1.65% in urine and faeces, respectively) and 16.6% of the dose being recovered as unchanged parent compound. Dapagliflozin has an elimination half life of approximately 12 hours.

No additional studies with the FDC were conducted. No additional excretion studies are considered necessary as no metabolism or transporter interactions are expected based on the available in vitro and in vivo interaction data.

Dose proportionality and time dependencies

Saxagliptin and dapagliflozin both display linear pharmacokinetics in the therapeutic range, do not exhibit time dependent PK and have a moderate variability. The FDC tablet contains 5mg saxagliptin and 10mg dapagliflozin, both concentrations are in the linear range. Both active substances in the FDC tablet do not exhibit time dependent PK, therefore there is also no need to conduct multiple dose PK studies.

Special populations

No additional “Intrinsic Factor PK Studies” were considered necessary for this application since both saxagliptin and dapagliflozin are registered medications, and a drug-drug interaction study between saxagliptin and dapagliflozin showed no clinically meaningful effect of saxagliptin on dapagliflozin PK parameters and vice versa.

As both saxagliptin and dapagliflozin are mainly renally excreted or metabolised, the exposure to both drugs is substantially increased by *renal impairment*. Saxagliptin AUC was increased approximately 2 fold by mild renal impairment and 3 fold by moderate renal impairment. In patients with, mild, moderate and severe renal impairment, the dapagliflozin AUC increased by 30%, 50% and 80% respectively. No dose adjustment is necessary for both active components in patients with mild renal impairment. However dapagliflozin is currently not recommended for use in patients with moderate to severe renal impairment and therefore the fixed dose combination is also not recommended in these patients. No additional information on this patient group is required for the FDC.

In patients with hepatic impairment the exposures to saxagliptin were 1.1-, 1.4- and 1.8-fold higher, respectively, and the exposures to 5-OH saxagliptin were 22%, 7%, and 33% lower, respectively, than those observed in healthy subjects. In patients with mild hepatic impairment dapagliflozin’s PK was similar to the control group. Moderate hepatic impairment had only a small effect on dapagliflozin’s

pharmacokinetics, 36% increase in AUC. In patients with severe hepatic impairment the mean increase in dapagliflozin exposure was 67%. In the SmPC of the monocomponent is mentioned that no dose adjustment in patients with mild or moderate hepatic impairment is necessary. However in patients with severe hepatic impairment, a lower starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg. Saxagliptin should be used with caution in patients with moderate hepatic impairment is not recommended in patients with severe hepatic impairment, and thus Qtern has the same recommendations. No additional information on this patient group is required for the FDC.

Small, non clinically significant differences between male and female subjects were observed for both active substances and also the differences due to race or weight were small and not considered clinically meaningful.

Elderly subjects (65 to 80 years) had 23% and 59% higher C_{max} and AUC_{INF} values of saxagliptin, respectively, than young subjects (18 to 40 years). For dapagliflozin there was no clinically meaningful increase in exposure based on age alone in subjects up to 70 years old. However, increased exposure due to age-related decrease in renal function can be expected.

There are no PK data in children for saxagliptin and dapagliflozin, which is considered acceptable for this type of product.

Drug interactions

In vitro

The *in vitro* drug interaction program of saxagliptin and dapagliflozin was extensive. The main metabolising enzymes have been evaluated.

Dapagliflozin is mainly metabolized via UGT1A9, but saxagliptin and its 5-OH metabolite both do not inhibit this enzyme.

The biotransformation of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5), but dapagliflozin does not inhibit this enzyme.

Saxagliptin and dapagliflozin are both substrates for P-gp.

Saxagliptin and 5-OH-saxagliptin neither inhibited CYP1A2, 2A6, 2B6, 2C9, 2C8, 2C19, 2D6, 2E1, or 3A4, nor induced CYP1A2, 2B6, 2C9, 3A4 or CYP2C19 in vitro. For saxagliptin no in vitro data on transporter inhibition are available, however clinical data indicate that saxagliptin does not inhibit P-gp, OATP1B1, OCT1 and OCT2 transporters at clinically relevant doses.

Dapagliflozin is not a substrate for OCT2, OAT1, OATP1B1 and OATP1B3. The presented data indicate that dapagliflozin does not inhibit P-gp, OAT1 or OCT1/OCT2 and is a weak inhibitor of OAT3, OATP1B1 and OATP1B3 transporters, but not an inhibitor at clinically relevant systemic exposures. Hence clinically relevant drug interactions via inhibition of these transporters are not expected. Dapagliflozin did not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 and induce CYP1A2, CYP2B6 and CYP3A4.

In vivo

A drug-drug interaction study (CV181191) showed no clinically meaningful effect of saxagliptin on dapagliflozin PK parameters and vice versa. This study was a single-dose, open-label, randomized, 3-period, 3-treatment crossover study to evaluate the pharmacokinetics of saxagliptin 5 mg and dapagliflozin 10 mg when co-administered. It should be noted that the identity and certificates of analysis of the investigational products used in study CV181191 were not entirely clear.

Table 9 Statistical analysis to assess effect interaction between dapagliflozin and saxagliptin (Pharmacokinetic evaluable population) Study CV181191

Analyte	Treatment and Comparison	Cmax (ng/mL) Adjusted GM [n]	AUC(0-T) (ng h/mL) Adjusted GM [n]	AUC(INF) (ng h/mL) Adjusted GM [n]
Dapagliflozin	B *	133 [41]	529 [41]	547 [41]
	C	125 [42]	523 [42]	539 [42]
		Ratio of Adjusted GM (90% CI)		
	C vs B	0.943 (0.867, 1.026)	0.990 (0.966, 1.014)	0.984 (0.961, 1.008)
Saxagliptin	A	23.6 [42]	87.8 [42]	89.0 [42]
	C	21.9 [42]	87.0 [42]	88.2 [42]
		Ratio of Adjusted GM (90% CI)		
	C vs A	0.927 (0.883, 0.972)	0.991 (0.960, 1.022)	0.991 (0.961, 1.022)
5-OH Saxagliptin	A	47.0 [42]	267 [42]	273 [42]
	C	49.6 [42]	289 [42]	296 [42]
		Ratio of Adjusted GM (90% CI)		
	C vs A	1.055 (1.004, 1.109)	1.085 (1.058, 1.113)	1.085 (1.058, 1.113)
Saxagliptin Total Active Moiety	A	138a [42]	694b [42]	702b [42]
	C	137a [42]	727b [42]	735b [42]
		Ratio of Adjusted GM (90% CI)		
	C vs A	0.994 (0.960, 1.030)	1.046 (1.029, 1.064)	1.046 (1.029, 1.064)

Treatment A Saxagliptin 5 mg
Treatment B Dapagliflozin 10 mg
Treatment C Saxagliptin 5 mg + Dapagliflozin 10 mg
a Units for Cmax are nM
b Units for AUC are nM hour

*Subject 10018 was excluded from the summaries for Cmax, Tmax, AUC(0-T), AUC(INF) and CLT/F for Treatment B.
AUC(0-T) Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration; AUC(INF) Area under the plasma concentration-time curve from time zero extrapolated to infinity; Cmax Maximum plasma concentration; CI confidence interval; GM geometric mean; n number of nonmissing observations.

The effect of other drugs on saxagliptin

The pharmacokinetic interaction with oral antidiabetic agents was evaluated. Metformin co-administration of 1000 mg did not affect the overall systemic exposure to saxagliptin, but has resulted in a modest decrease in the C_{max} of saxagliptin (21%) and BMS-510849. Saxagliptin C_{max} and AUC_{TAU} values were 20% higher and 18% higher, respectively, when pioglitazone was co-administered with saxagliptin compared to when saxagliptin was administered alone. Glyburide did not affect saxagliptin pharmacokinetics.

Interactions with the Gastric Acid Controllers Maalox Max®, omeprazole and famotidine was also studied. Co-administration of Gastric Acid Controllers did not profoundly affect saxagliptin and 5-OH-saxagliptin pharmacokinetics.

The strong CYP3A4/5 inhibitor ketoconazole had a pronounced effect on saxagliptin pharmacokinetics. The C_{max} and AUC_{INF} values for saxagliptin were 62% and 2.5-fold higher, upon coadministration with ketoconazole and the corresponding values for 5-OH-saxagliptin were 95% and 88% lower, respectively. The exposure AUC_{INF} values of the total active moiety (saxagliptin+5-OH-saxagliptin) increased by 13% compared to when saxagliptin was administered alone.

Co-administration of the moderate inhibitor of CYP3A4/5 diltiazem with saxagliptin increases the C_{max} and AUC_{INF} values of saxagliptin by 63% and 2.1-fold, respectively, and the corresponding values for the active metabolite were decreased by 44 and 34%, respectively.

Concomitant administration of the potent inducer of CYP3A4 rifampicin resulted in decreased saxagliptin exposure (C_{max} and AUC_{INF} were decreased by 53% and 76%, respectively), and 5-OH-saxagliptin C_{max} and AUC_{INF} increased by 39% and 3%, respectively. The co-administration of saxagliptin and CYP3A4/5 inducers, other than rifampicin (such as carbamazepine, dexamethasone, phenobarbital and phenytoin) has not been studied and may result in decreased plasma concentration of saxagliptin.

Co-administration of omeprazole (CYP2C19 substrate) to steady-state did not meaningfully alter the pharmacokinetics of saxagliptin or 5-OH-saxagliptin.

The effect of other drugs on dapagliflozin

The company evaluated the pharmacokinetic drug-drug interaction between dapagliflozin and several antidiabetic drugs (metformin, pioglitazone, sitagliptin, glimepiride and voglibose). These did not profoundly affect dapagliflozin pharmacokinetics.

The pharmacokinetic interactions with frequently used concomitant medication hydrochlorothiazide (25 mg), bumetanide (1 mg), valsartan (320 mg) and simvastatin (40 mg) were also evaluated. Valsartan slightly reduced dapagliflozin C_{max} (↓ 12%) but AUC was not affected. Hydrochlorothiazide, bumetanide and simvastatin did not affect dapagliflozin pharmacokinetics.

Concomitant administration with the metabolizing enzyme inducer rifampin (600 mg QD) resulted in a slight decrease of dapagliflozin C_{max} (↓7%) and AUC (↓22%), however as mean amount of glucose excreted in the urine over 24 h was not markedly affected by rifampin co-administration.

Co-administration of the UGT1A9 inhibitor mefenamic acid under steady state conditions with a single dose of dapagliflozin resulted in a 55% increase in dapagliflozin AUCt, 22% reduction in dapagliflozin 3-O-glucuronide AUC and an increase in urine excretion of glucose.

The effect of saxagliptin on other drugs

Saxagliptin did not meaningfully alter the PK of metformin (OCT2 and OCT3 substrate), glyburide (CYP2C9 substrate), pioglitazone (substrate CYP3A4 and CYP2C8), digoxin(P-gp substrate), simvastatin (CYP3A4 substrate and OATP1B1), diltiazem, ketoconazole, ethinyl estradiol, and norgestimate. Saxagliptin did not meaningfully alter the PK of metformin (OCT2 and OCT3 substrate), glyburide (CYP2C9 substrate), pioglitazone (substrate CYP3A4 and CYP2C8), digoxin (P-gp substrate), simvastatin (CYP3A4substrate and OATP1B1), diltiazem, ketoconazole, ethinyl estradiol, and norgestimate.

The effect of dapagliflozin on other drugs

Dapagliflozin did not meaningfully alter the PK of metformin (OCT2and OCT3 substrate), pioglitazone (SubstrateCYP3A4 and CYP2C8), sitagliptin (substrate CYP3A4 and CYP2C8), glimepiride, hydrochlorothiazide (OAT1), bumetanide (OAT3), valsartan, simvastatin(CYP3A4substrate and OATP1B1), digoxin(P-gp substrate), and warfarin(substrate CYP2C9).

5 mg saxagliptin / 10 mg dapagliflozin filmcoated tablets

No additional interaction studies have been conducted for the fixed dose combination product. The potential for interactions with other medicinal products has been extensively evaluated in the original saxagliptin and dapagliflozin applications. The overall potential for either saxagliptin or dapagliflozin to be involved in meaningful DDIs is assessed to be low, and is not expected to be increased due to combined use of both medicinal products. No additional information is required.

2.4.3. Pharmacodynamics

No new data were submitted on pharmacodynamics. The clinical pharmacology programme that supported the original saxagliptin and dapagliflozin clinical development programmes provides information to support the saxagliptin/dapagliflozin FDC programme. Key clinical pharmacology information about saxagliptin and dapagliflozin, with and without combination with metformin, are available in the respective product labels.

Mechanism of action

Saxagliptin is a highly potent (Ki: 1.3 nM), selective, reversible and competitive inhibitor of DPP4, an enzyme responsible for the breakdown of incretin hormones. This results in a glucose-dependent increase in insulin secretion, thus reducing fasting and post-prandial blood glucose concentrations.

Dapagliflozin is a highly potent (Ki: 0.55 nM), selective and reversible inhibitor of sodium-glucose co-transporter 2 (SGLT2). Dapagliflozin blocks reabsorption of filtered glucose from the S1 segment of the renal tubule, effectively lowering blood glucose in a glucose-dependent and insulin-independent manner. Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion.

Qtern combines the complementary mechanisms of action of both monocomponents. Actions of both medicines are regulated by the plasma glucose level. The combination of both agents delivers clinically meaningful reductions in HbA1c for improved glycaemic control in patients with T2DM. While saxagliptin has a neutral effect on weight, urinary glucose excretion (glucuresis) induced by dapagliflozin is associated with caloric and weight loss.

Primary and Secondary pharmacology

Saxagliptin

In patients with type 2 diabetes, administration of saxagliptin inhibited DPP4 enzyme activity throughout a 24-hour period. After an oral glucose load, this produced in a 2- to 3-fold increase in

circulating levels glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), decreased glucagon concentrations, and increased beta-cell responsiveness, resulting in higher insulin and C-peptide concentrations. The rise in insulin from pancreatic betacells and the decrease in glucagon from pancreatic alpha-cells were associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

Dapagliflozin
Dapagliflozin's glucuretic effect is observed after the first dose, is continuous over the 24-hour dosing interval, and is sustained for the duration of treatment. Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in subjects with type 2 diabetes mellitus following the administration of dapagliflozin. Approximately 70 g of glucose was excreted in the urine per day (corresponding to 280 kcal/day) at a dapagliflozin dose of 10 mg/day in subjects with type 2 diabetes mellitus for 12 weeks. Evidence of sustained glucose excretion was seen in subjects with type 2 diabetes mellitus given dapagliflozin 10 mg/day for up to 2 years. Urinary uric acid excretion was also increased transiently (for 3-7 days) and accompanied by a sustained reduction in serum uric acid concentration. At 24 weeks, reductions in serum uric acid concentrations ranged from –48.3 to –18.3 micromoles/l (–0.87 to –0.33 mg/dl). The increased urinary excretion with SGLT2 inhibition produces an osmotic diuresis, and can result in a reduction in systolic BP.

2.4.4. Discussion on clinical pharmacology

The applicant conducted two pharmacokinetic studies to bridge the pharmacokinetic data of the monocomponents to the FDC tablets.

Bridging of the results obtained in the phase 3 studies performed with the combination of the monotherapies to the to-be-marketed FDC formulation has sufficiently been justified.

Although the sampling schedule of BE Study CV181341 was suboptimal for dapagliflozin, the study has shown that the PK of the FDC tablet is comparable to the dapagliflozin monocomonent tablet. It is considered unlikely that the finding of BE for dapagliflozin between the FDC tablet and the 10 mg dapagliflozin mono component tablet would have been different if an earlier time point would have been studied in study CV18134. The following points have been taken into account:

- The initial findings of the full study population were confirmed in the reanalysis without subjects having their C_{max} in the first sampling point. The recalculated ratio of the FDC vs the individual components show a 90% CI around C_{max} of 79.7-103.5 which is only slightly outside the 80-125% acceptance interval and is most probably due to a reduced power. The recalculated 90% CI around AUC is 99.3-106.1%.

- The applicant has appropriately justified that the 0.5 h time point is representative of early individual C_{max} values. Therefore the C_{max} data of the subjects that had a first time-point C_{max} are considered sufficiently reliable.

The pharmacokinetics of saxagliptin and dapagliflozin are well established for both active substances and no additional data with respect to the absorption, distribution, metabolism or excretion are required. Also the use in special populations of both monocomponents of the FDC tablets has been sufficiently characterized.

