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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Qtrilmet

International non-proprietary name: metformin hydrochloride / saxagliptin / dapagliflozin

Procedure No. EMEA/H/C/004910/0000

Note

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

Medicinal product no longer authorised



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List of abbreviations

Abbreviation or special term	Explanation
AACE	American Association of Clinical Endocrinologists
ADA	American Diabetes Association
alu/PVC/alu	aluminium/polyvinyl chloride/aluminium
BMI	Body mass index
CEP	Certificate of Suitability of the European Pharmacopoeia
CGM	Continuous glucose monitoring
CK	Creatine phosphokinase
C _{max}	Maximum plasma concentration
CQA	Critical quality attribute
CRF	Case report form
CSR	Clinical study report
CV	Cardiovascular
DAE	Discontinuation due to adverse events
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
DKA	Diabetic ketoacidosis
DoE	Design of Experiments
DPP4	Dipeptidyl peptidase 4
DSC	Differential scanning calorimetry
EASD	European Association for the Study of Diabetes
eGFR	Estimated glomerular filtration rate
FCMP	Fixed combination medicinal product
FPG	Fasting plasma glucose
GC	Gas Chromatography
GI	Gastrointestinal
GLP-1	Glucagon-like peptide 1
HbA1c	Glycated haemoglobin
HCl	Hydrochloride
HDL-C	High-density lipoprotein cholesterol
HDPE	High-density polyethylene
HPLC	High performance liquid chromatography
IPC	In-process control
IR	Immediate-release or Infrared
KF	Karl Fischer titration
LDPE	Low-density polyethylene

Abbreviation or special term	Explanation
MI	Myocardial infarction
MOA	Mechanism(s) of action
MTT	Meal tolerance test
PAR	Proven acceptable range
Ph. Eur.	European Pharmacopoeia
PPG	Postprandial glucose
PVC/PCTFE/alu	polyvinyl chloride/poly-chloro-tri-fluoro-ethylene/aluminium
QbD	Quality by Design
SBP	Systolic blood pressure
SGLT2	Sodium-glucose cotransporter 2
SU	Sulphonylurea
T2DM	Type 2 diabetes mellitus
TG	Triglyceride
TGA	Thermogravimetric analysis
Total-C	Total cholesterol
UGT1A9	Uridine diphosphate glucuronosyl transferase
ULN	Upper limit of normal
UTI	Urinary tract infection
UV-Vis	Ultraviolet-visible
XR	Extended release

Nomenclature used in this Assessment Report

In consequence to a change in order of the INN for Qtrilmet (metformin hydrochloride / saxagliptin / dapagliflozin) during the procedure, Qtrilmet is also referred to as dapagliflozin/saxagliptin/metformin or saxagliptin/dapagliflozin/metformin in this Assessment Report.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 27 June 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Qtrilmet, 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 14 September 2017.

The applicant applied for the following indication (as initially proposed):

“Tradename (combination of dapagliflozin, saxagliptin, and metformin) is indicated in adults aged 18 years and older with type 2 diabetes mellitus:

- to improve glycaemic control when metformin with or without sulphonylurea (SU) does not provide adequate glycaemic control and where simultaneous addition of dapagliflozin and saxagliptin is considered necessary because a single addition of any oral monotherapy is not expected to provide adequate glycaemic control.
- to improve glycaemic control when metformin with or without sulphonylurea (SU) and either dapagliflozin or saxagliptin does not provide adequate glycaemic control.
- when already being treated with dapagliflozin and saxagliptin and metformin.

(See sections 4.2, 4.4, 4.5, 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 fixed combination products

The application submitted is a fixed combination medicinal product.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0092/2018 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.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: Alar Irs

The application was received by the EMA on	27 June 2018
The procedure started on	19 July 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	8 October 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	08 October 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	22 October 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	15 November 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	28 March 2019
The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at 1 investigator site in Canada between 22 Oct 2018 and 26 Oct 2018, 1 investigator site in Russia between 12 Nov 2018 and 16 Nov 2018 and 1 sponsor site in the United States between 03 Dec 2018 and 07 Dec 2018. The outcome of the inspection carried out was issued on	01 March 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	06 May 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 May 2019
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	29 May 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	15 August 2019

The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	04 September 2019
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
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 Qtrilmet on	19 September 2019

Medicinal product no longer authorised

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The indication proposed for Qtrilmet (final wording) is:

"Qtrilmet is indicated in adults aged 18 years and older with type 2 diabetes mellitus:

- to improve glycaemic control when metformin with or without sulphonylurea (SU) and either saxagliptin or dapagliflozin does not provide adequate glycaemic control.
- when already being treated with metformin and saxagliptin and dapagliflozin."

2.1.2. Epidemiology

According to the World Health Organization (WHO) (World Health Organisation 2015), there are 60 million people with diabetes in the European Region. The increasing domestic and global burden of T2DM has made it a disease of considerable concern at both the individual patient and the public health levels.

2.1.3. Clinical presentation

T2DM, the predominant type of diabetes accounting for >90% of all diabetes cases, is a progressive disease involving parallel defects of glucose metabolism in multiple tissues. Key processes leading to T2DM include peripheral insulin resistance, insulin secretory dysfunction, and hepatic glucose overproduction. The condition is associated with hypertension, hyperlipidaemia and increased body weight. The co-morbidities associated with uncontrolled diabetes are significant. Diabetes is the major cause of kidney failure, blindness, and non-traumatic leg amputations among adults in the US and the United Kingdom (UK), and is a leading cause of coronary heart disease and stroke. Cardiovascular (CV) disease is the leading cause of mortality in patients with diabetes, with life expectancy reduced by as much as 10 years in people with T2DM.

Common risk factors for T2DM include increasing age, smoking, being overweight or obese, physical inactivity and poor nutrition, family history of T2DM, race/ethnicity, hypertension, impaired glucose metabolism ("prediabetes"), and gestational diabetes.

2.1.4. Management

An important goal of diabetes care is to achieve and maintain adequate glycaemic control as HbA1c levels over 7% are associated with an increased risk of microvascular and macrovascular complications in T2DM patients.

The European Association for the Study of Diabetes (EASD), American Diabetes Association (ADA), and American Association of Clinical Endocrinologists (AACE) algorithms advocate initiating T2DM treatment with lifestyle modifications and metformin monotherapy. If treatment goals (e.g., lowering plasma glucose, non-glycaemic benefits such as weight loss) have not been reached, diabetes treatment should be intensified after

3 months by introducing a second antidiabetic agent and later a third agent is introduced in a stepwise treatment approach. However, a very large percentage of patients on second-line (81%) or third-line (77%) treatment who do not meet their treatment goal remain on unchanged treatment for 24 months (Adelphi Real World Diabetes DSP XII, 2015).

In newly diagnosed patients who have HbA1c $\geq 9\%$, the ADA recommends initiating dual therapy (Inzucchi et al 2015). However, the AACE algorithm for T2DM management recommends a more intensive approach with initial dual combination therapy for patients with HbA1c $\geq 7.5\%$ and initial dual or even triple combination therapy in patients with HbA1c > 9.0 (Garber et al 2017). Despite these differences, both the EASD/ADA and AACE guidelines highlight the need for individualised treatment where factors such as lifestyle, age, and comorbidities guide treatment plans should be taken into consideration. Patient attributes and preferences are also important in therapeutic decisions (Inzucchi et al 2012; Inzucchi et al 2015).

Nearly half of all T2DM patients require combinations of 2 or more classes of non-insulin, oral antidiabetic agents (Bailey et al 2016), and approximately one-third of them eventually require insulin (Home et al 2014). Among different countries in the EU, the percentage of patients with T2DM who fail to achieve HbA1c $< 7\%$ range from 25.9% in the Netherlands to 68% in the United Kingdom (Adelphi Real World Diabetes DSP XII, 2015, de Pablos-Velasco et al 2014).

The pathophysiologic complexity of T2DM involves changes in multiple key organs together contributing to the development and progression of hyperglycaemia. Because of this complexity, using a combination of antidiabetes agents, which can correct multiple pathophysiological disturbances through complementary mechanisms of actions is more likely to result in sustainable glycaemic control (De Fronzo et al 2013).

The importance of good adherence and persistence with treatments for chronic diseases such as those with T2DM and associated comorbidities is well accepted. Apart from glycaemic control, treatment of T2DM is associated with the use of multiple medications for accompanying disorders such as dyslipidaemia, hypertension, and depression (Bailey and Kodack 2011). As a result, taking multiple drugs simultaneously is common in patients with T2DM. In this context, FCMPs should be considered for improving medication adherence by reducing pill burden, which can translate into better clinical outcomes.

About the product

Qtrilmet is a triple fixed combination medicinal product (FCMP) containing metformin extended release (XR), saxagliptin and dapagliflozin as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM when treatment with metformin, saxagliptin and dapagliflozin is appropriate.

Dapagliflozin is a sodium glucose transporter 2 (SGLT2) inhibitor that inhibits renal glucose reabsorption (and thereby decreases hyperglycaemia) and acts independently of insulin. Saxagliptin is a dipeptidyl peptidase-4 (DPP4) inhibitor that enhances insulin secretion by a glucose-dependent mechanism (via the incretins GLP-1 and GIP). Metformin, which belongs to the biguanide class of drugs, is not chemically or pharmacologically related to any other class of oral antidiabetic drugs (OAD); it decreases hepatic glucose production and intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Dapagliflozin, saxagliptin and metformin, owing to their distinct pharmacology, contribute to the efficacy of Dapa/Saxa/Met XR through complementary mechanisms of action (MOAs), thereby having an additive effect on glycaemic control in T2DM patients.

The FCMP is proposed to be available at the following strengths:

Planned Tablet Strengths - metformin XR/ saxagliptin/ dapagliflozin (mg)	Dosage	Daily Dose- Metformin XR/ saxagliptin/ dapagliflozin (mg)
850/2.5/5	2 tablets once a day	1700/5/10
1000/2.5/5	2 tablets once a day	2000/5/10

With the dual drug combinations, patients who have been prescribed a combination of metformin IR, saxagliptin and dapagliflozin, have to take their medication twice daily, as 3 or more tablets, for glycaemic control; Met XR/Saxa/Dapa would reduce this number to 2 tablets once daily.

Type of Application and aspects on development

The dapagliflozin and saxagliptin mono-components included in the proposed Met XR/Saxa/Dapa formulation are approved within the European Union (EU); dual combinations of dapagliflozin, saxagliptin, and/or metformin are also approved. In the EU, metformin IR is nationally approved although harmonised in a referral procedure; however, FCMPs containing metformin IR are centrally approved. There are a limited number of EU Member States that have approved metformin HCl XR products on a national basis.

The Met XR/Saxa/Dapa clinical development programme was informed by the CHMP Guideline on clinical development of FCMPs and CHMP Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CHMP/EWP/240/95, Rev.1, 2009, CHMP/EWP/1080/00, Rev.1, 2012).

Met XR/Saxa/Dapa is referred to as a modified release tablet, providing an extended release formulation for metformin and immediately release for dapagliflozin and saxagliptin. The Met XR/Saxa/Dapa clinical development programme is consistent with the EMA Guideline on the Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98, Rev. 1, 2010). For metformin the EMA Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1, 2014) also apply.

The QTERN (dapagliflozin and saxagliptin) MAA was submitted in April 2015 (EMA/H/C/004057) and received a positive CHMP opinion on May 2016 and European Commission Decision on 15 July 2016 with the following 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.

The foundation for Met XR/Saxa/Dapa is the dapagliflozin/saxagliptin FCMP (QTERN) MAA (EMA/H/C/004057), clinical development program. In addition, safety and efficacy data from other supporting studies are included in this MAA. Since the FMCP is only indicated in patients already treated with

metformin, i.e. substitution therapy, no additional data on the contribution of the metformin component to the effect of the FMCP is deemed necessary.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a modified-release tablet containing 5 mg/2.5 mg/850 mg or 5 mg/2.5 mg/1000 mg of dapagliflozin/saxagliptin/metformin hydrochloride.

Other ingredients are: croscarmellose sodium, crospovidone, hypromellose, lactose anhydrous, magnesium stearate, microcrystalline cellulose, silica dental type, macrogol, polyvinyl alcohol, titanium dioxide, talc, iron oxide yellow, iron oxide red, iron oxide black.

The product is available in PVC/PCTFE/alu or alu/PVC/alu blister as described in section 6.5 of the SmPC.

2.2.2. Active Substance

Full quality information regarding the active substances dapagliflozin and saxagliptin were provided in the dossier. This information has been previously submitted and assessed with regards to the centrally authorised products Onglyza, Forxiga, Xigduo, Komboglyze and Qtern. For the active substance metformin hydrochloride, the applicant makes use of the EDQM's Certificate of Suitability (CEP) procedure.

2.2.2.1 Dapagliflozin

General information

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

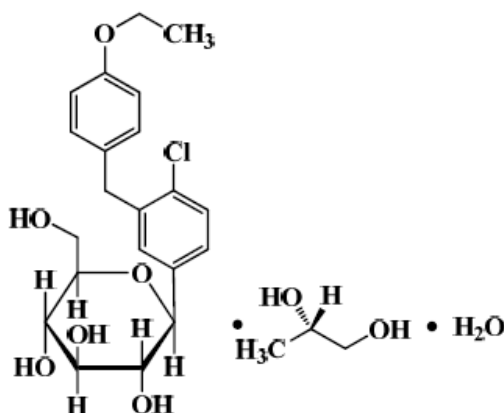


Figure 1: Dapagliflozin active substance structure

The chemical structure of dapagliflozin propanediol was elucidated by a combination of elemental analysis, (UV)-Vis spectroscopy, (IR) spectroscopy, Raman spectroscopy, Nuclear Magnetic Resonance, Mass Spectrometry and X-ray crystallography. The solid state properties and physical characteristics of the active substance have also been determined by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) studies.

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

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. Dapagliflozin is a chiral molecule with five stereogenic centres. The relative and absolute stereochemistry is derived from the chosen starting material and by a stereoselective step during the synthesis.

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 process controls implemented in the manufacturing process of dapagliflozin propanediol ensures the desired crystalline form of the active substance.

Manufacture, characterisation and process controls

The commercial manufacturing process for the synthesis of dapagliflozin propanediol is the same as approved for Forxiga and Qtern. It 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. Process controls including temperature control and the endpoint check for water during the drying step are in place to prevent desolvation during the manufacturing process. Storage and shipment controls are appropriate to ensure the quality of the dapagliflozin propanediol. The reprocessing/reworks presented are considered justified as no new solvents are introduced.

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 route.

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 or VHPLC), assay (HPLC or VHPLC), impurities (HPLC or VHPLC), 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 for total volatiles, benzene, polymorphic form, heavy metals and residue on ignition 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 from three pilot scale batches of dapagliflozin propanediol stored in the intended commercial package up 36 months under long-term conditions (25 °C ± 2 °C/60% ± 5%RH and 30 °C/65% RH), 24 months at 5 °C and 6 months at accelerated conditions (40 °C ± 2 °C/75% ± 5% RH) have been provided. Studies have been carried out in accordance with current ICH guidelines.

Forced degradation studies have been carried out. The different degradation pathways have been identified and presented in the documentation. All the stability results remain within the acceptance limits at all conditions tested, no trends can be observed. The defined re-test period of 36 months with no storage restrictions is considered justified.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 36 months with no storage restrictions in the proposed container.

2.2.2.2 Saxagliptin

General information

The chemical name of saxagliptin monohydrate is (1S,3S,5S)-2-((2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl)-2-azabicyclo[3.1.0]hexane-3-carbonitrile hydrate corresponding to the molecular formula C₁₈H₂₅N₃O₂·H₂O and a relative molecular mass of 333.43 g/mol (315.41 g/mol anhydrous). It has the following structure:

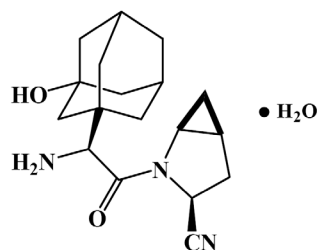


Figure 2: Saxagliptin active substance structure

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 H-1 (free base monohydrate) has been observed to date. An anhydrous crystalline form of the free base (Form N-3) has been characterised. No stable solvate forms have been observed.

Manufacture, characterisation and process controls

The commercial manufacturing process for the synthesis of saxagliptin is the same as approved for Onglyza and Qtern. 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 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). The CPPs defined for the manufacturing process 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 HPLC impurity method used for control of active substance is specific for detecting the three potential diastereoisomers. The omission of routine testing for some residual solvents, water content, polymorphism, heavy and trace metals and isopropyl methanesulfonate (a potential genotoxic impurity) has been satisfactorily justified based on batch data and 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 controlled in the starting materials and do not epimerise 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

Stability data has been provided from three pilot scale batches of saxagliptin manufactured according to a previous (but representative) process, two pilot scale batches manufactured according to current commercial process at the commercial site and three commercial scale batches produced 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.

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 of 36 months when stored in a refrigerator (2-8 °C) is acceptable and remains unchanged in comparison with the already authorised saxagliptin containing products of the same applicant.

2.2.2.3 Metformin Hydrochloride

General information

The chemical name of metformin hydrochloride is 1,1-Dimethylbiguanide hydrochloride corresponding to the molecular formula $C_4H_{12}ClN_5$. It has a relative molecular mass of 165.62 g/mol and the following structure:

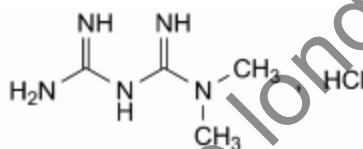


Figure 3: Metformin Hydrochloride active substance structure

Metformin (INN) consists of white crystals, freely soluble in water, slightly soluble in alcohol, practically insoluble in acetone and in methylene chloride. Polymorphism is inexistent. The substance is non-hygroscopic.

As there is a monograph of metformin hydrochloride in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for metformin hydrochloride which has been provided within the current Marketing Authorisation Application (CEP No: R1-CEP 1997-029-REV 04, Holder: Merck Santé s.a.s.).

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Specification

The active substance specification complies with the specifications and test methods of the Ph. Eur. Monograph and the Certificate of Suitability.

The active substance specification includes tests for appearance (visual), filter test (visual), appearance of aqueous solution (Ph Eur), identification (IR), identification of chlorides (Ph Eur), related substances (HPLC), heavy metals (Ph Eur), loss on drying (Ph Eur), sulphated ash (Ph Eur), assay (HPLC) and microbiological testing (Ph Eur).

The analytical methods used are all compendial and satisfactory batch analysis data on three recent manufactured batches is provided. The results are within the specifications and consistent from batch to batch.

Stability

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability. A re-test period of 5 years is included in the Certificate of Suitability.

2.2.3. Finished Medicinal Product

Qtrilmet extended release tablets (Dapa/Saxa/Met XR) are manufactured in the strengths of 5/2.5/850 mg and 5/2.5/1000 mg.

The 5 mg/2.5 mg/850 mg modified-release tablets are beige, biconvex, 11 x 21 mm oval tablets with 3005 debossed on one side. The 5 mg/2.5 mg/1000 mg modified-release tablets are green, biconvex, 11 x 21 mm oval tablet, with 3002 debossed on one side. The tablets will be supplied commercially in either Alu/PVC/Alu blisters or PVC/PCTFE/Alu blisters. Each will be sealed with an aluminium lid foil.

The formulation design principle is a tablet core containing dapagliflozin and metformin HCl (similar to XIGDUO XR) coated with a three-layer film-coating containing saxagliptin (similar to ONGLYZA). In the tablet core, the dapagliflozin is formulated for immediate-release, whereas the metformin HCl is formulated to provide extended release.

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

The starting points for formulation development were the commercial products XIGDUO XR (dapagliflozin and metformin HCl XR, approved in the US 2014) and ONGLYZA (saxagliptin, approved in EU and in the US 2009). Prior knowledge from the development of the commercial combination products, QTERN (dapagliflozin and saxagliptin, approved in EU 2016), XIGDUO (dapagliflozin and metformin HCl, approved in EU 2014), KOMBOGLYZE (saxagliptin and metformin HCl, approved in EU 2011) and KOMBIGLYZE XR (saxagliptin and metformin HCl XR, approved in the US 2010), was also considered since they build on the same active substances and, for most products, the same formulation design principles. The development of these combination products was in turn built on their respective mono-component products. The tablet core of Dapa/Saxa/Met XR 5/2.5/1000 mg (Qtrilmet) and Dapa/Met XR 5/1000 mg (XIGDUO XR) are identical. This core has been commercially manufactured for the US market since 2014.

The quality target product profile (QTPP) is a summary of the quality characteristics which guided the formulation and process development work. The control strategy includes control of input materials, controls of unit operations, in-process controls (IPC), and end-product testing.

The manufacturing process for Dapa/Met XR 5/1000 mg tablet core was already developed and approved in the US. The manufacturing process for Dapa/Met XR 5/850 mg tablet core was developed for EU. The manufacturing process for dapagliflozin stock granules is identical to the process for dapagliflozin stock granules included in the Dapa/Met XR 5/1000 mg tablet core, and no further process development was deemed necessary. The manufacturing processes for metformin XR stock granules and the compaction process for Dapa/Met XR 5/850 mg were developed. The active coating process is similar to processes used

for other commercial products containing saxagliptin. A quality risk assessment (QRA) was conducted to identify risks for patient safety and drug product efficacy when combining dapagliflozin, saxagliptin and metformin HCl in one tablet.

A single method was developed for the dissolution testing of the immediate release dapagliflozin and saxagliptin components, and the extended release metformin component, for both strengths of Qtrilmet. *In vitro* dissolution profiles for dapagliflozin, saxagliptin and metformin from Qtrilmet, FORXIGA, ONGLYZA and GLUCOPHAGE XR were generated in dissolution media across three pH values. The dissolution studies were performed using the validated quality control method. *In vitro* dissolution data for both Qtrilmet tablet strengths support the BE study and results are in line with the dissolution from the individual mono components. The discriminatory power of the dissolution method has been demonstrated.

The compositions used for the primary stability studies and the bioequivalence study are representative of the commercial compositions. The primary packaging is PVC/PCTFE/Alu or Alu/PVC/Alu blister packs as stated in the SmPC. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product;

Manufacture of the product and process controls

The manufacturing process consists of four main steps:

1. Manufacture of metformin XR stock granules
2. Manufacture of dapagliflozin stock granules
3. Compression of Dapa/Met XR tablet cores
4. Coating of Dapa/Met XR cores with saxagliptin film-coat

The in-process controls are included as part of the overall control strategy and are applied to ensure the quality of the finished product throughout the manufacturing process. The metformin hydrochloride + magnesium stearate blend (metformin HCl/MgSt) is considered a drug product intermediate. The in-process controls are adequate for this type of manufacturing process / pharmaceutical form.

The manufacturing process is considered to be a non-standard manufacturing process. The manufacturing process is to an appreciable extent based on knowledge from the commercial products FORXIGA® (Dapagliflozin), ONGLYZA® (Saxagliptin), QTERN® (Dapagliflozin/Saxagliptin), XIGDUO XR® (Dapagliflozin/Metformin XR), KOMBIGLYZE® XR (Saxagliptin/Metformin XR) and KOMBOGLYZE® (Saxagliptin/Metformin IR). Through comprehensive pharmaceutical development work and extensive prior knowledge, a thorough understanding of the manufacturing process has been gained. This has allowed a control strategy to be established ensuring that the critical quality attributes are consistently delivered.

The applicant has presented process validation data of XIGDUO XR (Dapagliflozin/ Metformin HCl XR), QTERN (Dapagliflozin/ Saxagliptin) and KOMBIGLYZE XR (Saxagliptin/ Metformin HCl XR) along with explanation of relevance with the manufacturing process for Qtrilmet tablets. Based on the presented additional data, the prior knowledge of the manufacturer can be considered acceptable to justify the omission of commercial scale validation studies of Qtrilmet modified release tablets manufacturing process before granting the MA. The applicant confirms that prospective full scale process validation will be completed, in line with the approved Process Validation Protocol, prior to commercialization of the finished product from the commercial manufacturing site.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form; description, identification dapagliflozin (LC-UV), identification saxagliptin (LC-UV), identification metformin hydrochloride (LC-UV, IR), assay dapagliflozin (LC-UV), assay saxagliptin (LC-UV), assay metformin hydrochloride (LC-UV), degradation products dapagliflozin (HPLC/UHPLC), degradation products saxagliptin (LC-UV), degradation products metformin hydrochloride (LC-UV), dissolution dapagliflozin, saxagliptin, metformin hydrochloride (LC-UV), content uniformity dapagliflozin (LC-UV), content uniformity saxagliptin (LC-UV), mass variation metformin hydrochloride (Ph. Eur.), water content (KF) and microbiological quality (Ph. Eur.).

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

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 5 batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls.

Batch analysis results are provided for two batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data was presented from six primary stability batches, manufactured at commercial batch size and stored in PVC/PCTFE/Alu and Alu/PVC/Alu blister and stored up to 24 months at long term storage conditions (25 °C/60% RH), intermediate (30 °C/65% RH), 6 months at accelerated (40 °C/75% RH). A matrixing design (in accordance with ICH Q1D 'Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products') was applied for the different pack configurations at the long-term storage condition (25 °C/60% RH).

Stability testing was also performed on product batches stored in simulated bulk containers. In addition, stability data from stressed conditions (photo stability testing and open dish storage at 25 °C/60% RH) are presented to support the recommended storage condition and proposed shelf life of the product.

Stability data for the drug product in Alu/PVC/Alu blister shows all parameters were within the specification limits at the long term condition 25 °C/60% RH. Similarly, the data from accelerated condition (40 °C/75% RH, 6 months) shows no significant change in any of the stability indicating parameters. However, data indicated a slight change in some parameters from initial values. Therefore a statistical evaluation was performed on these parameters. The statistical analysis, based on stability data up to 24 months at long term condition 25 °C/60% RH, supports the proposed shelf life of 30 months without any special storage conditions.

Stability data for the drug product in PVC/PCTFE/Alu blister shows parameters were within the specification limits at the long term condition 25 °C/60% RH. The data from the accelerated condition (40 °C/75% RH, 6 months) did not meet all parameters in the specification which resulted in additional testing (all tests) at intermediate condition (30 °C/65% RH) for up to 12 months. All data from the 30 °C/65% RH condition is well within the specification.

For all parameters showing a change at the accelerated condition 40 °C/75% RH, a statistical analysis of the long term 25 °C/60% RH data was performed. The statistical analysis, based on stability data up to 24 months at long term condition 25 °C/60% RH, supports the proposed shelf life of 2 years when stored at 30 °C.

Adventitious agents

The finished product contains the following material of animal origin: Lactose anhydrous. Lactose anhydrous is derived from milk fit for human consumption. Lactose anhydrous meets the requirements of the CPMP Guideline 'Note for Guidance on Minimising Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products' (EMA/410/01).

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

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

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendation(s) for future quality development

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:

- At least one batch of each product strength will be placed into the annual stability program. In case of any adverse results this will be reported to the regulatory authorities.

2.3. Non-clinical aspects

2.3.1. Introduction

Qtrilmet combines the 3 oral antihyperglycaemic agents metformin hydrochloride, saxagliptin and dapagliflozin. It will be available as modified-release tablets containing 850 mg metformin hydrochloride/2.5 mg saxagliptin/5 mg dapagliflozin, or 1000 mg metformin hydrochloride/2.5 mg saxagliptin/5 mg dapagliflozin.

The pharmacological profiles of metformin hydrochloride, 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 the EU as monotherapy and in combination with other medicinal products.

The individual toxicities of dapagliflozin, saxagliptin and metformin as single entities as well as dual FCMP have been established in comprehensive developmental programs including studies of in vitro, in vivo PD, safety pharmacology, PK, TK and toxicity. These have been evaluated as parts of previous approval processes which were referred to in the application.

2.3.2. Pharmacology

Primary and secondary pharmacodynamic studies

No studies on the primary and secondary pharmacodynamics of Met XR/Saxa/Dapa fixed dose combination have been performed. Each compound contributes via different mechanisms to normalise the glucose concentration in plasma in type II diabetes patients.

Dapagliflozin is a novel SGLT2 inhibitor developed for the treatment of type2 diabetes. SGLT2 is the major luminal glucose transporter responsible for the reabsorption of glucose from the renal glomerular filtrate and its inhibition leads to substantial urinary excretion of glucose. Administration of dapagliflozin in mice and normal and diabetic rats increases the urinary excretion of glucose resulting in decreased serum glucose. These effects have also been observed in patients administered dapagliflozin.

DPP4 is the enzyme responsible for the inactivation of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Incretin hormones are gastrointestinal hormones that increase insulin secretion in response to enteral stimulation. These hormones contribute to the control of postprandial glucose excursions in a glucose dependent manner, which mitigates the risk of hypoglycaemia. In addition to enhanced postprandial insulin release, GLP-1 also reduces glucagon release from the pancreatic α -cells, thereby reducing hepatic glucose production. This effect is also glucose-dependent, such that when plasma glucose is normal or low, the counter-regulatory response of glucagon release is not impaired.

A comprehensive set of nonclinical studies has been established for metformin. Metformin acts by decreasing hepatic glucose production and intestinal absorption of glucose and improving insulin sensitivity by increasing peripheral glucose uptake and utilization. These effects have been demonstrated in both experimental animals and in patients.

Based on the different mechanisms that these substances exert their pharmacological effects no adverse pharmacodynamics interactions are expected.

Safety pharmacology programme

No specific safety pharmacology studies were conducted with the triple combination of dapagliflozin, saxagliptin and metformin. In vitro and in vivo safety pharmacology studies evaluating the cardiovascular, central nervous, and respiratory systems were previously conducted for dapagliflozin or saxagliptin. There were no adverse effects indicative of potential human safety concerns for either of these two drugs. Furthermore, assessments of effects on CNS and respiratory systems were evaluated for the dual

combinations dapagliflozin and metformin, saxagliptin and metformin and saxagliptin and dapagliflozin, and were concluded to have no concerns for human safety.

Therefore, evaluation of the triple combination of dapagliflozin, saxagliptin and metformin in a full battery of safety pharmacology studies was considered unwarranted. It is unlikely that the administration of the combination of the three drugs will result in significant safety concerns.

Pharmacodynamic drug interactions

Metformin, saxagliptin and dapagliflozin were all 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 and the available clinical data in patients with the 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

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. In humans, the major circulating metabolite is dapagliflozin 3-O-glucuronide (BMS-801576); while in animals, BMS-801576 is only a minor metabolite with the majority of the metabolites formed by oxidative metabolism. Human UGT1A9, which is preferentially expressed in human liver and kidney, is the major enzyme responsible for the formation of BMS-801576. In vitro profiling of the enzymes and transporters typically responsible for drug metabolism and disposition suggest that dapagliflozin has a low potential to inhibit these enzymes and transporters. Dapagliflozin is a weak P-gp substrate; however, since dapagliflozin's membrane permeability is high, little potential exists for its absorption and disposition to be affected by P-gp inhibitors. Also, UGT1A9 inhibitors and inducers could affect dapagliflozin exposures.

Saxagliptin is rapidly absorbed following oral administration in all species including human, and systemic exposure of saxagliptin in mouse, rat, dog, and monkey was comparable to or exceeding that in human. Saxagliptin is rapidly and primarily excreted in human urine mainly as a mixture of saxagliptin and its metabolite, 5-OH saxagliptin (BMS-510849), whereas urine and faeces were the primary routes of excretion in rats, dogs, and monkeys. All metabolites identified in human plasma were found in mouse, rat, dog, and monkey plasma; saxagliptin was primarily metabolized to BMS-510849 in these species, and together saxagliptin and BMS-510849 comprised the most abundant drug-related plasma components. In humans, CYP3A4 was identified as the major enzyme responsible for the formation of BMS-510849 from saxagliptin. Neither saxagliptin nor BMS-510849 induced CYP1A2, 2B6, 2C9 or 3A4 in primary human hepatocytes nor inhibited CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A4/5 in pooled human liver microsomes.

Metformin (also known as BMS-207150) is also an oral anti-diabetic drug, but of the biguanide class. A comprehensive set of nonclinical studies in pharmacokinetic evaluations similar to those described for dapagliflozin and saxagliptin has also been established for metformin. Therefore, no additional non-clinical studies have been conducted with metformin as an individual component.

No specific nonclinical or clinical drug-drug interaction studies were conducted with the triple combination of metformin, saxagliptin and dapagliflozin as an FCMP. Given the lack of clinical and non-clinical interactions between dapagliflozin and saxagliptin, or dapagliflozin with metformin or saxagliptin with metformin, the potential for drug-drug interaction with this triple combination is low. It is unlikely that the administration of the combination of metformin, saxagliptin and dapagliflozin will result in meaningful drug-drug interactions, either with one another or with other concomitant medications.

2.3.4. Toxicology

Single dose toxicity

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

Repeat dose toxicity

The toxicity observed in repeat-dose studies in rats, mice and dogs show that dapagliflozin decreased body weight/body gains. In rats an increase in serum calcium with associated tissue mineralization and increased bone formation was observed at very high exposure (>2000 x relative to MRHD). The toxicity concerns from repeat-dose studies of saxagliptin includes gastrointestinal toxicity characterized by blood/mucoid faeces and enteropathy (dogs (AUC 19x and 580x respectively) and erosive and/or ulcerative skin lesions (monkeys AUC 1 to 3 x). Metformin adverse findings includes increase incidence of minimal necrosis and inflammation of parotid salivary glands, body weight loss and minimal metabolic acidosis at doses >600 mg/kg/day in rats.

Moreover, the applicant has previously conducted repeat-dose toxicity studies for the dual combinations as part of approval processes for Qtern (3 months rat study), Xigafuze (3 months rat study) and Komboglyze (2 week and 3 months studies in dogs). No toxicokinetic interactions or any additive or synergistic toxicity were observed. Taken together the extensive studies done in the previous approval processes of the compound additional repeat-toxicity studies of Met/Saxa/Dapa are considered unwarranted.

Notably, metformin and the dual FCMPs with metformin approved in EU all include metformin with an immediate release (IR), whereas Met/Saxa/Dapa is a tablet where an extended (XR) release of metformin has been developed. No toxicity studies with Met XR tablets (alone or in FCMP) were submitted. Since metformin XR is absorbed more slowly than metformin IR i.e. have a longer GI residence an alteration in Met induced GI-toxicity (diarrhoea, dyspepsia, flatulence) may be noted. Clinical studies have shown that the use of metformin XR decrease the risk of GI side effects as compared to metformin IR (Blonde 2004) (Davidson 2004) (Kim 2012). Moreover, FCMP with metformin XR have been approved by FDA (Kombiglyze XR and Xigduo XR), and there are single metformin XR preparations approved in some EU countries where no GI or any other clinical concerns have been raised. The applicant provides a clinical human study comparing the safety of metformin IR and metformin XR where no safety concerns were noted, and hence no toxicity studies including metformin XR are considered warranted.

Genotoxicity

No genotoxicity studies were conducted with the metformin/saxagliptin/dapagliflozin fixed-dose combination. Individually, neither metformin, 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 metformin/saxagliptin/dapagliflozin fixed-dose combination. Individually, neither metformin, neither saxagliptin nor dapagliflozin was shown to be carcinogenic in rodents. There is sufficient knowledge 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 metformin/saxagliptin/dapagliflozin fixed-dose combination. In accordance with ICH M3 (R2), combination carcinogenicity studies are generally not recommended to support marketing of FDC if the individual agents have been tested according to current standards. No additional studies are considered necessary.

Reproduction Toxicity

No adverse effects on fertility or early embryonic development were previously observed with the individual compounds at clinically relevant exposures.

Both saxagliptin and dapagliflozin have shown to in embryo-foetal development studies to be toxic at very high doses and Met/Saxa/Dep is not recommended in WOCBP. During embryonic foetal development reduction in skeletal ossification was observed for saxagliptin and dapagliflozin was associated with an increased incidence and/or severity of renal pelvic and tubular dilatations in off-spring. Combination studies are not recommended as a potential human developmental hazard has already been identified.

These findings have been adequately reflected in sections 4.6 and 5.3 of the Qtrilmet SmPC and the Package Leaflet.

Toxicokinetic data

Toxicokinetics were assessed as a part of toxicity studies.

The AUC for dapagliflozin was decreased only at high doses of metformin used in the 7-day range-finding study in the rat. In the 3-month combination study in the rat, dapagliflozin did not affect metformin AUC and C_{max} nor did metformin affect dapagliflozin AUC and maximum concentration (C_{max}).

Systemic plasma exposures to saxagliptin, its major active metabolite, BMS-510849, and metformin were assessed in dogs and pregnant rats and rabbits following oral administration of saxagliptin in combination with metformin. In dogs, exposures to saxagliptin, BMS-510849, and metformin were similar regardless of individual or combination dosing, with no gender-related difference or accumulation. No toxicokinetic interaction was apparent in the rat at the lower dose of metformin in combination with saxagliptin (25/200 mg/kg/day, respectively). When the same saxagliptin dose was administered to rats with a higher metformin dose (600 mg/kg/day), there was a 46-70% decrease in C_{max} for saxagliptin and BMS-510849, with no substantive effect on AUC. Likewise, there was no effect on metformin exposure at either dose. In pregnant

rabbits, exposures to saxagliptin, BMS-510849, and metformin were similar regardless of individual or combination dosing.

Toxicokinetic parameters of the saxagliptin/dapagliflozin fixed-dose combination were obtained in the 3-month repeated dose toxicity in rats. Dapagliflozin at 0.4 mg/kg/day and saxagliptin at 2 mg/kg/day were administered individually and as a combination. 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 7x the MRHDs for both compounds.

No specific toxicological studies were conducted with the triple combination of Dapa/Saxa/Met. Given the lack of toxicological interactions between dapagliflozin and saxagliptin, or dapagliflozin with metformin or saxagliptin with metformin, the potential for drug-drug interaction with this triple combination is low.

Local Tolerance

The intended clinical route of administration is oral therefore no local tolerance studies have been conducted with the combination, which is agreed.

Other toxicity studies

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

The combination of metformin, 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

The applicant has provided individual environmental risk assessments for dapagliflozin, saxagliptin and metformin, including study reports. The same studies, mainly performed in 2011-2012, have been used for PBT assessment, for characterization of physical-chemical properties, fate and effects. A recently published detailed review of available fate data for metformin was submitted and used in the risk assessment.

The risk of an adverse environmental impact (Phase II assessment), resulting from use of each API for the treatment of adult patients with T2DM, has already been evaluated and approved by EMA for the different monotherapy and dual fixed dose combination products. The introduction of this modified release FDC is not expected to result in an increase in environmental exposure.

However, available recent literature data indicates that metformin may cause reproductive effects in fish and the applicant was asked to further update the ERA for metformin by focussing on effects on reproduction and to provide a fish full life cycle test for an appropriate PNEC value to be established.

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

A fish extended one generation reproduction test in accordance with OECD240, or any other suitable study, investigating possible reproductive effects in fish of metformin should be conducted and submitted post-approval.

Table 1. 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		Log Pow = 2.34 at pH 7		
				Potential PBT: No		
PBT-assessment						
Parameter		Result relevant for conclusion		Conclusion		
		No potential for PBT, tests not performed				
PBT-statement :		The compound is not considered as PBT nor vPvB				
Phase I						
Calculation		Value	Unit	Conclusion		
PEC _{surfacewater} , default or refined (e.g. prevalence, literature)		Default: 0.05 ($F_{pen} = 0.01$) Refined: 0.14 ($F_{pen} = 0.028$)	µg/L	> 0.01 threshold: Yes		
Other concerns (e.g. chemical class)		-	-	No		
Phase II Physical-chemical properties and fate						
Study type		Test protocol	Results		Remarks	
Hydrolysis		OECD 111	<10% Day 5 (pH 5 and 7) 11.5% Day 5 (pH 9) $t_{1/2}$ at 25°C ≥ 1 year			
Adsorption-Desorption		(OECD 106) OPPTS 835.1110	$K_d = 51$ $K_{oc} = 138$		Test was performed with one sludge sample $K_d < 3700$ $K_{oc} < 10000$ No assessment of the terrestrial compartment is required in Tier B	
Ready Biodegradability Test		OECD 301F	Negligible biodegradation (day 28: 11 %)		Not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems		OECD 308	DT _{50, whole system} = 128 / 94 respectively for high and low organic matter vessels Peak % shifting to sediment = 78 % / 45 % by day 15		As the total radioactivity associated with the sediment exceeded 10 %, the toxicity of dapagliflozin to sediment-dwelling organisms was investigated in Tier B. Dapagliflozin is potentially persistent in sediments.	
Phase IIa Effect studies						
Study type		Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/Species: green algae <i>Pseudokirchneriella</i>		OECD 201	NOEC	37000	µg/L	LOEC = 67000 (growth rate)

<i>subcapitata</i>					
<i>Daphnia magna</i> Reproduction Test	OECD 211	NOEC	10000	µg/L	21 day LOEC >10000 µg/L
Fish, Early Life Stage Toxicity Test/ <i>Species: Pimephales promelas</i>	OECD 210	NOEC	1000	µg/L	Species 32 day LOEC >1000 µg/L
Activated Sludge, Respiration Inhibition Test	OECD 209	(EC) NOEC	200 000	µg/L	3 hour EC ₅₀ > 200000 µg/L
<p>PECsurfacewater = 0.14 µg/L PNECmicroorganism = 20000 µg/L PNECsurfacewater = 100 µg/L PECgroundwater = 0.035 µg/L PNECgroundwater = 1000 µg/L</p> <p>PECsurfacewater/PNECmicroorganism = 7.0×10^{-6} (<0.1): Dapagliflozin is unlikely to present a risk to microorganisms PECsurfacewater/PNECsurfacewater = 1.4×10^{-3} (<1): Dapagliflozin is unlikely to present a risk to organisms in surface water PECgroundwater/PNECgroundwater = 3.5×10^{-5} (<1): Dapagliflozin is unlikely to present a risk to the groundwater environment</p>					
Phase IIb Studies					
Sediment dwelling organism	OECD 2018	NOEC	150	mg/kg	<i>Chironomus riparius</i> LOEC >150mg/kg
<p>PECsediment = 2.44 µg/kg (normalised to 10% o.c.) PNECsediment = 6250 µg/kg (NOEC from the Chironomus test (normalised to 10% o.c.) / 100)</p> <p>PEC/PNECsediment = 3.9×10^{-4} (<1): Dapagliflozin is unlikely to present a risk to the sediment environment</p>					

Substance (INN/Invented Name): SAXAGLIPTIN			
CAS-number (if available): 945667-22-1			
PBT screening		Result	Conclusion
<i>Bioaccumulation potential</i> - log K _{ow}	OECD107	LogD _{ow} = -1.74 at pH 4 LogD _{ow} = 0.114 at pH 8.2 LogD _{ow} = 0.169 at pH 9	Potential PBT: No
PBT-assessment			
Parameter	Result relevant for conclusion	No potential for PBT, tests not performed	Conclusion
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	Value	Unit	Conclusion
PEC _{surfacewater} default or refined (e.g. prevalence, literature)	Default: 0.025 (F _{pen} = 0.01) Refined: 0.07 (F _{pen} = 0.028)	µg/L	> 0.01 threshold: Yes
Other concerns (e.g. chemical class)	-	-	No
Phase II Physical-chemical properties and fate			
Study type	Test protocol	Results	Remarks
Water Solubility		46.9 g/L at pH 6.94	
Hydrolysis,	OECD 111	DT ₅₀ at pH 7 = 34.5 days DT ₅₀ at pH 9 = 41.0 days	
Adsorption-Desorption	OECD 106	<i>High organic carbon (sludge sample)</i>	Individual results, soil samples:

		$K_d = 19.6$ $K_{oc} = 71.6$ Low organic carbon (mean of 5 soil samples) $K_d = 13.7$ $K_{oc} = 700$	K_d 22.2 K_{oc} 525 K_d 9.08 K_{oc} 857 K_d 19.3 K_{oc} 992 K_d 7.48 K_{oc} 209 K_d 10.2 K_{oc} 915 Sludge K_d <3700 Sludge K_{oc} <10000 No assessment of the terrestrial compartment is required in Tier B		
(Ready Biodegradability Test) Aerobic Biodegradation Test	(OECD 301) OECD 310	5.9 % of degradation occurred by Day 28	Not readily biodegradable		
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, \text{water}} = 18.0-23.2$ days $DT_{50, \text{sediment}} =$ not assessed $DT_{50, \text{whole system}} = 20-31.5$ days The average amount of sediment-bound residue was 20.3 to 41.2 % at day 102. Four major degradation products, each accounting of > 10 %, were observed.	As the total radioactivity associated with the sediment exceeded 10 %, the toxicity of saxagliptin to sediment-dwelling organisms was investigated in Tier B		
Phase IIa Effect studies					
Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test <i>Pseudokirchneriella subcapitata</i>	OECD 201	NOEC	21000	µg/L	$E_r C_{50} > 140000$ LOEC = 54000
<i>Daphnia magna</i> Reproduction Test	OECD 211	NOEC	35000	µg/L	21 day LOEC = 94000 µg/L
Fish, Early Life Stage Toxicity Test <i>Pimephales promelas</i>	OECD 210	NOEC	9500	µg/L	32 day LOEC > 9500 µg/L
Activated Sludge, Respiration Inhibition Test	OECD 209	(EC_{10}) NOEC	82100 0	µg/L	3 hour EC_{50} > 1000000 µg/L
PECsurfacewater = 0.07 µg/L PNECmicroorganism = 82100 µg/L PNECsurfacewater = 950 µg/L PECgroundwater = 0.0175 µg/L PNECgroundwater = 3500 µg/L PECsurfacewater/PNECmicroorganism = 8.5×10^{-7} (<0.1): Saxagliptin is unlikely to present a risk to microorganisms PECsurfacewater/PNECsurfacewater = 7.4×10^{-5} (<1): Saxagliptin is unlikely to present a risk to organisms in surface water PECgroundwater/PNECgroundwater = 5.0×10^{-6} (<1): Saxagliptin is unlikely to present a risk to the groundwater environment					
Phase IIb Studies					
Sediment dwelling organism <i>Chironomus riparius</i>	OECD 218	NOEC	6.4	mg/kg	28 day LOEC = 16 mg/kg dry sediment
PECsediment = 5.15 µg/kg (normalised to 10% o.c.) PNECsediment = 356 µg/kg (NOEC from the Chironomus test (normalised to 10% o.c.) / 100) PEC/PNECsediment = 1.4×10^{-2} (<1): Dapagliflozin is unlikely to present a risk to the sediment environment					

Substance (INN/Invented Name): METFORMIN HYDROCHLORIDE			
CAS-number (if available): 1115-70-4			
PBT screening		Result	Conclusion
Bioaccumulation potential- log K_{ow}	OECD107	log K_{ow} = -1.43 log D_{ow} < -2.48	Potential PBT: No
PBT Assessment			
Parameter	Result relevant for conclusion	No potential for PBT, tests not performed	Conclusion
PBT-statement:		<i>The compound is not considered as PBT nor vPvB</i>	
Phase I			
Calculation	Value	Unit	Conclusion
PEC _{surfacewater} , default or refined (e.g. prevalence, literature)	Default: 10 ($F_{pen} = 0.01$) Refined: 28 ($F_{pen} = 0.028$)	$\mu\text{g/L}$	> 0.01 threshold: Yes
Other concerns (e.g. chemical class)			No
Phase II Physical-chemical properties and fate			
Study type	Test protocol	Results	Remarks
Hydrolysis	OECD 111	None at pH 5 and 50°C 1% at pH 7 and 50°C 1% at pH 9 and 50°C $t_{1/2}$ at 25°C ≥ 1 year	
Adsorption-Desorption in sludge	FDA 3.08	$K_d = 10.3$ $K_{oc} = 32.1$	$K_d < 3700$ $K_{oc} < 10000$ No assessment of the terrestrial compartment is required in Tier B
Adsorption-Desorption in soil	OECD 106	Geomean of 10 soils: $K_d = 65.8 \text{ L/kg}$	
Ready Biodegradability Test	FDA 3.11	Negligible biodegradation (day 28: 0.6%)	Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT_{50} aqueous system = 3.52 – 37.46 in high and low organic matter vessels respectively $DT_{50, total system} = 6.59$ and 55 for high and low organic matter vessels respectively	Metformin hydrochloride increased in the sediment up to a maximum of 13.8% by day 102. As the total radioactivity associated with the sediment exceeded 10%, the toxicity of metformin hydrochloride to sediment-dwelling

					organisms is investigated in Tier B.
Phase IIa Effect studies					
Study type	Test protocol	Endpoint	value	Unit	Remarks
Microbial Inhibition Test <i>Anabaena flos-aquae</i>	FDA 4.02	NOEC	80000	µg/L	Most sensitive of 7 tested species LOEC (MIC) = 100000 µg/L
Algae, Growth Inhibition Test <i>Pseudokirchneriella subcapitata</i>	OECD 201	NOEC	10000 0	µg/L	LOEC > 100000 µg/L
<i>Daphnia magna</i> Reproduction Test	OECD 211	NOEC	67000	µg/L	21 day LOEC = 140000 µg/L
Fish, Early Life Stage Toxicity Test <i>Pimephales promelas</i>	OECD 210	NOEC	10000	µg/L	32 day LOEC > 10000 µg/L
PECsurfacewater = 28 µg/L PNECmicroorganism = 8000 µg/L PNECsurfacewater = 1000 µg/L PECgroundwater = 7 µg/L PNECgroundwater = 6700 µg/L PECsurfacewater/PNECmicroorganism = 3.5×10^{-3} (<0.1): Metformin hydrochloride is unlikely to present a risk to microorganisms PECsurfacewater/PNECsurfacewater = 2.8×10^{-2} (<1): Metformin hydrochloride is unlikely to present a risk to organisms in surface water PECgroundwater/PNECgroundwater = 1.0×10^{-3} (<1): Metformin hydrochloride is unlikely to present a risk to the groundwater environment					
Phase IIb Studies					
Toxicity to <i>Chironomus riparius</i>	OECD 218	NOEC	100	mg/kg	28 d LOEC > 100 mg/kg dry sediment, (development rate and emergence)
PECsediment = 694 µg/kg (based on default PECsurfacewater to account for conservatism in ERA) PNECsediment = 1000 µg/kg (NOEC from the Chironomus test / 100) PEC/PNECsediment = 0.69 (<1): Metformin hydrochloride is unlikely to present a risk to the sediment environment					

2.3.6. Discussion on non-clinical aspects

No new non-clinical studies have been done in relation to this application. Considering that dapagliflozin, saxagliptin and metformin are approved products as single entities and as fixed dual combinations, it is agreed that no further non-clinical studies are needed. The components all exhibit different pharmacodynamics effects and hence no pharmacodynamic interactions are expected. Moreover the pharmacokinetics has been assessed with dual combinations and no interactions have been observed and therefore no pharmacokinetic interactions are expected with the three compounds.

There were no safety concerns identified in the repeat-dose toxicity studies conducted with the different dual combinations, and no safety concerns are expected with the metformin/saxagliptin/dapagliflozin combination.

AstraZeneca AB acknowledges the recommendations identified by the CHMP and indicated their willingness to address and implement these recommendations in the ongoing development of the medicinal product. A fish extended one generation reproduction test in accordance with OECD240, or any other suitable study, will be conducted post-authorisation to investigate possible reproductive effects in fish of metformin.

2.3.7. Conclusion on the non-clinical aspects

There are no non-clinical effects expected that preclude the safe administrations of the triple modified release fixed dose combination to the adult patients at doses up to 2000 mg metformin 5 mg saxagliptin and 10 mg dapagliflozin, respectively.

There are no objections to an approval of Qtrilmet from a non-clinical perspective.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 1 Phase 3/4 clinical studies in the Met XR/Saxa/Dapa clinical development programme

Study ID	# Study centers and locations	Design and duration	Study objective Primary endpoint	Treatment groups	# Subjects by arm Randomised/ completed	Sex M/F Mean age (range) at study start	Diagnosis Main inclusion criteria
CV181169 (Pivotal)	145 centers in 8 countries	Randomised double-blind, active-controlled, parallel group, multicenter study 24 weeks of randomised treatment	Efficacy and safety Change in HbA1c from baseline to Week 24	Dapagliflozin 10 mg + saxagliptin 5 mg + metformin ≥ 1500 mg Saxagliptin 5 mg + metformin ≥ 1500 mg Dapagliflozin 10 mg + metformin ≥ 1500 mg	Dapagliflozin + saxagliptin + metformin: 179/169 Saxagliptin + metformin: 176/161 Dapagliflozin + metformin: 179/160	268/266 (randomised subjects) 53.8 (24 to 81) years	T2DM Men and women ≥ 18 years with inadequate glycaemic control (HbA1c $\geq 8.0\%$ and $\leq 12.0\%$ at screening) under current metformin therapy stable at ≥ 1500 mg for at least 8 weeks prior to screening
CV181168 (Pivotal)	79 centers in 9 countries	Randomised, double-blind, placebo-controlled, parallel-group, multicenter study 24 weeks of randomised treatment followed by a 28-week extension period	Efficacy and safety Change in HbA1c from baseline to Week 24	Saxagliptin 5 mg + dapagliflozin 10 mg + metformin IR ≥ 1500 mg per day Placebo + dapagliflozin 10 mg + metformin IR ≥ 1500 mg per day	Saxagliptin + dapagliflozin + metformin: 153/142 Placebo + dapagliflozin + metformin: 162/156 Entered/completed the LT extension period: Saxagliptin + dapagliflozin + metformin: 142/133; Placebo + dapagliflozin + metformin: 155/147	149/166 (randomised subjects) 54.6 (27 to 78) years	T2DM Men and women ≥ 18 years with inadequate glycaemic control (HbA1c $\geq 7.0\%$ and $\leq 10.5\%$ at randomisation) under current metformin therapy stable at ≥ 1500 mg for at least 8 weeks prior to screening

Study ID	# Study centers and locations	Design and duration	Study objective Primary endpoint	Treatment groups	# Subjects by arm Randomised/ completed	Sex M/F Mean age (range) at study start	Diagnosis Main inclusion criteria
MB102129 (Pivotal)	55 centers in 8 countries	Randomised, double-blind, placebo-controlled, parallel group, multicenter study	Efficacy and safety Change in HbA1c from baseline to Week 24 24 weeks of treatment followed by a 28-week extension	Dapagliflozin 10 mg + Saxagliptin 5 mg + metformin ≥ 1500 mg per day Placebo + Saxagliptin 5 mg + metformin ≥ 1500 mg per day	Dapagliflozin + saxagliptin + metformin: 160/148 Placebo + saxagliptin + metformin: 160/153 Entered/completed the LT extension period: Dapagliflozin + saxagliptin + metformin: 147/141; Placebo + saxagliptin + metformin: 147/140	54%/44% Mean age was 55 years	T2DM Men and women ≥ 18 years with inadequate glycaemic control under current metformin therapy stable at ≥ 1500 mg for at least 8 weeks prior to screening <u>Stratum A</u> – HbA1c $\geq 8.0\%$ and $< 9.0\%$ at randomisation <u>Stratum B</u> – HbA1c $\geq 7.5\%$ and $\leq 10.5\%$ at randomisation
CV181365 (Supportive)	87 centers in 10 countries	Randomised, double-blind, active controlled, parallel group, multicenter study 52 weeks of randomised treatment followed by a 104-week extension period	Efficacy and safety Change in HbA1c from baseline to Week 24	Dapagliflozin 10 mg + saxagliptin 5 mg + metformin ≥ 1500 mg Glimepiride 1-6 mg + metformin ≥ 1500 mg	Dapagliflozin + saxagliptin + metformin: 227/197 Glimepiride + metformin: 217/188	218/225 56.1 (27 to 78) years	T2DM Men and women ≥ 18 years with inadequate glycaemic control (HbA1c $\geq 7.5\%$ and $\leq 10.5\%$ at randomisation) under current metformin therapy stable at ≥ 1500 mg for at least 8 weeks prior to screening.