The drug interaction study CV181191 is properly designed, and in this study the absence of an interaction between saxagliptin and dapagliflozin was shown. The applicant justified the choice of the single dose design for the drug-drug interaction study. Due to the lack of accumulation of both agents the plasma concentrations after a single dose are sufficient to assess the interaction between saxagliptin and dapagliflozin. In addition no interaction is expected due to their different routes of

metabolism and the lack of impact of either compound on drug metabolizing enzymes or transporters. Since the FDC is intended to be given in combination with metformin, potential drug-drug interactions between saxagliptin or dapagliflozin and metformin are of full interest. This issue has been sufficiently addressed during the MA assessment of the mono-components in dedicated DDI studies with metformin. Also the potential for interactions of both monocomponents of the FDC tablets with other relevant comedication have been sufficiently characterised. Based on the pharmacokinetic properties of saxagliptin and dapagliflozin and the results of previously conducted drug interaction studies the overall interaction potential of the fixed dose combination is assessed to be low. No additional drug-interactions are expected as saxagliptin and dapagliflozin are metabolized via different metabolic pathways. Both saxagliptin and its 5-OH metabolite and dapagliflozin demonstrated low potential to inhibit or induce CYP enzymes or to affect transporters. As a result, it is unlikely that the combination of saxagliptin and dapagliflozin will result in any previously unidentified drug-drug interactions with co-administered drugs that are CYP substrates or substrates for the relevant transporters. Therefore no additional drug interaction studies are required for Qtern.

No new studies were performed on pharmacodynamics. Key clinical pharmacology information about saxagliptin and dapagliflozin, with and without combination with metformin, is available in the respective product labels. For Qtern, effects on HbA1c and weight were shown in the clinical phase 3 trials. The mechanisms of action of dapagliflozin and saxagliptin are different and complementary but the fact that dapagliflozin lowers glucose might diminish the efficacy of saxagliptin because the effect of Saxagliptin is increased by increases in glycaemia. The Applicant has shown that the contribution of both components to the FDC depends on baseline HbA1c. Saxagliptin is contributing a larger proportion to the total combination effect at lower baseline HbA1c levels than at higher ones, and conversely, dapagliflozin is contributing a larger proportion to the total combination effect at higher baseline HbA1c levels than at lower ones.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics of saxagliptin and dapagliflozin are well established for both active substances and based and the results of previously conducted studies the overall interaction potential of the fixed dose combination is assessed to be low. Bioequivalence between the fixed dose combination 5 mg saxagliptin/10 mg dapagliflozin FDC tablets and the individual components has been studied in study CV181341.

The effect of food on the FDC tablets was similar to that for the monotherapy products. Study CV181191 confirmed the absence of a drug-drug interaction between saxagliptin on dapagliflozin. No additional studies of pharmacokinetic studies are considered necessary for this application.

No new pharmacodynamic studies were performed. Key clinical pharmacology information about saxagliptin and dapagliflozin, with and without combination with metformin, are available in the respective product labels. The contribution of both components to the FDC depends on baseline HbA1c, with saxagliptin more active at lower baseline HbA1c levels and dapagliflozin contributing more at higher baseline HbA1c levels.

2.5. Clinical efficacy

2.5.1. Dose response studies

Not applicable.

2.5.2. Main studies

In support of the application results of three Phase 3 studies were submitted (Table 16).

Study CV181169 is completed; from study CV181168 and MB102129 the Short-term phase is completed, the Long-term extension phase is still ongoing.

Methods

Study CV181169 was a multicentre, randomised, double-blind, active-controlled, parallel-group, 24-week Phase 3 trial in 534 subjects designed to evaluate the safety and efficacy (primary endpoint: mean change from baseline in HbA1c) of saxagliptin and dapagliflozin added concurrently to metformin compared with dapagliflozin added to metformin and saxagliptin added to metformin in subjects with T2DM with inadequate glycaemic control on metformin alone. The study consisted of a screening period, followed by a lead-in period (4-weeks), and then a 24-week double-blind treatment period.

Study CV181168 and *Study MB102129* were multicentre, randomised, double-blind, placebo-controlled, parallel-group, 24-week Phase 3 trials in 315 and 320 subjects, respectively, designed to evaluate the safety and efficacy (primary endpoint: mean change from baseline in HbA1c) of the sequential addition of saxagliptin to dapagliflozin and metformin (CV118168) or dapagliflozin to saxagliptin and metformin (MB102129) compared with the addition of placebo in subjects with T2DM with inadequate glycaemic control on metformin and dapagliflozin or saxagliptin. The studies had a screening period, followed by an OL treatment period (16 weeks), and then a 24-week double blind treatment period. Eligible subjects could enter the long-term (LT) extension for an additional 28 weeks (ongoing). In study MB102129, to facilitate recruitment, patients were divided into two strata, one of which comprised patients who were already being treated with a DPP4 inhibitor at the time of the screening visit.

Table 10 Description of the clinical efficacy and safety studies

Study ID	No. of study centres / locations	Design and duration	Study objective Primary endpoint	Treatment groups	Subjs by arm randomised / completed.	Gender M/F Median Age	Diagnosis Incl. criteria
CV181169	145 centres in 8 countries	Randomised double-blind, active-controlled, parallel-group, multicentre study 24 weeks of randomised treatment	Efficacy and Safety Change in HbA1c from baseline to Week 24	Saxagliptin 5 mg + dapagliflozin 10 mg + metformin XR 1500 to 2000 mg Saxagliptin 5 mg + metformin XR 1500 to 2000 mg Dapagliflozin 10 mg + metformin XR 1500 to 2000 Mg	**Table 3.** Saxagliptin + dapagliflozin + metformin: 179/169 Saxagliptin + metformin: 176/161 Dapagliflozin + metformin: 179/160	268/266 (randomised subjects) 53.8 (24 to 81) years	Type 2 diabetes mellitus Men and women ≥18 years with inadequate glycaemic control (HbA1c ≥8.0% and ≤12.0% at screening) under current metformin therapy stable at ≥1500 mg for at least 8 weeks prior to screening.
CV181168	79 centres in 9 countries	Randomised, double-blind, placebo-controlled, parallel-group, multicentre study 24 weeks of randomised treatment	Efficacy and Safety Change in HbA1c from baseline to Week 24	**Table 4.** Saxagliptin 5 mg + dapagliflozin 10 mg + metformin IR ≥1500 mg Placebo + dapagliflozin 10 mg + metformin IR ≥1500 mg	Saxagliptin + dapagliflozin + metformin: 153/142 Placebo + dapagliflozin + metformin: 162/156	149/166 (randomised subjects) 54.6 (27 to 78) years	Type 2 diabetes mellitus Men and women ≥18 years with inadequate glycaemic control (HbA1c ≥7.0% and ≤10.5% at randomisation) under current metformin therapy stable at ≥1500 mg for at least 8 weeks prior to screening.
MB102129	64 centres in 8 countries	Randomised, double-blind, placebo-controlled, parallel-group, multicentre study	Efficacy and Safety Change in HbA1c from	**Table 5.** Saxagliptin 5 mg + dapagliflozin 10 mg + metformin IR	Saxagliptin + dapagliflozin + metformin: 160/148 Placebo +	146/174 (randomised subjects) 55.1 (30 to 75) years	Type 2 diabetes mellitus Men and women ≥18 years with inadequate glycaemic control (HbA1c ≥7.0% and ≤10.5% at randomisation) under current metformin therapy stable at ≥1500 mg for at least 8 weeks prior to screening. A second stratum included subjects that had additionally been on the maximum approved dose of a DPP4 inhibitor for at least

24 weeks of randomised treatment	baseline to Week 24	≥1500 mg Placebo + saxagliptin 5 mg + metformin IR ≥1500 mg	saxagliptin + metformin: 160/153	8 weeks prior to screening.

Study participants

In all three studies, the target population was male and female subjects aged ≥18 years with T2DM and inadequate glycaemic control on metformin alone. Subjects were to have been on stable metformin therapy for at least 8 weeks prior to screening visit at a dose of ≥1500 mg per day, have a C-peptide value of ≥0.34 nmol/L, and have a body mass index (BMI) ≤45.0 kg/m2 at the screening visit. Subjects with moderate or severe impairment of renal function were excluded.

Objectives

The objective of the studies was to assess superiority of the combination of saxagliptin + dapagliflozin added concurrently or sequentially to metformin versus the monocomponents plus metformin in reducing HbA1c.

Outcomes/endpoints

The *primary efficacy endpoint* for all 3 studies was mean change from baseline in HbA1c at Week 24.

Secondary efficacy endpoints were: 1) Mean change from baseline in 2-hour PPG during a liquid meal tolerance test (120-minute Meal Tolerance Test [MTT]) at Week 24; 2) Mean change from baseline in FPG at Week 24; 3) Percent of subjects achieving a therapeutic glycaemic response, defined as a HbA1c <7.0% at Week 24, and 4) Mean change from baseline in body weight at Week 24.

Other efficacy endpoints were about rescue treatment or discontinuation for lack of efficacy, $AUC_{glucose}$ during MTT, serum lipids.

Sample size

In performing the sample size computations for all three studies, 90% power with a two-sided 0.05 significance level was targeted to detect a 0.4% difference in mean HbA1c between the saxagliptin + dapagliflozin + metformin treatment group versus the respective study-specific control(s) assuming a standard deviation of 1.0%. Statistical significance of the primary endpoint was claimed if the p-value for the comparison (and in the case of CV181169, the p-values for both comparisons) was significant at the 2-sided, 0.05 significance level.

Randomisation

At the screening visit, each subject was assigned a unique sequential Subject Number at each site through the Interactive Voice Response System (IVRS). This number was used for subject identification throughout the study and was not used for any other participant at the site. Central randomization (stratified by site) was used in all the three studies. For study MB102129, a central randomization was used within each stratum. Randomization schedules for both subject treatment assignments and containers was generated and kept in the Randomization Center within the Drug Supply Management Department of Bristol- Myers Squibb.

Blinding (masking)

The investigator, sponsor personnel, and subjects remained blinded to double-blinded treatment allocation throughout the short-term, double-blind treatment period. The database used for the analysis of the short-term double-blind data of the study was locked after all subjects terminated the short-term double-blind treatment period of the study. The locked database was unblinded for reporting purposes. In order to protect the integrity of the long-term treatment period of the

studies, the subjects and investigators will not have access to the individual treatment assignments until the long-term treatment period has been completed.

In order to maintain integrity of the studies, during the open-label or lead-in and the 24-week double-blind treatment periods, the HbA1C, plasma glucose MTT values, and the urinary glucose values including the urinary glucose:creatinine ratio will be masked to the Investigator and to the Sponsor. For each study, these values will be provided to the Investigator after the study has been completed.

In the event of a medical emergency or pregnancy, during which knowledge of the identity of the investigational product is critical to the subject's management, procedures are in place to have the blind broken for an individual subject. A separate procedure is in place for unblinding in case of expedited safety reporting to regulatory authorities.

Statistical methods

The primary efficacy analysis was performed using a longitudinal repeated measures analysis with terms for baseline value, treatment group, stratum (study MB102129 only), time, the interaction of treatment group and time, and the interaction of baseline value and time, including only observations prior to rescue. Point estimates and 95% confidence intervals (CIs) were calculated for the adjusted mean changes within each treatment group as well as for the differences in adjusted mean changes between treatment groups. For all three studies, in order to protect the overall type I error rate, the interpretation of the family-wise statistical significance of treatment comparisons for each secondary efficacy endpoint was done using a step-wise procedure (in CV181169, the test was simultaneously applied to the two treatment comparisons).

The analysis of mean change from baseline at Week 24 for the secondary efficacy endpoint 2-hour PPG was based on an analysis of covariance (ANCOVA) model using last observation carried forward (LOCF) methodology with terms for treatment group and baseline value in the model. Analyses of the mean change from baseline at Week 24 for FPG and total body weight were performed using the same longitudinal repeated measures model as for the primary efficacy endpoint. The proportion of subjects achieving therapeutic glycaemic response (defined as HbA1c <7.0%) at Week 24 (LOCF) was summarised by treatment group and compared between treatment groups using the methodology of Zhang et al (Zhang et al 2008) and Tsiatis et al (Tsiatis et al 2008). The 95% CIs for the response rate within each treatment group as well as for the difference in response rates between treatment groups was calculated with adjustment for baseline HbA1c.

Results

Participant flow
Patient disposition is shown in Table 12**Error! Reference source not found.**.

Table 11 Disposition of subjects – Studies CV181169, CV181168, and MB102129

	Concomitant add-on study				Sequential add-on studies					
	Study CV181169				Study CV181168			Study MB102129		
	Saxa + Dapa + Met	Saxa + Met	Dapa + Met	Total	Saxa + Dapa + Met	Pla + Dapa + Met	Total	Saxa + Dapa + Met	Pla + Saxa + Met	Total
Subjects enrolled	1282				857			818		
Subjects not entering treatment period (%)	643 (50.2)				373 (43.5)			335 (40.9)		
Subjects entering treatment period (%)	639 (49.8)				484 (56.5)			483 (59.0)		
Subjects not randomised	105 (16.4)				169 (34.9)			163 (33.8)		
Subject no longer meets study criteria					127 (26.3)			130 (26.9)		
HbA1c < 7%					106 (22.0)			61 (17.5)		
HbA1c>10%					8 (1.7)			12 (3.4)		
Subjects randomised	179	176	179	534	153	162	315	160	160	320
Subjects completing the short-term treatment (%)	169 (94.4)	161 (91.5)	160 (89.4)	490 (91.8)	142 (92.8)	156 (96.3)	298 (94.6)	148 (92.5)	153 (95.6)	301 (94.1)
Subjects not completing the short-term treatment (%)	10 (5.6)	15 (8.5)	19 (10.6)	44 (8.2)	11 (7.2)	6 (3.7)	17 (5.4)	12 (7.5)	7 (4.4)	19 (5.9)
Reasons for not completing the short- term treatment (%)										
Lack of efficacy[a]	0	0	0	0	0	0	0	0	0	0
Adverse event	1 (0.6)	0	1 (0.6)	2 (0.4)	0	1 (0.6)	1 (0.3)	3 (1.9)	0	3 (0.9)
Subject request to discontinue study treatment	1 (0.6)	0	2 (1.1)	3 (0.6)	1 (0.7)	0	1 (0.3)	0	0	0
Subject withdrew consent	1 (0.6)	8 (4.5)	6 (3.4)	15 (2.8)	4 (2.6)	2 (1.2)	6 (1.9)	2 (1.3)	0	2 (0.6)

Death	0	0	0	0	0	0	0	0	0	0
Lost to follow-up	5 (2.8)	6 (3.4)	8 (4.5)	19 (3.6)	4 (2.6)	2 (1.2)	6 (1.9)	4 (2.5)	4 (2.5)	8 (2.5)
Poor/non-compliance	0	1 (0.6)	0	1 (0.2)	1 (0.7)	1 (0.6)	2 (0.6)	0	0	0
Pregnancy	1 (0.6)	0	1 (0.6)	2 (0.4)	0	0	0	0	0	0
Subject no longer meets study criteria	0	0	0	0	1 (0.7)	0	1 (0.3)	0	1 (0.6)	1 (0.3)
Administrative reason by sponsor	0	0	0	0	0	0	0	0	0	0
Other	1 (0.6)	0	1 (0.6)	2 (0.4)	0	0	0	1 (0.6)	0	1 (0.3)
Not reported	0	0	0	0	0	0	0	2 (1.3)	2 (1.3)	4 (1.3)

[a] Does not include patients receiving rescue medication

Recruitment

Recruitment periods for each of the studies were as follows:

Study CV181168 :Study initiation date: 29-jun-2012, Study completion date: Jan 2015 .

Study CV181169 : Study initiation date: 05-jun-2012, Study completion date: 17 Jan 2014.

Study MB102129 : Study initiation date: 21-sep-2013, Study completion date: Feb 2015

Conduct of the study

In general, there were no important differences between treatment groups. In all studies, the most common reason for subjects enrolled but not entering treatment period was no longer meeting eligibility criteria (between 40 and 50%). As can be expected, in study CV181168 and MB102129 a number of subjects was sufficiently controlled after the OL treatment period, and thus were not randomised for additional treatment.

Baseline data

The demographics and disease characteristics of the subjects in study CV181169, CV181168, and MB102129 are summarized in Table13. The treatment groups within the respective studies were well-balanced with regard to demographic and baseline characteristics, including diabetes-related medical history (hyperlipidaemia, dyslipidaemia, hypertension, and CV disease). The majority of subjects were White; mean age was 53.8-55.1 years. There were few subjects ≥75 years of age (1 to 5 subjects per study). The entrance criterion of HbA1c ≥8.0%, ≤12.0% (Study CV181169) and ≥8.0%, ≤11.5% (Studies CV181168 and MB102129) in subjects not controlled on metformin monotherapy was selected to be more representative of patient populations with T2DM encountered in clinical practice. In Study CV181169, the mean baseline HbA1c was 8.9%. In Studies CV181168 and MB102129, the mean baseline HbA1c values after the pre-randomisation OL treatment period were 7.9% and 8.2%, respectively. Across studies, subjects had a high mean weight ≥87 kg and body mass index (BMI) ≥31 kg/m^2. Mean duration of T2DM was at least 7.6 years. Along with high mean baseline HbA1c, these characteristics suggest more advanced disease in these subjects and are representative of T2DM patients that present in clinical practice who have not achieved their target goals.