Study ID	# Study centers and locations	Design and duration	Study objective Primary endpoint	Treatment groups	# Subjects by arm Randomised/ completed	Sex M/F Mean age (range) at study start	Diagnosis Main inclusion criteria
D1689 C00014 (Supportive)	194 centers in 5 countries	Randomised, double-blind, active-controlled, parallel group, multicenter study	Efficacy and safety Change from baseline in HbA1c at Week 52	Dapagliflozin 10 mg + placebo (saxa) + placebo (glim) + metformin ≥ 1500 mg per day Dapagliflozin 10 mg + 5mg saxagliptin + Placebo (glim) + metformin ≥ 1500 mg per day Placebo (dapa) + placebo (saxa) + 1-6 mg glimepiride + metformin ≥ 1500 mg per day	Dapagliflozin + placebo (saxa) + placebo (glim) + metformin 314/281 Dapagliflozin+ 5 mg saxagliptin + Placebo (glim) + metformin 312/298 Placebo (dapa) + placebo (saxa) + glimepiride + metformin 313/ 288	339/600 58.4 (31 to 75) years	T2DM Men and women ≥ 18 to >75 years with inadequate glycaemic control (HbA1c $\geq 7.5\%$ and $\leq 10.5\%$ at randomisation) under current metformin therapy stable at ≥ 1500 mg for at least 8 weeks prior to Enrolment visit.
CV181369 (Supportive)	112 centers in 11 countries	Randomised, open-label, active-controlled, parallel group, multicenter study 24 weeks of treatment followed by a 28-week extension	Efficacy and safety Change in HbA1c from baseline to Week 24	Dapagliflozin 10 mg + saxagliptin 5 mg + metformin (≥ 1500 mg) \pm SU Insulin glargine + metformin (≥ 1500 mg) \pm SU	Dapagliflozin + saxagliptin + metformin \pm SU: 324/298 Insulin + metformin \pm SU: 326/286	347/296 55.5 (25 to 80) years	T2DM Men and women ≥ 18 years with inadequate glycaemic control (HbA1c $\geq 8.0\%$ and $\leq 12.0\%$ at randomisation) under current metformin therapy stable at ≥ 1500 mg for at least 8 weeks prior to screening

Study ID	# Study centers and locations	Design and duration	Study objective Primary endpoint	Treatment groups	# Subjects by arm Randomised/ completed	Sex M/F Mean age (range) at study start	Diagnosis Main inclusion criteria
CV181363 (Safety)	87 centers in 6 countries	Randomised, double-blind, active-controlled, parallel group, multicenter study 26 weeks of treatment followed by a 26-week extension	Efficacy and safety Change in HbA1c from baseline to Week 26	Dapagliflozin 10 mg + saxagliptin 5 mg + metformin ≥ 1500 mg per day Sitagliptin 100 mg + metformin ≥ 1500 mg per day	Dapagliflozin + saxagliptin + metformin 232/213 Sitagliptin + metformin 229/198 Entered/completed the LT extension period: Dapagliflozin + saxagliptin + metformin 209/198 Sitagliptin + metformin 193/180	45.6%/54.4% mean age was 55.9 years	T2DM Men and women ≥ 18 years with inadequate glycaemic control (HbA1c $\geq 8.0\%$ and $\leq 10.5\%$ at randomisation) under current metformin therapy stable at ≥ 1500 mg for at least 8 weeks prior to enrollment
D1683 C00005 (Safety)	119 centers in 6 countries	Randomised double-blind, active-controlled, parallel-group, multicenter study 24 weeks of randomised treatment	Efficacy and safety Change in HbA1c from baseline to Week 24	Dapagliflozin 5 mg + saxagliptin 5 mg + metformin ≥ 1500 mg Saxagliptin 5 mg + metformin ≥ 1500 mg Dapagliflozin 5 mg + metformin ≥ 1500 mg	Dapagliflozin + saxagliptin + metformin: 293/256 Saxagliptin + metformin: 296/243 Dapagliflozin + metformin: 294/255	451/419 56.7 (21 to 88) years	T2DM Men and women ≥ 18 years with inadequate glycaemic control (HbA1c $\geq 7.5\%$ to $\leq 10.0\%$ at screening) under current metformin therapy stable at ≥ 1500 mg for at least 8 weeks prior to screening

CSR Clinical study report; DPP4 Dipeptidyl peptidase 4; F Female; HbA1c Glycated haemoglobin A1c; IR Immediate release; LT Long-term; M Male; ST Short-term; SU Sulphonylurea; XR Extended release.

Table 2 Overview of studies included in the clinical pharmacology package

Description	n	Dose	Study no	Included in previous procedures
BE	126	Dapagliflozin 5 mg/ Saxagliptin 2.5 mg/ Metformin 1000 mg	D168AC00002	-
DDI - Saxa/Met		Saxagliptin 100 mg Metformin 1000 mg	CV181017	EMA/H/C/1039 (Onglyza®) 2009
DDI - Dapa/Met	18	Dapagliflozin 20 mg Metformin 1000 mg	MB102026	EMA/H/C/2322 (Forxiga®) 2011
DDI - Dapa/Saxa	72	Dapagliflozin 10 mg Saxagliptin 5 mg	CV181191	EMA/H/C/4057 (Qtern®) 2015
Supplied on request				
Publication BE - Glucophage® Merck (EU ref) and Glucophage® BMS (US ref)	56	Metformin 500 mg, 1000 mg	J Bioequiv Availab	2014
Relative F FCMP - saxa/met XR vs saxa + met (Merck) or metformin SR (Merck)	28	2.5/1000 mg 2.5 mg + 1000 mg 1000 mg	CV181209	2013
Relative F Glucophage XR® (BMS), Glucophage SR (Merck)	36	Metformin 500 mg	CV138088	2003
Steady state PK Modified release vs Glucophage bid	16	Metformin 500 - 2000 mg od 1000 mg bid	CV138028	1998
Relative F Xigduo™ XR steady state		Dapagliflozin/Metformin 10/1000 mg od	MB102092	2012

Glucophage (Merck) - immediate release, EU reference; Glucophage (BMS) - immediate release, US reference; Glucophage XR - modified release BMS, US reference; Glucophage SR - modified release Merck, available in some EU MS; Xigduo™ XR - FDC dapagliflozin/metformin XR

2.4.2. Pharmacokinetics

Introduction

This is a full application of a fixed combination medicinal product (FCMP) of three known compounds dapagliflozin, saxagliptin and metformin intended for treatment of type 2 diabetes mellitus (T2DM). The individual components are licensed in EU as mono-components and as dual FCMP tablets. A limited number of member states have approved Glucophage SR® for once daily dosing. Metformin should be taken together with food while dapagliflozin and saxagliptin can be either with or without.

Evaluation of bioequivalence between co-administration of mono-components and administration of the triple FCMP has been assessed in the current procedure. Basic PK of the three active components have been assessed in earlier procedures and no additional information for the triple FCMP is required. The basic PK presented below are based on available SmPCs.

Table 3 Metformin formulations used in the efficacy/safety studies included in the submission

Study	Metformin formulation
CV181169 ^a	metformin XR
CV181168 ^a	metformin
MB102129 ^a	metformin
CV181365	metformin XR, metformin
D1689C00014	Metformin
CV181369	metformin XR, metformin

^a pivotal

Absorption

Dapagliflozin (SmPC)

Dapagliflozin was rapidly and well absorbed after oral administration with C_{max} . The absolute oral bioavailability (F) was 78%. The exposure increased proportionally with dose over the range of 0.1-500 mg. The PK intra- and inter-individual variability were low to moderate.

Saxagliptin (SmPC)

Saxagliptin was rapidly absorbed after oral administration. C_{max} of saxagliptin and 5-OH-saxagliptin (major metabolite) was attained within 2 and 4h (t_{max}), respectively. The exposure of saxagliptin and 5-OH-saxagliptin increased proportionally with dose up to 400 mg. The intra-subject variability was <12%.

Metformin (SmPC)

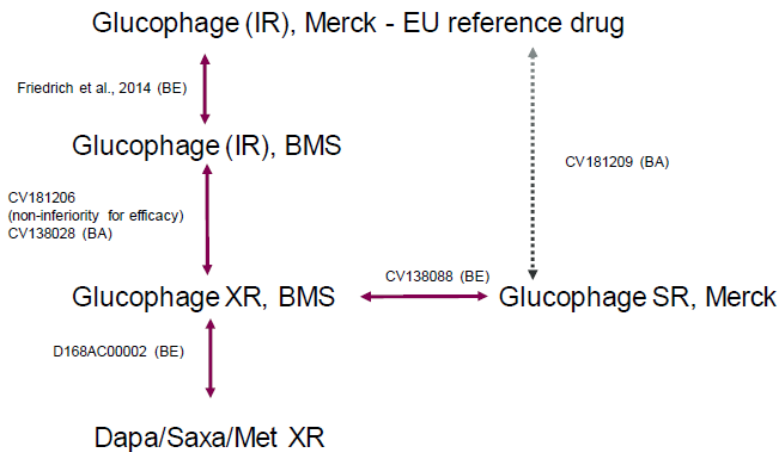
C_{max} was reached in *ca* 2.5h after administration of metformin as an immediate release tablet. The absolute bioavailability of a 500-mg tablet given under fasted conditions was *ca* 50-60%. The absorption was decreased with increasing dose. Steady state was reached within 24-48 h. Food decreases the extent and slightly delays the absorption. Metformin shows high PK inter-individual variability.

● **Bioequivalence**

Qtrilmet is referred to as a modified release (MR) tablet, providing an extended release formulation for metformin and immediately release (IR) for dapagliflozin and saxagliptin. The current FCMP formulation has not been administered in the clinical studies except in the BE-study.

Bridging strategy within the program is shown in Figure 41.

Figure 4 Bridging strategy



The exposure of both dapagliflozin and saxagliptin following administration of the triple FCMP Qtrilmet can be claimed BE compared to co-administration of single components. The 90%CI for the ratio of the mean C_{max} of saxagliptin in fasted subjects was slightly above, 103-127%, compared to the BE criteria, which is not considered clinical relevant.

The 90%CI of the ratio of the exposure of metformin after a single dose of the FCMP compared to administration of the three mono-components concomitantly were within the BE criteria 80-125%.

The EU reference Glucophage® (Merck) 500 and 1000 mg tablets are BE to the US reference Glucophage® (BMS) 500 and 1000 mg tablets.

The relative bioavailability of metformin after a single dose of Glucophage XR® 500 mg (BMS US) and Glucophage SR® 500 mg (Merck EU) in fasted condition were within the BE criteria 90%CI 80-125%.

Comparable C_{max} and AUC of metformin were seen following single doses of as saxagliptin/metformin XR 2.5/1000 mg and Glucophage SR 1000 mg, Merck (fed condition).

A lower C_{max} of metformin (0.7-fold) but comparable AUC were seen after a single dose of saxagliptin/metformin XR 2.5/1000 mg compared to after Glucophage® Merck 1000 mg (fed condition).

Comparable exposure of metformin was seen between a single dose and at steady state after dosing with a modified release 500 mg od. The exposure was ca 7% lower at steady state compared to after a single dose.

Steady state exposure after metformin modified release tablet 2000 mg od and Glucophage® 1000 mg bid was comparable (total exposure) but with a 1.4-fold higher C_{max} after once daily dosing.

Comparable exposure of metformin, was seen after a single dose and at steady state following repeated dosing once daily (od) with Xigduo XR (dapagliflozin/metformin XR) 10/1000 mg with a low-fat meal for four days.

(MB102092), the systemic exposure of metformin was ca 7% higher after four doses (steady state) compared to after a single dose

- **Influence of food**

Dapagliflozin (SmPC)

Administration with a high-fat meal decreased $C_{max} \leq 50\%$ but did not alter AUC as compared with the fasted state.

Saxagliptin (SmPC)

Co-administration with food (a high-fat meal) resulted in no change in C_{max} and a 27% increase in AUC compared with the fasted state.

Metformin (SmPC)

Food decreased the extent and slightly delayed the absorption of metformin. Following an oral dose of 850 mg, a 40% lower C_{max} and a 25% decrease in AUC was seen.

Metformin/saxagliptin/dapagliflozin (FCMP)

C_{max} of dapagliflozin after co-administered with a light meal was ca 0.6-fold compared to in fasted state. No differences in total exposure of dapagliflozin were seen compared to when administered together with food or without.

The total exposure of saxagliptin was about 1.5-fold and C_{max} 0.9-fold when co-administered with a light meal compared to in fasted state.

C_{max} of metformin was about 0.8-fold when administered with a light meal but AUC was unchanged independently if dosed with food or not.

Distribution

Dapagliflozin (SmPC)

The fraction unbound (f_u) was determined to ca 9% and the volume of distribution 118L.

Saxagliptin (SmPC)

The *in vitro* protein binding of saxagliptin and its major metabolite in human serum was negligible.

Metformin (SmPC)

Plasma protein binding of metformin is negligible. The volume of distribution ranged between 63-276L.

Elimination

• **Excretion**

Dapagliflozin (SmPC)

The terminal $t_{1/2}$ was calculated to ca 13h after an oral dose. The total clearance (CL) was determined to 207 ml/min after an iv dose. Dapagliflozin and its metabolites are primarily excreted in the urine with <2% as unchanged dapagliflozin. After a 14C-labelled dose, 75% of the dose was recovered in the urine and 21% in faeces. In faeces, approximately 15% of the dose was excreted as parent drug.

Saxagliptin (SmPC)

The terminal plasma $t_{1/2}$ for saxagliptin and 5-OH-saxagliptin was ca 2.5h and 3h respectively. The mean $t_{1/2}$ for plasma DPP4 inhibition was 27h.

The renal clearance (CL_R) of saxagliptin of ~230 ml/min suggests active secretion as a compliment to the glomerular filtration. The CL_R of the 5-OH-saxagliptin was comparable to the glomerular filtration rate.

Metformin (SmPC)

The terminal $t_{1/2}$ was ca 7h. CL_R is >400 ml/min indicating that metformin is eliminated by glomerular filtration and tubular secretion.

- **Metabolism**

Dapagliflozin (SmPC)

Dapagliflozin was extensively metabolised, primarily to dapagliflozin-3-O-glucuronide mediated by UGT1A9. UGT1A9 is a known polymorphic enzyme but the polymorphism does not have any clinical relevant impact. UGT1A9 is present in the liver and kidney. CYP-mediated metabolism was of minor importance. Dapagliflozin has five stereocenters, no interconversion is expected.

Saxagliptin (SmPC)

The biotransformation of saxagliptin was primarily mediated by CYP3A4/5. The major metabolite, 5-OH-saxagliptin, is also a selective, reversible, competitive DPP4 inhibitor, half as potent as saxagliptin. Saxagliptin is chiral with four stereogenic centres, all centres have the S-configuration. Interconversion is not expected.

Metformin (SmPC)

Metformin is excreted unchanged in the urine.

Pharmacokinetics in target population

Dapagliflozin (SmPC)

Steady state exposure, C_{max} and AUC_{τ} , after dapagliflozin 10 mg od (recommended clinical dose) was 158 ng/ml and 628 ng/ml.h, respectively.

Saxagliptin (SmPC)

The total systemic exposure of saxagliptin and 5-OH-saxagliptin was determined to 78 and 214 ng/ml.h, respectively, following a single dose of saxagliptin 5 mg (recommended clinical dose od). The corresponding C_{max} were 24 and 47 ng/ml.

Metformin

At clinical relevant doses, a steady state C_{trough} level of about 1 µg/ml is expected. C_{max} values in clinical studies, including patients with impaired renal function, are in general reported to <5 µg/ml.

Special populations

- **Impaired renal function**

Dapagliflozin (SmPC)

At steady-state, subjects with T2DM and mild, moderate or severe renal impairment had mean systemic exposure of 32, 60 and 87% higher, respectively, than those of with normal renal function.

Saxagliptin (SmPC)

The total exposure of saxagliptin and 5-OH-saxagliptin was 1.7- and 1.2-fold higher, respectively, in subjects with mild renal impairment compared to subjects with normal renal function. In subjects with moderate or severe renal impairment or in subjects with ESRD on haemodialysis, the AUC of saxagliptin and 5-OH-saxagliptin were up to 2.1- and 4.5-fold higher, respectively, than in subjects with normal renal function.

Metformin (SmPC)

When renal function is impaired, CL_R is decreased in proportion to that of creatinine clearance resulting in prolonged $t_{1/2}$ and increased plasma levels.

- **Impaired hepatic function**

Dapagliflozin (SmPC)

The total exposure was comparable in subjects with mild and normal liver function. Subjects with moderate hepatic impairment had a 1.4-fold higher exposure and in severe hepatic impairment 1.7-fold higher compared to healthy subjects.

Saxagliptin (SmPC)

In subjects with mild, moderate and severe hepatic impairment, the exposure to saxagliptin was 1.1-, 1.4- and 1.8-fold higher, respectively, compared to in healthy subjects. The exposure 5-OH-saxagliptin was 22, 7 and 33% lower, respectively, than those observed in healthy subjects.

Metformin (SmPC)

Metformin is excreted unchanged.

- **Gender, race, weight, age**

Dapagliflozin (SmPC)

About 22% higher exposure was seen in females compared males. The difference is not considered clinical significant. No clinically relevant differences in systemic exposures between White, Black or Asian have been reported. Exposure decreased with increased weight but was not considered clinical relevant. An increased exposure due to age-related decrease in renal function can be expected.

Saxagliptin (SmPC)

Females had approximately 25% higher exposure of 5-OH-saxagliptin than males. The difference is not considered clinical significant. No differences in the PK due to race have been reported. Body weight did influence the PK of saxagliptin and 5-OH-saxagliptin (population PK analysis). Elderly patients (65-80 years) had about 60% higher total systemic exposure of saxagliptin than young patients (18-40 years), which is not considered clinical relevant.

Metformin (SmPC)

No clinical relevant increase in exposure based on age alone has been reported. An increased exposure due to age-related decrease in renal function can be expected. Comparable PK have been shown in paediatric and adult patients following a single dose of 500 mg metformin. A decreased exposure by 35-40% has been reported in paediatric patients compared to adults, as dosing is individualised this is of limited clinical relevance.

Pharmacokinetic interaction studies

- **In vitro**

Dapagliflozin (SmPC)

Dapagliflozin is a P-gp substrate.

Dapagliflozin did not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4 *in vitro*. Neither did dapagliflozin induce CYP1A2, 2B6 or 3A4.

Saxagliptin (SmPC)

Saxagliptin is a P-gp substrate.

Saxagliptin and its major metabolite did not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4. Neither did saxagliptin induce CYP1A2, 2B6, 2C9, or 3A4.

Metformin (SmPC)

- **In vivo**

Dapagliflozin (SmPC)

Victim

Co-administration with mefenamic acid (UGT1A9 inhibitor) resulted in a 55% increase in systemic exposure but with no clinically meaningful effect on 24-h urinary glucose excretion. No dose adjustment is recommended.

A 22% decrease in systemic exposure was observed following co-administration with rifampicin (inducer) but with no clinically meaningful effect on 24-h urinary glucose excretion.

The PK of dapagliflozin is not altered by co-administration of saxagliptin, metformin, pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin.

Perpetrator

A single dose of dapagliflozin 20 mg resulted in 19% and 31% increase in systemic exposure of simvastatin (CYP3A4, OATP1B1 substrate) and simvastatin acid, respectively. The increases were not considered clinically relevant.

Dapagliflozin did not alter the PK of metformin (OCT2 substrate), pioglitazone (CYP2C8 substrate), sitagliptin (OAT3 substrate), glimepiride (CYP2C9 substrate), hydrochlorothiazide (OAT substrate), bumetanide (OAT substrate), valsartan (OATP, OAT, MRP substrate), digoxin (P-gp substrate) or warfarin (S-warfarin CYP2C9 substrate).

Saxagliptin (SmPC)

Victim

Concomitant administration with diltiazem (moderate CYP3A4/5 inhibitor) increased C_{max} and AUC of saxagliptin by 1.6- and 2.1-fold, respectively. The corresponding C_{max} and AUC for the active metabolite were 0.6-fold and 0.7-fold, respectively. The changes are not considered clinically relevant.

Co-administration with ketoconazole (potent CYP3A4/5 inhibitor) increased C_{max} and AUC of saxagliptin by 1.6-fold and 2.5-fold, respectively. C_{max} and AUC for the active metabolite were 0.05- and 0.1-fold, respectively. These changes are considered clinically relevant.

Concomitant administration with rifampicin (potent inducer) reduced C_{max} and AUC of saxagliptin by 53% and 76 %, respectively. The exposure of the active metabolite was not influenced. Glycaemic control should be assessed when saxagliptin is used concomitantly with a potent inducer.

The PK of saxagliptin or the active metabolite was not altered by co-administration with dapagliflozin, metformin, glibenclamide, pioglitazone, digoxin, simvastatin, omeprazole, antacids or famotidine.

Perpetrator

Saxagliptin did not alter the PK of metformin (OCT2 substrate), glibenclamide (CYP2C9, CYP3A4, Pgp, OATP1B1 substrate), pioglitazone (CYP2C8 substrate), digoxin (Pgp substrate), simvastatin (CYP3A4

substrate), diltiazem (CYP3A substrate), ketoconazole (CYP3A4 substrate), ethinyl estradiol and norgestimate).

Metformin (SmPC)

Victim

Co-administration of multiple doses of dapagliflozin and metformin does not alter the PK of metformin.

Co-administration of multiple doses of saxagliptin and metformin did not alter the PK of metformin in patients with T2DM.

Cationic substances that are eliminated by renal tubular secretion (e.g. cimetidine) may interact with metformin by competing for common renal tubular transport systems. Cimetidine (OCT inhibitor), administered as 400 mg bid, increased metformin C_{max} and AUC by 1.8- and 1.5-fold, respectively. Close monitoring of glycaemic control and dose adjustment is recommended.

Perpetrator

Co-administration of multiple doses of metformin and dapagliflozin does not alter the PK of dapagliflozin.

Co-administration of multiple doses of metformin and saxagliptin did not alter the PK of either saxagliptin patients with T2DM.

2.4.3. Pharmacodynamics

Introduction

Qtrilmet combines 3 oral antidiabetic drugs - dapagliflozin, saxagliptin, and metformin.

No new data were submitted on pharmacodynamics. The clinical pharmacology programme that supported the original dapagliflozin and saxagliptin clinical development programmes provides information to support the dapagliflozin/saxagliptin/metformin FCMP programme. Key clinical pharmacology information about the respective components, are available in the product information for each product.

Mechanism of action

Dapagliflozin

The SGLT2, expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen and is an inhibitor of SGLT2. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion. This, in turn, reduces fasting plasma glucose (FPG), postprandial glucose (PPG), and HbA1c resulting in improved glycaemic control with weight loss and low risk of hypoglycaemia. SGLT2 inhibitors have a MOA that is independent of beta-cell function or the degree of insulin resistance.

Saxagliptin

Under normal conditions, incretin hormones such as GLP-1 and glucose-dependent insulinotropic polypeptide are released into the bloodstream from the small intestine in response to meals. In turn, these hormones stimulate insulin release from the pancreatic β -cells in a glucose-dependent manner but are inactivated by the DPP4 enzyme within minutes. Saxagliptin is a competitive DPP4 inhibitor that slows the inactivation of the incretin hormones, thereby increasing their bloodstream concentrations which reduces

fasting and PPG concentrations in a glucose-dependent manner in patients with T2DM. Furthermore, saxagliptin is weight neutral with a low risk of hypoglycaemia.

Metformin

Metformin hydrochloride (metformin), a biguanide, lowers HbA1c, FPG, and PPG concentrations in patients with T2DM, by reducing hepatic glucose production, decreasing intestinal absorption of glucose, and improving insulin sensitivity, increasing peripheral glucose uptake and utilisation. In addition, there is no associated weight gain with metformin use (Tan et al 2016).

Complementary mechanisms of action of dapagliflozin, saxagliptin, and metformin

By combining the MOAs of dapagliflozin, saxagliptin, and metformin, there is a potential for effective HbA1c reduction (dapagliflozin, saxagliptin, and metformin), improvement in insulin sensitivity (dapagliflozin), body weight reduction (dapagliflozin), reduction in blood pressure (dapagliflozin), glucose-dependent insulin secretion (saxagliptin), and reduced hepatic glucose output (metformin), with no change in the risk profile when compared with the monocomponents.

Primary pharmacology

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).

Saxagliptin

In patients with type 2 diabetes, administration of saxagliptin inhibited DPP-4 enzyme activity throughout a 24-hour period. The inhibition of plasma DPP-4 activity by saxagliptin for at least 24 hours after oral administration of saxagliptin is due to high potency, high affinity, and extended binding to the active site. 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 beta-cells 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.

Metformin

In clinical studies, the major non-glycaemic effect of metformin is either weight stability or modest weight loss. In humans, independently of its action on glycaemia, immediate release metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-

term clinical studies: immediate release metformin reduces total cholesterol, LDL cholesterol and triglyceride levels. A similar action has not been demonstrated with the prolonged release formulation, possibly due to the evening administration, and an increase in triglycerides may occur.

- *Study CV181206*

Study CV181206 was a multicentre, randomised, parallel-group, double-blind, 24-week study in 568 patients to evaluate metformin XR monotherapy compared to metformin IR in adult subjects with T2DM with inadequate glycaemic control with diet and exercise; >30% of subjects had baseline HbA1c \geq 8.0%.

The primary objective of the study was to determine whether monotherapy with 2000 mg metformin XR is non-inferior to monotherapy with 2000 mg metformin IR. The primary efficacy analysis was change in HbA1c from baseline to Week 24. Secondary objectives were to compare the effects of metformin XR versus metformin IR after a 24-week double-blind treatment period for (i) Change from baseline to Week 24 in fasting plasma glucose (ii) Change from baseline to Week 24 in mean daily glucose; and (iii) the proportion of subjects achieving a therapeutic glycaemic response, defined as HbA1c <7.0% at Week 24.

Results of the primary efficacy analysis for the adjusted mean change from baseline in HbA1c at Week 24 demonstrated non-inferiority of metformin XR compared with metformin IR using the predefined 0.3% noninferiority margin for the upper bound of the CI.

Additional evidence for the non-inferiority of metformin XR compared with metformin IR was provided by data from analyses of the secondary endpoints. Baseline to 24-week change in fasting plasma glucose and mean daily glucose, and proportion of subjects achieving a therapeutic glycaemic response of HbA1c <7.0% at 24 weeks, showed similar results for both metformin XR and metformin IR.

2.4.4. Discussion on clinical pharmacology

The current application includes six clinical phase 3/4 studies (three pivotal), the commercial triple FCMP Qtrilmet tablets were not used in any of the studies. All subjects had background therapy with metformin and the dapagliflozin and saxagliptin were then added on. Both metformin IR- and/or MR-formulations were used and sources of the tablets are unclear whether US or EU products. Comparison of systemic exposure following co-treatment with single components with exposure after administration with the applied product is needed to bridge available efficacy and safety data from the single components to the triple FCMP.

A single dose BE study, comparing systemic exposure of dapagliflozin, saxagliptin and metformin following Qtrilmet with co-administration of single components in both fasted and fed condition has been performed.

BE can be claimed between the FCMP-commercial tablet to be and co-administration of the single component dapagliflozin. For saxagliptin the 90CI for the C_{max} ratio in fasted subjects was 103-127% and does not fulfil the BE criteria of 80-125%. Similar PK are required but strict BE does not have to be shown. The effect of saxagliptin is mainly driven by total exposure and the dose recommendation for the FCMP, is to be taken together with food (C_{max} and AUC were within 80-125%) therefore the C_{max} ratio, in fasted state, outside the BE-criteria is probably not clinically relevant. The sampling time points around the determined C_{max} (t_{max}) may not be optimal as C_{max} was determined in the first sample.

The relative bioavailability of metformin between Qtrilmet and a single dose of the US reference Glucophage XR® 500 mg BMS was within the defined BE criteria 90%CI 80-125% interval.

However, for a modified release component (metformin), exposure comparison between test and reference products after repeated dosing are required, according to the guideline on PK of modified release formulations (EMA/CHMP/EWP/280/96 Corr1), if not justified. In the BE study with the FCMP-commercial tablet, it was shown in a *posthoc* comparison that the AUC_{0-24h} (recommended dosing interval at repeated dosing) represents >90% of AUC_{inf} after both 1000 and 850 mg together with a light fat/low calorie meal. Thus, a low extent of accumulation is expected following repeated dosing.

Steady state exposure after metformin MR-tablet 2000 mg od and Glucophage® 1000 mg bid was comparable (total exposure) but with a 1.4-fold higher C_{max} after once daily dosing. Comparable the systemic exposure of metformin was seen at steady state (*ca* 7% higher) and after a single dose following repeated dosing once daily (od) with Xigduo XR (dapagliflozin/metformin XR) 10/1000 mg.

As stated above, no new studies were performed on pharmacodynamics. Key clinical pharmacology information about the respective components, are available in the respective product information.

Clinical data was provided to support the bridging between metformin IR and metformin XR, the latter being included in the fixed dose combination. Data from this study showed that metformin XR was non-inferior to metformin IR with regards to HbA1c reduction, with upper limit of the 95% CI well within the non-inferiority margin of 0.3%. This finding was supported by comparable outcomes also for the secondary endpoints. Thus, the clinical data presented does not raise any concerns with regards to the use of metformin XR in the FCMP.

2.4.5. Conclusions on clinical pharmacology

Qtrilmet is a FCMP of three known active components and will be available in two tablet strengths. The basic Pharmacokinetics of the mono-components is known. One BE study, comparing the exposure following co-administration of a single dose of the three mono-components with a single dose of the FCMP, in both fasted and fed condition, has been performed. Comparable bioavailability can be claimed, between the two administration ways, for dapagliflozin (BE) and for saxagliptin.

The relative bioavailability of metformin between the FCMP (metformin MR-component) and the mono-component was within the defined BE criteria. AUC_{0-24h} (recommended dosing interval at repeated dosing) represents >90% of AUC_{inf} after both 1000 and 850 mg together with a light fat/low calorie meal. Thus, a low extent of accumulation is expected following repeated dosing. Comparable exposure of metformin after a single dose and at state has been shown, following repeated dosing with metformin MR-tablet 2000 mg od, Glucophage® 1000 mg bid and Xigduo XR (dapagliflozin/metformin XR) 10/1000 mg od.

The pharmacodynamics for the three components is well known and no new data has been provided, which is acceptable. Key clinical pharmacology information about the respective components, are available in the respective product information. Clinical data presented does not raise any concerns with regards to the use of metformin XR in the FCMP.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

No dose response studies were submitted. The planned tablet strengths for Met XR/Saxa/Dapa include dapagliflozin 5 mg/saxagliptin 2.5 mg/metformin 850 mg (daily dosage 10 mg/5 mg/1700 mg) and 5

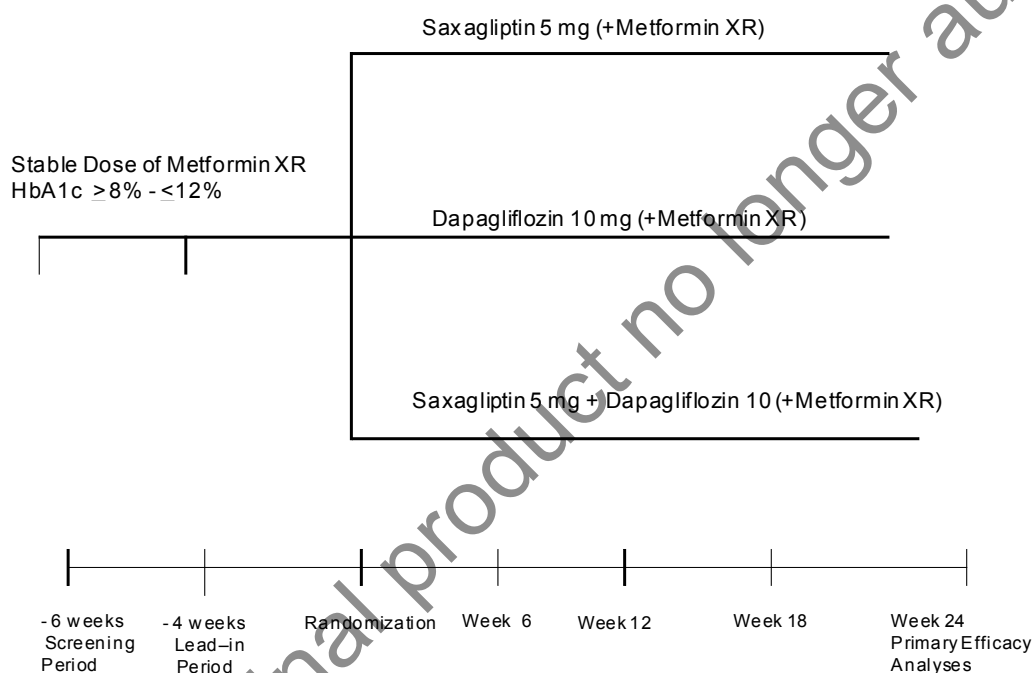
mg/saxagliptin 2.5 mg/ metformin 1000 mg (daily dosage 10 mg/5 mg/2000 mg). These tablet strengths were selected to match the recommended daily doses of the mono components available in the EU.

2.5.2. Main study(ies)

Study CV181169

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 dapagliflozin and saxagliptin 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 design of Study CV181169 is illustrated in Figure 5.

Figure 5 Design of Study CV181169

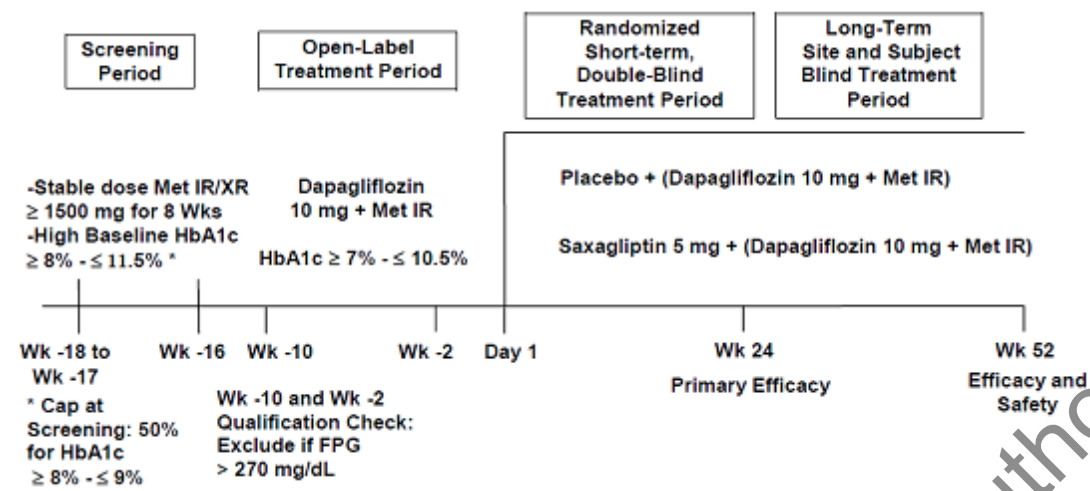


HbA1c Glycated haemoglobin A1c; XR Extended release.

Study CV181168

Study CV181168 was a multicentre, randomised, double-blind, placebo-controlled, parallel-group, 24-week Phase 3 trial in 315 subjects 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 compared with the addition of placebo to dapagliflozin and metformin in subjects with T2DM with inadequate glycaemic control on metformin and dapagliflozin. Eligible subjects could enter the long-term (LT) extension for an additional 28 weeks. The design of Study CV181168 is illustrated in Figure 6.

Figure 6 Design of Study CV181168

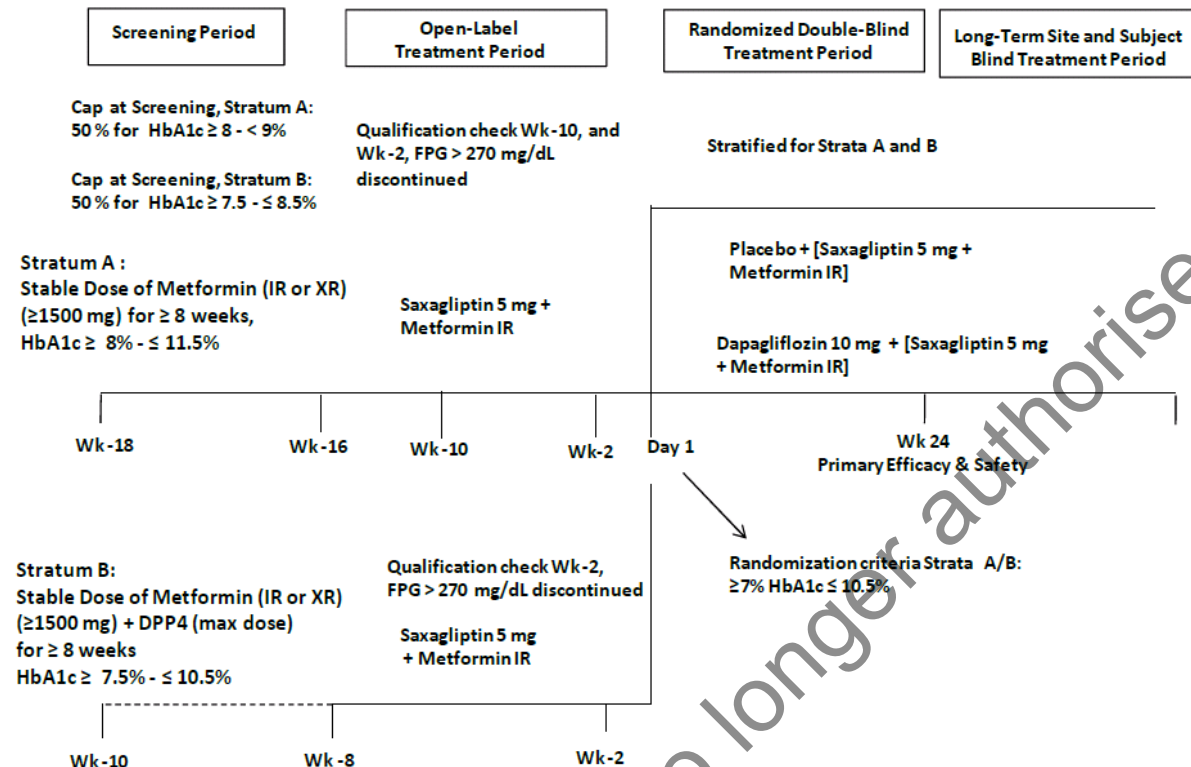


FPG Fasting plasma glucose; HbA1c Glycated haemoglobin A1c; IR Immediate release; XR Extended release.

Study MB102129

Study MB102129 was a multicentre, randomised, double-blind, placebo-controlled, parallel-group, 24-week Phase 3 trial designed to evaluate the safety and efficacy (primary endpoint: mean change from baseline in HbA1c) of the sequential addition of dapagliflozin to saxagliptin and metformin compared with the addition of placebo to saxagliptin and metformin in subjects with T2DM who had inadequate glycaemic control on metformin and saxagliptin. Eligible subjects could enter the LT extension for an additional 28 weeks. The design of Study MB102129 is illustrated in Figure 7. 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.

Figure 7 Design of Study MB102129



DPP4 Dipeptidyl peptidase 4; FPG Fasting plasma glucose; HbA1c Glycated haemoglobin A1c; IR Immediate release; XR Extended release.

Methods

Study Participants

The target populations in all studies were male and female subjects aged ≥ 18 years with T2DM and inadequate glycaemic control on metformin alone (Studies CV181169), metformin + saxagliptin (MB102129), or on metformin + dapagliflozin (CV181168). 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 ≥ 1.0 ng/mL (0.33-0.34 nmol/L), and have a BMI ≤ 45.0 kg/m² at the screening visit. Subjects with moderate or severe impairment of renal function were excluded.

Treatments

In all studies, dapagliflozin 10 mg and saxagliptin 5 mg were used as study medication. These dapagliflozin and saxagliptin doses are approved within the EU for the individual drugs and are the recommended doses.

In Study CV181169, dapagliflozin 10 mg and matching placebo tablets, saxagliptin 5 mg and matching placebo tablets, and metformin XR 500 mg tablets were used as study medication.

In Study CV181168, saxagliptin 5 mg and matching placebo tablets, dapagliflozin 10 mg tablets, and metformin IR 500 mg tablets were used as study medication.

In Study MB102129, dapagliflozin 10 mg and matching placebo tablets, saxagliptin 5 mg tablets, and metformin IR 500 mg tablets were used as study medication.

Rescue medication

In all studies, subjects were eligible for treatment with open-label rescue medication, in addition to their treatment regimen, in order to treat ongoing hyperglycaemia. Prespecified glycaemic criteria based upon central laboratory FPG and repeated, confirmatory FPG were established to determine eligibility for initiation of open-label rescue medication during the double-blind treatment period.

Rescued subjects were given open-label antidiabetic rescue medication, in addition to their double-blinded study drug. Rescued subjects continued in the double-blind treatment period according to their original visit schedule.

Objectives

The primary objectives are listed below.

Study CV181169

- To compare the mean change from baseline in HbA1c achieved with concurrent addition of dapagliflozin and saxagliptin to metformin versus the addition of placebo and saxagliptin to metformin and versus the addition of placebo + dapagliflozin to metformin after 24 weeks of double-blind treatment

Study CV181168

- To compare the mean change from baseline in HbA1c achieved with saxagliptin added to dapagliflozin + metformin versus placebo added to dapagliflozin + metformin after 24 weeks of ST double-blind treatment

Study MB102129

- To compare the mean change from baseline in HbA1c achieved with dapagliflozin added to saxagliptin + metformin versus placebo added to saxagliptin + metformin after 24 weeks of oral administration of double-blind treatment

Outcomes/endpoints

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

Main **secondary efficacy endpoints** were:

- Mean change from baseline in 2-hour PPG during a liquid meal tolerance test (120-minute Meal Tolerance Test [MTT]) at Week 24
- Mean change from baseline in FPG at Week 24
- Percent of subjects achieving a therapeutic glycaemic response, defined as a HbA1c <7.0% at Week 24

- Mean change from baseline in body weight at Week 24

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). The subject number consisted of five digits which were assigned sequentially (00001, 00002, 00003, etc) by the 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, BMS personnel, and subjects will remain 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 will be locked after all subjects have terminated the short-term double-blind treatment period of the study. The locked database will be 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.

Blinding is critical to the integrity of this clinical trial. However, 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

For all three studies, the primary efficacy endpoint was the change in HbA1c from baseline to Week 24.

The primary efficacy analyses were 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.

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 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 continuous secondary endpoints such as the mean change from baseline for FPG, total body weight (CV181169, and MB102129) were performed using a similar longitudinal repeated measures model as for the primary efficacy endpoint. The proportion of subjects achieving therapeutic glycaemic response (defined as HbA1c <7.0%; all studies) were based on the methodology of Zhang et al 2008 and Tsiatis et al 2007 with adjustment for baseline HbA1c value.

The following order was used for the step-wise analysis of secondary efficacy endpoints:

CV181169

- Mean change from baseline in 2-hour PPG at Week 24
- Mean change from baseline in FPG at Week 24
- Percent of subjects achieving therapeutic glycaemic response at Week 24
- Mean change from baseline in total body weight at Week 24 (only comparing dapagliflozin + saxagliptin + metformin versus saxagliptin + metformin)

CV181168

- Mean change from baseline in 2-hour PPG at Week 24
- Mean change from baseline in FPG at Week 24
- Percent of subjects achieving therapeutic glycaemic response at Week 24

MB102129

- Mean change from baseline in FPG at Week 24
- Mean change from baseline in 2-hour PPG at Week 24
- Mean change from baseline in total body weight at Week 24
- Percent of subjects achieving therapeutic glycaemic response at Week 24

Analysis sets

Data from all randomised subjects who took at least one dose of double-blind study drug during the ST double-blind periods were included in the Randomised Subjects Data Sets. When the Randomised Subjects

Data Sets are used, subjects are presented in the treatment group to which they were randomised at the start of the double-blind treatment period, even if the treatment they received was different. For all studies, the primary data set for efficacy analysis was the respective Randomised Subjects data set.

Results

Participant flow

Study CV181169

There were 1282 subjects enrolled in study CV181169, of whom 639 subjects (49.8%) entered the treatment period. The most common reason for not entering the treatment period was no longer meeting eligibility criteria (620 subjects [48.4%]).

Study CV181168

There were 857 subjects enrolled in study CV181168, of whom 484 subjects (56.5%) entered the open-label treatment period. The most common reason for not entering the open-label period was no longer meeting eligibility criteria (353 subjects [41.2%]).

Study MB102129

A total of 818 subjects were enrolled in study MB102129. Of the enrolled subjects, 483 subjects (59%) entered the open-label period. The most common reason for not entering the open-label treatment period was no longer meeting eligibility criteria (318 subjects [38.9%]).

Table 4 Disposition of subjects – Studies CV181169, CV181168, and MB102129

	Concomitant add-on study				Sequential add-on studies					
	Study CV181169				Study CV181168			Study MB102129		
	Dapa + Saxa + Met	Saxa + Met ^a	Dapa + Met ^b	Total	Saxa + Dapa + Met	Pla + Dapa + Met	Total	Dapa + Saxa + Met	Pla + Saxa + Met	Total
Subjects	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 ^c	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)

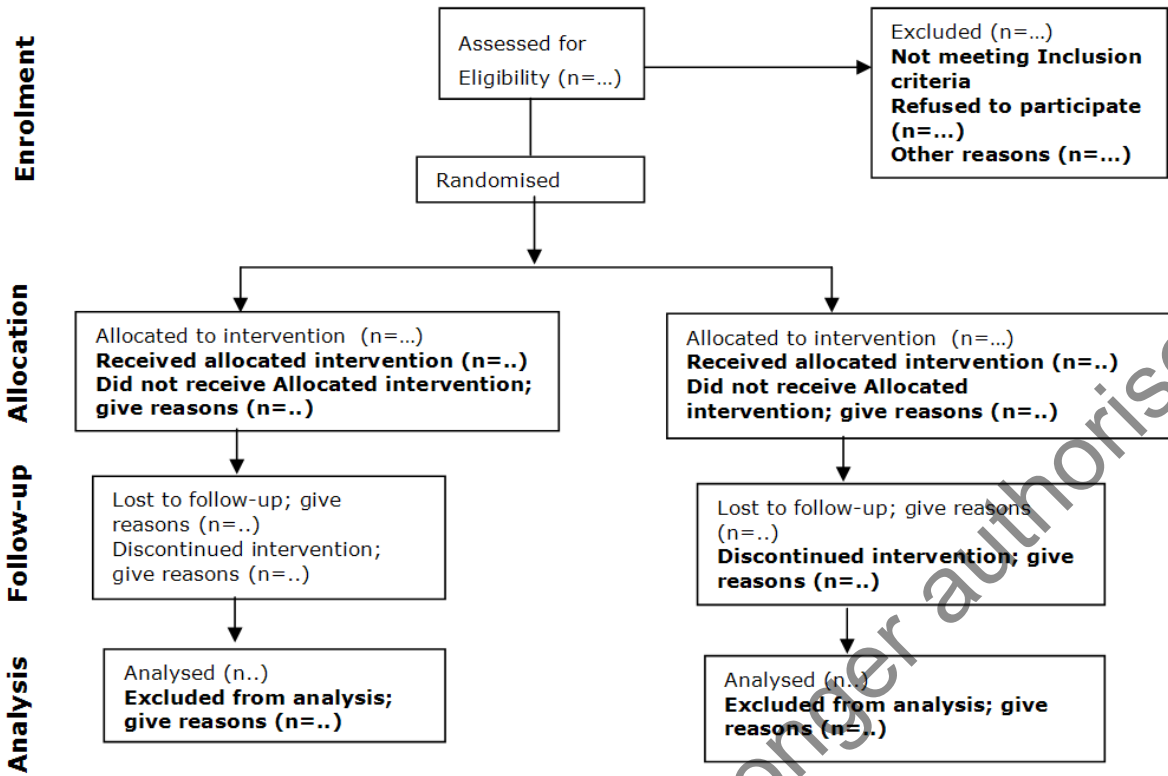
^a Placebo matching dapagliflozin 10 mg was used.

^b Placebo matching saxagliptin 5 mg was used.

^c Does not include patients receiving rescue medication.

Randomised subjects are those who were randomised and received at least one dose of double-blind medication during the short-term double-blind treatment period. Percentages based on subjects randomised in the respective treatment group.

Dapa Dapagliflozin; Met Metformin; Pla Placebo; Saxa Saxagliptin.



Baseline data

The demographics and disease characteristics of the subjects are summarised for Study CV181169, CV181168, and MB102129 in Table 5. The study populations were representative of subjects with T2DM with high HbA1c that present in clinical practice who have not achieved their target goals. The study populations can be considered representative of the target population, with the exception of the small number of subjects ≥ 75 years old.

In Study CV181169, the mean age was 53.8 years, there was an equal sex distribution, the mean duration of T2DM was 7.6 years, and the mean baseline HbA1c was 8.9% (Table 5). Approximately half (55.6%) of the subjects were from North America while 21.9% were from Latin America, 21.3% were from Europe, and 1.1% were from Asia/the Pacific. The majority of subjects were White (69.7%), 11.2% were Black, 6.2% were Asian, and 12.9% were of other racial origin.

In study CV181168, the mean age was 54.6 years, 52.7% of subjects were female, the mean duration of T2DM was 7.7 years, and the mean baseline HbA1c was 7.9% (Table 5). Approximately half (52.1%) of the subjects were from North America while 34.9% were from Europe and 13.0% were from Latin America. The majority of subjects were White (87.9%), 6.3% were Black, 4.1% were Asian, and 1.6% were of other racial origin.

In study MB102129, the mean age was 55.1 years, 54.4% of subjects were female, the mean duration of T2DM was 7.6 years, and the mean baseline HbA1c was 8.2% (Table 5). Similar proportions of subjects were from Europe (35.6%), North America (32.2%), and Latin America (32.2%). The majority of subjects (92.8%) were White, 5.6% were Black, 0.6% were Asian, and 0.9% were of other racial origin.

Table 5 Subject demographics and baseline characteristics – Studies CV181169, CV181168, and MB102129 (randomised subjects) (abbreviated by assessor)

	Concomitant add-on study				Sequential add-on studies					
	Study CV181169				Study CV181168			Study MB102129		
	Dapa + Saxa + Met (N=179)	Saxa + Met ^a (N=176)	Dapa + Met ^b (N=179)	Total (N=534)	Saxa + Dapa + Met (N=153)	Pla + Dapa + Met (N=162)	Total (N=315)	Dapa + Saxa + 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	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	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	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)
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)
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)

	Concomitant add-on study				Sequential add-on studies					
	Study CV181169				Study CV181168			Study MB102129		
	Dapa + Saxa + Met (N=179)	Saxa + Met ^a (N=176)	Dapa + Met ^b (N=179)	Total (N=534)	Saxa + Dapa + Met (N=153)	Pla + Dapa + Met (N=162)	Total (N=315)	Dapa + Saxa + Met (N=160)	Pla + Saxa + Met (N=160)	Total (N=320)
eGFR (mean [SD] ml/min/1.73 m ²)	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)

^a Placebo matching dapagliflozin 10 mg was used.

^b Placebo matching saxagliptin 5 mg was used.

BMI Body mass index; Dapa Dapagliflozin; eGFR Estimated glomerular filtration rate; FPG Fasting plasma glucose; HbA1c Glycated haemoglobin A1c; Met Metformin; Pla Placebo; PPG Post-prandial glucose; Saxa Saxagliptin, SD Standard deviation; T2DM Type 2 diabetes mellitus.

Study treatment compliance

Almost all subjects were compliant with study medication across the 3 studies.

In Study CV181169, all subjects were compliant (i.e. took $\geq 80\%$ to $\leq 120\%$ of prescribed medication) with administration of dapagliflozin and/or saxagliptin during the double-blind treatment period. Eight randomised subjects (1.5%) were $< 80\%$ compliant with metformin dose treatment.

In Study CV181168, almost all subjects (98.8%) were compliant with dapagliflozin administration during the pre-randomisation open-label treatment period. During the 24-week, ST, double-blind treatment period, all subjects in the saxagliptin + dapagliflozin + metformin treatment group and 161 (99.4%) subjects in the placebo + dapagliflozin + metformin treatment group were compliant with double-blind medication.

In Study MB102129, almost all subjects (99.2%) were compliant with saxagliptin administration during the pre-randomisation open-label treatment period. During the 24-week ST double-blind treatment period, 98.8% of the subjects in the dapagliflozin + saxagliptin + metformin treatment group and all subjects in the placebo + saxagliptin + metformin group were compliant with double-blind study medication. Three randomised subjects received no double-blind study medication for ≥ 2 consecutive weeks.

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 4.

Outcomes and estimation

Primary efficacy endpoint: Change in HbA1c from baseline

The primary efficacy endpoint was met for all three studies (Table 6).

Table 6 HbA1c change from baseline at Week 24 excluding data after rescue – Studies CV181169, CV181168, and MB102129

	Concomitant add-on study			Sequential add-on studies			
	Study CV181169			Study CV181168		Study MB102129	
	Dapa + Saxa + Met (N=179)	Saxa + Met ^a (N=176)	Dapa + Met ^b (N=179)	Saxa + Dapa + Met (N=153)	Pla + Dapa + Met (N=162)	Dapa + Saxa + Met (N=160)	Pla + Saxa + Met (N=160)
HbA1c (%) at Week 24							
N#	176	175	172	150	160	158	158
Baseline Mean (SD)	8.93 (1.186)	9.03 (1.053)	8.87 (1.174)	7.95 (0.826)	7.85 (0.920)	8.24 (0.970)	8.16 (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							
Dapa + Saxa + Met vs Saxa + Met^a				Dapa + Saxa + 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	-
Dapa + Saxa + Met vs Dapa + Met^b				Dapa + Saxa + 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	-	-	-

N is the number of randomised subjects who took at least one dose of double-blind study medication. N# corresponds to the number of randomised subjects with non-missing baseline value and at least one post-baseline value. N## is the number of randomised subjects with non-missing baseline and Week 24 values. Primary endpoint is tested at alpha=0.05. Logistic regression based on the method of Zhang, Tsiatis and Davidian and Tsiatis, Davidian, Zhang and Lu, with the adjustment for baseline HbA1c.

^a Placebo matching dapagliflozin 10 mg was used.

Placebo matching saxagliptin 5 mg was used.

CI Confidence interval; Dapa Dapagliflozin; HbA1c Glycated haemoglobin A1c; Met Metformin; Pla Placebo; Saxa Saxagliptin; SD Standard deviation; vs Versus

Secondary endpoints

120-minute PPG change from baseline

In Study CV181169, the dapagliflozin + saxagliptin + metformin group had a greater adjusted mean reduction from baseline only when compared with the saxagliptin + metformin group (-2.44 mmol/L, $p < 0.0001$), while the difference from the dapagliflozin + metformin group was non-significant (-0.51 mmol/L, $p = 0.0640$).

In Study CV181168, the difference between the saxagliptin + dapagliflozin + metformin group and the placebo + dapagliflozin + metformin group was non-significant (-0.32 mmol/L, $p = 0.2054$).

In Study MB102129, the adjusted mean changes from baseline in 120-minute PPG at Week 24 were -4.08 mmol/L in the dapagliflozin + saxagliptin + metformin group and -2.11 mmol/L in the placebo + saxagliptin + metformin group. The difference in the adjusted mean change from baseline between the treatment groups was -1.97 mmol/L ($p < 0.0001$).

FPG change from baseline

Note, no formal statistical testing was performed for FPG or subsequent secondary endpoints in studies CV181169 and CV181168 as the previous secondary efficacy endpoint (PPG) had not been met and hierarchical significance testing for the other secondary endpoints was therefore stopped.