Table 12: Subject demographics and baseline characteristics – studies CV181169, CV181168, and MB102129

	Concomitant add-on study				Sequential add-on studies					
	Study CV181169				Study CV181168			Study MB102129		
	Saxa + Dapa + Met (N=179)	Saxa + Met (N=176)	Dapa + Met (N=179)	Total (N=534)	Saxa + Dapa + Met (N=153)	Pla + Dapa + Met (N=162)	Total (N=315)	Saxa + Dapa + Met (N=160)	Pla + Saxa + Met (N=160)	Total (N=320)
Age (mean [SD] years)	53.4 (9.8)	54.6 (9.6)	53.5 (9.7)	53.8 (9.7)	54.7 (9.83)	54.5 (9.32)	54.6 (9.56)	55.2 (8.61)	55.0 (9.60)	55.1 (9.10)
Age (n, %)										
<65 years old	160 (89.4)	148 (84.1)	158 (88.3)	466 (87.3)	132 (86.3)	140 (86.4)	272 (86.3)	137 (85.6)	132 (82.5)	269 (84.1)
≥65 years old	19 (10.6)	28 (15.9)	21 (11.7)	68 (12.7)	21 (13.7)	22 (13.6)	43 (13.7)	23 (14.4)	28 (17.5)	51 (15.9)
≥75 years old	2 (1.1)	0	1 (0.6)	3 (0.6)	2 (1.3)	3 (1.9)	5 (1.6)	0	1 (0.6)	1 (0.3)
Sex (n, %)										
Male	85 (47.5)	94 (53.4)	89 (49.7)	268 (50.2)	73 (47.7)	76 (46.9)	149 (47.3)	70 (43.8)	76 (47.5)	146 (45.6)
Female	94 (52.5)	82 (46.6)	90 (50.3)	266 (49.8)	80 (52.3)	86 (53.1)	166 (52.7)	90 (56.3)	84 (52.5)	174 (54.4)
Race, n (%)										
White	120 (67.0)	121 (68.8)	131 (73.2)	372 (69.7)	136 (88.9)	141 (87.0)	277 (87.9)	150 (93.8)	147 (91.9)	297 (92.8)
Black	22 (12.3)	22 (12.5)	16 (8.9)	60 (11.2)	11 (7.2)	9 (5.6)	20 (6.3)	8 (5.0)	10 (6.3)	18 (5.6)
Asian	12 (6.7)	11 (6.3)	10 (5.6)	33 (6.2)	5 (3.3)	8 (4.9)	13 (4.1)	1 (0.6)	1 (0.6)	2 (0.6)
Other	25 (14.0)	22 (12.5)	22 (12.3)	69 (12.9)	1 (0.7)	4 (2.5)	5 (1.6)	1 (0.6)	2 (1.3)	3 (0.9)
Weight (mean [SD] kg)	87.16 (17.96)	88.19 (18.84)	86.28 (18.57)	87.20 (18.44)	88.10 (20.04)	87.93 (17.06)	88.01 (18.54)	85.92 (18.44)	88.11 (18.07)	87.01 (18.26)
BMI (mean [SD] kg/m^2)	31.76 (4.79)	31.80 (5.14)	31.46 (5.32)	31.67 (5.08)	31.40 (5.20)	31.35 (5.35)	31.37 (5.27)	31.20 (4.73)	32.20 (5.33)	31.70 (5.06)
T2DM duration (mean [SD] years)	7.13 (5.04)	8.16 (5.52)	7.40 (5.40)	7.56 (5.33)	8.08 (7.02)	7.40 (5.82)	7.73 (6.43)	7.23 (5.66)	7.95 (6.55)	7.59 (6.13)

	Concomitant add-on study				Sequential add-on studies					
	Study CV181169				Study CV181168			Study MB102129		
	Saxa + Dapa + Met (N=179)	Saxa + Met (N=176)	Dapa + Met (N=179)	Total (N=534)	Saxa + Dapa + Met (N=153)	Pla + Dapa + Met (N=162)	Total (N=315)	Saxa + Dapa + Met (N=160)	Pla + Saxa + Met (N=160)	Total (N=320)
HbA1c (mean [SD])	8.92 (1.18)	9.03 (1.05)	8.87 (1.16)	8.94 (1.13)	7.97 (0.83)	7.86 (0.93)	7.91 (0.88)	8.24 (0.96)	8.17 (0.98)	8.20 (0.97)
FPG (mean [SD] mmol/L)	10.01 (2.53)	10.64 (2.52)	10.26 (2.69)	10.30 (2.59)	9.09 (1.91)	8.75 (1.92)	8.92 (1.92)	9.95 (2.71)	9.81 (2.60)	9.88 (2.65)
120-minute PPG (mean [SD] mmol/L)	13.45 (3.03)	14.19 (3.45)	13.64 (3.30)	13.76 (3.27)	11.57 (2.78)	11.45 (2.95)	11.51 (2.86)	13.41 (3.38)	13.49 (3.20)	13.45 (3.28)
C-peptide (mean [SD] nmol/L)	0.723 (0.332)	0.706 (0.300)	0.739 (0.343)	0.723 (0.325)	0.792 (0.318)	0.852 (0.402)	0.823 (0.364)	0.836 (0.371)	0.873 (0.360)	0.855 (0.366)
eGFR (mean [SD] ml/min/1.73m2)	96.57 (19.60)	92.54 (19.47)	93.93 (19.91)	94.35 (19.70)	92.82 (21.57)	93.88 (20.64)	93.36 (21.07)	93.47 (20.81)	91.62 (23.15)	92.55 (22.00)
Metformin dose N (%)	Metformin XR				Metformin IR			Metformin IR		
1500-1700 mg	64 (35.8)	56 (31.8)	70 (39.1)	190 (35.6)	48 (31.4	52 (32.1)	100 (31.7)	26 (37.7)	23 (30.7)	49 (34.0)
1701-2500 mg	115 (64.2)	120 (68.2)	109 (60.9)	344 (64.4)	77 (50.3)	72 (44.4)	149 (47.3)	31 (44.9)	28 (37.3)	59 (41.0)
> 2500 mg	0	0	0	0	28 (18.3)	38 (23.5)	66 (21.0)	12 (17.4)	24 (32.0)	36 (25.0)

Numbers analysed

For all three studies, the primary data set for efficacy analysis was the respective Randomised Subjects data set. These consisted of data from all randomised subjects who took at least one dose of double-blind study drug during the ST double-blind periods. Numbers are shown in Table 12 (Disposition of subjects).

Outcomes and estimation

The endpoints are presented in the tables summarizing the efficacy results in the following section.

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 13 Summary of efficacy for trial CV181169

Title: A Multicenter, Randomized, Double-Blind, Active-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Add-On Therapy with Saxagliptin and Dapagliflozin Added to Metformin Compared to Add-On Therapy with Saxagliptin in Combination with Metformin or Dapagliflozin in Combination with Metformin in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Alone.		
Study identifier	CV181169 (EudraCT No. 2012-000679-18)	
Design	This was a Phase 3, randomized, double-blind, active-controlled study in 534 subjects with T2DM designed to compare the mean change from baseline in HbA1c achieved with saxagliptin + dapagliflozin + metformin vs. saxagliptin + metformin and vs. dapagliflozin + metformin after 24 weeks of double-blind treatment. The target population was male and female subjects aged ≥18 years with T2DM and inadequate glycaemic control on metformin alone. Subjects were to have been on stable metformin therapy for at least 8 weeks prior to screening visit at a dose of ≥1500 mg per day, have a C-peptide value of ≥0.34 nmol/L, and have a body mass index (BMI) ≤45.0 kg/m2 at the screening visit. Subjects with moderate or severe impairment of renal function were excluded.	
	Screening period:	Up to 2 weeks
	Lead-in period:	4 weeks
	Main treatment phase	24 weeks
	Efficacy and safety Extension phase:	28 weeks

Title: A Multicenter, Randomized, Double-Blind, Active-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Add-On Therapy with Saxagliptin and Dapagliflozin Added to Metformin Compared to Add-On Therapy with Saxagliptin in Combination with Metformin or Dapagliflozin in Combination with Metformin in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Alone.		
Study identifier	CV181169 (EudraCT No. 2012-000679-18)	
Statistical methods	The mean change from baseline in HbA1c at Week 24 was assessed comparing the saxagliptin + dapagliflozin + metformin treatment group vs. the saxagliptin + metformin treatment group and vs. the dapagliflozin + metformin treatment group. The min test approach of Laska and Meisner was implemented to test saxagliptin + dapagliflozin + metformin vs. saxagliptin + metformin and vs. dapagliflozin + metformin. Statistical significance of the primary endpoint would be claimed if the p-values for both comparisons were significant at the 2-sided, 0.05 significance level. Power calculations for longitudinal repeated measures analyses depend on many factors, including the pattern of drop out over time and correlations among the various time points included in the model. Power calculations were based on ANCOVA with LOCF, with the expectation that this would provide a good estimate of the power for the primary analysis using a longitudinal repeated measures model. With 163 subjects per treatment group, there was 90% power to detect a difference in mean HbA1c of 0.4% between the saxagliptin + dapagliflozin + metformin treatment group vs. the saxagliptin + metformin treatment group and vs. the dapagliflozin + metformin treatment group, assuming a standard deviation of 1.0%. Assuming that 5% of subjects would not have a post-baseline assessment, a total of approximately 516 subjects (172 subjects per treatment arm) needed to be randomized. Assuming that 50% of screened subjects would fail to meet screening criteria, a total of 1032 subjects needed to be screened.	
Treatments groups	Saxa+Dapa+Met 179 patients randomised	5mg+10mg+≥1500mg
	Saxa+Met 176 patients randomised	5mg+≥1500mg
	Dapa+Met 179 patients randomised	10mg+≥1500mg
Endpoints and definitions	Primary endpoint	
	Change in HbA1c (%)	Change from baseline to week 24
	Secondary endpoints	
	2-hour PPG from a liquid MTT	Mean change from baseline in 2-hour post-prandial glucose during a MTT at Week 24.
	FPG	Mean change from baseline in FPG at Week 24.
	Responders	Percent of subjects achieving a therapeutic glycemic response, defined as a HbA1c < 7.0% at Week 24.
	Body weight	Mean change in total body weight.
	Glycemic rescue	The percent of subjects who required glycemic rescue or discontinuation of study treatment for lack of efficacy up to Week 24, and the time to glycemic rescue or discontinuation for lack of efficacy in the double-blind treatment period.
	Glucose, insulin, C-peptide, glucagon	Mean change from baseline in AUC glucose, AUC insulin, AUC C-peptide and AUC glucagon obtained during the MTT at Week 24.
	Lipids	Mean percent change from baseline in fasting serum lipids (Total-C, LDL-C, HDL-C, TG) during the double-blind treatment period.
	Hypoglycaemia	Hypoglycaemic events, AEs, ECGs, serum creatinine.
Results and Analysis		
Analysis description	**Primary Analysis**	

Title: A Multicenter, Randomized, Double-Blind, Active-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Add-On Therapy with Saxagliptin and Dapagliflozin Added to Metformin Compared to Add-On Therapy with Saxagliptin in Combination with Metformin or Dapagliflozin in Combination with Metformin in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Alone.					
Study identifier	CV181169 (EudraCT No. 2012-000679-18)				
Analysis population and time point description	Longitudinal repeated measures analysis - change in HbA1c from baseline to Week 24				
Descriptive statistics, point estimate, and effect estimate	Primary endpoint	Treatment group	Saxa + Dapa +Met (N=179)	Saxa + Met (N=175)	Dapa + Met (N=179)
	HbA1c (%)	n	176	175	172
		Baseline: Mean (SD)	8.93	9.03	8.87
		Change from baseline to endpoint (Week 24): Adj mean (SE) [95% CI]	-1.47 (0.078) [-1.62, -1.31]	-0.88 (0.0795) [-1.03, -0.72]	-1.20 (0.0789) [-1.35, -1.04]
		Change from baseline to endpoint (Week 24): difference Saxa+Dapa+Met vs Saxa+Met [95% CI]		-0.59% [-0.81, -0.37] P<0.0001	
		Change from baseline to endpoint (Week 24): difference Saxa+Dapa+Met vs Dapa+Met [95% CI]		-0.27% [-0.48, -0.05] P=0.0166	
Analysis description	**Secondary analysis**				
	120-min PPG (mmol/L)	n	154	147	144
		Baseline: Mean (SD)	13.49 (3.078)	14.19 (3.567)	13.71 (3.132)
		Change from baseline to endpoint (Week 24): Adj Mean (SE) [95% CI]	-4.42 (0.1903) [-4.79, -4.04]	-1.97 (0.1950) [-2.36, -1.59]	-3.91 (0.1965) [-4.29, -3.52]
		Change from baseline to endpoint (Week 24): difference (SE) Saxa+Dapa+Met vs Saxa+Met [95% CI]		-2.44 (0.2730) (-2.98, -1.91) p<0.0001	
		Change from baseline to endpoint (Week 24): difference (SE) Saxa+Dapa+Met vs Dapa+Met [95% CI]		-0.51 (0.2735) (-1.05, 0.03) p=0.0640	
	FPG (mmol/L)	n	155	142	148
		Baseline: Mean (SD)	10.04 (2.525)	10.63 (2.520)	10.26 (2.643)
		Change from baseline to endpoint (Week 24): Adj Mean (SE) [95% CI]	-2.10 (0.1540) [-2.40, -1.79]	-0.78 (0.1587) [-1.09, -0.47]	-1.76 (0.1565) [-2.07, -1.45]
		Change from baseline to endpoint (Week 24): difference (SE) Saxa+Dapa+Met vs Saxa+Met [95% CI]		-1.32 (0.2214) [-1.76, -0.88]	

Title: A Multicenter, Randomized, Double-Blind, Active-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Add-On Therapy with Saxagliptin and Dapagliflozin Added to Metformin Compared to Add-On Therapy with Saxagliptin in Combination with Metformin or Dapagliflozin in Combination with Metformin in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Alone.					
Study identifier		CV181169 (EudraCT No. 2012-000679-18)			
		Change from baseline to endpoint (Week 24): difference (SE) Saxa+Dapa+Met vs Dapa+Met [95% CI]		-0.34 (0.2197) [-0.77, 0.09]	
	Number (%) of patients at endpoint	n	177	175	173
		HbA1c<7%	74 (41.8)	29 (16.6)	40 (23.1)
		Difference (SE) Saxa+Dapa+Met vs Saxa+Met [95% CI]		23.1 (4.3) [14.7, 31.5]	
		Difference (SE) Saxa+Dapa+Met vs Dapa+Met [95% CI]		19.1 (4.6) [10.1, 28.1]	

Table 14 Summary of efficacy for trial CV181168

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Triple Therapy with Saxagliptin added to Dapagliflozin in Combination with Metformin compared to Therapy with Placebo added to Dapagliflozin in combination with Metformin in Subjects with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin and Dapagliflozin.		
Study identifier	CV181168 (EudraCT No. 2011-006323-37)	
Design	This was a Phase 3, randomized, double-blind, placebo-controlled, study in 315 subjects with Type 2 diabetes mellitus (T2DM) designed to compare the mean change from baseline in HbA1c achieved with saxagliptin + dapagliflozin + metformin vs. placebo + dapagliflozin + metformin after 24-weeks of ST double-blind treatment.	
	Screening period:	Up to 2 weeks
	Open-Label treatment phase:	14-16 weeks
	Main treatment phase	24 weeks
	Efficacy and safety Extension phase:	28 weeks
Statistical methods	The primary endpoint was the mean change from baseline in HbA1c at Week 24 (using longitudinal repeated measures analysis) comparing the saxagliptin + dapagliflozin + metformin treatment group and the placebo + dapagliflozin + metformin treatment group. Statistical significance would be claimed if the p-value for the comparison was significant at the 2-sided, 0.05 significance level. Power calculations were based on ANCOVA with LOCF, with the expectation that this would provide a good estimate of the power for the primary analysis using a longitudinal repeated measures model. With 133 subjects per treatment group, there was 90% power to detect a difference in mean HbA1c of 0.4% between the saxagliptin + dapagliflozin + metformin treatment group and the placebo + dapagliflozin + metformin group, assuming a standard deviation of 1.0%. Assuming that 5% of subjects would not have a post-baseline assessment, a total of approximately 280 subjects (140 subjects per treatment arm) needed to be randomized. Assuming that 50% of screened subjects would fail to meet screening criteria, a total of 934 subjects needed to be screened. The number of subjects with HbA1c ≥ 8.0% and ≤ 9.0% at the start of the open-label treatment period was to be capped at 50%.	
Treatments groups	Saxa+Dapa+Met 153 patients randomised	5mg+10mg+≥1500mg
	Pla+Dapa+Met 162 patients randomised	Pla+10mg+≥1500mg