In Study CV181169, the adjusted mean changes in FPG from baseline at Week 24 (excluding data after rescue) for the dapagliflozin + saxagliptin + metformin group, saxagliptin + metformin group, and dapagliflozin + metformin group were -2.10 mmol/L, -0.78 mmol/L, and -1.76 mmol/L, respectively). The 95% CI for the difference between the treatment groups excluded zero for the comparison of dapagliflozin + saxagliptin + metformin versus saxagliptin + metformin (-1.32 mmol/L [95% CI: -1.76, -0.88]), but not for the comparison versus dapagliflozin + metformin (0.34 mmol/L [95% CI: -0.77, 0.09]).

In Study CV181168, the adjusted mean changes from baseline in FPG at Week 24 in the saxagliptin + dapagliflozin + metformin group and placebo + dapagliflozin + metformin group were -0.50 mmol/L, and -0.30 mmol/L, respectively, with a difference of -0.20 mmol/L (95% CI; -0.61, 0.20) between the treatment groups.

In Study MB102129, the adjusted mean changes from baseline in FPG at Week 24 in the dapagliflozin + saxagliptin + metformin group and placebo + saxagliptin + metformin group were -1.81 mmol/L, and -0.29 mmol/L, respectively, with a statistically significant difference of -1.52 mmol/L ($p < 0.0001$) between the treatment groups.

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

In Study CV181169, the proportion of subjects achieving HbA1c <7% at Week 24 was nearly 2-fold higher in the dapagliflozin + saxagliptin + metformin group (41.4%) compared with the saxagliptin + metformin group (18.3%) and the dapagliflozin + metformin group (22.2%). The adjusted differences between the dapagliflozin + saxagliptin + metformin group and the saxagliptin + metformin and dapagliflozin + metformin groups were 23.1% (95% CI: 14.7, 31.5) and 19.1% (95% CI: 10.1, 28.1), respectively. The 95% CIs for the differences excluded zero for both comparisons.

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 ($p < 0.0001$).

Body weight change from baseline

The mean change from baseline in total body weight after 24 weeks of treatment was a secondary efficacy endpoint for studies CV181169, and MB102129, while for Study CV181168 it was an exploratory efficacy endpoint.

In Study CV181169, the adjusted mean change from baseline in body weight at Week 24 (excluding data after rescue) was -2.05 kg in the dapagliflozin + saxagliptin + metformin group and -2.39 kg in the dapagliflozin + metformin group, while the saxagliptin + metformin group had no change (0.00). Almost 20% of subjects with a baseline BMI of ≥ 25 kg/m² achieved at least a 5% decrease in body weight in the dapagliflozin-containing treatment groups: the proportions were 17.5% for dapagliflozin + saxagliptin + metformin, 7.0% for saxagliptin + metformin, and 19.0% for dapagliflozin + metformin.

In Study CV181168, both treatment groups had similar small mean changes in body weight at Week 24 from baseline: -0.53 kg for the saxagliptin + dapagliflozin + metformin group and -0.51 kg for the placebo + dapagliflozin + metformin group. Both groups had been treated with dapagliflozin during the open-label treatment period preceding randomisation. The mean change in body weight after 14 weeks of open-label treatment (at the double-blind treatment period baseline) was -1.85 kg.

In Study MB102129, the adjusted mean changes from baseline at Week 24 in body weight were -1.91 kg in the dapagliflozin + saxagliptin + metformin group and -0.41 kg in the placebo + saxagliptin + metformin group. The difference between the treatment groups, -1.50 kg, was statistically significant ($p < 0.0001$).

Change in HbA1c and FPG 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.

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). Open-label treatment with dapagliflozin and metformin led to a 2.64 mmol/L decrease in FPG (95% CI: 2.93, -2.35) from open-label baseline to Week 2.

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). The mean change in FPG from baseline to Week -2 with saxagliptin + metformin treatment was -1.58 mmol/L for Stratum A (95% CI: -1.98, -1.17) and -0.68 mmol/L (95% CI: -1.16, -0.21) in Stratum B.

After the open-label treatment period in Studies CV181168 and MB102129, 1 of the entry criteria for the double-blind treatment period was HbA1c $\geq 7\%$ and $\leq 10.5\%$. In Study CV181168, 315 of the 431 subjects

who completed the open-label period met the entry criteria for the 24-week, ST, double-blind treatment period; in Study MB102129, 320 of the 402 subjects who completed the open-label period met the entry criteria. This means that at least 73% of subjects in CV181168 did not achieve a therapeutic glycaemic response after open-label treatment with dapagliflozin 10 mg + metformin and at least 80% of subjects in MB102129 did not achieve a therapeutic glycaemic response with saxagliptin 5 mg + metformin. This shows that, even in a randomised controlled trial environment, most patients do not achieve HbA1c treatment goals with the individual mono-components added to metformin.

Ancillary analyses

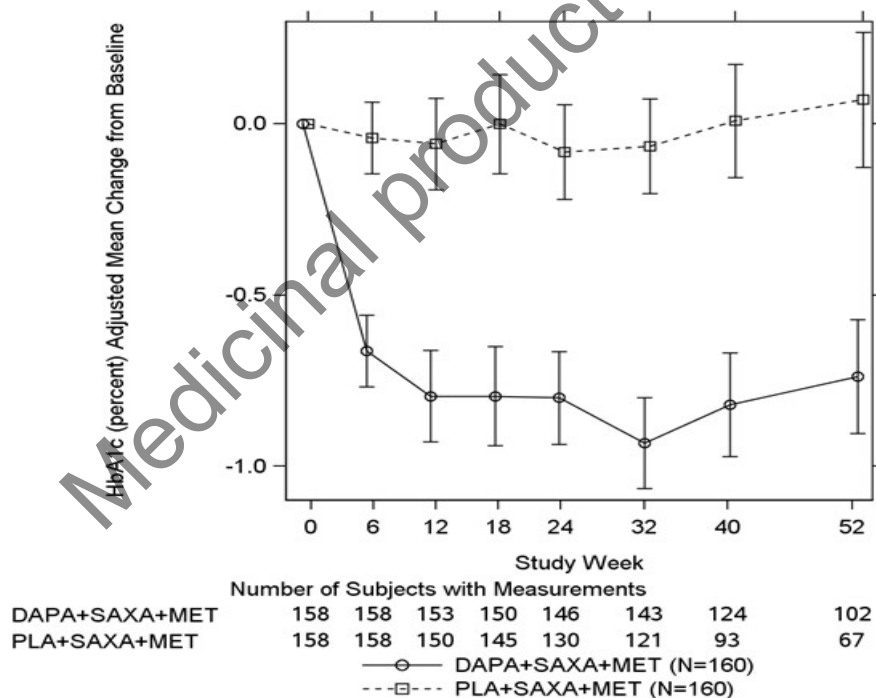
Analysis of efficacy in long-term extension studies (MB102129 and CV181168)

HbA1c change from baseline at Week 52

Study MB102129

The exploratory analysis of adjusted mean change from baseline in HbA1c over time in the ST + LT (52-week) treatment period, excluding data after rescue, showed larger reductions at each time point in the dapagliflozin + saxagliptin + metformin group compared with the placebo + saxagliptin + metformin group (Figure 8). At Week 52, the adjusted mean changes from baseline in HbA1c (excluding data after rescue) in the dapagliflozin + saxagliptin + metformin and placebo + saxagliptin + metformin groups were -0.74% (95% CI: -0.90, -0.57) and 0.07% (95% CI: -0.13, 0.27), respectively. The difference in the adjusted mean change from baseline between the treatment groups was -0.81% (95% CI: -1.06, -0.55).

Figure 8 Longitudinal plot of change from baseline in HbA1c, short-term plus long-term treatment period, excluding data after rescue, randomised subjects, Study MB102129



Randomised subjects are those who were randomised and received at least one dose of double-blind medication during the short-term plus long-term treatment.

Mean refers to mean change from baseline based on a mixed model with treatment, baseline value, week, stratum, week-by-treatment interaction, and week-by-baseline interaction as independent variables.

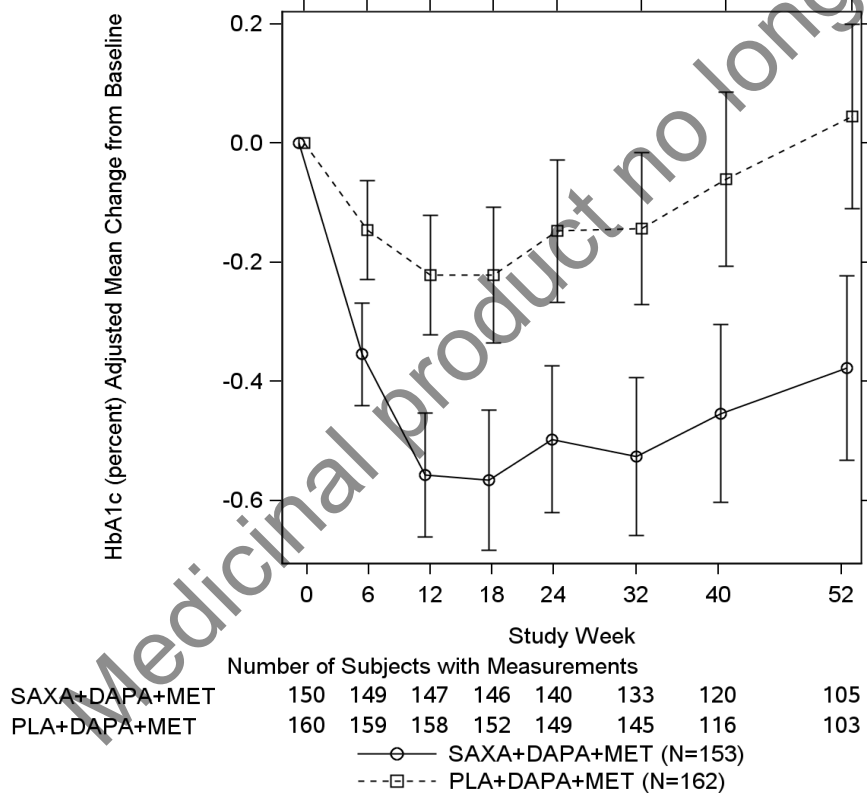
Error bars represent 95% confidence intervals for the adjusted mean change from baseline.

DAPA Dapagliflozin; HbA1c Glycated haemoglobin A1c; MET Metformin; N Number of randomised subjects who took at least one dose of double-blind study medication; PLA Placebo; SAXA Saxagliptin.

Study CV181168

The exploratory analysis of adjusted mean change from baseline in HbA1c over time in the ST + LT (52-week) treatment period, excluding data after rescue, demonstrated greater reductions at each time point in the saxagliptin + dapagliflozin + metformin group than in the placebo + dapagliflozin + metformin group (Figure 9). Adjusted mean reductions from baseline in HbA1c with saxagliptin + dapagliflozin + metformin were seen as early as Week 6, the earliest time point assessed, and continued through the long-term period. At Week 52, the adjusted mean changes from baseline in HbA1c (excluding data after rescue) in the saxagliptin + dapagliflozin + metformin and placebo + dapagliflozin + metformin groups were -0.38% (95% CI: -0.53, -0.22) and 0.05% (95% CI: -0.11, 0.20), respectively. The difference in adjusted mean change from baseline in HbA1c between the 2 treatment groups was -0.42% (95% CI: -0.64, -0.20).

Figure 9 Longitudinal plot of adjusted mean change from baseline in HbA1c during the 52 week double-blind period in Study CV181168, excluding data after rescue, randomised subjects



Randomised subjects are those who were randomised and received at least one dose of double-blind medication during the short-term plus long-term treatment.

Mean refers to mean change from baseline based on a mixed model with treatment, baseline value, week, week-by-treatment interaction, and week-by-baseline interaction as independent variables.

Error bars represent 95% confidence intervals for the adjusted mean change from baseline.

Dapa Dapagliflozin; HbA1c Glycated haemoglobin A1c; Met Metformin; Saxa Saxagliptin.

FPG adjusted mean change in from baseline at Week 52

Study MB102129

At Week 52, the adjusted mean changes from baseline in FPG in the dapagliflozin + saxagliptin + metformin and placebo + saxagliptin + metformin groups were -1.49 mmol/L and 0.57 mmol/L, respectively. The difference in adjusted mean change from baseline for dapagliflozin + saxagliptin + metformin versus placebo + saxagliptin + metformin was -2.06 mmol/L (95% CI: -2.68, -1.44).

Study CV181168

At Week 52, the difference in adjusted adjusted mean change from baseline in FPG in the saxagliptin + dapagliflozin + metformin and placebo + dapagliflozin + metformin groups were -0.51 mmol/L and -0.05 mmol/L, respectively. The difference between the treatment groups in adjusted mean change from baseline in FPG at Week 52 was -0.45 mmol/L (95% CI: -0.90, 0.00).

Proportion of subjects achieving therapeutic glycaemic response of HbA1c <7% at Week 52

Study MB102129

At Week 52, the adjusted percentage of subjects with HbA1c <7.0% was 29.4% in the dapagliflozin + saxagliptin + metformin group and 12.6% in the placebo + saxagliptin + metformin group. The adjusted percent difference between the treatment groups was 16.8% (95% CI: 8.4, 25.2).

Study CV181168

At Week 52, the adjusted percentage of subjects achieving a therapeutic glycaemic response was 29.3% in the saxagliptin + dapagliflozin + metformin group and 13.1% in the placebo + dapagliflozin + metformin group. The adjusted percent difference at between the treatment groups was 16.2% (95% CI: 8.1, 24.2).

Body weight change from baseline at Week 52

Study MB102129

At Week 52, adjusted mean change from baseline in body weight was -2.13 kg in the dapagliflozin + saxagliptin + metformin group and -0.37 in the placebo + saxagliptin + metformin group. The difference in the adjusted mean change from baseline between the treatment groups was -1.76 kg (95% CI: -2.61, -0.90).

Study CV181168

Subjects in the saxagliptin + dapagliflozin + metformin and placebo + dapagliflozin + metformin groups demonstrated similar mean changes in body weight (-1.13 kg versus -1.50 kg, respectively) at Week 52.

Summary of main study(ies)

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 7 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/m ² at the screening visit. Subjects with moderate or severe impairment of renal function were excluded.							
	<table border="1"> <tr> <td>Screening period:</td> <td>Up to 2 weeks</td> </tr> <tr> <td>Lead-in period:</td> <td>4 weeks</td> </tr> <tr> <td>Main treatment phase</td> <td>24 weeks</td> </tr> <tr> <td>Efficacy and safety Extension phase:</td> <td>28 weeks</td> </tr> </table>	Screening period:	Up to 2 weeks	Lead-in period:	4 weeks	Main treatment phase	24 weeks	Efficacy and safety Extension phase:
Screening period:	Up to 2 weeks							
Lead-in period:	4 weeks							
Main treatment phase	24 weeks							
Efficacy and safety Extension phase:	28 weeks							
Hypothesis	Superiority							
Treatments groups	Saxa+Dapa+Met 179 patients randomised	5mg+10mg+ ≥ 1500 mg						
	Saxa+Met 176 patients randomised	5mg+ ≥ 1500 mg						
	Dapa+Met 179 patients randomised	10mg+ ≥ 1500 mg						
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								

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 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=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)	

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): 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]	
		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 8 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
Hypothesis		Superiority
Treatments groups		Saxa+Dapa+Met 153 patients randomised
		5mg+10mg+≥1500mg
		Pla+Dapa+Met 162 patients randomised
		Pla+10mg+≥1500mg
Endpoints and definitions		Primary endpoint
		Change in HbA1c (%) Change from baseline to week 24
		Secondary endpoints

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)	
	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]
		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

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)			
	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) [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 9 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:	Up to 2 weeks	
	Open-Label treatment phase:	Up to 16 weeks	
	Main treatment phase	24 weeks	
	Efficacy and safety Extension phase:	28 weeks	
Hypothesis	Superiority		
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	Primary endpoint		

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)	
definitions	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
		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]

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)		
		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
		Baseline: Mean (SD)	9.91 (2.700)
		Change from baseline to endpoint (Week 24): Adj mean (SE) [95% CI]	-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
		HbA1c<7%	58 (36.7)
		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

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials	598/3192	26/3192	0
- Dapa 10 + Saxa 5 + Met	243/598	10/26	0
Non Controlled trials	0	0	0

No studies were conducted specifically to address the efficacy of dapagliflozin + saxagliptin in special populations. In all 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, Sex, Age, Female/Age, Region, Duration of T2DM and Baseline eGFR.

Treatment with sequential or concomitant administration of dapagliflozin and saxagliptin on a background of metformin, glimepiride + metformin, or metformin ± SU resulted in reductions in HbA1c irrespective of the

baseline level of HbA1c. There were no interactions between baseline HbA1c and treatment (the interaction p-values were above the 0.1 threshold) in any of the studies.

No potential treatment interactions (p-values >0.10) were detected for age or sex subgroups in CV181169, CV181168, MB102129, or CV181369, or for race in studies CV181169 and CV181168. In Studies MB102129 and D1689C00014, over 90% of the subjects were White, and potential interactions based on race could therefore not be evaluated.

Potential treatment interactions were detected for race in Study CV181369, age in Studies CV181365 and D1689C00014, region in Study CV181169, and female age in Study CV181169. It should be noted that the subgroup analyses were exploratory in nature and included subgroups with few subjects.

A subgroup analysis by disease duration was performed in Study CV181169. No potential treatment-by-disease duration interaction was observed.

A subgroup analysis by GFR was performed in Studies CV181365, D1689C00014, and CV181369. No potential treatment-by-GFR interactions were observed in any of the studies.

Supportive study(ies)

Three supportive studies have been submitted. The studies compared dapagliflozin + saxagliptin + metformin with glimepiride + metformin (CV181365 and D1689C00014) and dapagliflozin + saxagliptin + metformin ± SU with insulin + metformin ± SU (CV181369).

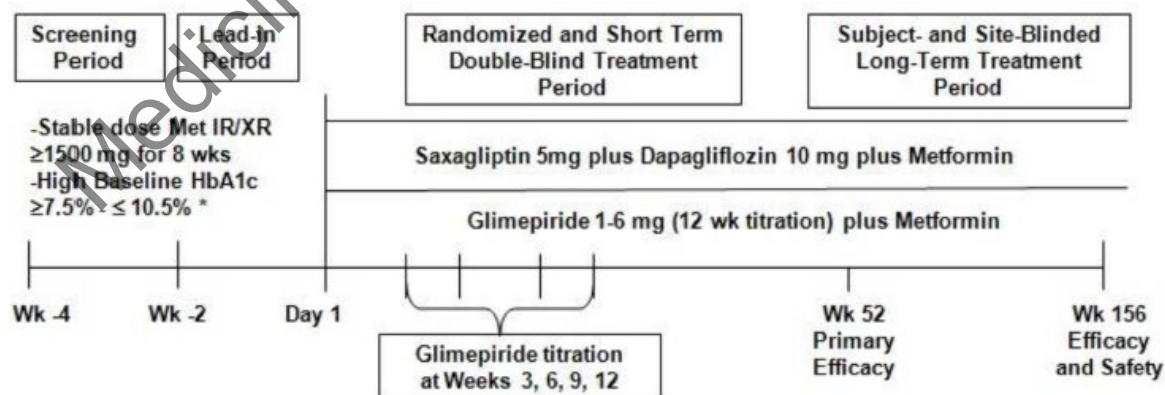
Methods

Study CV181365

Study CV181365 was a 52-week international, multicentre, randomised, double-blind, active-controlled, parallel group, Phase 3b trial with a blinded 104-week long-term extension period to evaluate the efficacy and safety co-administered dapagliflozin 10 mg and saxagliptin 5 mg added to metformin compared with glimepiride (1 mg to 6 mg) added to metformin in adult subjects with T2DM who had inadequate glycaemic control on metformin monotherapy. Study data from the first 52-week period is submitted.

The study design is illustrated in Figure 10.

Figure 10 Design of Study CV181365



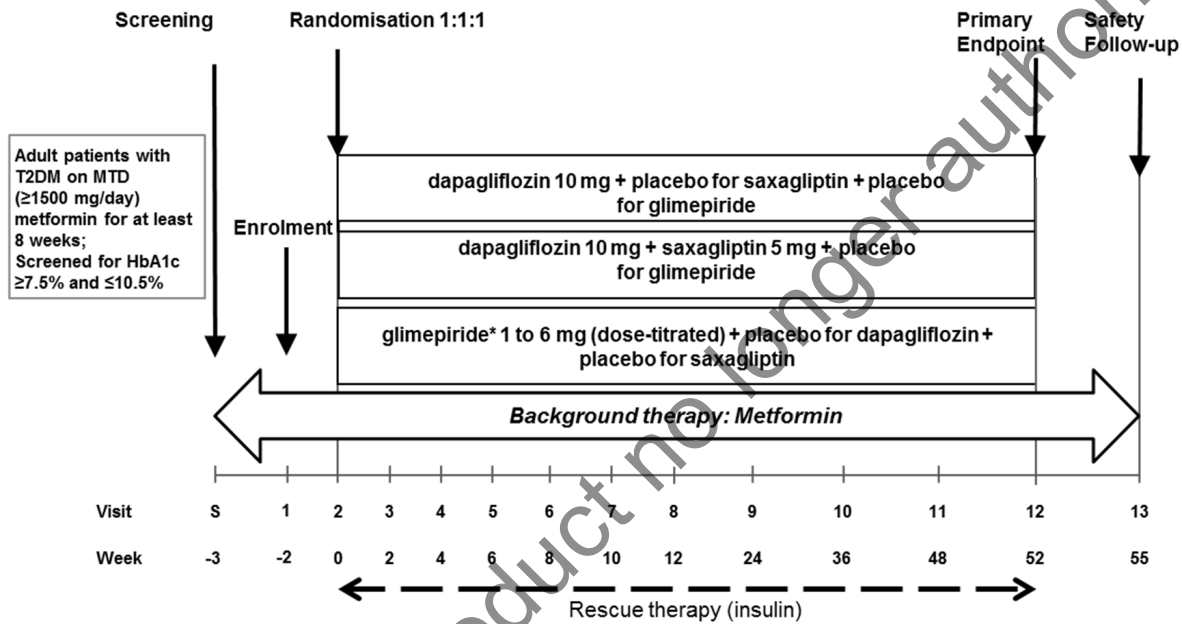
HbA1c Glycated haemoglobin A1c; IR Immediate release; Met Metformin; Wk Week; XR Extended release.

Study D1689C00014

Study D1689C00014 was a 52-week, multicentre, randomised, parallel-group, double-blind, double-dummy, active-controlled, Phase 4 study to evaluate the efficacy and safety of dapagliflozin added to metformin and dapagliflozin and saxagliptin added to metformin compared with SU (glimepiride) added to metformin in adult subjects with T2DM who had inadequate glycaemic control on a maximum tolerated dose of ≥ 1500 mg of metformin monotherapy and with individual need for therapy escalation.

The study design is illustrated in Figure 11.

Figure 11 Design of Study D1689C00014



*Note: Glimepiride treatment began at 1 mg/day and was titrated (upwards or downwards) in 1-mg increments at subsequent visits, as needed. In the event that a subject developed recurrent hypoglycaemia episodes with the 1-mg dose, down titration to 0 mg was allowed during the study.

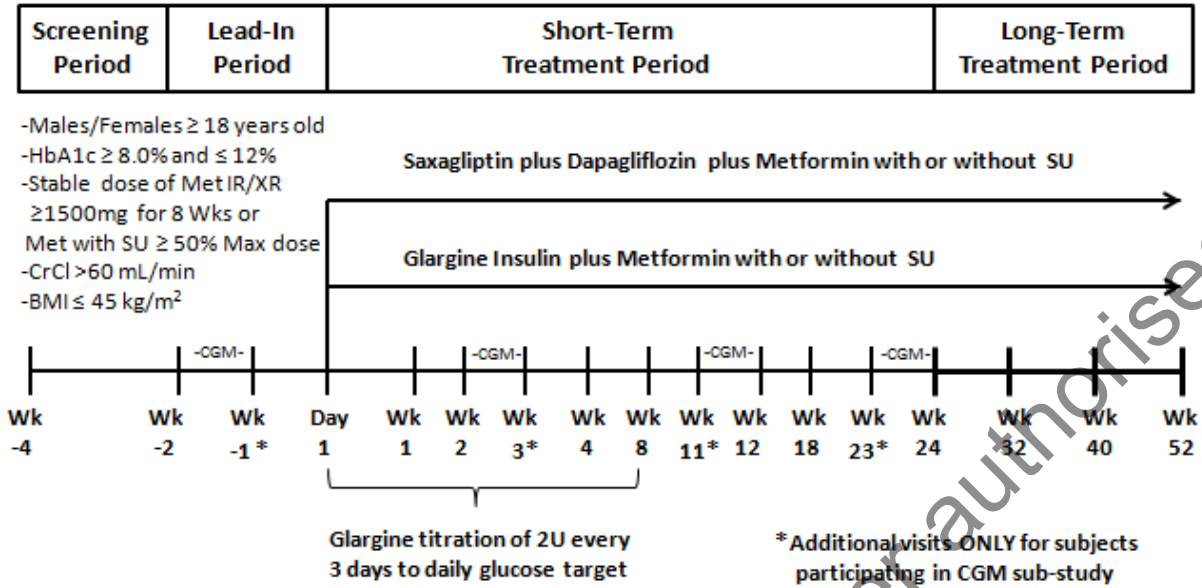
HbA1c Glycated haemoglobin A1c; MTD Maximum tolerated dose; T2DM Type 2 diabetes mellitus.

Study CV181369

Study CV181369 was a multicentre, randomised, open-label, 2-arm, parallel-group, active controlled, Phase 3b study to evaluate the efficacy and safety of saxagliptin co administered with dapagliflozin compared to insulin glargine in adult subjects with T2DM who had inadequate glycaemic control on metformin with or without SU therapy. The study included a 24-week short-term (ST) treatment period followed by a 28-week LT extension period. The subjects continued on the same open-label randomised medication and the stable dose of metformin with or without SU during the LT extension period. Only the data up to 24 weeks are included in this submission.

The study design is illustrated in Figure 12.

Figure 12 Design of study CV181369



BMI Body mass index; CGM Continuous glucose monitoring; CrCl Creatinine clearance; HbA1c Glycated haemoglobin A1c; IR Immediate release; Max Maximum; Met Metformin; SU Sulphonylurea; U Unit; Wk Week; XR Extended release.

• **Study population**

The target populations in all studies were male and female subjects aged ≥18 years (≥18 years to <75 years in Study D1689C00014) with T2DM and inadequate glycaemic control on metformin alone (Studies CV181365, and D1689C00014), or on metformin with or without a stable dose of SU (CV181369). 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 ≥1.0 ng/mL (0.33-0.34 nmol/L), and have a BMI ≤45.0 kg/m² at the screening visit. Subjects with moderate or severe impairment of renal function were excluded.

• **Dose selection and control treatment**

In all studies, dapagliflozin 10 mg and saxagliptin 5 mg were used as study medication. These dapagliflozin and saxagliptin doses are approved within the EU for the individual drugs and are the recommended doses.

In Studies CV181365 and D1689C00014, dapagliflozin 10 mg and matching placebo tablets, saxagliptin 5 mg and matching placebo tablets, and glimepiride 1-, 2-, or 4-mg capsules and matching placebo capsules were used as study medication.

In Study CV181369, dapagliflozin 10 mg, saxagliptin 5 mg, and insulin glargine 100 units/mL were used as study medication.

Rescue medication

In all studies, subjects were eligible for treatment with open-label rescue medication, in addition to their treatment regimen, in order to treat ongoing hyperglycaemia. Prespecified glycaemic criteria based upon central laboratory FPG and repeated, confirmatory FPG were established to determine eligibility for initiation of open-label rescue medication during the double-blind treatment period.

Following completion of the rescue visit procedures, rescued subjects were given open-label antidiabetic rescue medication, in addition to their double-blinded study drug. Rescued subjects continued in the double-blind treatment period according to their original visit schedule.