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Triple Therapy with Saxagliptin added to Dapagliflozin in Combination with Metformin compared to Therapy with Placebo added to Dapagliflozin in combination with Metformin in Subjects with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin and Dapagliflozin.				
Study identifier	CV181168 (EudraCT No. 2011-006323-37)			
Endpoints and definitions	Primary endpoint			
	Change in HbA1c (%)	Change from baseline to week 24		
	Secondary endpoints			
	2-hour PPG from a liquid MTT	Mean change from baseline in 2-hour post-prandial glucose during a MTT at Week 24.		
	FPG	Mean change from baseline in FPG at Week 24.		
	Responders	Percent of subjects achieving a therapeutic glycemic response, defined as a HbA1c < 7.0% at Week 24.		
	Glycemic rescue	The percent of subjects who required glycemic rescue or discontinuation of study treatment for lack of efficacy up to Week 24, and the time to glycemic rescue or discontinuation for lack of efficacy in the double-blind treatment period.		
	Glucose	Mean change from baseline in AUC glucose obtained during the MTT at Week 24.		
	Lipids	Mean percent change from baseline in fasting serum lipids (Total-C, LDL-C, HDL-C, TG) during the double-blind treatment period.		
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Longitudinal repeated measures analysis - change in HbA1c from baseline to Week 24			
Descriptive statistics, point estimate, and effect estimate	Primary endpoint	Treatment group	Saxa+Dapa+Met (N=153)	Pla+Dapa+Met (N=162)
	HbA1c (%)	n	139	149
		Baseline: Mean (SD)	7.95 (0.826)	7.85 (0.920)
		Change from baseline to endpoint (Week 24): Adj mean (SE) [95% CI]	-0.51 (0.0624) [-0.63, -0.39]	-0.16 (0.0605) [-0.28, -0.04]
		Change from baseline to endpoint (Week 24): difference Saxa+Dapa+Met vs Pla+Dapa+Met [95% CI]		-0.35 (-0.52, -0.18) P<0.0001
Analysis description	**Secondary Analysis**			
	120-min PPG (mmol/L)	n	135	144
		Baseline: Mean (SD)	11.53 (2.811)	11.31 (2.887)
		Change from baseline to endpoint (Week 24): Adj mean (SE) [95% CI]	-2.06 (0.1824) [-2.42, -1.71]	-1.74 (0.1766) [-2.09, -1.39]

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Triple Therapy with Saxagliptin added to Dapagliflozin in Combination with Metformin compared to Therapy with Placebo added to Dapagliflozin in combination with Metformin in Subjects with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin and Dapagliflozin.				
Study identifier	CV181168 (EudraCT No. 2011-006323-37)			
		Change from baseline to endpoint (Week 24): difference (SE) Saxa+Dapa+Met vs Pla+Dapa+Met [95% CI]		-0.32 (0.2539) (-0.82, 0.18) P=0.2054
	FPG (mmol/L)	n	139	146
		Baseline: Mean (SD)	9.07 (1.905)	8.71 (1.879)
		Change from baseline to endpoint (Week 24): Adj mean (SE) [95% CI]	-0.50 (0.1468) [-0.79, -0.21]	-0.30 (0.1438) [-0.58, -0.02]
		Change from baseline to endpoint (Week 24): difference (SE) Saxa+Dapa+Met vs Pla+Dapa+Met [95% CI]		-0.20 (0.2061) [-0.61, 0.20]
	Number (%) of patients at endpoint	n	150	160
		HbA1c<7%	51 (34)	39 (24.4)
		Difference (SE) Saxa+Dapa+Met vs Pla+Dapa+Met		12.2 (4.504) [3.4, 21.0]

Table 15 Summary of efficacy for trial MB102129

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Therapy with Dapagliflozin added to Saxagliptin in Combination with Metformin compared to Therapy with Placebo added to Saxagliptin in Combination with Metformin in Subjects with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin and Saxagliptin.		
Study identifier	MB102129 (EudraCT No. 2011-006324-20)	
Design	This was a Phase 3, randomized, double-blind, placebo-controlled, study in 320 subjects with Type 2 diabetes mellitus (T2DM) designed to compare the mean change from baseline in HbA1c achieved with saxagliptin + dapagliflozin + metformin vs. placebo + saxagliptin + metformin after 24-weeks of ST double-blind treatment.	
	Screening period: Open-Label treatment phase: Main treatment phase Efficacy and safety Extension phase:	Up to 2 weeks Up to 16 weeks 24 weeks 28 weeks

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Therapy with Dapagliflozin added to Saxagliptin in Combination with Metformin compared to Therapy with Placebo added to Saxagliptin in Combination with Metformin in Subjects with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin and Saxagliptin.				
Study identifier	MB102129 (EudraCT No. 2011-006324-20)			
Statistical methods	With 133 subjects per treatment group, there was 90% power to detect a difference in means of 0.4% between the dapagliflozin + saxagliptin + metformin treatment group and the placebo + saxagliptin + metformin treatment group, assuming a standard deviation of 1.0%. Assuming that 5% of subjects would not have a post-baseline assessment, a total of approximately 280 subjects (140 subjects per treatment group) were to be randomized. The mean change from baseline in HbA1c at Week 24 was assessed comparing the dapagliflozin + saxagliptin + metformin treatment group with the placebo + saxagliptin + metformin treatment group. The primary efficacy analysis was performed using a longitudinal repeated measures analysis with terms for baseline value, treatment group, time, stratum, the interaction of treatment group and time, and the interaction of baseline value and time, including observations prior to rescue.			
Treatments groups	Saxa+Dapa+Met 160 patients randomised	5mg+10mg+≥1500mg		
	Pla+Saxa+Met 160 patients randomised	Pla+5mg+≥1500mg		
	During the open-label, pre-randomisation treatment period of the study, subjects were divided into two strata (Stratum A and Stratum B), depending on whether or not they had been on DPP4 inhibitor therapy prior to the screening visit. Subjects in Stratum B had been on the maximum approved dose of a DPP4 inhibitor for at least 8 weeks prior to the screening visit.			
Endpoints and definitions	Primary endpoint			
	Change in HbA1c (%)	Change from baseline to week 24		
	Secondary endpoints			
	FPG	Mean change from baseline in FPG at Week 24.		
	2-hour PPG from a liquid MTT	Mean change from baseline in 2-hour post-prandial glucose during a MTT at Week 24.		
	Body weight	Change from baseline to Week 24 in body weight		
	Responders	Percent of subjects achieving a therapeutic glycemic response, defined as a HbA1c < 7.0% at Week 24.		
	Glycemic rescue	The percent of subjects who required glycemic rescue or discontinuation of study treatment for lack of efficacy up to Week 24, and the time to glycemic rescue or discontinuation for lack of efficacy in the double-blind treatment period.		
	Glucose	Mean change from baseline in AUC glucose obtained during the MTT at Week 24.		
	Lipids	Mean percent change from baseline in fasting serum lipids (Total-C, LDL-C, HDL-C, TG) during the double-blind treatment period.		
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Longitudinal repeated measures analysis - change in HbA1c from baseline to Week 24			
Descriptive statistics, point estimate, and effect estimate	Primary endpoint	Treatment group	Saxa+Dapa+Met (N=153)	Pla+Saxa+Met (N=162)
	HbA1c (%)	n	146	129

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 3 Trial to Evaluate the Safety and Efficacy of Therapy with Dapagliflozin added to Saxagliptin in Combination with Metformin compared to Therapy with Placebo added to Saxagliptin in Combination with Metformin in Subjects with Type 2 Diabetes who have Inadequate Glycemic Control on Metformin and Saxagliptin.				
Study identifier	MB102129 (EudraCT No. 2011-006324-20)			
		Baseline: Mean (SD)	8.24 (0.970)	8.16 (0.987)
		Change from baseline to endpoint (Week 24): Adj mean (SE) [95% CI]	-0.82 (0.0686) [-0.93, -0.69]	-0.10 (0.0704) [-0.24, 0.04]
		Change from baseline to endpoint (Week 24): difference Saxa+Dapa+Met vs Pla+Saxa+Met [95% CI]		-0.72 (-0.91, -0.53) P<0.0001
Analysis description	**Secondary Analysis**			
	120-min PPG (mmol/L)	n	134	132
		Baseline: Mean (SD)	13.31 (3.376)	13.40 (3.172)
		Change from baseline to endpoint (Week 24): Adj mean (SE) [95% CI]	-4.08 (0.2252) [-4.53, -3.64]	-2.11 (0.2279) [-2.56, -1.66]
		Change from baseline to endpoint (Week 24): difference (SE) Saxa+Dapa+Met vs Pla+Saxa+Met [95% CI]		-1.97 (0.3050) (-2.57, -1.37) P<0.0001
	FPG (mmol/L)	n	146	129
		Baseline: Mean (SD)	9.91 (2.700)	9.80 (2.599)
		Change from baseline to endpoint (Week 24): Adj mean (SE) [95% CI]	-1.81 (0.1567 [-2.12, -1.50]	-0.29 (0.1649) [-0.62, 0.03]
		Change from baseline to endpoint (Week 24): difference (SE) Saxa+Dapa+Met vs Pla+Saxa+Met [95% CI]		-1.52 (0.2230) [-1.96, -1.08]
	Number (%) of patients at endpoint	n	158	158
		HbA1c<7%	58 (36.7)	21 (13.3)
		Difference (SE) Saxa+Dapa+Met vs Pla+Saxa+Met		25.5 (4.5) [16.7, 34.4] P<0.0001

Clinical studies in special populations

No separate studies were conducted specifically to address the efficacy of dapagliflozin + saxagliptin in special populations. In all three studies, treatment-by-subgroup interaction testing was used to evaluate treatment effects on the primary endpoint (adjusted mean change in HbA1c) in subgroups

where the effect might vary (from the primary endpoint analysis). Subgroups analysed were Baseline HbA1c, Race, Gender, Age, Female/Age and Region.

There were no interactions between baseline HbA1c and treatment (the interaction p-values were above the 0.1 threshold) in all 3 studies. In all studies, mean reductions from baseline in HbA1c at Week 24 were generally greater for subjects with higher baseline values. No potential treatment interactions (p-values >0.10) were detected for age or gender subgroups or race.

The subgroup analysis for disease duration subgroups in Study CV181169 did not reveal any interaction between disease duration and treatment.

In Study CV181169, a potential interaction was detected for region. However, no such interaction was seen in study CV181168 and MB102129 and an interaction is also not representative of the broader saxagliptin and dapagliflozin experience.

Potential treatment interactions were detected for female age in Studies CV181169 (p=0.0082) and MB102129 (p=0.0154). In Studies CV181169 and MB102129, the reduction of HbA1c in saxagliptin-containing treatment groups was diminished in women ≤50 years of age. Results are shown in Table 22. However, as the studies were not designed to detect such subgroup differences, and due to the small sample size in the female ≤50 groups, these results should be interpreted with caution.

Table 16 HbA1c Subgroup Analysis by Age and Gender at 24 Weeks, study CV181169

Treatments	**Interaction Tested for Adjusted Mean HbA1c Change From Baseline**					
	Age (years) (p = 0.7758)		**Female Age (years) (p = 0.0082)**		**Gender (p = 0.4124)**	
	< 65	**≥ 65**	**< 50**	**≥ 50**	**Male**	**Female**
N	466	68	87	175	268	266
Saxa+Dapa+Met (n=179)	-1.47	-1.40	-1.28	-1.39	-1.58	-1.37
Saxa+Met (n= 176)	-0.85	-1.04	-0.13	-0.97	-1.01	-0.72
Dapa+Met (n=179)	-1.22	-1.05	-1.25	-1.14	-1.21	-1.19
Treatment comparisons	**Difference (95% CI)**		**Difference (95% CI)**		**Difference (95% CI)**	
Saxa+Dapa+Met vs Saxa+Met	-0.63 (-0.86, -0.39	-0.37 (-0.97, 0.24)	-1.16 (-1.7, -0.61)	-0.42 (-0.77, -0.07)	-0.56 (-0.87, -0.26)	-0.65 (-0.96, -0.34)
Saxa+Dapa+Met vs Dapa+Met	-0.26 (-0.49, -0.02)	-0.35 (-1.00, 0.30)	0.03 (-0.54, 0.47)	-0.25 (-0.60, 0.10)	-0.37 (-0.68, -0.05)	-0.17 (-.048, 0.13)

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

Primary efficacy endpoint: HbA1c change from baseline at Week 24

The primary efficacy endpoint was met for all three studies. Repeated measures analysis of the primary endpoint (excluding data after rescue) demonstrated a clinically relevant effect of saxagliptin + dapagliflozin + metformin treatment (added concurrently or sequentially) in lowering HbA1c at Week 24 which was statistically significant versus the addition of saxagliptin to metformin (studies CV181169 and MB102129) and versus the addition of dapagliflozin to metformin (studies CV181169 and CV181168).

Secondary endpoints

120-minute PPG change from baseline at week 24

The saxagliptin + dapagliflozin + metformin group had a greater adjusted mean reduction from baseline only when compared with the saxagliptin + metformin group: -2.44 and -1.97 in study CV181169 and MB102129, respectively. The difference between the saxagliptin + dapagliflozin + metformin group and the dapagliflozin + metformin was non-significant: -0.51 and -0.32 in study CV181169 and CV181168, respectively.

FPG change from baseline at week 24

The adjusted mean change in FPG from baseline at Week 24 (excluding data after rescue) for the saxagliptin + dapagliflozin + metformin group was larger than that of the saxagliptin + metformin group and similar to that of the dapagliflozin + metformin group. Differences between the triple therapy and dapagliflozin + metformin treated group were -0.34 and -0.20 mmol/L, respectively in trial CV181169 and CV181168 (non-significant). Differences with saxagliptin + metformin group were -1.32 and -1.52, respectively, in study CV181169 and MB102129. The endpoint was met in study MB102129.

Proportion of subjects achieving therapeutic glycaemic response (HbA1c<7%) at Week 24

In study CV181169, the proportion of subjects achieving HbA1c <7% at Week 24 was nearly 2-fold higher in the saxagliptin + dapagliflozin + metformin group (41.4%) compared with the saxagliptin + metformin group (18.3%) and the dapagliflozin + metformin group (22.2%). The adjusted differences between the saxagliptin + dapagliflozin + metformin group and the saxagliptin + metformin and dapagliflozin + metformin groups were 23.1% and 19.1%, respectively. The 95% CIs for the differences excluded zero for the comparison versus the saxagliptin + metformin (14.7, 31.5) and dapagliflozin + metformin (10.1, 28.1) treatments.
In study CV181168, the proportion of subjects achieving HbA1c <7.0% at Week 24 was greater in the saxagliptin + dapagliflozin + metformin group (35.3%) than in the placebo + dapagliflozin + metformin group (23.1%). The difference between the 2 groups was 12.2%.
In study MB102129, the proportion of subjects achieving the glycaemic target of HbA1c <7.0% at Week 24 was over 3-fold higher in the dapagliflozin + saxagliptin + metformin group (38.0%) compared with the placebo + saxagliptin + metformin group (12.4%). The difference between the treatment groups was 25.5% and statistically significant (p<0.0001) and this endpoint was met.

Body weight change from baseline at Week 24

in all three studies, the dapagliflozin-containing treatment groups showed a decrease from baseline in mean adjusted body weight at Week 24 (0.51 kg to 2.39 kg). The weight reduction observed in groups

treated with both saxagliptin and dapagliflozin suggests that the dapagliflozin-induced weight loss is maintained in the presence of saxagliptin.

Table 17 HbA1c change from baseline at Week 24 excluding data after rescue for randomised subjects – studies CV181169, CV181168, and MB102129

	Concomitant add-on study			Sequential add-on studies			
	Study CV181169			Study CV181168		Study MB102129	
	Saxa+Dapa+ Met (N=179)	Saxa+Met (N=176)	Dapa+Met (N=179)	Saxa+Dapa+ Met (N=153)	Pla+Dapa+ Met (N=162)	Saxa+Dapa+ Met (N=160)	Pla+Saxa+ Met (N=160)
HbA1c (%) at Week 24							
N#	176	175	172	150	160	158	158
Baseline	8.93	9.03	8.87	7.95	7.85	8.24	8.16
Mean (SD)	(1.186)	(1.053)	(1.174)	(0.826)	(0.920)	(0.970)	(0.987)
N##	158	143	151	139	149	146	129
Adj. mean change from baseline (SE)	-1.47 (0.0778)	-0.88 (0.0795)	-1.20 (0.0789)	-0.51 (0.0624)	-0.16 (0.0605)	-0.82 (0.0686)	-0.10 (0.0704)
95% CI	(-1.62, -1.31)	(-1.03, -0.72)	(-1.35, -1.04)	(-0.63, -0.39)	(-0.28, -0.04)	(-0.96, -0.69)	(-0.24, 0.04)
Comparison of adjusted mean change from baseline							
Saxa + Dapa+ Met vs Saxa + Met						**Saxa + Dapa+ Met vs Pla + Saxa + Met**	
Difference	-0.59%					-0.72	
95%CI for difference	(-0.81, -0.37)	-	-	-	-	(-0.91, -0.53)	--
p-value	P<0.0001					p<0.0001	
Saxa + Dapa+ Met vs Dapa + Met				**Saxa + Dapa+ Met vs Pla + Dapa + Met**			
Difference	-0.27			-0.35			
95%CI for difference	(-0.48, -0.05)	-	-	(-0.52, -0.18)	-	-	-
p-value	P=0.0166			p<0.0001			

Change in HbA1c during the pre-randomisation open-label period

Data were collected for mean changes in HbA1c and FPG during the pre-randomisation open-label treatment period (from open-label baseline at Week -16 to Week -2) for studies CV181168 and MB102129, although mean changes in HbA1c and FPG during the open-label treatment period were not defined as efficacy objectives in study MB102129. Results for HbA1c are shown in Table 24.