- **Objectives**

The primary objectives are listed below.

Study CV181365

To compare the mean change from baseline in HbA1c achieved with dapagliflozin + saxagliptin + metformin, compared with glimepiride + metformin at Week 52.

Study D1689C00014

To compare the absolute change from baseline in HbA1c at Week 52 between dapagliflozin + metformin and dapagliflozin + saxagliptin + metformin with glimepiride + metformin.

Study CV181369

To examine whether the mean change from baseline in HbA1c with co administered dapagliflozin 10 mg + saxagliptin 5 mg plus metformin with or without SU is non-inferior to titrated insulin glargine plus metformin with or without SU after 24 weeks of open-label treatment.

- **Statistical methodology**

All efficacy analyses were based on all randomised patients who took at least one dose of the study medication with no exclusions based on protocol deviations.

For Study CV181369, the primary efficacy endpoint was the change in HbA1c from baseline to Week 24. For Studies CV181365 and D1689C00014, the primary efficacy endpoint was the change in HbA1c from baseline to Week 52.

The primary efficacy analyses were performed using a longitudinal repeated measures analysis with terms for baseline value, treatment group, 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.

In Study CV181369, the primary endpoint was tested for noninferiority for saxagliptin plus dapagliflozin versus insulin at the $\alpha=0.025$ level (1-sided), within a noninferiority margin of 0.30%. If noninferiority was demonstrated for the primary endpoint, the statistical tests within the hierarchy for the secondary efficacy endpoints, including superiority testing, were to be performed.

The following sensitivity analyses were carried out for the primary endpoint:

- Primary analysis was repeated using evaluable subjects data set.
- Primary analysis was repeated using all available values regardless of rescue or treatment discontinuation.

- An analysis of covariance (ANCOVA) analysis using values prior to rescue or treatment discontinuation (LOCF was used if the Week 52 value was not available)
- Analysis using multiple imputation return-to-baseline (not performed in D1689C00014)
- Tipping point analysis (not performed in D1689C00014).

Secondary endpoints were assessed at Week 24 for Study CV181369, and Week 52 in Studies CV181365 and D1689C00014.

Analyses of continuous secondary endpoints such as the mean change from baseline for FPG (CV181365), total body weight (D1689C00014, CV181369), mean value of 24-hour glucose readings from CGM (CV181369), or SBP (CV181365) were performed using a similar longitudinal repeated measures model as for the primary efficacy endpoint. The proportion of subjects achieving therapeutic glycaemic response (defined as HbA1c <7.0%; all studies) were based on the methodology of Zhang et al 2008 and Tsiatis et al 2007 with adjustment for baseline HbA1c value. The proportion of subjects reporting confirmed hypoglycaemia (CV181365, D1689C00014, and CV181369) were summarised by treatment group and compared between treatment groups using logistic regression with baseline HbA1c as a covariate. Time to rescue was analysed using a Cox proportional hazards model; estimates of the hazard ratio and 95% CI are provided (CV181365 and D1689C00014). Analyses of the mean change from baseline in MAGE at Week 52 were performed using the ANCOVA model based on LOCF data (CV181365).

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. The order was pre-specified.

Results

• Participant flow

Study CV181365

Of the 823 subjects enrolled in study CV181365, 466 (56.6%) entered the treatment period. The most common reason for not entering the treatment period was failure to meet inclusion/exclusion criteria (326 subjects).

Of the 466 subjects who entered the treatment (lead-in) period, 444 subjects were randomised. The most common reason for not completing the lead-in period was failure to meet inclusion/exclusion criteria (9 subjects).

Study D1689C00014

A total of 1358 subjects were enrolled in Study D1689C00014, of which 939 subjects were randomised and a total of 867 (92.3%) subjects completed the study.

Table 10. Disposition of subjects – Studies D1689C00014 and CV181365

	Study D1689C00014 (52 weeks)				Study CV181365 (52 weeks)		
	Dapa + Saxa + Met	Dapa + Met	Glim + Met	Total	Dapa + Saxa + Met	Glim + Met	Total
Subjects randomised	312	314	313	939	227	217	444

	Study D1689C00014 (52 weeks)				Study CV181365 (52 weeks)		
	Dapa + Saxa + Met	Dapa + Met	Glim + Met	Total	Dapa + Saxa + Met	Glim + Met	Total
Subjects who did not receive randomised treatment					0	1 (0.5)	1 (0.2)
Subjects who completed the study ^a	298 (95.5)	281 (89.5)	288 (92.0)	867 (92.3)	197 (86.8)	188 (87.0)	385 (86.9)
Subjects who discontinued the study ^a	14 (4.5)	33 (10.5)	25 (8.0)	72 (7.7)	17 (7.5)	23 (10.6)	40 (9.0)
Adverse event	1 (0.3)	7 (2.2)	2 (0.6)	10 (1.1)	1 (0.4)	1 (0.5)	2 (0.5)
Death	0	0	0	0	0	2 (0.9)	2 (0.5)
Lost to follow-up	1 (0.3)	1 (0.3)	3 (1.0)	5 (0.5)	6 (2.6)	6 (2.8)	12 (2.7)
Development of study-specific withdrawal criteria ^b	1 (0.3)	4 (1.3)	2 (0.6)	7 (0.7)	-	-	-
Protocol violation/Non-compliance with study medication ^c	0	1 (0.3)	0	1 (0.1)	0	2 (0.9)	2 (0.5)
Withdrawal by subject	4 (1.3)	8 (2.5)	5 (1.6)	17 (1.8)	9 (4.0)	9 (4.1)	18 (4.1)
Failure to meet randomisation (inclusion/exclusion) criteria	0	2 (0.6)	1 (0.3)	3 (0.3)	-	-	-
Subject request to discontinue study treatment ^d	-	-	-	-	1 (0.4)	1 (0.5)	2 (0.5)
Other	7 (2.2)	10 (3.2)	12 (3.8)	29 (3.1)	0	2 (0.9)	2 (0.5)

^a For Study D1689C00014, the completion (and discontinuation) status was determined from the disposition page of the CRF. For Study CV181365, the numbers represent the number of subjects who completed (or discontinued) the 52-week open-label treatment period.

^b This criterion was used in Study D1689C00014.

^c Protocol violation in Study D1689C00014 and non-compliance with study medication used in Study CV181365.

^d This criterion was used in Study CV181365.

Note: Percentages were based on the number of subjects randomised.

Dapa Dapagliflozin; Glim Glimepiride; Met Metformin; Saxa Saxagliptin; SU Sulphonylurea.

Study CV181369

A total of 1163 subjects were enrolled in Study CV181369, of which 707 subjects entered the lead-in period. A total of 650 subjects were randomised. Seven subjects in the insulin + metformin group never received study medication, and 643 subjects were randomised and received treatment.

Table 11 Disposition of subjects – Study CV181369

	Study CV181369 (24 weeks)		
	Dapa + Saxa + Met ± SU	Insulin + Met ± SU	Total
Subjects randomised	324	326	650
Subjects who completed the study ^a	298 (92.0)	286 (89.7)	584 (90.8)
Subjects who discontinued the study ^a	26 (8.0)	33 (10.3)	59 (9.2)
Adverse event	5 (1.5)	1 (0.3)	6 (0.9)
Death	1 (0.3)	0	1 (0.2)
Lost to follow-up	8 (2.5)	11 (3.4)	19 (3.0)
Non-compliance with study medication	0	3 (0.9)	3 (0.5)
Withdrawal by subject	6 (1.9)	10 (3.1)	16 (2.5)
Failure to meet randomisation (inclusion/exclusion) criteria	4 (1.2)	0	4 (0.6)
Administrative reason by sponsor	0	1 (0.3)	1 (0.2)
Subject request to discontinue study treatment	2 (0.6)	3 (0.9)	5 (0.8)
Other	0	4 (1.3)	4 (0.6)

^a The number of subjects who completed (or discontinued) the 24-week open-label treatment period.

Note: Percentages were based on the number of subjects randomised.

Dapa Dapagliflozin; Glim Glimepiride; Met Metformin; Saxa Saxagliptin; SU Sulphonylurea.

- **Baseline data**

The demographics and disease characteristics of the subjects are summarised for Study D1689C00014 and CV181369 in Table 12.

In study CV181365, the overall mean age was 56.1 years, sex distribution was balanced, the mean duration of T2DM was 7.8 years, and the mean baseline HbA1c was 8.45% (Table 12). Two hundred and fifty-five (57.6%) subjects were from Europe while 25.3% were from North America, and 17.2% were from Latin America. The majority of subjects were White (90.1%), 4.7% were American Indian or Alaska Native, 2.0% were Black or African American, 0.2% were Native Hawaiian or other Pacific Islander, and 2.9% were of other racial origin.

In Study D1689C00014, the overall mean age was 58.4 years, 339 (36.1%) subjects were female, the mean duration of T2DM was 6.96 years, and the mean baseline HbA1c was 8.28% (Table 12). All subjects were from Europe and almost all subjects were White (98.9% subjects).

The subjects enrolled in Study CV181369 were more advanced in the disease state than the other studies. The overall mean age was 55.5 years, 296 (46.0%) subjects were female, the mean duration of T2DM was 9.41 years, and the mean baseline HbA1c was 9.05% (Table 13). Approximately half (52.3%) of the subjects were from North America, while 35.5% were from Europe, and 12.3% were from Latin America. The majority of subjects were White (80.4%), while 9.8% were Black or African American, 3.7% were Asian, 3.1% were Other ethnic origin, 2.8% were American Indian or Alaska Native, and 0.2% were Native Hawaiian or Other Pacific Islander.

Table 12 Subject demographics and baseline characteristics – Studies D1689C00014 and CV181365 (randomised subjects) (abbreviated)

	Study D1689C00014 (52 weeks)				Study CV181365 (52 weeks)		
	Dapa + Saxa + Met (N=312)	Dapa + Met (N=314)	Glim + Met (N=313)	Total (N=939)	Dapa + Saxa + Met (N=227)	Glim + Met (N=216)	Total (N=443)
Age (mean [SD]), years	59.2 (7.87)	57.4 (9.36)	58.6 (8.38)	58.4 (8.58)	56.1 (10.11)	56.1 (9.23)	56.1 (9.68)
Age, n (%)							
<65 years	226 (72.4)	232 (73.9)	226 (72.2)	684 (72.8)	182 (80.2)	171 (79.2)	353 (79.7)
≥65 to <75 years	86 (27.6)	81 (25.8)	85 (27.2)	252 (26.8)	43 (18.9)	42 (19.4)	85 (19.2)
≥75 years	0	1 (0.3)	2 (0.6)	3 (0.3)	2 (0.9)	3 (1.4)	5 (1.1)
Sex, n (%)							
Male	190 (60.9)	202 (64.3)	208 (66.5)	600 (63.9)	117 (51.5)	101 (46.8)	218 (49.2)
Female	122 (39.1)	112 (35.7)	105 (33.5)	339 (36.1)	110 (48.5)	115 (53.2)	225 (50.8)
Weight (mean [SD] kg)	95.33 (17.42)	97.73 (18.91)	97.30 (17.88)	96.79 (18.09)	91.0 (19.76)	88.4 (17.09)	89.7 (18.53)
BMI (mean [SD] kg/m ²)	32.53 (5.11)	33.07 (5.16)	33.04 (5.13)	32.88 (5.13)	32.4 (5.33)	32.2 (5.12)	32.3 (5.23)
T2DM duration (mean [SD] years)	7.33 (5.94)	6.85 (5.20)	6.71 (5.09)	6.96 (5.42)	7.70 (6.35)	7.90 (6.46)	7.80 (6.40)
HbA1c (mean [SD] %)	8.26 (0.67)	8.27 (0.73)	8.31 (0.75)	8.28 (0.72)	8.41 (0.82)	8.50 (0.82)	8.45 (0.82)
FPG (mean [SD] mmol/L) ^a	10.5 (2.01)	10.6 (2.29)	10.4 (2.10)	10.5 (2.14)	9.51 (2.30)	9.71 (2.35)	9.69 (2.33)
C-peptide (mean [SD] nmol/L)	0.920 (0.373)	0.926 (0.357)	0.933 (0.343)	0.926 (0.358)	-	-	-
eGFR (mean [SD] mL/min/1.73 m ²)	88.01 (19.61)	87.24 (19.42)	86.02 (17.47)	87.09 (18.86)	93.67 (23.028)	92.96 (21.147)	93.33 (22.109)

^a The unit for FPG measurements was mg/dL (mmol/L=[mg/dl]/18) in Study CV181369 and mmol/L in Study D1689C00014.

BMI Body mass index; Dapa Dapagliflozin; eGFR Estimated glomerular filtration rate; FPG Fasting plasma glucose; Glim Glimepiride; HbA1c Glycated haemoglobin A1c; Max Maximum; Met Metformin; Min Minimum; N Number of subjects in treatment group; n Number of subjects in analysis; ND Not done; Saxa Saxagliptin; SD Standard deviation; SU Sulphonylurea; T2DM Type 2 diabetes mellitus.

Table 13 Subject demographics and baseline characteristics – Study CV181369 (randomised subjects) (abbreviated)

	Dapa + Saxa + Met ± SU (N=324)	Insulin + Met ± SU (N=319)	Total (N=643)
Age (mean [SD]), years			
Age, n (%)			
<65 years	265 (81.8)	260 (81.5)	525 (81.6)
≥65 to <75 years	55 (17.0)	54 (16.9)	109 (17.0)
≥75 years	4 (1.2)	5 (1.6)	9 (1.4)
Sex, n (%)			
Male	176 (54.3)	171 (53.6)	347 (54.0)
Female	148 (45.7)	148 (46.4)	296 (46.0)
Weight (mean [SD] kg)	89.8 (17.65)	89.4 (18.44)	89.6 (18.03)
BMI (mean [SD] kg/m ²)	32.5 (5.29)	32.0 (5.35)	32.2 (5.32)
T2DM duration (mean [SD] years)	9.56 (6.47)	9.26 (6.19)	9.41 (6.33)
HbA1c (mean [SD] %)	9.04 (1.02)	9.05 (1.05)	9.05 (1.04)
FPG (mean [SD] mmol/L) ^a	189.53 (55.53)	188.55 (53.82)	189.04 (54.65)
eGFR (mean [SD] mL/min/1.73 m ²)	94.57 (23.65)	97.26 (21.75)	95.91 (22.75)

^b The unit for FPG measurements was mg/dL (mmol/L=[mg/dL]/18) in Study CV181369.

BMI Body mass index; Dapa Dapagliflozin; eGFR Estimated glomerular filtration rate; FPG Fasting plasma glucose; HbA1c Glycated haemoglobin A1c; Max Maximum; Met Metformin; Min Minimum; N Number of subjects in treatment group; n Number of subjects in analysis; ND Not done; Saxa Saxagliptin; SD Standard deviation; SU Sulphonylurea; T2DM Type 2 diabetes mellitus.

Study treatment compliance

Almost all subjects were compliant with study medication across the 3 studies.

In CV181365, almost all (99.1%) subjects were compliant (ie, took ≥80% to ≤120% of prescribed medication) with administration of study treatment during the 52-week double-blind treatment period. Four randomised subjects (0.9%) took <80% of prescribed medication.

In Study D1689C00014, almost all subjects were compliant study treatment: 99.1% in the dapagliflozin + saxagliptin + metformin group, 98.8% in the dapagliflozin + metformin group, and 98.7 in the glimepiride + metformin group.

In Study CV181369, almost all subjects were compliant study treatment: 99.4% in both the dapagliflozin + saxagliptin + metformin ± SU and insulin ± SU treatment groups.

● Outcomes and estimation

Primary efficacy endpoint: Change in HbA1c from baseline

The primary endpoint was met in all three studies as shown in Table 14 (Study CV181365 and Study D1689C00014) and Table 15 (Study CV181369).

Table 14 Change in HbA1c from baseline to endpoint – Studies D1689C00014 and CV181365

	Study D1689C00014 (52 weeks)			Study CV181365 (52 weeks)	
Statistic	Dapa + Saxa + Met (N=312)	Dapa + Met (N=311)	Glim + Met (N=309)	Dapa + Saxa + Met (N=227)	Glim + Met (N=216)
HbA1c (%) at Week 52					
N#	311	309	305	218	212
Baseline mean (SD)	8.26 (0.666)	8.27 (0.732)	8.31 (0.751)	8.40 (0.826)	8.49 (0.819)
	Week 52			Week 52	
N##	257	202	222	193	171
Mean (SD)	6.95 (0.655)	7.21 (0.672)	7.05 (0.737)	6.98 (0.987)	7.29 (1.028)
Adjusted mean change from baseline (SE)	-1.20 (0.046)	-0.82 (0.049)	-0.99 (0.048)	-1.35 (0.069)	-0.98 (0.071)
95% CI for adjusted mean change from baseline	-1.29, -1.11	-0.92, -0.73	-1.08, -0.89	-1.49, -1.22	-1.12, -0.84
	Dapa + Saxa + Met versus Glim + Met	Dapa + Met versus Glim + Met		Dapa + Saxa + Met versus Glim + Met	
Difference (SE)	-0.21 (0.067)	0.16 (0.069)	NA	-0.37 (0.099)	NA
95% CI for difference ^a	-0.3443, -0.0825	0.0294, 0.2986	NA	-0.57, -0.18	NA
p-value (2-sided)	0.001 ^b (*)	NA	NA	<0.001(*)	NA

^a An upper limit of the 2-sided 95% CI below 0.30% implies non-inferiority of Dapa + Saxa + Met or Dapa + Met compared with Glim + Met. The MMRM model included terms for treatment, baseline HbA1c, visit, treatment-by-visit interaction, and baseline HbA1c-by-visit interaction.

^b Superiority p-value for Dapa + Saxa + Met versus Glim + Met in Study D1689C00014 following the hierarchical closed testing procedure.

Note: Efficacy results are based on the randomised subject data set for Study CV181365 and the FAS for Study D1689C00014. N# is the number of subjects in the analysis data set with non-missing baseline and at least 1 post-baseline HbA1c value. N## is the number of subjects in the analysis data set with non-missing baseline and Week 52 HbA1c values. Values recorded after rescue treatment or collected more than 8 days after the last dose date were excluded from the analysis. (*) indicates a significant p-value.

CI Confidence interval; Dapa Dapagliflozin; FAS Full analysis set; Glim Glimperide; HbA1c Glycated haemoglobin A1c; Met Metformin; MMRM Mixed-model repeated measures; N Number of subjects in treatment group; NA Not applicable; Saxa Saxagliptin; SD Standard deviation; SE Standard error; SU Sulphonylurea.

Table 15 Change in HbA1c from baseline to endpoint – Study CV181369

Statistic	Dapa + Saxa + Met ± SU (N=324)	Insulin + Met ± SU (N=319)
HbA1c (%)		
N#	319	312
Mean (SD)	9.04 (1.023)	9.04 (1.054)
Week 24		
N##	285	283
Mean (SD)	7.27 (0.972)	7.44 (1.221)
Adjusted mean change from baseline (SE)	-1.67 (0.060)	-1.54 (0.061)
95% CI for adjusted mean change from baseline	-1.79, -1.55	-1.66, -1.42
Dapa + Saxa + Met versus Insulin + Met		
Difference (SE)	-0.13 (0.085)	
95% CI for difference ^a	-0.30, 0.03	NA
p-value (2-sided)	0.118	NA

^a An upper limit of the 2-sided 95% CI below 0.30% implies non-inferiority of Dapa + Saxa + Met compared with Insulin + Met (Study CV181369). The MMRM model included terms for treatment, baseline HbA1c, randomisation stratification factor (background medication of metformin with or without SU), visit, treatment-by-visit interaction, and baseline HbA1c-by-visit interaction.

Note: Efficacy results are based on the randomised subject data set. N# is the number of subjects in the analysis data set with non-missing baseline and at least 1 post-baseline HbA1c value. N## is the number of subjects in the analysis data set with non-missing baseline and Week 24 HbA1c values. Values recorded after rescue treatment or collected more than 8 days after the last dose date were excluded from the analysis. (*) indicates a significant p-value.

CI Confidence interval; Dapa Dapagliflozin; HbA1c Glycated haemoglobin A1c; Met Metformin; MMRM Mixed-model repeated measures; N Number of subjects in treatment group; NA Not applicable; Saxa Saxagliptin; SD Standard deviation; SE Standard error; SU Sulphonylurea.

In Study CV181369, the randomization was stratified by current use of background medication (metformin ± SU). Overall, 331 (51.5%) subjects received SU in addition to metformin as background medication, including 166 (51.2%) subjects in the dapagliflozin + saxagliptin + metformin group and 165 (51.7%) subjects in the insulin + metformin group. The change from baseline in HbA1c by the stratification factor (± SU) is summarised in Table 16. Firm conclusions are not possible because this analysis does not account for multiplicity.

Table 16 Change from baseline in HbA1c at Week 24 stratified by background medication - Study CV181369 (randomised subject set)

Statistic	With SU		Without SU	
	Dapa 10 mg + Saxa 5 mg + Met	Insulin + Met	Dapa 10 mg + Saxa 5 mg + Met	Insulin + Met
Baseline				
N#	164	161	155	151
Mean (SD)	8.94 (0.991)	9.06 (1.045)	9.15 (1.048)	9.02 (1.066)
Week 24				
N##	147	145	138	138
Mean (SD)	7.15 (0.873)	7.53 (1.237)	7.39 (1.056)	7.34 (1.200)
Adjusted LS mean change from baseline (SE)	-1.76 (0.083)	-1.43 (0.084)	-1.58 (0.086)	-1.66 (0.087)
95% CI for adjusted mean change from baseline	-1.93, -1.60	-1.59, -1.26	-1.74, -1.41	-1.83, -1.49
Difference (SE)	-0.34 (0.119)	NA	0.08 (0.122)	NA
95% CI for difference	-0.57, -0.10	NA	-0.16, 0.32	NA
p-value	0.005	NA	0.501	NA
Treatment by stratification factor interaction p-value ^a : 0.014				

^c LS mean, LS mean treatment difference, SE, CI, and p-value are obtained from an MMRM model with terms for treatment, baseline HbA1c, visit, subgroup, treatment-by-visit, baseline HbA1c-by-visit, treatment-by-subgroup, visit-by-subgroup, and treatment-by-visit-by-subgroup interaction. The unstructured covariance matrix was used to model the covariance structure. Test of the treatment-by-subgroup interaction has been assessed using contrasts of the treatment effect by subgroups at Week 24.

Note: N# is the number of subjects in the randomised subject data set with non-missing baseline and at least 1 post-baseline HbA1c value. N## is the number of subjects in the randomised subject data set with non-missing baseline and Week 24 HbA1c values. Values recorded after rescue treatment or collected more than 8 days after the last dose date were excluded from the analysis.

CI Confidence interval; Dapa Dapagliflozin; HbA1c Glycated haemoglobin A1c; LS Least squares; Met Metformin; MMRM Mixed-model repeated measures; NA Not applicable; Saxa Saxagliptin; SD Standard deviation; SE Standard error; SU Sulphonylurea.

Secondary endpoints

FPG change from baseline

In Study CV181365, the adjusted mean changes from baseline in FPG at Week 24 in the dapagliflozin + saxagliptin + metformin group and glimepiride + metformin group were -1.99 mmol/L, and -0.95 mmol/L, respectively, with a statistically significant difference of -1.04 mmol/L ($p < 0.001$) between the treatment groups.

In Study D1689C00014, the adjusted mean changes from baseline in FPG at Week 52 in the dapagliflozin + saxagliptin + metformin group, dapagliflozin + metformin group, and glimepiride + metformin group were -2.08 mmol/L, -1.62 mmol/L, and -1.49 mmol/L, respectively. The change from baseline in FPG in the dapagliflozin + saxagliptin + metformin group was significantly greater than the change in the glimepiride + metformin group (treatment group difference: -0.59 mmol/L, $p < 0.001$). The mean change from baseline was also nominally significantly greater between the dapagliflozin + saxagliptin + metformin group and the

dapagliflozin + metformin group based on a post hoc analysis (treatment group difference: -0.46; 95% CI: -0.75, -0.17; nominal p=0.002).

In Study CV181369, the mean change from baseline in FPG was not a pre-specified endpoint but FPG was collected throughout the study. The mean FPG value at Week 24 was 7.99 mmol/L (baseline value: 10.52 mmol/L) in the dapagliflozin + saxagliptin + metformin ± SU group and 7.61 mmol/L (baseline value: 10.46 mmol/L) in the insulin + metformin ± SU group.

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

In Study CV181365, the proportion of subjects achieving the glycaemic target of HbA1c <7.0% at Week 52 was 44.3% in the dapagliflozin + saxagliptin + metformin group and 34.3% in the glimepiride + metformin group. The odds ratio for the difference between the dapagliflozin + saxagliptin + metformin group and glimepiride + metformin group was 1.5 (95% CI: 1.01, 2.29, p=0.044).

In Study D1689C00014, the proportion of subjects achieving HbA1c <7.0% at Week 52 was numerically greater in the dapagliflozin + saxagliptin + metformin group (40.3%) than the dapagliflozin + metformin group (20.3%) and the glimepiride + metformin group (33.9%). The odds ratio for the difference between the dapagliflozin + saxagliptin + metformin group and glimepiride + metformin group was 1.31 (95% CI: 0.94, 1.84, p=0.112) and the odds ratio for the difference between the dapagliflozin + metformin and the glimepiride + metformin group was 0.50 (95% CI: 0.34-0.71; nominal p <0.001).

In Study CV181369, the proportion of subjects achieving HbA1c <7.0% at Week 24 was similar in the dapagliflozin + saxagliptin + metformin ± SU group and in the insulin + metformin ± SU group (33.2% and 33.5%, respectively; treatment difference: -0.4%; 95% CI: -7.42, 6.54). Non-inferiority of dapagliflozin + saxagliptin + metformin ± SU compared with insulin + metformin ± SU was demonstrated (non-inferiority defined by lower bound of 95% CI >-10%). The treatment by stratification factor interaction was nominally significant (nominal p=0.089). In the subgroup of subjects receiving metformin + SU at baseline, treatment with dapagliflozin + saxagliptin showed a greater relative difference versus insulin (odds ratio 1.3; 95% CI 0.81, 2.13; nominal p=0.262) compared with subjects receiving only metformin at baseline (odds ratio 0.7; 95% CI 0.44, 1.19; nominal p=0.200).

Body weight change from baseline

In Study CV181365, the adjusted mean changes from baseline at Week 52 in body weight were -3.11 kg in the dapagliflozin + saxagliptin + metformin group and 0.95 kg in the glimepiride + metformin group. The difference between the treatment groups, -4.06 kg (95% CI: -4.84, -3.28), was statistically significant (p<0.001).

In Study D1689C00014, the adjusted mean changes in body weight from baseline to Week 52 were -3.15 kg in the dapagliflozin + saxagliptin + metformin group, -3.54 kg in the dapagliflozin + metformin group, and 1.76 kg in the glimepiride + metformin group. The differences in mean change in body weight between the dapagliflozin + saxagliptin + metformin group and the glimepiride + metformin group (-4.91 kg; 95% CI: -5.52, -4.29) and between the dapagliflozin + metformin group and the glimepiride + metformin group (-5.30 kg; 95% CI: -5.93, -4.67) were significant (p<0.001 for both comparisons).

In Study CV181369, the adjusted mean (95% CI) change in body weight from baseline to Week 24 was -1.50 kg in the dapagliflozin + saxagliptin + metformin ± SU group and 2.14 kg in the insulin + metformin ± SU group. The mean difference between the treatment groups of -3.64 kg (95% CI: -4.20, -3.09) was statistically significant (p<0.001). The mean difference between treatment groups was evident already at

the first analysed time point (Week 4) (LS mean difference -1.46 kg; 95% CI -1.72, -1.20; nominal $p < 0.001$).

Proportion of subjects with confirmed hypoglycaemia

The proportion of subjects with confirmed hypoglycaemia was a key secondary endpoint in Studies D1689C00014 and Study CV181369. The results are presented separately below as confirmed hypoglycaemia was defined differently in the 2 studies.