In study CV181168, the mean HbA1c was 9.33% (N=479) prior to open-label treatment at Week -16 (the open-label baseline). At Week -2, after 14 weeks of open-label treatment with dapagliflozin + metformin, the mean HbA1c was 7.70% and the change in HbA1c was -1.61% (95% CI: -1.74, -1.49).
In 22% the reduction resulted in an HbA1c value below 7%.

In study MB102129, the mean HbA1c at Week -16 (open-label baseline) was 9.36% (n=348) in Stratum A and 8.56% (n=134) in Stratum B. At Week –2, after 14 (Stratum A) or 6 (Stratum B) weeks of open-label treatment with saxagliptin + metformin, the mean HbA1c was 8.06% for both strata. The mean change in HbA1c from baseline to Week -2 was -1.32% for Stratum A (95% CI: -1.46, -1.17) and -0.46% for Stratum B (95% CI: -0.63, -0.29). In 17.5% and 14% the reduction resulted in an HbA1c value below 7%.

Table 18 Change in HbA1c in the pre-randomisation open-label period

	Study CV181168	**Study MB102129**	
	Dapa + Met	**Saxa + Met**	
		Stratum A	**Stratum B**
	(N=482)	**(N=348)**	**N=134)**
HbA1c (%)			
Baseline (Week -16) (Mean, SD)	9.33 (0.945)	9.36 (0.892)	8.56 (0.814)
Week -2	7.70 (1.123)	8.06 (1.275)	8.06 (1.064)
Change (Mean, SE)	-1.61 (0.0642)	-1.32 (0.0730)	-0.46 (0.0863)
95% CI	(-1.74, -1.49)	(-1.46, -1.17)	-0.40 (-0.63, -0.29)
Numbers (%) at specified value, Week -2			
HbA1c <7	106 (22.0)	61 (17.5)	19 (14.2)
7 < HbA1c < 10.5	320 (66.4)	234 (67.0)	107 (79.9)
HbA1c > 10.5	8 (1.7)	12 (3.4)	1 (0.7)
Not reported	48 (10.0)	42 (12.0)	7 (5.2)

Supportive study(ies)

No supportive studies were submitted.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

In support of the Application, data from three clinical Phase 3 studies were submitted. All three were multicentre, randomised, double-blind, active (CV181169) or placebo-controlled (CV181168 and MB102129), parallel-group studies. Study CV181169 consisted of a screening period, followed by a lead-in period (4-weeks), and then a 24-week double-blind treatment period. Study CV181168 and MB102129 had a screening period, followed by an OL treatment period (16 weeks), and then a 24-week double-blind treatment period.

Study CV181169 was a concomitant add-on study: patients inadequately controlled by metformin only, were randomised to receive saxagliptin + dapagliflozin + metformin or saxagliptin + metformin or dapagliflozin + metformin.

Study CV181168 and MB102129 had a sequential design. During the OL treatment period subjects received dapagliflozin (study CV181168) or saxagliptin (study MB102129) in addition to metformin. Subjects insufficiently controlled on this combination after 14 weeks of treatment received the additional drug (saxagliptin or dapagliflozin) or placebo for the 24 double-blind treatment period.

In all three studies the target population was male and female subjects aged ≥18 years with T2DM and inadequate glycaemic control on metformin alone. Subjects had to be on stable metformin therapy for at least 8 weeks prior to screening visit at a dose of ≥1500 mg per day, with a C-peptide value of ≥0.34 nmol/L, and a body mass index (BMI) ≤45.0 kg/m^2 at the screening visit. Subjects with moderate to severe renal impairment (eGFR < 60 mL/min/1.73 m^2) were excluded.

Inadequate glycaemic control was defined as central laboratory HbA1c at screening visit of ≥8.0% and ≤12.0% for study CV181169 and ≥8.0% and ≤11.5% for study CV181168. Study MB102129 was comprised of two strata: Stratum A, with subjects who had been on stable metformin therapy alone, and Stratum B, with subjects who had been on a maximum dose of a DPP4 inhibitor for ≥8 weeks prior to screening visit in addition to metformin. For Stratum A, inadequate glycaemic control was defined as central laboratory HbA1c ≥8.0% and ≤11.5% at the screening visit, while for Stratum B it was defined as central laboratory HbA1c ≥7.5% and ≤10.5% at the screening visit. For both study CV181168 and study MB102129, inadequate glycaemic control for randomisation into the 24-week short-term (ST) study periods (after the open-label treatment periods), was defined as central laboratory HbA1c of ≥7.0% and ≤10.5%, slightly lower than the ≥8.0% and ≤12.0% criterion for randomisation into study CV181169.

The design and conduct of the studies were appropriate to establish the efficacy and safety of saxagliptin + dapagliflozin + metformin vs the monocomponents added to metformin. For approval it is important to know whether the addition of two products at once is better than sequential treatment in terms of magnitude of effect and time to response. However, concomitant add-on treatment and sequential treatment were not used in the same study, which makes a comparison more difficult. Furthermore, the treatment period in study CV181169 was 24 weeks, while the open-label (OL) treatment period in study CV181168 and study MB102129 was 14 weeks (Week -16 to Week -2) for Stratum A and 6 weeks for Stratum B (subjects already on DPP4-inhibitor for 8 weeks at least). Although the duration of the OL period is considered sufficient for the

added treatment to reach its optimal effect, the design of the studies does not allow for a time-to-effect analysis.

Percentage responders (HbA1c < 7%) in study CV181169 and after the OL treatment period in the sequential add-on studies, can be another parameter for the comparison between direct add-on treatment and sequential add-on treatment. Percentage of responders was a secondary endpoint in study CV181169, was part of other efficacy endpoints in study CV181168, but was not defined as efficacy objective in study MB102129.

In study CV181169, metformin XR release tablets were used as background therapy. Metformin XR tablets are not registered in all EU countries. There are no formal studies that have demonstrated non-inferiority compared to Metformin IR. In the MAA for dapagliflozin and for Komboglyze (FDC of saxagliptin + met) Metformin XR has been used in trials, but not in the pivotal trials. Two thirds of subjects used metformin XR in a dose between 1700 and 2500 mg daily, and one third used 1500-1700 mg daily. Maximum recommended dose of metformin XR is 2000 mg, while maximum daily dose for metformin IR is 2550 to 3000 mg. That is probably the reason why more patients in the two sequential studies used metformin in higher doses (above 2500 mg) as in these studies metformin IR was used. Mean metformin doses were not presented, but these will be lower in study CV181169. This makes a comparison between studies more complicated.

The randomisation and blinding procedures were adequate. The analysis populations, analysis of the primary and secondary endpoints and the step-wise procedure to ensure control of the overall type I error rate are acceptable.

Efficacy data and additional analyses

The study population of the three studies can be considered representative of the target population. However, few subjects ≥75 years old were included.

Baseline HbA1c was rather high in study CV181169 (8.94%). In study CV181168 and MB102129 baseline HbA1c was initially also high (9.33 % in Study CV181168 and around 9% in MB102129 at Week -16). Due to treatment with, respectively, dapagliflozin and saxagliptin, HbA1c decreased during OL treatment, and "baseline" HbA1c as defined by the Applicant at randomisation was 7.91 and 8.20%, respectively.

Primary endpoint

Primary endpoint (change in HbA1c at Week 24) was met in all three studies. Repeated measures analysis of the primary endpoint (excluding data after rescue) demonstrated a clinically relevant effect of saxagliptin + dapagliflozin + metformin treatment (added concurrently or sequentially) in lowering HbA1c at Week 24 which was statistically significant versus the combination of saxagliptin and metformin (studies CV181169 and MB102129) and versus the combination of dapagliflozin and metformin (studies CV181169 and CV181168). Results show that both components contribute to the effect of the combination, although dapagliflozin seems to be more effective than saxagliptin.

The difference of Saxa + Dapa + metformin vs Dapa + Met is considered to be of doubtful clinical relevance: only -0.27% in study CV181169. This is below the accepted delta for non-inferiority trials in diabetes. Apparently, the additional value of saxagliptin on top of dapagliflozin and metformin is small. In the fixed combination guideline (EMA/CHMP/689925/2014), it is stated that each component should contribute to the

efficacy. This trial does not prove that this is the fact although one could argue that the response rate is different (22% Dapa + Met vs 41% Dapa/Saxa +Met). The finding observed in Study CV181169 is confirmed in Study CV181168: the additional efficacy of Saxagliptin on top of Dapa + Met is limited (HbA1c = -0.35%). This figure is very close to the delta of 0.30% used in non-inferiority trials. Although this difference is statistically significant, the clinical relevance is doubtful. Even the response rate Saxa + Dapa + Met is not convincingly superior to Dapa+Met (35% vs 23%). In answer to a question on this issue, the Applicant has shown that the contribution of both components to the FDC depends on baseline HbA1c. Saxagliptin is contributing a larger proportion to the total combination effect at lower baseline HbA1c levels than at higher ones, and conversely, dapagliflozin is contributing a larger proportion to the total combination effect at higher baseline HbA1c levels than at lower ones. Furthermore, the difference measured between the FDC and the monocomponents is not quite representative for the actual contribution of each component. Although there is no direct pharmacodynamic interaction, when combined, both the effect of saxagliptin and dapagliflozin seems to be reduced, as the total effect of the combination is not the sum of the individual effects. This is because both components for their action are dependent on plasma glucose levels. This seems reasonable, but it should be recognised that in the add-on study the added effect was -0.35% after 24 weeks and -0.42% after 52 weeks.

Compared to sequential add-on treatment, concomitant add-on treatment can result in a gain in time of 3 months to reach glycaemic targets. There is no evidence that a delay of 3 months in intensification of treatment will result in increased risk of micro- and macrovascular complications. This should be balanced against the over-treatment in 20% of patients, who would be sufficiently controlled by adding one medicine. Concomitant add-on treatment could be considered in patients well above target (≥9%). However, that is the range that there is no additive value of saxagliptin to the effect of dapagliflozin to the decrease in HbA1c (decrease in HbA1c saxa+dapa+met -2.03%, vs dapa+met -1.87%). The percentage responders was only slightly higher in these subjects when treated with the FDC (23.5% saxa+dapa+met vs 14.6% dapa+met). For subjects with rather low HbA1c (< 8%), concomitant treatment does not result in much more responders than the monocomponents.

Saxagliptin has potential benefits apart from HbA1c reduction, such as effect on glucagon and C-peptide, but their clinical relevance remains unproven.

Nevertheless, there might be patients who can benefit from the addition of saxagliptin. However, as the response is variable and it is not known which patient will benefit, treatment effects should be monitored in individual patients. This argues in favour of sequential treatment.

Secondary endpoints

120-minute PPG
In all treatment groups a reduction in 120-minute PPG was observed. Reductions were numerically greater in the saxagliptin + dapagliflozin + metformin group. However, only the difference between saxagliptin + dapagliflozin + metformin and saxagliptin + metformin was statistically significant, suggesting that adding dapagliflozin has more effect on 120-minute PPG than adding saxagliptin.

FPG
Reductions in FPG were seen in all dapagliflozin-treated groups. Numerically, these decreases were largest in the saxagliptin + dapagliflozin +metformin groups, but the differences with dapagliflozin + metformin treated groups were not statistically significant. Significance was reached for the comparison between saxagliptin +

dapagliflozin +metformin and saxagliptin + metformin groups. For FPG too, results suggest that dapagliflozin has more effect than saxagliptin.

Responders

In study CV181169, treatment with saxagliptin + dapagliflozin + metformin resulted in 41% responders (HbA1c < 7%) after 24 weeks, compared to 18% for the saxagliptin + metformin group and 22% for the dapagliflozin + metformin group. In the sequential add-on studies percentages responders after the OL treatment period were 22% for the dapagliflozin + metformin group and 14-17% for the saxagliptin + metformin group (14% for stratum B and 17% for stratum A). Adding the second drug in the 24 week treatment period resulted in an increase in responders (35-38%) that was larger than in the placebo group (12-23%). Because of the design of the studies, a comparison between studies of total number of responders on triple therapy during the whole study period is difficult to make, as responders on OL treatment were discontinued from the studies. Thus, it is not possible to evaluate whether concomitant add-on and sequential add-on result in the same percentage responders. Results from studies suggest that about 20% of subjects will benefit from the addition of one drug in patients failing on metformin treatment. Most patients, however, will need additional treatment for their glucose regulation.

Body weight

Dapagliflozin treatment resulted in moderate weight loss of around 2 kg. Treatment with saxagliptin was weight neutral.

Subgroups

The total number of elderly patients is limited in the three trials, and especially the number of subjects of 75 years and above: total number of 9. The Applicant has proposed to make a statement in section 4.2 of the SmPC.

In female subjects < 50 year, saxagliptin was virtually ineffective. Although the numbers of females < 50 was limited, the contrast with older females and males is large. Reduction in HbA1c was only -0.13 in the younger female group in study CV181169, and there was no statistical significant difference between the saxagliptin + dapagliflozin + metformin group vs dapagliflozin + metformin group, suggesting that the effect in the triple therapy group was due to the addition of dapagliflozin and not by saxagliptin. In Study MB102129, HbA1c increased in females < 50 years treated with saxagliptin + metformin. The Applicant has conducted a number of exploratory analyses to investigate if evidence exists for a smaller treatment effect in younger females. There were no indications that baseline characteristics C-peptide, T2DM duration, BMI, FPG, PPG, and eGFR could explain the difference in study CV181169. Individual effects in younger females showed large variability. An analysis of 10 pooled studies did not reveal a treatment-by-female age for saxagliptin 5 mg. However, for saxagliptin 2.5 mg, the possibility of female age interaction cannot be excluded. But the clinical consequences, if any, are limited.

Long-term results

Updates of the study reports have been provided during the procedure. Results indicate that glucose control was sustained at week 52; therefore a statement in the SmPC on this was accepted.

2.5.4. Conclusions on the clinical efficacy

Studies indicate that the combination of saxagliptin and dapagliflozin is effective in subjects failing on metformin monotherapy. However, the effect of adding saxagliptin to dapagliflozin is limited, in particular in patients with a high baseline HbA1c (≥ 9%). Nevertheless, there might be patients who can benefit from the addition of saxagliptin. However, as the response is variable and it is not known which patient will benefit, treatment effects should be monitored in individual patients. This argues in favour of sequential treatment.

2.6. Clinical safety

For the purpose of this submission for marketing authorisation of the saxagliptin/dapagliflozin FDC, data were pooled from the 24-week, double-blind treatment periods of the 3 studies (CV181169, CV181168, and MB102129). The rationale for pooling the safety data from the 3 clinical studies was based on similarity in study design and the possibility of identifying potential safety signal(s) in a larger subject population.

Patient exposure

A total of 1169 subjects were included in the Treated Subjects dataset. Of these, 492 received saxagliptin + dapagliflozin + metformin, 336 received saxagliptin + metformin, and 341 received dapagliflozin + metformin. The median exposure to double-blind study treatment in each treatment group was 169 days. The majority of subjects across the 3 treatment groups received their respective study treatment between 121 and 180 days.

Adverse events

Overall AEs in the Integrated ST Pool are summarised in Table 25.

Of the 1169 subjects in the Integrated ST Pool, 594 reported at least 1 AE. The proportion of subjects who reported at least 1 AE was 250 subjects (50.8%) in the saxagliptin + dapagliflozin + metformin group, 187 subjects (55.7%) in the saxagliptin + metformin group, and 157 subjects (46.0%) in the dapagliflozin + metformin group. There were no differences in hypoglycaemia, SAEs, related AEs or SAEs and no deaths occurred during the studies.

Table 19 Overall adverse event summary – treated subjects

	Treatment groups		
	Saxa + Dapa + Met	Saxa + Met	Dapa + Met
	N=492	N=336	N=341
At least 1 AE	250 (50.8)	187 (55.7)	157 (46.0)
At least 1 hypoglycaemia	6 (1.2)	3 (0.9)	6 (1.8)
At least 1 AE or hypoglycaemia	250 (50.8)	188 (56.0)	160 (46.9)
At least 1 related AE	32 (6.5)	23 (6.8)	21 (6.2)
Deaths	0	0	0
At least 1 SAE	12 (2.4)	9 (2.7)	7 (2.1)
At least 1 related SAE	1 (0.2)	1 (0.3)	0
SAE leading to discontinuation of study medication	3 (0.6)	2 (0.6)	0

AE leading to discontinuation of study medication	10 (2.0)	2 (0.6)	4 (1.2)
Hypoglycaemia leading to discontinuation of study medication	0	0	0

Common adverse events

Common AEs (reported in ≥2.0% of subjects in any treatment group) in the Integrated ST Pool are summarised by PT in Table 21.