In Study D1689C00014, confirmed hypoglycaemia was defined as symptomatic blood glucose ≤ 50 mg/dL (2.8 mmol/L). The proportion of subjects who had at least 1 episode of confirmed hypoglycaemia was significantly lower in the dapagliflozin + saxagliptin + metformin group than the glimepiride + metformin group (difference of -3.89%; 95% CI: -6.21, -1.56; $p < 0.001$); the comparison between the dapagliflozin + metformin group and glimepiride + metformin group was also significant (-4.21%; 95% CI: -6.45, -1.97; $p < 0.001$).

In Study CV181369, confirmed hypoglycaemia was defined as glucose ≤ 70 mg/dL (3.9 mmol/L). The proportion of subjects who had at least 1 episode of confirmed hypoglycaemia at Week 24 was significantly lower in the dapagliflozin + saxagliptin + metformin \pm SU group (21.3%) than in the insulin + metformin \pm SU group (38.4%) (odds ratio 0.4; 95% CI: 0.30, 0.62; $p < 0.001$). The treatment by stratification factor interaction was nominally significant ($p = 0.017$) but in both SU subgroups fewer subjects experienced confirmed hypoglycaemia in the dapagliflozin + saxagliptin + metformin group (with SU: 36.8%; without SU: 8.9%) than in the insulin + metformin group (with SU: 49.2%; without SU: 29.7%).

The adjusted percentage of subjects with symptomatic confirmed hypoglycaemia (defined as symptomatic blood glucose ≤ 50 mg/dL [2.8 mmol/L]) at Week 24 was 2.2% in the dapagliflozin + saxagliptin + metformin \pm SU group and 5.9% in the insulin + metformin \pm SU group (odds ratio: 0.4 [95% CI: 0.16, 0.79], nominal $p = 0.011$).

Proportion of subjects achieving a therapeutic glycaemic response defined as HbA1c <7.0% without any reported hypoglycaemia

The proportion of subjects who achieved a therapeutic glycaemic response (HbA1c <7.0%) without any reported hypoglycaemia was defined as a key secondary endpoint in Study CV181369 only.

In Study CV181365, the proportion of subjects achieving therapeutic glycaemic response without any reported hypoglycaemia (blood glucose ≤ 70 mg/dL) was greater in the dapagliflozin + saxagliptin + metformin group than in the glimepiride + metformin group (34.8% versus 14.8% of subjects, odds ratio: 3.1 [95% CI: 1.93, 4.88], nominal p -value <0.001).

In Study D1689C00014, the proportion of subjects achieving therapeutic glycaemic response without any confirmed hypoglycaemia (blood glucose ≤ 50 mg/dL) was greater in the dapagliflozin + saxagliptin + metformin group than in the glimepiride + metformin group (40.0% versus 31.2% of subjects, odds ratio: 1.47 [95% CI: 1.05, 2.06], nominal p -value=0.027). Post hoc analyses comparing the proportion of subjects achieving therapeutic glycaemic response, without any reported hypoglycaemia, in the dapagliflozin + saxagliptin + metformin group versus the dapagliflozin + metformin group favoured the concomitant addition of dapagliflozin and saxagliptin to metformin compared to dapagliflozin added to metformin (40.0% versus 20.3% of subjects, odds ratio: 2.61 [95% CI: 1.82, 3.76], nominal $p < 0.001$).

In Study CV181369, significantly more subjects in the dapagliflozin + saxagliptin + metformin \pm SU group achieved therapeutic glycaemic response without any reported hypoglycaemia (blood glucose ≤ 70 mg/dL)

than in the insulin + metformin ± SU group (20.9% versus 13.1%, odds ratio: 1.8 [95% CI: 1.16, 2.67], p=0.008).

Systolic blood pressure change from baseline

In Study CV181365 and D1689C00014, the mean change in SBP from baseline to Week 52 was a secondary efficacy variable.

In Study CV181365, the adjusted mean change from baseline in SBP at Week 52 was -2.6 mmHg (95% CI: -4.4, -0.8) in the dapagliflozin + saxagliptin + metformin group and 1.0 mmHg (95% CI: -0.9, 2.9] in the glimepiride + metformin group. The difference between the treatment groups in adjusted mean change from baseline in SBP at Week 52 was -3.6 mmHg (95% CI: -6.3, -1.0; p=0.007).

In Study D1689C00014, the adjusted mean change from baseline in SBP at Week 52 was -6.42 (95% CI: -7.81, -5.02) in the dapagliflozin + saxagliptin + metformin group, -5.61 (95% CI: -7.12, -4.09) for the dapagliflozin + metformin group, and -1.59 (95% CI: -3.08, -0.11) for the glimepiride + metformin group. The difference between the dapagliflozin + saxagliptin + metformin group and the glimepiride + metformin group was -4.82 (95% CI: -6.86, -2.78, p<0.001). The difference between the dapagliflozin + metformin group and the glimepiride + metformin group was -4.01 (95% CI: -6.14, -1.89, p<0.001).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

In support of this application, data from six Phase 3/4 studies have been submitted. Three of these studies (CV181169, CV181168 and MB102129) were submitted with the QTERN MAA and, together with data on the mono-components, formed the basis of the QTERN marketing approval in the EU. These studies compared the safety and efficacy of dapagliflozin + saxagliptin + metformin with dapagliflozin + metformin and/or saxagliptin + metformin after 24 weeks of treatment (sequential and concomitant add-on to metformin). These studies are considered pivotal to this application.

In addition, the current application for Met XR/Saxa/Dapa includes 3 additional, supportive, clinical studies: CV181365 and D1689C00014 and CV181369.

No dose response studies were submitted. The doses have been selected based on the recommended doses for the mono-components, taking restrictions in special populations into account. The tablet strengths allow for two different doses of metformin to be administered according to the proposed posology (1700 mg daily and 2000 mg daily). The FCMP is to be taken once daily but has to be given as two (rather large) tablets. With the responses, the applicant has stated that the FCMP was administered in the Phase 1 BE study without challenges.

Pivotal studies

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 (16weeks), 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 dapagliflozin + saxagliptin + 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, 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 to severe renal impairment (eGFR < 60 mL/min/1.73 m²) were excluded.

Inadequate glycaemic control was defined as central laboratory HbA1c at screening visit of $\geq 8.0\%$ and $\leq 12.0\%$ for study CV181169 and $\geq 8.0\%$ and $\leq 11.5\%$ 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 $\geq 8.0\%$ and $\leq 11.5\%$ at the screening visit, while for Stratum B, it was defined as central laboratory HbA1c $\geq 7.5\%$ and $\leq 10.5\%$ 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 $\geq 7.0\%$ and $\leq 10.5\%$, slightly lower than the $\geq 8.0\%$ and $\leq 12.0\%$ criterion for randomisation into study CV181169.

The design and conduct of the studies were appropriate to establish the efficacy and safety of dapagliflozin + saxagliptin + metformin vs the mono-components added to metformin. As the triple combination is to be initiated in patients already on the corresponding metformin dose, i.e. substitution therapy, there is no need to further evaluate the contribution of metformin to the combination.

In all of the studies, study medication was given as free combinations. Both metformin IR and metformin XR were used. Clinical data have been provided with this application to ensure that the effect of these formulations is comparable (see PD section of this report).

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.

Three supportive studies have been submitted. In the three supportive studies, concomitant initiation of dual therapy with Dapa+Saxa on a background treatment with metformin was evaluated. Study CV181368 and D1689C00014 compared the effect of triple therapy with Glimepiride+Met and study D1689C00014 also included a comparison with Dapa+Met. The study duration was 52 weeks. Study CV181369 included subject with or without SU in combination with metformin and compared Dapa+Saxa therapy with insulin glargine. The study duration was 24 weeks.

The design and conduct of the supportive studies were adequate and in all essentials similar to the methodology used in the pivotal studies. The studies provide additional data on the concomitant initiation of

Dapa + Saxa to metformin, but none of the studies provide data on sequential treatment with dapagliflozin and saxagliptin. In addition, limited data on the concomitant use of SU with the triple combination is provided.

Across the six studies the completion rates were high. Drop-outs were rather few and the most common reasons for not completing the studies were either withdrawal-of-consent or lost-to-follow-up. These reasons varied between treatment groups and were not consistent.

In general, protocol deviations were rare. Not taking study medication or taking study medication outside of the dose range for ≥ 2 consecutive weeks was considered a relevant protocol deviation. Especially for the evaluation of the triple combination, such protocol deviations could affect the outcome and interpretation of data. These protocol deviations were, however, few.

Concomitant add-on treatment and sequential treatment were not compared in any of the studies.

Percentage responders (HbA1c < 7%) in study CV181169 and study D1689C00014 and after the OL treatment period in the sequential add-on studies, can be another parameter for the comparison between concomitant add-on treatment and sequential add-on treatment. Percentage responders was a secondary endpoint in study CV181169 but not in study D1689C00014. It was also defined as a secondary endpoint in studies CV181168 and MB102129 during the double blind phase but not over the open label treatment period.

Statistical methods were similar across the individual phase 3 studies, both pivotal and supportive. The estimand for all of the primary hypotheses was the difference in mean change from baseline in HbA1c in all randomised subjects at the primary time point, if all subjects tolerated or adhered to therapy, although not explicitly expressed by the applicant. This will reflect efficacy in a hypothetical setting where patients are treatment compliant which may not obviously apply in normal clinical practice. The preferred primary scientific question of interest should rather focus on a treatment policy estimand, as discussed in diabetes indications recently. Analysing a treatment policy estimand is expected to result in a smaller estimated treatment effect than the estimand used for the primary analysis, however the conclusion is not expected to change.

To assess the robustness of the primary analyses to departures from the missing at random assumption used in the primary statistical analysis sensitivity analyses were performed. Analyses using the tipping-point approach and multiple-imputation with return-to-baseline method were performed in the supportive studies CV181369 and CV181365. These are considered appropriate methods and a reasonably conservative method for treatment of missing data that is not considered missing at random.

Efficacy data and additional analyses

The study population can be considered representative of the target population. However, across the six studies, only 26 subjects ≥ 75 years old were included out of which 10 were treated with Met+Saxa+Dapa.

HbA1c at enrolment was rather high in study CV181169 (8.94%). In study CV181168 and MB102129 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 HbA1c at randomisation was 7.91 and 8.20%, respectively. At the end of the pre-randomisation period about 20% in study MB102129 and 27% in study CV181168 were no longer eligible since they had a HbA1c <7.0%.

Baseline characteristics in the supportive studies D1689C00014 and CV181365 were comparable to the baseline characteristics in the pivotal studies with a baseline HbA1c of 8.28 and 8.45%, whereas subjects in study CV181369 had a more advanced disease and a higher HbA1c at inclusion (9.05%), consistent with a population in need for insulin treatment.

At screening, most patients (81.3%) were treated with 1500 to 2500 mg metformin daily. Treatment compliance was generally high. This is of importance since study medication was administered as free combination.

Pivotal studies

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 Met+Saxa+Dapa treatment (added concurrently or sequentially) in lowering HbA1c at Week 24 which was statistically significant versus the combination of Saxa+Met (studies CV181169 and MB102129) and versus the combination of Dapa+Met (studies CV181169 and CV181168). Results show that both dapagliflozin and saxagliptin contribute to the effect of the combination, although dapagliflozin seems to be more effective than saxagliptin. The estimated treatment difference when dapagliflozin was added to saxagliptin + metformin ranged between -0.59 to -0.72%, whereas when saxagliptin was added to dapagliflozin+metformin the estimated treatment difference ranged between -0.27 to -0.35%. The difference measured between the combined treatment (dapa+saxa) and the dapagliflozin and saxagliptin 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 possibly because both components for their action are dependent on plasma glucose levels.

Compared to sequential add-on treatment, concomitant add-on treatment could potentially result in a gain in time to reach glycaemic targets. This should be balanced against the risk of over-treatment. As seen from the data from the OL period, about 20% of patients could be sufficiently controlled by adding one medicine. In this context it should be considered that due to the MOA of dapagliflozin and saxagliptin, the risk for hypoglycaemias is rather low and in the absence of hypoglycaemias there are no symptoms that could indicate that the patient is unnecessarily treated. Furthermore, although current treatment guidelines state that concomitant add-on treatment could be considered in selected patients, the recommendations diverge on how to select these patients, and patient related characteristics beyond HbA1c should be taken into account. The applicant proposed that concomitant add-on could be used in patients who require $\geq 1.5\%$ reduction in HbA1c to reach glycaemic target, However, assessment of the B/R balance in this population is not possible due to the lack of data.

A statistically significant decrease in PPG was observed in both study CV181169 and MB102129, when Dapa+Saxa+Met was compared to Saxa+ Met. When triple therapy was compared with Dapa+Met, no significant difference was observed, suggesting that adding dapagliflozin has more effect on 120-minute PPG than adding saxagliptin.

A statistically significant decrease in FPG was observed in study MB102129, when Met+ Saxa+Dapa was compared to Saxa+ Met. A comparable outcome was observed in study CV181169, although no formal testing was performed. When triple therapy was compared with Dapa+Met in studies CV181168 and CV181169, no significant differences was observed (not formally tested). For FPG too, results suggest that dapagliflozin has more effect than saxagliptin.

The proportion of patients achieving HbA1c <7.0% was consistently higher in the groups treated with the triple combination compared to either Dapa+Met or Saxa+Met. Formal testing was only performed in study MB102129, where the difference was statistically significant. 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 the OL part of the 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.

Dapagliflozin treatment resulted in a body weight reduction of about 2 kg whereas treatment with saxagliptin was weight neutral.

Long-term data

Data up to week 52 for studies MB102129 and CV181168 show that the effect on HbA1c was somewhat attenuated in all treatment groups except for Saxa+Met, but the difference between treatment groups was maintained as was the effect on FPG. The proportion of responders decreased somewhat up to week 52, but the difference between treatment groups was largely maintained in both studies. A body weight reduction of about 1-2 kg was maintained in the dapagliflozin treated groups up to week 52.

Supportive studies

The primary endpoint was met in all three studies. In study CV181365, triple combination was superior to Glim+Met. Non-inferiority was shown for both Met+Saxa+Dapa and Dapa+Met vs Glim+Met in study D1689C00014, and a subsequent analysis showed that triple therapy was superior to Glim+Met. In study CV181369, non-inferiority for Met+Saxa+Dapa vs Insulin+Met was shown and an analysis by SU treatment indicates that the outcome was driven by a larger treatment effect in the group on concomitant SU treatment. About 50% of subjects were treated with SU in both groups.

The change in HbA1c from baseline for Met+Saxa+Dapa in studies CV181365 and D1689C00014 was comparable to that observed in study CV181169. A larger reduction was observed in Study CV181369, where the baseline HbA1c was higher. In studies CV181365 and D1689C00014, a greater effect on FPG was observed with the triple combination compared to Glim+Met. Numerically higher proportions of subjects achieved the target of HbA1c <7.0% with Met+Saxa+Dapa compared to Dapa+Met and Glim+Met whereas no differences were observed when compared to insulin glargine. Notably, in Study D1689C00014, 40.3% of subjects achieved HbA1c <7.0% in the Met+Saxa+Dapa group compared to 20.3% in the Dapa+Met group, indicating that about 20% of subject were potentially over-treated in the Met+Saxa+Dapa group.

In the two studies of 52 weeks duration, Met+Saxa+Dapa and Dapa+Met treatment resulted in a body weight reduction of about 4-5 kg whereas Glim+Met resulted in a slight weight gain. In study CV181369, which was of shorter duration, the body weight reduction was -1.50 kg with Met+Saxa+Dapa whereas the body weight increased by 2.14 kg in the Insulin+Met treated group.

Confirmed hypoglycaemia (defined as blood glucose <2.8 mmol/L in study D1689C00014 and as blood glucose <3.9 mmol/L in study CV181369) was more common with Glim+Met or Insulin+Met than with Met+Saxa+Dapa or Dapa+Met. The proportion of subjects achieving therapeutic glycaemic response without any hypoglycaemia was significantly higher for Met+Saxa+Dapa than for Insulin+Met in study CV181369. The same pattern was observed when comparing Met+Saxa+Dapa with Glim+Met in studies D1689C00014 and CV181365.

The mean change in SBP from baseline was a secondary endpoint in studies CV181365 and D1689C00014. The treatment difference between Met+Saxa+Dapa and Glim+Met was 4-5 mmHg in both studies.

The data from the supportive studies confirm the outcome in the pivotal studies and also provide data on the effects of Met+Saxa+Dapa therapy compared to other potential therapies to be used in patients not achieving glycaemic target on metformin or metformin in combination with SU. With regards to the effect on HbA1c reduction, triple therapy was superior (vs glimepiride) or non-inferior (vs insulin glargine) and the effect was achieved with less hypoglycaemias and without weight gain. The supportive studies do however not provide any new data on whether concomitant add-on is more beneficial than sequential add-on.

No pooled subgroup analyses were conducted. Subgroup analyses performed for the individual studies could not detect any relevant treatment interaction by subgroups tested.

The total number of elderly patients is limited in the studies and especially the number of subjects of 75 years and above was low: in total 26 subjects out of which 10 were treated with the triple combination. The applicant proposes that treatment with Met/Saxa/Dapa should not be initiated in subjects of 75 years and above due to the limited data. This is endorsed.

2.5.4. Conclusions on the clinical efficacy

The studies indicate that the combination of dapagliflozin and saxagliptin is effective in subjects failing on metformin monotherapy and the FCMP with dapagliflozin and saxagliptin has been approved for sequential add-on and substitution therapy (QTERN). The FCMP with metformin, saxagliptin and dapagliflozin is considered approvable for the same indications as a means of improving compliance by reducing the number of tablets.

The initially proposed concomitant add-on indication is however not accepted. The main objections against an indication allowing concomitant add-on are the lack of data supporting a benefit of reaching HbA1c target faster compared to sequential add on of one product at the time, and the disadvantage of risking adverse events from two products instead of just one. Thus, this part of the indication has been removed.

2.6. Clinical safety

To support safety of the combined use of metformin and saxagliptin and dapagliflozin in the intended population a summary of safety data analysed from 8 Phase 3/4 randomised, controlled studies in the Met XR/Saxa/Dapa FCMP programme was submitted. The safety assessment was focused on the 7-study pool based on the three studies (CV181169, CV181168 and MB102129) that supported safety in the QTERN MAA (EMA/H/C/004057/0000) and four additional studies (CV181365, CV181363, D1689C00014 and D1683C00005) that have been finalised after the approval of Qtern. The three studies that supported safety in the Qtern MAA (CV181169, CV181168 and MB102129) constituted the 3-study pool in the present application and have been served as a reference to the 7-study pool.

Two of the studies in the 7-study pool were not included in the assessment of efficacy. These were:

- Study CV181363 was a 26-week, 2-arm, randomised, double-blind, placebo-controlled, parallel-group Phase 3b study followed by a 26-week, site- and subject-blind LT extension treatment period to evaluate the efficacy and safety of the concomitant addition of dapagliflozin 10 mg and saxagliptin 5 mg compared with sitagliptin in adult patients with T2DM who had inadequate glycaemic control

(screening HbA1c $\geq 8.0\%$ and $\leq 10.5\%$) on a stable metformin therapy at a dose of ≥ 1500 mg per day.

- Study D1683C00005 was initiated after a request from FDA to confirm efficacy and safety of a low dose of Qtern. This was a 24-week, 3-arm, randomised, double-blind, placebo-controlled, parallel-group Phase 3 study that evaluated the efficacy and safety of the concomitant addition of dapagliflozin 5 mg and saxagliptin 5 mg compared with dapagliflozin 5 mg or saxagliptin 5 mg in T2DM patients who had inadequate glycaemic control (screening HbA1c $\geq 7.5\%$ and $\leq 10.0\%$) on a stable metformin therapy at a dose of ≥ 1500 mg per day.

The applied indication includes use in subjects with type 2 diabetes when simultaneous addition (concomitant add-on) of dapagliflozin and saxagliptin treatment to metformin is considered necessary. Safety in this population was studied in five of the studies in the 7-study pool: Study CV181169, Study D1689C00014, Study CV181363, Study CV181365 and Study D1683C00005. These studies have been referred to as the 5-study pool in the ISS.

In addition, safety data from the Dapa10 mg/Saxa 5mg/Met \pm SU study (CV181369) were submitted. This study was not included in the pooled analyses since some subjects were on background treatment that included SU, which was not a relevant comparison for pooling, and because it was an open-label study. These results are presented separately when considered relevant.

Patient exposure

In none of the studies patients received the Fixed Combination Medicinal Product (FCMP) tablets.

7-study pool

In the 7-study pool, a total of 3134 subjects were included, and of these, 1263 subjects were included in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin (Dapa10mg/Saxa5mg/Met) group. The median exposure time for all three monocomponents in this group was 364 days.

The exact dose of metformin is not reported, however at inclusion, $> 90\%$ received doses above 1500 mg and the exposure of metformin *per se* was within the same time range as dapagliflozin 10 mg and saxagliptin 5 mg (Table 1).

The maximum recommended daily dose of dapagliflozin is 10 mg and saxagliptin is 5 mg with the FCMP Met XR/Saxa/Dapa and the exposure with these doses is considered sufficiently covered in the 7-study pool (Table 17).

5-study pool

The applied indication includes simultaneous (concomitant) add-on of dapagliflozin 10 mg and saxagliptin 5 mg of the Met XR/Saxa/Dapa FCMP in patients inadequately controlled on metformin. According to information in the Integrated Summary of Safety (ISS) this was studied in 950 subjects with a median duration of 363.0 days in five of the studies in the 7-study-pool (Study CV181169, Study D1689C00014, Study CV181363, Study CV181365 and Study D1683C00005). Thus, the extent of exposure in this population is considered sufficient.

Study CV181369

In study CV181369 324 subjects were randomised in the Dapa 10mg/Saxa 5mg/Met ± SU arm. Of these Dapa10 mg and Saxa5 mg to metformin and SU were studied in 166 subjects with a median duration of 168 days (Study CV181369). Thus, the exposure of Dapa 10 mg/Saxa 5mg/Met + SU is not extensive and safety analysis in this population compared with Dapa 10 mg/Saxa 5mg/Met group without SU (n=158) was difficult to perform. However, the size is sufficient for comparisons of safety results with the 7-study pool.

Table 17 Extent of exposure to study treatment regardless of interruption - 7-Study Pool - safety analysis set

Days on treatment, n (%)	Dapa 10 + Saxa 5 + Met (N=1263)	Dapa 10 + Met (N=654)	Saxa 5 + Met (N=631)	Dapa 5 + Saxa 5+ Met (N=293)	Dapa 5 + Met (N=293)	Total (N=3134)
Dapagliflozin 5 mg						
N				293	293	586
Mean (days)				156.2	154.8	155.5
Median				168.0	168.0	168.0
Range				1-206	1-212	1-212
Dapagliflozin 10 mg						
N	1263	654				1917
Mean (days)	312.1	281.2				301.6
Median	364.0	357.0				363.0
Range	1-412	1-395				1-412
Saxagliptin 5 mg						
N	1263		630	293		2186
Mean (days)	312.3		204.6	156.2		260.3
Median	364.0		169.0	168.0		345.0
Range	1-412		1-404	1-206		1-412
Metformin						
N	1262	652	630	293	293	3130
Mean (days)	312.7	282.0	204.4	156.1	154.8	255.1
Median	364.0	357.0	169.0	168.0	168.0	202.5
Range	1-412	1-395	1-404	1-206	1-212	1-412

Adverse events

Overall adverse events

7-study pool

A summary of overall AEs in the 7-study pool is presented in Table 18.

In total, 1652 of the 3134 subjects (52.7%) in the 7-study pool reported at least one AE. The proportion of subjects with at least one AE was similar in the Dapa10mg/Saxa5mg/Met group (56.7%) compared to the group treated with Dapa10mg/Met (56.4%) but slightly higher compared to treatment without dapagliflozin (Saxa 5mg/Met: 51.2%) or dapagliflozin in low dose (Dapa 5 mg containing groups; 41.6% [mean of the two groups]). The AE category at least one hypoglycaemia was higher in the Dapa10mg/Saxa5mg /Met group compared to the same group in the 3-study pool and the other treatment groups. Hypoglycaemia is an adverse event of special interest and further discussed in the corresponding section below.

5-study pool

In the population treated simultaneous with Dapa10 mg/Saxa5 mg to metformin the proportion of subjects with at least one AE was 54.8% (521/950) (data not shown).

Study CV181369

In Study CV181369 the overall incidence of AEs was similar as in the 7-study pool (54%). The frequency of SAEs and DAE in the Dapa 10mg/Saxa 5mg/Met \pm SU group was 2.8% and 1.9%, respectively.

Table 18 Overall AE summary, during treatment period from 7-study pool, safety analysis set

AE category	N (%) of subjects					
	Dapa 10 + Saxa 5 + met (N=1263)	Dapa 10 + Met (N=654)	Saxa 5 + Met (N=631)	Dapa 5 + Saxa 5 + Met (N=293)	Dapa 5+ Met (N=293)	Total (N=3134)
At least 1 AE	716 (56.7)	369 (56.4)	323 (51.2)	121 (41.3)	123 (42.0)	1652 (52.7)
At least 1 hypoglycaemia	99 (7.8)	18 (2.8)	16 (2.5)	19 (6.5)	9 (3.1)	161 (5.1)
At least 1 related AE	129 (10.2)	76 (11.6)	40 (6.3)	39 (13.3)	32 (10.9)	316 (10.1)
Deaths	2 (0.2)	1 (0.2)	0	1 (0.3)	2 (0.7)	6 (0.2)
At least 1 SAE	61 (4.8)	52 (8.0)	17 (2.7)	7 (2.4)	8 (2.7)	145 (4.6)
At least 1 related SAE	4 (0.3)	1 (0.2)	1 (0.2)	0	0	6 (0.2)
SAE leading to discontinuation of study medication.	7 (0.6)	14 (2.1)	3 (0.5)	1 (0.3)	2 (0.7)	27 (0.9)
AE leading to discontinuation of study medication.	38 (3.0)	33 (5.0)	9 (1.4)	19 (6.5)	15 (5.1)	114 (3.6)

Common adverse events

7-study pool

The SOCs with most commonly reported PTs in total for the 7-study pool and for the dapagliflozin 10 mg + saxagliptin 5 mg + metformin group were the SOCs *Infections and infestations* (25.5% and 28.1% respectively) and the SOC *Gastrointestinal disorders* (9.9% and 11.2% respectively).

The most common PTs reported in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin group, were *viral upper respiratory tract infection* (5.9%), *UTI* (4.5%) and *headache* (3.7%). The PTs *viral upper respiratory tract infection* and *vulvovaginal mycotic infections* were reported in higher frequencies in both the Dapa 10 mg groups compared with treatment groups without dapagliflozin or dapagliflozin in low dose (5 mg) (Table 19).

Overall, no new safety concern was identified in the safety assessment of the 7-study pool and the AE profile observed with the combined use of dapagliflozin + saxagliptin added to metformin was consistent with the known safety profiles of dapagliflozin and saxagliptin and the findings in the 3-study pool.

To note is that only hypoglycaemia reported as SAEs were included in the AE categories/tables.

5-study pool (simultaneous vs sequential add-on of dapagliflozin and saxagliptin to metformin)

In general, subjects treated with the dapagliflozin 10 mg and saxagliptin 5 mg simultaneously added to metformin, had a similar common AE pattern and percentages of common AEs as was reported for subjects treated with the dapagliflozin 10 mg and saxagliptin 5 mg sequentially added to metformin in the 7-study pool.

Study CV181369

The AE profile observed with the combined use of dapagliflozin 10 mg + saxagliptin 5 mg added to metformin ± SU in Study CV181369 was in line with the results in the 7-study pool.