Overall, the common AEs reported in the Integrated ST Pool were generally consistent with the known safety profiles of saxagliptin or dapagliflozin. The 3 most common AEs reported in the saxagliptin + dapagliflozin + metformin group were nasopharyngitis (3.7%), headache (3.5%), and UTI (3.5%). The 3 most common AEs reported in the saxagliptin + metformin group were UTI (5.4%), influenza (4.5%), and headache (4.2%). The 3 most common AEs reported in the dapagliflozin + metformin group were UTI (3.8%), influenza (3.2%), and nasopharyngitis and headache (2.9% each).

Table 20 Most common adverse events (reported in ≥2.0% of subjects in any treatment group) – treated subjects

Preferred term	Treatment groups		
	Saxa + Dapa + Met	Saxa + Met	Dapa + Met
	N=492	N=336	N=341
Total subjects with an event	**250 (50.8)**	**187 (55.7)**	**157 (46.0)**
Nasopharyngitis	18 (3.7)	12 (3.6)	10 (2.9)
Headache	17 (3.5)	14 (4.2)	10 (2.9)
Urinary tract infection	17 (3.5)	18 (5.4)	13 (3.8)
Influenza	14 (2.8)	15 (4.5)	11 (3.2)
Back pain	13 (2.6)	8 (2.4)	6 (1.8)
Arthralgia	12 (2.4)	4 (1.2)	3 (0.9)
Diarrhoea	11 (2.2)	11 (3.3)	6 (1.8)
Dyslipidaemia	11 (2.2)	8 (2.4)	7 (2.1)
Hypertriglyceridaemia	11 (2.2)	13 (3.9)	9 (2.6)
Nausea	8 (1.6)	9 (2.7)	5 (1.5)
Upper respiratory tract infection	8 (1.6)	7 (2.1)	9 (2.6)
Vulvovaginal mycotic infection	7 (1.4)	1 (0.3)	8 (2.3)

Serious adverse event / deaths / other significant events

Deaths

No subject died due to an AE during the 24 week, double-blind treatment period of the Integrated ST Pool. In Study CV181169, 1 subject died 6 months after the final treatment and post database lock (gastric neoplasm). In Study CV181168, 1 subject died prior to receiving study treatment (rectal adenocarcinoma), and 1 subject died during the OL treatment period (dapagliflozin + metformin) (pulmonary embolism).

Serious adverse events

Overall, the incidence of SAEs was low and balanced across the 3 treatment groups. A total of 28 subjects experienced at least 1 SAE: 12 subjects (2.4%) in the saxagliptin + dapagliflozin + metformin group, 9 subjects (2.7%) in the saxagliptin + metformin group, and 7 subjects (2.1%) in the dapagliflozin + metformin group. Two SAEs, hyperkalaemia reported in 1 subject in Study CV181169 and thrombocytopenia reported in 1 subject in Study MB102129, were considered by the Investigator to be treatment-related. Five subjects discontinued study treatment due to an SAE: 3 subjects in the saxagliptin + dapagliflozin + metformin group (cardiac failure, thrombocytopenia, and invasive ductal breast carcinoma, respectively) and 2 subjects in the saxagliptin + metformin group (ankle fracture and gangrene, respectively). All subjects who discontinued study treatment due to an SAE were from Study MB102129.

Adverse events of special interest

Hypoglycaemia

Overall, the incidence of hypoglycaemia was low (≤1.8% in any treatment group). Hypoglycaemia events, excluding data after rescue, were reported in a total of 13 subjects: 6 subjects (1.2%) in the saxagliptin + dapagliflozin + metformin group, 1 subject (0.3%) in the saxagliptin + metformin group, and 6 subjects (1.8%) in the dapagliflozin + metformin group. None of the reported hypoglycaemia events was a major episode of hypoglycaemia, and no subject discontinued the study treatment due to hypoglycaemia. Confirmed hypoglycaemia, defined as fingerstick glucose value ≤50 mg/dL with associated symptoms, was reported in 1 subject each in the saxagliptin + dapagliflozin + metformin group and the dapagliflozin + metformin group. Both events of confirmed hypoglycaemia were minor episodes.
In a sensitivity analysis, including data after rescue, 2 additional events of hypoglycaemia were reported in the saxagliptin + metformin treatment group. Both events were minor episodes.

Renal impairment/failure

In the Integrated ST Pool, the incidence of AEs of renal impairment/failure was balanced, with an AE of renal impairment/failure reported in 15 subjects: 7 (1.4%) in the saxagliptin + dapagliflozin + metformin group, 6 (1.8%) in the saxagliptin + metformin group and 2 (0.6%) in the dapagliflozin + metformin group. These included AEs of the PT renal impairment, an AE of renal failure, AEs of renal failure chronic, AEs of GFR decrease. No AEs of renal impairment/failure or decreased GFR were reported as SAEs. Two subjects in the saxagliptin + dapagliflozin + metformin group and 1 subject in the dapagliflozin + metformin group discontinued study treatment due to decreased GFR.

Infections

In the Integrated ST Pool, the overall incidence of AEs of the SOC Infections and infestations was balanced across the 3 treatment groups, with at least 1 AE reported in 102 subjects (20.7%) in the saxagliptin + dapagliflozin + metformin group, 80 subjects (23.8%) in the saxagliptin + metformin group, and 79 subjects (23.2%) in the dapagliflozin + metformin group.

Genital infections were reported in 24 subjects. The proportion of subjects who reported an AE of genital infection in the Integrated ST Pool was higher in the 2 dapagliflozin-containing treatment groups: 8 (1.6%)

subjects in the saxagliptin + dapagliflozin + metformin group and 14 (4.1%) subjects in the dapagliflozin + metformin group compared to 2 (0.6%) subjects in the saxagliptin + metformin group.

UTIs were balanced across the 3 treatment groups (49 subjects total): 17 subjects (3.5%) in the saxagliptin + dapagliflozin + metformin group, 19 subjects (5.7%) in the saxagliptin + metformin group, and 13 subjects (3.8%) in the dapagliflozin + metformin group (including 1 subject with cystitis).

Malignancies

Six subjects in the Integrated ST Pool reported AEs in the SOC Neoplasms benign, malignant, and unspecified (including cysts and polyps): 4 (0.8%) subjects in the saxagliptin + dapagliflozin + metformin group, 1 (0.3%) subject in the saxagliptin + metformin group, and 1 (0.3%) subject in the dapagliflozin + metformin group. Of these 6 subjects, 3 subjects in the saxagliptin + dapagliflozin + metformin group had events that were reported as SAEs: gastric neoplasm, hepatic cancer, and invasive ductal breast carcinoma. Considering the short latency between first drug exposure and tumour diagnosis, a causal relationship to any specific tumour type is considered unlikely.

The malignancies that are defined as AEoSI in the saxagliptin/dapagliflozin FDC clinical programme include bladder neoplasm, breast neoplasm, and pancreatic cancer. No case of bladder neoplasm was reported in the Integrated ST Pool. One case of invasive ductal breast carcinoma was reported in 1 subject in the saxagliptin + dapagliflozin + metformin group. No AE of the PT pancreatic cancer was reported in the Integrated ST Pool; however, the malignancy of hepatic cancer reported at Week 16 in 1 subject in the saxagliptin + dapagliflozin + metformin group during the double-blind treatment period was, upon adjudication, determined to be pancreatic cancer that metastasised to the liver.

Fractures

AEs of fractures were reported in a total of 7 subjects: 1 subject (0.2%) in the saxagliptin + dapagliflozin + metformin group, 4 subjects (1.2%) in the saxagliptin + metformin group, and 2 subjects (0.6%) in the dapagliflozin + metformin group.

Cardiovascular events and Cardiac Failure

CV events that were adjudicated and confirmed as CV events were reported in a total of 8 subjects: 4 subjects (0.8%) in the saxagliptin + dapagliflozin + metformin group, 2 subjects (0.6%) in the saxagliptin + metformin group, and 2 subjects (0.6%) in the dapagliflozin + metformin group.

AEs suggestive of heart failure were reported in a total of 10 subjects: 5 subjects (1.0%) in the saxagliptin + dapagliflozin + metformin group, 3 subjects (0.9%) in the saxagliptin + metformin group, and 2 subjects (0.6%) in the dapagliflozin + metformin group. In the saxagliptin + dapagliflozin + metformin group, an AE of oedema peripheral was reported in 3 subjects, cardiac failure in 1 subject, oedema in 1 subject, and orthopnoea in 1 subject (1 subject had AEs of both oedema peripheral and orthopnoea). The AE of cardiac failure was reported as an SAE and led to discontinuation of study treatment. Cardiac failure was based on severe bicuspid valve aortic stenosis and was resolved by surgery. In the saxagliptin + metformin group, an AE of oedema peripheral was reported in 3 subjects. In the dapagliflozin + metformin group, an AE of oedema peripheral was reported in 1 subject, and an AE of cardiac failure congestive was reported in 1 subject.

Other AEs of special interest

There were no unexpected findings for lymphocyte/thrombocyte counts, pancreatitis, severe cutaneous adverse events, hypersensitivity, hepatic events and volume depletion.

Laboratory findings

Haematology values and blood chemistry values were generally within the normal range throughout the 24-week treatment period.

Small mean increases from baseline in haemoglobin, haematocrit, and platelet count were seen in the dapagliflozin-containing treatment groups for these analytes, consistent with the dapagliflozin clinical programme.

Both albumin/creatinine ratio and urine albumin decreased in the dapagliflozin-containing groups and increased in the saxagliptin + metformin group. The mean changes over time in these parameters were not considered to be clinically meaningful.

The frequency of Marked abnormalities (Mas) in laboratory test results in Integrated ST Pool was generally low and similar across the 3 treatment groups.

Evaluation of overall AEs, SAEs, and AEs leading to discontinuation did not indicate any clinical concern regarding findings for potassium values. For CK values, further discussion taking also into account the data from the LT extension periods is necessary.

Consistent with its mild diuretic effect, dapagliflozin-containing treatments were associated with larger decreases from baseline in systolic and diastolic BP; these small effects on BP were consistent over time.

Safety in special populations

Subgroup analyses of AEs were performed for age, gender, and race.

Age

Of the 1169 subjects in the Integrated ST Pool, 1007 subjects (86.1%) were aged <65 years, 162 subjects (13.9%) were aged ≥65 years, and 9 subjects (0.8%) were aged ≥75 years. The distribution of subjects by age was balanced across the treatment groups. No clinically meaningful difference in the AE incidence was observed in the age subgroup <65 years and ≥65 years. There were too few subjects (0.8%) in the ≥75 year age group to evaluate the AE reporting in this group.

Gender

The incidence of AEs was comparable between female and male subjects in the saxagliptin + dapagliflozin + metformin (51.9% vs 49.6%, respectively) and the dapagliflozin + metformin (48.3% vs 43.6%, respectively) groups. In the saxagliptin + metformin group, the proportion of subjects who had an AE was slightly higher in females than males (63.3% vs 48.2%, respectively). The increased proportion of females reporting AEs was, in part, due to an increased frequency of UTIs and vulvovaginal mycotic infections in the female subgroup. Apart from this observation, the most common AEs in both males and females were similar to those observed in the overall Integrated ST Pool.

Race

The majority of subjects in the Integrated ST Pool were White (80.9%). The most common AEs were similar in both the White and Black subgroups and were consistent with the overall AEs in the Integrated ST Pool. Because of the low numbers of subjects who were of Asian or Other racial origin, no conclusions could be drawn based on an analysis of AEs.

Safety related to drug-drug interactions and other interactions

No additional drug interaction studies were required for Qtern. Based on the pharmacokinetic properties of saxagliptin and dapagliflozin and the results of previously conducted drug interaction studies the overall interaction potential of the fixed dose combination is assessed to be low. The relevant information with regard to interactions from Forxiga and Onglyza has been included in the QTERN SmPC section 4.5 :

Discontinuation due to adverse events

Overall, the incidence of subjects who discontinued study treatment due to an AE was low (≤2.0% in any treatment group). A total of 16 subjects discontinued study medication due to an AE in the Integrated ST Pool: 10 (2.0%) in the saxagliptin + dapagliflozin + metformin group, 2 (0.6%) in the saxagliptin + metformin group, and 4 (1.2%) in the dapagliflozin + metformin group. Subjects who discontinued the study treatment were numerically greater in the saxagliptin + dapagliflozin + metformin group, however AE PTs that led to discontinuation were dispersed across various SOC in this group and did not occur in more than 2 subjects.

Post marketing experience

No post-marketing data are available for saxagliptin/dapagliflozin FDC, but these are available for the monocomponents.

Saxagliptin

In 2013 results of the SAVOR trial (CV outcomes trial) were presented. This randomised, double-blind, placebo-controlled study included 16492 subjects with T2DM with a history of either established CV disease or multiple CV risk factors. The study achieved the primary safety endpoint, demonstrating no increased risk of CV death, myocardial infarction (MI), or stroke. While SAVOR met its primary safety and secondary CV composite endpoints, an analysis of the individual components of the secondary composite endpoint revealed an imbalance in hospitalisation for HF. This issue has been discussed extensively in a type 2 variation that was finalized in 2014 and is reflected in the QTERN SmPC. After reanalysis of the overall mortality data by FDA raised an issue on non-cardiovascular death at the expense of saxagliptin, the data have been re-discussed in CHMP/PRAC, and a further Type 2 variation has been finalised to implement results in section 5.1 of the saxagliptin SmPC. Relevant information has been included also in the QTERN SmPC.

Furthermore, a pharmacoepidemiology program consisting of 6 studies that further assess hospitalisation for acute kidney injury, hospitalisation with acute hepatic failure, major CV events, hospitalisation for infections, hospitalisation for severe hypersensitivity reactions, and risk factors for lymphopaenia among patients with T2DM exposed to saxagliptin has been implemented. First and second interim reports have been presented in the first half of 2015.

Dapagliflozin

A pharmacoepidemiology program consisting of 4 studies to further study the risk of severe complications of UTIs, risk of acute hepatic failure, risk of acute renal failure, and risk of cancer among patients with T2DM exposed to dapagliflozin has been implemented. For SGLT2-inhibitors in general, a referral on cases of

ketoacidosis was concluded in February 2016. The referral outcome is also relevant for Qtern and has been taken into account in its Product information and RMP.

2.6.1. Discussion on clinical safety

For the purpose of this submission for marketing authorisation of the saxagliptin/dapagliflozin FDC, data were pooled from the 24-week, double-blind treatment periods of the 3 studies (CV181169, CV181168, and MB102129). The rationale for pooling the safety data from the 3 clinical studies was based on similarity in study design and the possibility of identifying potential safety signal(s) in a larger subject population. However, all relevant safety data should be taken into account in the safety summary, not only safety data originating from the Integrated ST Pool. Analyses should be conducted on the largest possible pool of data. Therefore, on request, the Applicant has submitted data from the open label studies preceding the double blind treatments and from the LT extension periods.

It can be accepted that frequencies of adverse reactions are determined on the basis of the double blind, placebo controlled ST study period of 24 weeks, in combination with frequencies emerging from saxagliptin, dapagliflozin clinical trials and postmarketing experience of saxagliptin. On request, the Applicant has clarified the determination of frequency of adverse reactions for the saxagliptin/dapagliflozin combination. However, in line with the SmPC Guideline, the most appropriate frequencies to be mentioned in section 4.8 of the SmPC of Qtern are those calculated from the pooled data of the Phase III studies in the clinical development programme for the saxa/dapa FDC, not the ones of the monocomponents in the respective clinical development programmes as was initially proposed by the Applicant. In response, the Applicant has amended the data accordingly.

A total of 1169 subjects were included in the Treated Subjects dataset. Of these, 492 received saxagliptin + dapagliflozin + metformin, 336 received saxagliptin + metformin, and 341 received dapagliflozin + metformin. The median exposure to double-blind study treatment in each treatment group was 169 days. The majority of subjects across the 3 treatment groups received their respective study treatment between 121 and 180 days. Exposure was similar in the treatment groups.

Numerically more patients in the saxagliptin + metformin group (55.7%) reported at least 1 AE compared to the dapagliflozin + metformin group (46%) and the saxagliptin + dapagliflozin + metformin group (50.8%). The difference consisted primarily in slight differences in percentage of infections and headache. The triple combination was not associated with more AEs. No new safety concerns were noted.

There were no remarkable differences between groups in serious adverse events. Also, incidence of subjects who discontinued study treatment due to an AE was low.

The incidence of hypoglycaemia events was low. Numerically, there were more events of hypoglycaemia in the saxagliptin + dapagliflozin + metformin group and dapagliflozin + metformin group as compared to the saxagliptin + metformin group. This is to be expected, as glucose control with saxagliptin + metformin was less than that with the other two groups.

With regard to adverse events of special interest, there were also no differences between treatment groups, and there were no unexpected findings. Especially, no differences were seen in incidence of cardiovascular events and heart failure events. Overall, numbers were small, and studies were not powered to detect differences in these AEs.

In the safety conclusion, the Applicant states that concomitant addition of saxagliptin and dapagliflozin to metformin was not associated with an increase in the incidence of AEs when compared to the sequential addition of saxagliptin and dapagliflozin to metformin. However, safety data from the three trials were pooled, and no analysis according to concomitant or sequential add-on treatment was presented. When results of individual studies are compared, the percentage of subjects with at least 1 AE in the saxagliptin + dapagliflozin + metformin groups was 48.6% in study CV181169 (concomitant add-on), 47.7% in study CV181168 (sequential add-on), and 56.3% in study MB102129 (sequential add-on), thus suggesting no increase in AEs in the concomitant add-on group. However, as also discussed in the efficacy paragraph, a comparison between concomitant add-on treatment and sequential add-on treatment is difficult, as these regimens were not performed in the same study. Also, the number of patients tested is small. It is to be expected that the FDC will increase risk of specific side effects compared to monocomponents, e.g. the risk of urinary tract infections will increase when dapagliflozin is added to saxagliptin and the risk of GI events will increase when saxagliptin is added to dapagliflozin.

The Applicant performed a number of subgroup analyses. With respect to age, it should be remarked that the number of elderly subjects (>65 years) was limited: 162. Especially, the number of subjects >75 was low: only 9, thus limiting the extent of the analysis. For subjects > 65 years, compared to subjects < 65 years, no unexpected findings were observed. The older age group experienced some more SAEs and events in the category of accidents and injuries, Anticholinergic syndrome, and Cardiac disorders. These are not unexpected.
Female subjects experienced more AEs than males, especially UTIs and vulvovaginal mycotic infections.

No efficacy/safety trials were executed in special populations.

Immunocompromised patients were not investigated. However, based on the discussed data available for the monocomponents, there is no evidence for a direct immunotoxic or immunosuppressive effect.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

As expected, specific side effects related to the monocomponents, such as UTI for dapagliflozin and GI events for saxagliptin may occur when the two products are given together such as in a fixed dose combination, but in general the FDC was tolerated reasonably well. It is acknowledged that only a relatively small number of uncomplicated patients was tested.

The number of elderly subjects, and especially subjects >75 years was limited. This has been reflected in the SmPC.

2.7. Risk Management Plan

Safety concerns

Important identified risks	Hypersensitivity reactions

	Infections (including genital infections and urinary tract infections) Pancreatitis Gastrointestinal-related AEs Diabetic ketoacidosis with atypical presentation
Important potential risks	Hypoglycaemia Lymphopaenia Severe cutaneous adverse reactions Pancreatic cancer Skin lesions (ulcer, erosion, necrosis) Opportunistic infections Cardiac failure Volume depletion Clinical consequences of increased haematocrit Renal impairment/failure Bone fracture Liver injury Bladder cancer Breast cancer Prostate cancer Off-label use of saxagliptin/dapagliflozin FDC in specific populations
Missing information	Paediatric population Elderly population Pregnancy and lactation/breastfeeding Moderate and severe hepatic impairment Severe renal impairment Patients with immunocompromised conditions Use in patients with malignancy/neoplasm Use in patients with CHF defined as NYHA class III and IV

Pharmacovigilance plan

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Saxagliptin Studies:				
CV181058 A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of saxagliptin as monotherapy in pediatric patients with type 2 diabetes (Category 3)	To evaluate the efficacy, safety, tolerability, of saxagliptin in paediatric patients with type 2 diabetes	Safety in paediatric patients	Started	Last patient last visit planned: fourth quarter 2017
CV181147 A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of saxagliptin in combination with metformin in pediatric patients with type 2 diabetes who have inadequate glycemic control on metformin alone (Category 3)	To evaluate the efficacy, safety, tolerability, of saxagliptin in combination with metformin in pediatric patients with type 2 diabetes	Safety in paediatric patients	Started	Last patient last visit planned: fourth quarter 2017
CV181099 Observational cohort study Comparison of risk of major cardiovascular events between patients with type 2 diabetes initiating saxagliptin and those initiating other oral antidiabetic treatments (Category 3)	To compare the incidence of major cardiovascular events among patients with type 2 diabetes who are new initiators of saxagliptin and those who are new initiators of OADs in classes other than DPP-4 inhibitors.	Major cardiovascular events	Started	Final CSR: May 2016
CV181100 Observational cohort study Comparison of risk of hospitalization with acute liver failure between patients with type 2 diabetes initiating saxagliptin and those initiating other oral antidiabetic treatments (Category 3)	To compare the incidence of hospitalisation with acute liver failure among patients with type 2 diabetes who are new users of saxagliptin and those who are new users of other OADs	Acute liver failure	Started	Final CSR: May 2016

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
CV181101 Observational cohort study Comparison of risk of hospitalization for infections between patients with type 2 diabetes exposed to saxagliptin and those exposed to other oral antidiabetic treatments (Category 3)	To compare the incidence of hospitalisations for infections, including infections associated with T-lymphocyte dysfunction (ie, herpes zoster, tuberculosis, or non-tuberculous mycobacterial infections) among patients with type 2 diabetes mellitus who are new initiators of saxagliptin and those who are new initiators of OADs in classes other than DPP-4 inhibitors	Infection	Started	Final CSR: May 2016
CV181103 Observational cohort study Comparison of risk of hospitalization for severe hypersensitivity (including severe cutaneous reactions) between patients with type 2 diabetes initiating saxagliptin and those initiating other oral antidiabetic treatments (Category 3)	To compare the incidence hospitalisation for severe hypersensitivity and cutaneous reactions among patients with type 2 diabetes who are new users of saxagliptin and those who are new users of other OADs	Severe hyper-sensitivity reactions	Started	Final CSR: May 2016
CV181157 ST Observational cohort study Comparison of risk of hospitalization for acute kidney injury between patients with type 2 diabetes initiating saxagliptin and those initiating other oral antidiabetic treatments (Category 3)	To compare the incidence of hospitalization for acute kidney injury among patients with type 2 diabetes who are new initiators of saxagliptin and those who are new initiators of other OADs in classes other than DPP-4 inhibitors	Acute kidney injury	Started	Final CSR: May 2016

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
D1680C00016 Study title: Mechanistic Evaluation of Glucose-Lowering Strategies in Patients with Heart Failure A 24-Week, Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled Study to Investigate the Effects of Saxagliptin and Sitagliptin in Patients with Type 2 Diabetes Mellitus and Heart Failure (Category 3)	Primary objective: To exclude an increase in left ventricular end diastolic volume (LVEDV) index of greater than 10% in patients with T2DM and HF treated with saxagliptin for 24 weeks, compared to placebo	To further evaluate the imbalance in number of events of hospitalization for heart failure finding from the SAVOR Study	Planned; anticipated to begin recruitment in the United States in 3-4Q 2016 and 1Q2017 in the rest of world	Final report planned: 2019
Dapagliflozin Studies:				
MB102-138 A 24 Week, Multicenter, Randomized, Double-Blind, Parallel Group, Phase 3 Trial with a 28 Week Long Term Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin 10 mg in T2DM Patients aged 10-24 years	To evaluate the efficacy, safety, tolerability, of saxagliptin in paediatric patients with type 2 diabetes	Safety in paediatric patients	Started	Last patient last visit planned: third quarter 2019

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
CV181-375 A 24 Week, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Parallel Group, Phase 3 Trial with a 28 Week Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin 5 and 10 mg, and Saxagliptin 2.5 and 5 mg in Pediatric Patients with Type 2 Diabetes Mellitus who are between 10 and below 18 years of age	To evaluate the efficacy, safety, tolerability, of saxagliptin and Dapagliflozin in paediatric patients with type 2 diabetes	Safety in paediatric patients	Planned	Last patient last visit planned: fourth quarter 2020
MB102103 Non-interventional study evaluating the risk of severe complications of urinary tract infections (Category 3)	To compare the incidence of hospitalisation or emergency department visit for severe complications of urinary tract infections among patients with type 2 diabetes who are new users of dapagliflozin with those who are new users of other antidiabetic treatments	Severe complications of urinary tract infections	Started	Interim report planned: 2014 Final report planned: 2019
MB102104 Non-interventional study evaluating the risk of acute liver failure (Category 3)	To compare the incidence of hospitalisation for acute liver injury among patients with type 2 diabetes who are new users of dapagliflozin with those who are new users of other antidiabetic treatments	Acute liver failure	Started	Final report planned: 2019
MB102110 Non-interventional study evaluating the risk of acute kidney failure (Category 3)	To compare the incidence of hospitalisation for acute kidney injury among patients with type 2 diabetes who are new users of dapagliflozin with those who are new users of other antidiabetic treatments	Hospitalisation for acute kidney failure	Started	Final report planned: 2019

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
MB102118 Non-interventional study evaluating the risk of cancer (Category 3)	To compare the incidence of breast cancer among females with type 2 diabetes who are new users of dapagliflozin with those who are new users of other antidiabetic treatments To compare the incidence of bladder cancer among male and female patients with type 2 diabetes who are new users of dapagliflozin with those who are new users of other antidiabetic treatments	Cancer	Started	Interim data reported every 2 years for up to 10 years Final report planned: 2024
MB102117/ D1693C00001 Dapagliflozin effect on cardiovascular events A multicenter, randomized, double-blind, placebo-controlled trial to evaluate the effect of dapagliflozin 10 mg once daily on the incidence of cardiovascular death, myocardial infarction or ischaemic stroke in patients with type 2 diabetes (DECLARE) (Category 3)	To investigate if dapagliflozin, when added to a patients' current anti-diabetes therapy, is effective in reducing CV events such as myocardial infarction (heart attack), ischaemic stroke, and CV- related death, compared with placebo. To evaluate the incidence of adjudicated bladder cancer and liver injury	CV risk, bladder cancer, liver injury	Started	Final report planned: 2020.
D1690R00013: DKA incidence in SGLT2 users. Non-interventional (Category 3) A Post-Authorization Safety Study on incidence of diabetic ketoacidosis (DKA) in new users of different antidiabetic medication classes and combination of classes using observational data from the	Primary objective: To estimate the incidence of DKA among patients diagnosed with T2D initiating prescribed antidiabetes medication by antidiabetes medication class and combinations of classes. Secondary objective: To compare the	Ketoacidosis.	Planned	Final report planned: Q1 2017

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
MarketScan database.	incidence of DKA in patients diagnosed with T2DM between different medication classes and combination of classes. This objective will only be assessed if this is determined to be feasible based on the analysis of the first objective.			
Externally research sponsored independent investigator initiated nonclincial mechanistic model studies (postdoc project).	Studies aimed to elucidate the metabolic adaptations in term of glucose flux, lipolysis and ketogenesis following insulin withdrawal in subjects with diabetes mellitus and absolute or relative endogenous insulin deficiency, when treated with dapagliflozin.	Ketoacidosis	Planned	Update report: Q1 2017

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks		
Hypersensitivity reactions	Product labelling is sufficient to address the safety concern. Listed in the SmPC under Sections 4.3 (Contraindications), 4.4 (Special warnings and precautions for use), and 4.8 (Undesirable effects). Contraindicated in hypersensitive patients.	No additional measures are proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Infections (including genital infections and urinary tract infections)	Product labelling is sufficient to address the safety concern. Listed in the SmPC under Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects)	No additional measures are proposed.
Pancreatitis	Product labelling is sufficient to address the safety concern Listed in the SmPC under Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects). Patients to be informed of symptoms of acute pancreatitis. Discontinue if pancreatitis suspected.	No additional measures are proposed.
Gastrointestinal-related AEs	Product labelling is sufficient to address the safety concern Listed in the SmPC under Section 4.8 (Undesirable effects).	No additional measures are proposed.
Diabetic Ketoacidosis with atypical presentation	Product labelling is sufficient to address the safety concern. Listed in the SmPC under Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects)	DHPC distributed according to EMA dissemination plan, and is now completed
Important Potential Risks		
Hypoglycaemia	Product labelling is sufficient to address the safety concern. Listed in the SmPC under Sections 4.4 (Special warnings and precautions for use), 4.7 (Effects on ability to drive and use machines), and 4.8 (Undesirable effects).	No additional measures are proposed.
Lymphopaenia	Product labelling is sufficient to address the safety concern. Listed in the SmPC under Section 4.8 (Undesirable effects).	No additional measures are proposed.
Severe cutaneous adverse reactions	No risk minimisation measures are proposed.	Not applicable.
Pancreatic cancer	No risk minimisation measures are proposed.	Not applicable.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Skin lesions (ulcer/erosion/necrosis)	Product labelling is sufficient to address the safety concern. Listed in the SmPC under Sections 4.4 (Special warnings and precautions for use) and 5.3 (Preclinical safety data). Monitoring for skin disorders recommended.	No additional measures are proposed.
Opportunistic infections	No risk minimisation measures are proposed.	Not applicable.
Cardiac failure	Product labelling is sufficient to address the safety concern. Listed in the SmPC under Sections 4.4 (Special warnings and precautions for use), 4.8 (Undesirable effects), and 5.1 (Pharmacodynamic properties).	No additional measures are proposed.
Volume depletion	Product labelling is sufficient to address the safety concern. Listed in the SmPC under Sections 4.2 (Posology and method of administration), 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects). Monitoring of volume status in at-risk patients recommended. Not recommended in patients on loop diuretics or volume depleted. Use caution in patients for whom dapagliflozin-induced reduction in blood pressure could pose a risk. Renal function and the risk of volume depletion should be considered in elderly patients.	No additional measures are proposed.
Clinical consequences of increased haematocrit	Product labelling is sufficient to address the safety concern. Listed in the SmPC under Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects). Use caution in patients with already elevated haematocrit. Monitoring of volume status in at-risk patients recommended.	No additional measures are proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Renal impairment/ failure	Product labelling is sufficient to address the safety concern. Listed in the SmPC under Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects). Should not be used in patients with moderate to severe renal impairment.	No additional measures are proposed.
Bone fracture	No risk minimisation measures are proposed.	Not applicable.
Liver injury	No risk minimisation measures are proposed.	Not applicable.
Bladder cancer	Product labelling is sufficient to address the safety concern. Listed in the SmPC under Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects). Not recommended in patients on concomitant pioglitazone.	No additional measures are proposed.
Breast cancer	Product labelling is sufficient to address the safety concern. Listed in the SmPC under Section 4.8 (Undesirable effects).	No additional measures are proposed.
Prostate cancer	Product labelling is sufficient to address the safety concern. Listed in the SmPC under Section 4.8 (Undesirable effects).	No additional measures are proposed.
Off-label use in specific populations	Product labelling is sufficient to address the safety concern. Listed in the SmPC under Section 4.4 (Special warnings and precautions for use). Not recommended in patients with moderate to severe renal impairment, patients at-risk of volume depletion, hypotension and/or electrolyte imbalance, patients aged >75 years, and patients on comcomitant pioglitazone.	No additional measures are proposed.

Missing information

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Paediatric population	Product labelling is sufficient to address the safety concern. Listed in the SmPC under Sections 4.1 (Therapeutic indication), 4.2 (Posology and method of administration), and 5.1 (Pharmacodynamic properties).	No additional measures are proposed.
Elderly population	Product labelling is sufficient to address the safety concern. Listed in the SmPC under Sections 4.2 (Posology and method of administration), 4.4 (Special warnings and precautions for use), 4.8 (Undesirable effects), and 5.2 (Pharmacokinetic properties). Renal function and the risk of volume depletion should be considered. Not recommended in patents aged >75 years. Use caution in patients for whom dapagliflozin-induced reduction in blood pressure could pose a risk.	No additional measures are proposed.
Pregnancy and lactation/breastfeeding	Product labelling is sufficient to address the safety concern. Listed in the SmPC under Sections 4.6 (Fertility, pregnancy and lactation) and 5.3 (Preclinical safety data). Not recommended during pregnancy. If a patient wishes to become pregnant, or if pregnancy is detected, treatment with saxagliptin/dapagliflozin FDC should be discontinued. Should not be used while breast feeding.	No additional measures are proposed.
Patients with moderate and severe hepatic impairment	Product labelling is sufficient to address the safety concern. Listed in the SmPC under Sections 4.2 (Posology and method of administration), and 5.2 (Pharmacokinetic properties). Patients with moderate hepatic impairment should be evaluated prior to initiation and during treatment. Not recommended in patients with severe hepatic impairment.	No additional measures are proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Patients with severe renal impairment	Product labelling is sufficient to address the safety concern. Listed in the SmPC under Sections 4.2 (Posology and method of administration), 4.4 (Special warnings and precautions for use), and 5.2 (Pharmacokinetic properties). Should not be used in patients with moderate to severe renal impairment, or end-stage renal disease. Renal function and the risk of volume depletion should be considered in elderly patients. Monitoring of renal function recommended as follows: at inititiation of saxagliptin/dapagliflozin FDC treatment and at least yearly thereafter; prior to initiation of concomitant treatment that may reduce renal function and periodically thereafter; at least 2 to 4 times per year when renal function is approaching moderate impairment.	No additional measures are proposed.
Patients with immunocompromised conditions	Product labelling is sufficient to address the safety concern. Listed in the SmPC under Section 4.4 (Special warnings and precautions for use).	No additional measures are proposed.
Use in patients with malignancy/neoplasm	No risk minimisation measures are proposed.	Not applicable.
Use in patients with CHF defined as NYHA class III and IV.	Product labelling is sufficient to address the safety concern. Listed in the SmPC under Section 4.4 (Special warnings and precautions for use). No experience in clinical trials with dapagliflozin and limited with saxagliptin.	No additional measures are proposed.

Conclusion

The CHMP and PRAC considered that the risk management plan version 2.2 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.

2.9. Product information

2.9.1. 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.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Qtern (saxagliptin/dapagliflozin) 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

Benefits

Beneficial effects

Qtern is a fixed dose combination (FDC) of saxagliptin and dapagliflozin. Both components are approved for treatment of type 2 diabetes mellitus as monotherapy and as add-on treatment. Dapagliflozin has the add-on indication with a DPP4-inhibitor, while saxagliptin does not have the add-on indication to an SGLT2-inhibitor. The pharmacokinetics of saxagliptin and dapagliflozin are well established for both active substances and based on the results of previously conducted studies. The overall interaction potential of the fixed dose combination is assessed to be low. The applicant conducted two pharmacokinetic studies to bridge the pharmacokinetic data of the monocomponents to the FDC tablets. Based on the results of these studies, bridging of the results obtained in the phase 3 studies performed with the combination of the monotherapies to the FDC formulation has sufficiently been justified. Bioequivalence between the fixed dose combination 5 mg saxagliptin/10 mg dapagliflozin FDC tablets and the individual components has been evaluated in Study CV181341 and the drug-drug interaction between saxagliptin on dapagliflozin has been evaluated in study CV181191. Bioequivalence between the fixed dose combination 5 mg saxagliptin/10 mg dapagliflozin FDC tablets and the individual components has been shown and the absence of a drug-drug interaction between saxagliptin on dapagliflozin has been confirmed.

In support of the current application, data from three clinical studies were submitted: one concomitant add-on study (CV181169) and two sequential add-on trials (CV181168 and MB102129). Repeated measures analysis of the primary endpoint demonstrated a clinically relevant effect of saxagliptin + dapagliflozin + metformin treatment (added concomitantly or sequentially) in lowering HbA1c at Week 24 which was statistically significant versus the combination of saxagliptin and metformin (studies CV181169 and MB102129) and versus the combination of dapagliflozin and metformin (studies CV181169 and CV181168). Difference versus saxagliptin + metformin was -0.59% in study CV181169 and -0.72% in study MB102129. Difference versus dapagliflozin + metformin was -0.27% in study CV181169 and -0.35% in study CV181168. Results show that both components contribute to the effect of the combination; however, the contribution of both components to the FDC depends on baseline HbA1c. Saxagliptin is contributing a larger proportion to the total combination effect at lower baseline HbA1c levels than at higher ones, and conversely, dapagliflozin is contributing a larger proportion to the total combination effect at higher baseline HbA1c levels than at lower ones. Furthermore, the difference measured between the FDC and the monocomponents is not quite representative for the actual contribution of each component. As both components for their action are dependent on plasma glucose levels, when combined, both the effect of saxagliptin and dapagliflozin seems to be reduced, as the total effect of the combination is not the sum of the individual effects.

Results of secondary endpoints were in line with the primary analysis, although not all comparisons reached statistical significance. In study CV181169, the proportion of subjects achieving HbA1c <7% at Week 24 was nearly 2-fold higher in the saxagliptin + dapagliflozin + metformin group (41.4%) compared with the saxagliptin + metformin group (18.3%) and the dapagliflozin + metformin group (22.2%). However, the difference in responders depended on baseline HbA1c with the largest difference for subjects with baseline HbA1c of 8 – 9% (± 30%), and smallest for subjects with HbA1c <8% (7% vs saxa+met) or >9% (9% vs dapa+met).
In study CV181168, the proportions were 35.5% in the saxagliptin + dapagliflozin + metformin group and 23.1% in the dapagliflozin + metformin group. In study MB102129, the proportion of subjects achieving the glycaemic target of HbA1c <7.0% at Week 24 was over 3-fold higher in the dapagliflozin + saxagliptin + metformin group (38.0%) compared with the placebo + saxagliptin + metformin group (12.4%). The difference between the treatment groups was 25.5% and statistically significant ($p<0.0001$) and this endpoint was met. Dapagliflozin treatment resulted in moderate weight loss of around 2 kg; treatment with saxagliptin was weight neutral. In both studies effects on HbA1c were sustained at week 52.
Incidence of hypoglycaemia was low. Numerically, there were more events of hypoglycaemia in the saxagliptin + dapagliflozin + metformin group and dapagliflozin + metformin group as compared to the saxagliptin + metformin group, but differences were small.

Uncertainty in the knowledge about the beneficial effects.
The indication for Qtern as initially claimed by the applicant was for combination with other oral glucose lowering medicinal products when these alone do not provide adequate control, without further specification whether patients were already being treated with the monocomponents. The design and conduct of the studies were appropriate to establish the efficacy and safety of saxagliptin + dapagliflozin + metformin vs the monocomponents when added to metformin. However, they do not allow for a decision whether concomitant add-on treatment is better than sequential add-on.
In the sequential add-on studies percentages responders after the OL treatment period were 22% for the dapagliflozin + metformin group and 14-17% for the saxagliptin + metformin group (14% for stratum B and 17% for stratum A). Adding the second drug in the 24 week treatment period resulted in an increase in responders (to 35-38%) that was larger than in the placebo group (12-23%). Because of the design of the

studies, a comparison between studies of total number of responders on triple therapy during the whole study period is difficult to make, as responders on OL treatment were discontinued from the studies.
In response to this issue, the Applicant argued that early intensive treatment is important for preventing micro- and macrovascular complications. Compared to sequential add-on treatment, concomitant add-on treatment could result in a gain in time of 3 months to reach glycaemic targets.
Data from mechanistic studies suggest that very short-term hyperglycaemia and variations in glucose level can increase the risk for developing a negative metabolic memory. However, the clinical relevance of these findings is not clear.

The number of elderly subjects (>65 years) was limited: 162. Number of subjects > 75 was only 9. Data from these subjects and data from the individual monocomponent clinical programmes in elderly patients are reassuring. However, section 4.2 of the SmPC has been amended to reflect the limited experience.
Benefit in female subjects < 50 year was uncertain. In the studies saxagliptin showed very little effect in this patient group. Additional analyses did not reveal a treatment-by-female age interaction for saxagliptin 5 mg, but for saxagliptin 2.5 mg an interaction could not be excluded.

In study CV181169, metformin XR tablets were used. These tablets are not registered in all EU countries. In the other two studies metformin IR tablets were used. Two thirds of subjects used metformin XR in a dose between 1700 and 2500 mg daily, and one third used 1500-1700 mg daily. Maximum recommended dose of metformin XR is 2000 mg, while maximum daily dose for metformin IR is 2550 to 3000 mg. That is probably the reason why more patients in the two sequential studies used metformin in higher doses (above 2500 mg) as in these studies metformin IR was used. This makes a comparison between studies in terms of background therapy more complicated.

Switching from other DPP4-inhibitors and SGLT2-inhibitors other than the monocomponents to saxagliptin/dapagliflozin combination has not been studied.

Risks

Unfavourable effects

For the purpose of this submission for marketing authorisation of the saxagliptin/dapagliflozin FDC, data were pooled from the 24-week, double-blind treatment periods of the 3 studies (CV181169, CV181168, and MB102129). A total of 1169 subjects were included. Of these, 492 received saxagliptin + dapagliflozin + metformin, 336 received saxagliptin + metformin, and 341 received dapagliflozin + metformin. The median exposure to double-blind study treatment in each treatment group was 169 days.

Numerically more patients in the saxagliptin + metformin group (55.7%) reported at least 1 AE compared to the dapagliflozin + metformin group (46%) and the saxagliptin + dapagliflozin + metformin group (50.8%). The difference consisted primarily in slight differences in percentage of infections and headache. The triple combination was not associated with more AEs. No new safety concerns were noted.

There were no remarkable differences between groups in serious adverse events. Also, incidence of subjects who discontinued study treatment due to an AE was low.

The incidence of hypoglycaemia events was low. Numerically, there were more events of hypoglycaemia in the saxagliptin + dapagliflozin + metformin group and dapagliflozin + metformin group as compared to the saxagliptin + metformin group.

With regard to adverse events of special interest, there were no differences between treatment groups, and there were no unexpected findings. Especially, no differences were seen in incidence of cardiovascular events and heart failure events. Overall, numbers were small, and studies were not powered to detect differences in these AEs.

Female subjects experienced more AEs than males, especially UTIs and vulvovaginal mycotic infections.

Uncertainty in the knowledge about the unfavourable effects

The Applicant performed a number of subgroup analyses. With respect to age, it should be remarked that the number of elderly subjects was limited. The number of subjects > 75 years was too low for drawing meaningful conclusions. For subjects > 65 years, compared to subjects < 65 years, no unexpected findings were observed.

On request, the Applicant submitted data from the open label studies preceding the double blind treatments and from the LT extension periods.

No efficacy/safety trials were conducted in special populations.

Immunocompromised patients were not investigated. However, based on the data available for the monocomponents, there is no evidence for a direct immunotoxic or immunosuppressive effect. Qtern has only been studied with metformin as background therapy. Combination with SUs was studied for the individual components. Main issue is the risk for hypoglycaemia. Based on the MOA and the data from the individual components, no additional safety concerns of hypoglycaemia are to be expected.

The Applicant did not seek combination with insulin as indication.

Results from the SAVOR trial (cardiovascular outcome trial for saxagliptin) have been discussed in separate Type 2 variations, the most recent one regarding a numerical imbalance in non-cardiovascular death at the expense of saxagliptin. This information has been implemented in section 5.1 of the Qtern SmPC.

For SGLT2-inhibitors in general, there has been a referral reviewing cases of ketoacidosis. A small excess risk of DKA/related diagnosis in T2DM-patients on dapagliflozin cannot be ruled out. However, the conclusions of the referral were that the benefit/risk remains positive, with an additional warning in the SmPC section 4.4.

Benefit-risk balance

Importance of favourable and unfavourable effects

For a FDC, pharmacokinetic studies showing bioequivalence with the monocomponents and evaluating drug-drug-interactions are important. Based on the results of the bioequivalence and the interaction study, it can be concluded that bridging of the results obtained in the phase 3 studies performed with the combination of the monotherapies to the to-be-marketed FDC formulation has sufficiently been justified.

The effect of fixed-dose combination (FDC) of saxagliptin + dapagliflozin on HbA1c was statistically significant in all three studies when comparison was made with the monocomponents against a background therapy of metformin, both in a concomitant and a sequential add-on design.

With FDC's, it is required that all active ingredients contribute to the product's therapeutic effect. In combination with saxagliptin, dapagliflozin was associated with modest, but clinically relevant reductions in HbA1c. However, the relevance of the contribution of saxagliptin to the FDC was less clear, in particular in patients with high HbA1c who may represent a considerable part of the target population in clinical practice.

The concomitant add-on design was not compared in one study with the sequential add-on design. Furthermore, switching from other DPP4-inhibitors and SGLT2-inhibitors other than the monocomponents to saxagliptin/dapagliflozin combination has not been studied.

The Applicant pointed to the benefits of early intensification and the importance of metabolic memory. However, data were based on UKPDS and mechanistic studies, and the CHMP was not convinced that the findings are comparable to the results of the current FDC.

Secondary efficacy endpoints were supportive for the effect. Reduction in weight, induced by the dapagliflozin component, can be important for type 2 diabetes mellitus patients.

In general, the FDC was tolerated well. Common AEs are infections and headache. There is a small increase in hypoglycaemia, but this is not considered a major issue when combined with metformin. As expected, additional specific side effects related to the monocomponents, such as UTI and vulvovaginal mycotic infections in female patients for dapagliflozin and GI events for saxagliptin may occur when the fixed dose combination is given, but in general the FDC is tolerated reasonably well. Final conclusions are difficult as only a relatively small number of uncomplicated patients was tested. Reviews of ongoing safety issues for the monocomponents, related to non-cardiovascular deaths for saxagliptin and the potential risk for euglycaemic ketoacidosis, with the use of SGLT2-inhibitors were finalised in parallel with the current assessment, and the benefit/risk balance is still considered to be positive for both monocomponents.

The use of two different forms of metformin (XR and IR) was noted, but not considered very important. The effect of add-on treatment can be measured and compared in one and the same study. Between study comparison is not optimal, but the differences between both forms of metformin are not considered to have great impact on the effects of additive drugs.

Benefit-risk balance

The B/R of the fixed dose combination of saxagliptin and dapagliflozin is positive but only as sequential add-on treatment, or substitution in patients already being treated with the free combination of dapagliflozin and saxagliptin. The initially pursued indication, allowing concomitant add-on treatment, cannot be approved. Switching from other DPP-4 inhibitors and SGLT2 inhibitors is not considered sufficiently justified. Combination with SU is acceptable.

Discussion on the benefit-risk balance

The pursued indication as initially proposed by the applicant, would allow for initial concomitant treatment with the FDC. It should be considered that sequential treatment allows the physician to evaluate the value of each added drug individually and thus avoids not only over-treating patients, but also avoids treating patients with a drug that has only limited efficacy. The Applicant pointed to the benefits of early intensification and the importance of metabolic memory. Early hyperglycaemia may induce marked changes in cellular function and patho-histological changes that may not be reversible and may result in complications as long as 10 years later. This was based on the DCCT and UKPDS data and supported by mechanistic studies. However, the clinical relevance of results of mechanistic studies in mice is not clear. Also the UKPDS concerned a difference in HbA1c of 0.9% during 10 years. It is not clear if these findings are comparable to improvements in HbA1c of 0.27% during a few months of treatment with the FDC of saxagliptin and dapagliflozin. Therefore, concomitant add-on treatment is not considered justified. This could have been justified in case a group of patients were identified for which one could predict that the patients would need the two drugs

anyway. It was assumed that most likely, this would be patients with high initial HbA1c levels. However, the effect of the FDC shown in this group was limited.

Furthermore, adding saxagliptin to dapagliflozin showed limited effect. Although the difference measured between the FDC and the monocomponents is not quite representative for the actual contribution of each component, the measured difference is clinically the most relevant. As the response may be variable, there might be patients who can benefit from the addition of saxagliptin. However, as it is not known which patient will benefit, treatment effects should be evaluated in individual patients. This also argues in favour of sequential add-on treatment.

Although triple therapy did not result in more or unexpected adverse events, both saxagliptin and dapagliflozin are substances from rather new classes of glucose lowering drugs. Each component has its own specific side effects, e.g. GI side effects for DPP-4 inhibitors and UTI for dapagliflozin. Therefore, it can be expected that an increase in specific side effects will occur when starting with the FDC (concomitant add-on of saxagliptin and dapagliflozin) instead of one of the components, although in general the FDC was well tolerated.

The assessment of the safety issues for the monocomponents - ketoacidosis for SGLT2-inhibitors and non-cardiovascular death in the SAVOR trial with saxagliptin - have been finalised. The SmPC sections 4.8 and 4.4 and section 5.1 respectively have been amended in this regard.

The CHMP also considered whether the indication would also cover the switch from other DPP4-inhibitors and SGLT2-inhibitors than saxagliptin and dapagliflozin, and for add-on to other oral glucose lowering drugs than metformin. FDCs of DPP4-inhibitors plus metformin and SGLT2-inhibitors plus metformin currently do not have a switch indication from other DPP4-inhibitors or SGLT2-inhibitors. The interchangeability of all DPP4-inhibitors and all SGLT2 inhibitors is not considered proven. Once a patient is treated with a specific DPP4-inhibitor or a specific SGLT2 inhibitor, it is therefore not wise to switch to another one. This is common sense unless specific studies have proven the interchangeability, which is not the case.

Main oral classes which initially have not been discussed for combination treatment are SUs and TZDs. Dapagliflozin should not be used with pioglitazone because of the risk of bladder cancer, and thus the FDC should also not be combined with pioglitazone. This is adequately reflected in the SmPC.

Although combination with SUs has not been studied for the FDC, it has been investigated for the individual components. Based on the MOA and the data provided for the individual studies, no additional safety concerns of hypoglycaemia are to be expected when saxagliptin and dapagliflozin are used together. Therefore, the combination with SU is acceptable. The corresponding warnings as in the SmPCs of the monocomponents were reflected in the SmPC of Qtern.

The combination with insulin is not sought and is not in the indication.

The overall B/R of Qtern as sequential add-on treatment or substitution in patients already being treated with the free combination of dapagliflozin and saxagliptin is considered positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Qtern in the indication:
Qtern, fixed dose combination of saxagliptin and dapagliflozin, is indicated in adults aged 18 years and older with type 2 diabetes mellitus:

- to improve glycaemic control when metformin and/or sulphonylurea (SU) and one of the monocomponents of Qtern do not provide adequate glycaemic control,
- when already being treated with the free combination of dapagliflozin and saxagliptin.

(See sections 4.2, 4.4, 4.5 and 5.1 for available data on combinations studied.),
is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

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

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

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

Not applicable.

Literature references

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