Table 19 Most common adverse events (reported in ≥2.0% of subjects in any treatment group) by preferred term - 7-study pool - safety analysis set

Preferred term n (%)	N (%) of subjects					Total (N=3134)
	Dapa 10 + Saxa 5 + met (N=1263)	Dapa 10 + Met (N=654)	Saxa 5 + Met (N=631)	Dapa 5 + Saxa 5 + Met (N=293)	Dapa 5 + Met (N=293)	
Viral upper respiratory tract infection	74 (5.9)	42 (6.4)	20 (3.2)	5 (1.7)	9 (3.1)	150 (4.8)
Urinary tract infection	57 (4.5)	31 (4.7)	29 (4.6)	7 (2.4)	3 (1.0)	127 (4.1)
Headache	47 (3.7)	24 (3.7)	22 (3.5)	3 (1.0)	3 (1.0)	99 (3.2)
Upper respiratory tract infection	41 (3.2)	14 (2.1)	14 (2.2)	3 (1.0)	4 (1.4)	76 (2.4)
Back pain	36 (2.9)	21 (3.2)	17 (2.7)	4 (1.4)	4 (1.4)	82 (2.6)
Influenza	36 (2.9)	18 (2.8)	22 (3.5)	3 (1.0)	9 (3.1)	88 (2.8)
Diarrhoea	32 (2.5)	16 (2.4)	17 (2.7)	2 (0.7)	3 (1.0)	70 (2.2)
Bronchitis	30 (2.4)	16 (2.4)	6 (1.0)	4 (1.4)	0	56 (1.8)
Arthralgia	28 (2.2)	6 (0.9)	5 (0.8)	0	5 (1.7)	44 (1.4)
Vulvovaginal mycotic infection	20 (1.6)	14 (2.1)	1 (0.2)	2 (0.7)	1 (0.3)	38 (1.2)
Hypertriglyceridaemia	16 (1.3)	10 (1.5)	14 (2.2)	0	0	40 (1.3)
Pollakiuria	15 (1.2)	9 (1.4)	1 (0.2)	7 (2.4)	1 (0.3)	33 (1.1)
Nausea	14 (1.1)	8 (1.2)	14 (2.2)	6 (2.0)	5 (1.7)	47 (1.5)
Glomerular Filtration Rate decreased	8 (0.6)	3 (0.5)	6 (1.0)	12 (4.1)	11 (3.8)	40 (1.3)

Adverse events related to study treatment

7-study pool

In total, 316 subjects (10.1%) had an adverse event judged by the investigator to be related to study treatment in the 7-study pool. A slightly higher frequency of AEs related to study treatment were noted for the four dapagliflozin containing groups compared to the non-dapagliflozin treatment group (saxagliptin 5 mg + metformin) (Table 18). Differences in frequencies were noted in PTs within the SOCs *Infections and*

infestations (genital mycotic infections) and the SOC *Renal and Urinary disorders* (pollakiuria), respectively. This is expected taking the safety profile of dapagliflozin into consideration.

The most common treatment-related PTs in the overall dapagliflozin 10 mg + saxagliptin 5 mg + metformin group in order of frequency were UTI (1.7%), pollakiuria (1.0%) and vulvovaginal mycotic infections / polyuria / balanoposthitis (0.6% for respective PTs).

5-study pool

A slightly higher frequency of subjects with at least one related AE was reported in the group of subjects receiving dapagliflozin 10 mg and saxagliptin 5 mg simultaneous to metformin (10.7%) compared with the group receiving these substances sequential to metformin (8.6%). The main difference in the pattern of the most common AEs judged as related to study drug in the population among subjects treated with dapagliflozin 10 mg and saxagliptin 5 mg as simultaneous addition to metformin compared to subjects treated sequentially were within the SOC *Reproductive system and breast disorders*. All 15 cases in this SOC, including 8 cases of balanoposthitis and 3 cases of vulvovaginal pruritus, were reported in the group of subjects receiving dapagliflozin 10 mg and saxagliptin 5 mg simultaneous added to metformin compared to no event within this SOC reported among the subjects treated with dapagliflozin 10 mg and saxagliptin 5 mg sequentially added to metformin. This might partly reflect that subjects with sequential treatment in one of the studies (CV181168) already were treated with dapagliflozin when saxagliptin was added.

Study CV181369

In study CV181369, the pattern of adverse events related to study treatment was similar in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin ± SU group as in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin group in the 7-study pool.

Adverse events of special interest

In summary, events of, "pancreatitis", "lactic acidosis", "lower limb amputation", "malignancies", "fractures" "decreased lymphocyte count", "decreased thrombocyte count" and "potential DKA" were reported in few or no subjects in the 7-study pool. Thus, no clinically significant safety conclusions could be drawn regarding these adverse events of special interest and the safety issues regarding these remain unchanged.

Neither was any new safety issues identified in the data presented for the known adverse events related to genital infections, UTI, renal impairment/failure and volume depletion or the potential risks of CV events or hepatic related events

- Genital infections

Use of DPP-4 inhibitors and SGLT2 inhibitors is known to be associated with an increased incidence of genital infection. No new safety issue was raised regarding genital infections in the data presented. Genital infections were reported in 4.0% in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin group in the 7-study pool. No SAE were reported, and the majority of subjects had a single event.

- Urinary tract infections

Increased incidences of UTI are known to be associated with use of both dapagliflozin and saxagliptin. No new safety issue was raised regarding UTI in the data presented. Overall, UTI was reported in 70 subjects (5.5%) in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin group in the 7-study pool.

- Hypoglycaemia

Definitions of hypoglycaemia

Overall hypoglycaemia: Includes all reported episodes of hypoglycaemia on the hypoglycaemia CRF page(s) regardless of the self-monitoring blood glucose value and all episodes identified from central lab FPG values ≤ 70 mg/dL (≤ 3.9 mmol/L)

Confirmed hypoglycaemia: Defined as a blood glucose value ≤ 70 mg/dL (≤ 3.9 mmol/L) regardless of the method or associated symptoms.

Confirmed symptomatic hypoglycaemia: A confirmed hypoglycaemic episode was considered symptomatic if symptoms were indicated on the hypoglycaemia CRF page(s) on the date the glucose value was obtained which was ≤ 70 mg/dL (≤ 3.9 mmol/L).

Clinically significant hypoglycaemia: Blood glucose value < 54 mg/dL (< 3 mmol/L)

Severe hypoglycaemia: At least one episode of neuroglycopenic symptoms requiring third party help for neuroglycopenic recovery, prompt recovery, and a glucose value either not present or if glucose measured it must be ≤ 70 mg/dL (≤ 3.9 mmol/L)

7-study pool

The incidences of hypoglycaemia varied widely among the different studies in the 7-study pool (Table 20).

The incidence of overall hypoglycaemia in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin group in the 7-study pool was significantly higher (7.5%) compared with the same group in the studies included in the 3-study pool (2.0%). See Table 21. These differences were driven by remarkably higher incidences of overall hypoglycaemia rates reported in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin arm in Study CV181365 (18.5%) and Study CV181363 (12.9%) compared to the other studies (varying between 1.1% and 6.5%). However, there were several cross-study differences between the studies such as patient self-reporting, protocol-defined testing frequency, and further evaluation/validation by clinical study personnel.

No study in the clinical program compared concomitant treatment to sequential treatment. To assess potential differences in the rate of hypoglycaemia following concomitant addition of dapagliflozin and saxagliptin to metformin, randomised within-study comparisons with control groups were made. The 5 concomitant add-on studies that included a dapagliflozin 10 mg + saxagliptin 5 mg + metformin treatment arm were studies CV181169, CV181365, CV181363, D1689C00014 and CV181369. Based on the within-study comparisons in these studies, the following conclusions were drawn about the rate of hypoglycaemia following concomitant addition of dapagliflozin 10 mg and saxagliptin 5 mg (Table 20):

- The rate was the same as dapagliflozin 10 mg and similar to saxagliptin 5 mg in Study CV181169 and slightly higher than dapagliflozin 10 mg in Study D1689C00014.
- The rate was similar as for sitagliptin (Study CV181363).
- The rate was much lower than with SU (Study CV181365 and Study D1689C00014) or insulin (Study CV181369; not part of the 7-study pool).

Severe hypoglycaemia was reported in low frequency ($< 1\%$) across all studies and treatment groups in the 7-study pool (Table 21).

Table 20 Overall hypoglycaemia rates in the individual Phase 3/4 clinical studies excluding data after rescue (safety analysis sets)

	n/N (%) of subjects					
	Dapa+Saxa+Met	Dapa+Met	Saxa+Met	SU+Met	Insulin+Met	Sita+Met
CV181169	2/179 (1.1)	2/179 (1.1)	1/176 (0.6)	NA	NA	NA
MB102129	5/160 (3.1)	NA	1/160 (0.6)	NA	NA	NA
CV181168	3/153 (2.0)	6/162 (3.7)	NA	NA	NA	NA
CV181365	42/227 (18.5)	NA	NA	93/216 (43.1)	NA	NA
CV181363	30/232 (12.9)	NA	NA	NA	NA	28/229 (12.2)
D1689C00014	13/312 (4.2)	9/313 (2.9)	NA	87/312 (27.9)	NA	NA
D1683C00005^a	19/293 (6.5)	9/293 (3.1)	11/295 (3.7)	NA	NA	NA
CV181369 (minus SU)^b	17/158 (10.8)	NA	NA	NA	51/154 (33.1)	NA

^a All studies used dapagliflozin 10 mg, except for study D1683C00005 that used dapagliflozin 5 mg.

^b Study CV181369 was not a part of the study pools. This study was an open-label study and subjects were on a background of metformin ± SU. The frequency shown is for subjects who were not on background SU.

Table 21 Model-adjusted summary of hypoglycaemia episodes during the double-blind treatment period excluding data after rescue - 7-study pool - safety analysis set

	N (%) of subjects						
	Dapa 10 + Saxa 5 + Met (N=1263)	Dapa 10 + Met (N=654)	Saxa 5 + Met (N=631)	Dapa 5 + Saxa 5 + Met (N=293)	Dapa 5 + Met (N=293)	Glim 1-6 (N=528)	Sita (N=229)
Overall hypoglycaemia							
n	95	17	13	19	9	180	28
Crude %, Adj%	(7.5) (6.0)	(2.6) (3.5)	(2.1) (2.0)	(6.5) (3.8)	(3.1) (1.8)	(34.1) (25.1)	(12.2) (5.9)
95% CI	(3.2, 11.0)	(1.6, 7.5)	(0.7, 5.5)	(1.2, 11.5)	(0.5, 6.1)	(14.3, 40.2)	(2.6, 12.6)
Confirmed hypoglycaemia							
n	77	10	11	15	9	166	27
Crude%, Adj%	(6.1) (4.8)	(1.5) (2.3)	(1.7) (1.4)	(5.1) (2.4)	(3.1) (1.4)	(31.4) (24.5)	(11.8) (5.1)
95% CI	(2.3, 9.7)	(0.9, 5.7)	(0.4, 4.9)	(0.6, 9.1)	(0.3, 5.9)	(12.9, 41.6)	(2.1, 11.9)

	N (%) of subjects						
	Dapa 10 + Saxa 5 + Met (N=1263)	Dapa 10 + Met (N=654)	Saxa 5 + Met (N=631)	Dapa 5 + Saxa 5+ Met (N=293)	Dapa 5 + Met (N=293)	Glim 1-6 (N=528)	Sita (N=229)
Confirmed symptomatic hypoglycaemia							
n	37	4	4	6	1	116	8
Crude%, Adj%	(2.9) (2.7)	(0.6) (0.7)	(0.6) (0.6)	(2.0) (1.5)	(0.3) (0.2)	(22.0) (18.1)	(3.5) (2.3)
95% CI	(1.6, 4.5)	(0.2, 2.0)	(0.2, 2.0)	(0.4, 5.2)	(0.0, 2.2)	(10.6, 29.1)	(0.8) (6.3)
Clinically significant hypoglycaemia							
n	25	1	3	1	0	36	10
Crude %, Adj%	(2.0) (1.9)	(0.2) (0.2)	(0.5) (0.5)	(0.3) (0.2)	(0) (NA)	(6.8) (6.7)	(4.4) (2.8)
95% CI	(1.1, 3.2)	(0, 1.5)	(0.1, 1.6)	(0, 2.2)	(0, 1.3)	(3.7, 11.9)	(1.0, 7.5)
Severe hypoglycaemia							
n	1	0	0	1	1	5	0
Crude %, Adj%	(<0.1) (<0.1)	(0) (NA)	(0) (NA)	(0.3) (0.3)	(0.3) (0.3)	(0.9) (0.9)	0 (NA)
95% CI	(0, 0.6)	(0, 0.6)	(0, 0.6)	(0, 2.4)	(0, 2.4)	(0.4, 2.3)	(0, 1.6)

3-study pool

As mentioned above, no study in the clinical program compared concomitant treatment to sequential treatment. The 3-study pool is probably the most reliable data pool for assessing the hypoglycaemia risk for between-study comparisons of the two treatment strategies. These studies were conducted around the same time so the individual protocols for these studies were based on the same guidelines for defining hypoglycaemia, the study designs were aligned across the 3 studies, and each study included 1 or both monocomponents as control groups. In the 3-study pool, there was no indication of increased risk of hypoglycaemia with concomitant versus sequential add-on treatment. The overall incidence of hypoglycaemia was 1.1% with concomitant addition of dapagliflozin and saxagliptin to metformin (Study CV181169) and 2.0% and 3.1% with sequential addition (Studies CV181168 and MB102129, respectively; Table 22). Furthermore, within the concomitant add-on Study CV181169, the incidence of hypoglycaemia with concomitant treatment was the same as that for dapagliflozin. This makes it unlikely that concomitant use increases the risk of hypoglycaemia and suggests that other factors contribute to the higher frequency of hypoglycaemia observed in some of the 7-study pool studies.

Table 22 Overall hypoglycaemia in the individual clinical studies in the 3-study pool, excluding data after rescue

	n/N (%) of subjects		
	Dapa 10 + Saxa 5 + Met	Dapa 10 + Met	Saxa 5 + Met
Concomitant addition			
CV181169	2/179 (1.1)	2/179 (1.1)	1/176 (0.6)
Sequential addition			
MB102129	5/160 (3.1)	NA	1/160 (0.6)
CV181168	3/153 (2.0)	6/162 (3.7)	NA

Overall episodes of hypoglycaemia (reported on CRF or central lab FPG ≤ 70 mg/dL [3.9 mmol/L]). All studies used dapagliflozin 10 mg + saxagliptin 5 mg + metformin.

Study CV181369

Treatment with SU is known to cause hypoglycaemia. Thus, as expected, the overall incidence of hypoglycaemia was higher in subjects treated with SU (39.8%) in compared to treatment without SU (10.8%) in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin treatment group in Study CV181369.

In the SmPC section 4.8 "*hypoglycaemia (when used with SU)*" is labelled as very common. However, the presented data from the 7-study pool confirmed symptomatic hypoglycaemia was reported in 2.9% in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin group which reflects a higher risk for hypoglycaemia also when the treatment is used without SU. Renal impairment/failure

Dapagliflozin is associated with renal-related adverse events (Blood creatinine increased, creatinine renal clearance decreased, Blood urea increased; SmPC Forxiga). No new safety issue was raised regarding renal impairment/failure in the data presented. Overall, events of Renal impairment/failure were reported in 2.2% of subjects in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin group in the 7-study pool.

- Malignancies

In the 7-study pool a total of 25 events (0.8%) in the SOC *Neoplasm benign, malignant and unspecified (incl cysts and polyps)*, were reported. Sixteen of these (1.3%) were reported in the Dapa 10/Saxa5/Met group. The number of specific malignancies defined as potential risks with dapagliflozin (pancreatic cancer, breast cancer, bladder cancer and prostate cancer) were low (n=3; 0.2%).

- Fractures

Overall, the incidence of fracture was low (0.6%; n=20) without any clinically significant difference between the treatment groups.

- Cardiac failure and adjudicated cardiovascular events

In the 7-study pool, the total incidence rate for AEs of cardiac failure was 0.8% (n=25 subjects). Eleven of these (0.9%) were reported in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin group. The most common AEs of cardiac failure were oedema peripheral (n=6) and oedema (n=2). No clinically significant differences were seen for events of cardiac failure and adjudicated CV events between the different treatment groups.

Overall, no new safety issue was raised regarding CV events in the data presented.

- Decreased lymphocyte count (lymphopenia)

No adverse events of decreased lymphocyte count were reported in any of the studies in the 7-study pool.

- Decreased thrombocyte count (thrombocytopenia)

Adverse events of thrombocytopenia were reported in 5 (0.2%) subjects across the treatment groups in the 7-study pool. Three subjects (0.2%) had thrombocytopenia in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin group and 1 subject had platelet count decreased. In the saxagliptin 5 mg + metformin group 1 (0.2%) subject had thrombocytopenia.

- Pancreatitis

In the 7-study pool, one subject reported an SAE of pancreatitis chronic. This subject was in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin group.

- Severe Cutaneous Adverse Reactions (SCARs)

Potential SCAR events were identified in the 7-study pool by using the PTs in the SMQ for SCAR (broad definition). This search identified 17 non-serious adverse events in 15 subjects. None of the 17 events were considered as serious. The overall frequency of the events identified in the SCAR SMQ search was low and balanced across the different treatment groups (0.3-0.8%). The most common PTs across all treatment groups were *conjunctivitis* (10 events in 9 subjects) and *skin exfoliation* (6 events in 5 subjects). In addition, one event of "blisters" was reported. Most of the events were reported as mild (12/17) or moderate (4/12). Only one event was reported as severe (*PT conjunctivitis*). However, this event occurred in a patient treated with Dapa 10 + Met and not with the triple combination and the event was not considered as related to study drug according to the investigator. In total, two (mild) events of skin exfoliation in one patient were considered as possible related to study drug in the Dapa10/Saxa5/Met treatment group and the study drug was withdrawn.

Overall, frequencies of events identified in the broad SMQ for SCAR were low and based on available data, it is not considered that concomitant treatment with Dapa 10 + Saxa 5 to metformin is associated with an increased risk of SCARs compared with sequential add-on treatment.

- Hypersensitivity reactions

In total, hypersensitivity reactions were reported in 59 subjects (1.9%) in the 7-study pool.

In the dapagliflozin 10 mg + saxagliptin 5 mg + metformin group, the overall incidence of hypersensitivity reactions was 2.1% (n=26). The most common PTs were *rash* (n=7, 0.6%) and *dermatitis allergic* (n=4; 0.3%).

There was 1 SAE of *angioedema* in the dapagliflozin 5 mg + saxagliptin 5 mg + metformin group (Study D1683C00005).

A slightly higher incidence of hypersensitivity reactions was reported in subjects treated with the simultaneous add-on treatment of Dapa 10 mg/Saxa 5 mg (2.2%) compared with subjects treated with Dapa 10 mg/Saxa 5 mg sequential to metformin (1.6%). The most common PTs were *rash* and *allergic dermatitis*.

- Hepatic-related events

In the 7-study pool, a total, 47 subjects (1.5%) reported AEs or measured laboratory values suggestive of hepatic disorders. Two subjects reported both an AE and measured laboratory value suggestive of hepatic disorder. The differences in proportions of these events between the treatment groups in the 7-study pool

were small. The incidence in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin group was 1.5% (n=19).

In the 3 study-pool (Study CV181169, CV181168, and MB102129), 14 events fulfilled the criteria for hepatic adjudication based on the independent adjudication database and assessment. After assessment by the Hepatic Adjudication committee five subjects in these studies had hepatic events considered as probable (n=1) and possible (n=4) related to study drug (DILI). For the four additional studies included in the 7-study pool, the criteria for hepatic adjudication were changed (more "narrow" criteria) and no events were identified for adjudication and no events fulfilled the criteria for hepatic adjudication.

- Volume depletion

Volume depletion is known to be associated with use of dapagliflozin and in the 7-study pool, treatment groups with dapagliflozin had frequencies of volume depletion related events between 0.4% and 0.8%, without any clinically significant difference between the treatment groups. Five (0.4%) subjects reported events related to volume depletion in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin group. No new safety issue was raised regarding volume depletion in the data presented.

- Diabetic ketoacidosis (DKA)

Diabetic ketoacidosis has been reported during use with both dapagliflozin and saxagliptin as monotherapies. In total, potential events of DKA were reported in 0.2% (n=5) of the subjects in the 7-study pool. Of these 0.2% (n=2) were reported in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin group.

- Lower limb amputations

In the 7-study pool, lower limb amputations were reported for 3 subjects including one subject in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin group. The number of cases of lower limb amputations in the 7-study pool is too low to draw clinically significant conclusions. The potential risk for an increase of lower limb amputations with SGLT-2 inhibitors in general is reflected in the SmPC.

Serious adverse event/deaths/other significant events

Deaths

Overall six fatal cases (0.2%) were reported in the 7-study pool, equally distributed between the treatment groups (Table 18).

Two of these cases (*cardiac failure acute/acute MI* and *pneumonia*) were reported in the Dapa10mg/Saxa5mg/Met group.

None of the six fatal cases were considered as related to IP.

Serious adverse events

7-study pool

In total, 145 (4.6%) SAEs were reported in the 7-study pool (Table 18). The frequency of SAEs was 4.8% (n=61) in the Dapa10mg/Saxa5mg/Met group. As for the total population in the 7-study group, the most common reported PTs in the triple combination group (Dapa10mg/Saxa5mg/Met) were within the SOCs

Cardiac Disorders (0.9%; n=11 including four cases of coronary artery disease and three cases of AMI and *SOC Infections and infestations* (0.7%; n=9 divided by different PT with maximum 2 events per PT).

5-study pool

A slightly higher incidence of SAEs was noted with simultaneous add-on of Dapa 10 mg and Saxa 5 mg to metformin (4.9%) compared with sequential add-on treatment of these substances to metformin (3.8%).

No differences in pattern or cluster with regards to PTs between these two groups could be identified.

Study CV181369

SAEs were reported by 9 subjects (2.8%) in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin ± SU group; 7 (4.2%) of the SAEs were reported among subjects who used dapagliflozin 10 mg + saxagliptin 5 mg + metformin group with an SU and 2 (1.3%) in subjects who used dapagliflozin 10 mg + saxagliptin 5 mg + metformin group without an SU. The events were distributed among the system organ class (SOCs) and none of the preferred terms (PTs) occurred in more than 1 subject. In total, 5 subjects (1.6%) in the insulin + metformin ± SU group reported an SAE.

Laboratory findings

Overall, there were no new or unexpected findings with regard to laboratory findings.

- Haematology

Small changes in haemoglobin, haematocrit, platelet and leukocyte counts occurred in the 7-study pool. Mean values were contained within the normal range. Small mean increases from baseline were observed in haemoglobin and haematocrit in the dapagliflozin-treated subjects.

In all groups with dapagliflozin-treated subjects a similar, small and stable increase in haemoglobin and haematocrit over time (52 weeks) was noted.

- Clinical chemistry

Creatinine, CrCL, FPG

In line with earlier findings for dapagliflozin, changes in renal function laboratory tests (increase in creatinine, decrease in creatinine clearance) were noted in the groups treated with dapagliflozin compared to non-dapagliflozin treated subjects.

Small mean increases from baseline in blood creatinine were observed in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin group and the dapagliflozin 10 mg + metformin group. These changes started at week 6 (mean change in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin group from baseline was 2.9 ± 15.2 $\mu\text{mol/L}$ at week 6) and decreased towards baseline by Week 52 (mean change from baseline in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin group was 1.0 ± 9.6 $\mu\text{mol/L}$ by week 52).

The trend toward smaller increases from baseline in blood creatinine by week 52 was similar in the two dapagliflozin 10 mg groups. However, in the Saxa5 /Met group a trend toward a greater mean reduction from baseline by week 52 was noted instead.

Small decreases in CrCl and FPG were also observed across the treatment groups at all time points.

The changes from baseline in electrolytes, CK, and total protein in the 7-study pool were considered as not clinically meaningful.

Hepatic laboratory values

Mean changes in hepatic laboratory values in both the 7-study and 5-study pools were small, stable, and consistent over time, and stayed within normal range.

In total 4 subjects, in the 7-study pool, of which two were in the Dapa10mg/Saxa5mg/Met group, had combinations of ALT or AST >3X ULN with total bilirubin elevations >2X ULN within 14 days of each other.

- Lipids

Dyslipidaemia is included as an adverse reaction in the approved SmPC. The percentage of subjects with treatment-emergent AEs of dyslipidaemia was similar across treatment the treatment groups: 44 (3.5%) subjects in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin group, 26 (4.0%) subjects in the dapagliflozin 10 mg + metformin group, 23 (3.6%) subjects in the Saxa5/Met group, 2 (0.7%) subjects in the Dapa5/Saxa5/Met group, and 2 (0.7%) subjects in the Dapa5/Met group.

- Urinalysis

Urine albumin and albumin/creatinine decreased from baseline in the dapagliflozin-containing treatment groups. These changes started at Week 6 and were observed through Week 52. In the saxagliptin 5 mg + metformin group, there was no notable change in urine albumin and a small increase in albumin/creatinine.

- Vital signs

Overall, there were no unexpected results for vital signs. In the 7-study pool there was a mean decrease in heart rate by 1.0 BPM after 52 weeks (from 74.4±9.67 BPM at baseline to 73.7±9.60 BPM after 52-weeks) with a similar reduction across the treatment groups.

Overall in the 7-study pool, diastolic blood pressure was decreased from 79.3±8.51 mmHg at baseline to 78.7±8.58 mmHg after 52 weeks (a mean decrease by 1.3 mmHg) and systolic blood pressure from 131.0±13.86 mmHg to 129.4±13.46 mmHg at week 52 (a mean decrease of 3.2 mmHg). A similar decrease from baseline was noted for diastolic and systolic blood-pressure over time in all dapagliflozin treatment groups.

Safety in special populations

	Number of subjects (%) ^a			
	Age <65 N=1034 (81.9%) ^b	Age 65-74 N=220 (17.4%) ^b	Age 75-84 N=9 (0.7%) ^b	Age 85+ N=0
Total AEs	583 (56.4)	129 (58.6)	4 (44.4)	0
Serious AEs – Total	45 (4.4)	14 (6.4)	2 (22.2)	0
- Fatal	0	2 (0.9)	0	0
- Hospitalization/prolong existing hospitalization	38 (3.7)	13 (5.9)	2 (22.2)	0
- Life-threatening	1 (0.1)	0	0	0
- Disability/incapacity	1 (0.1)	0	0	0
- Other (medically significant)	7 (0.7)	3 (1.4)	0	0
AE leading to drop-out	20 (1.9)	16 (7.3)	2 (22.2)	0
Psychiatric disorders	17 (1.6)	3 (1.4)	0	0
Nervous system disorders	92 (8.9)	23 (10.5)	1 (11.1)	0
Accidents and injuries	33 (3.2)	9 (4.1)	0	0
Cardiac disorders	29 (2.8)	9 (4.1)	2 (22.2)	0
Vascular disorders	31 (3.0)	9 (4.1)	0	0
Cerebrovascular disorders	3 (0.3)	0	0	0
Infections and infestations	286 (27.7)	67 (30.5)	2 (22.2)	0
Anticholinergic syndrome	21 (2.0)	10 (4.5)	1 (11.1)	0
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	16 (1.5)	6 (2.7)	1 (11.1)	0
Creatinine renal clearance decreased ^c	2 (0.2)	4 (1.8)	1 (11.1)	0

^a The percentages for AEs are based on the total number of subjects in each age subgroup in the Dapa 10 + Saxa 5 + Met treatment group in the 7-study pool.

^b The percentages for each age group are based on the total number of subjects in the Dapa 10 + Saxa 5 + Met group in the 7-study pool (N=1263).

^c The only other AE appearing more frequently in subjects aged >65 years in the 7-study pool.

AE Adverse event; Dapa 10 Dapagliflozin 10 mg; Met Metformin; N Number of subjects in each age group; Saxa 5 Saxagliptin 5 mg.

Immunological events

See section "Hypersensitivity reactions" above.

Safety related to drug-drug interactions and other interactions

There are no specific non-clinical or clinical studies conducted with the Dapa/Saxa/Met XR FCMP tablet.

In study D168AC00002 it was concluded that administration of the triple FCMP of dapagliflozin/saxagliptin/metformin 5/2.5/1000 mg and 5/2.5/850 mg XR tablets (with metformin dose normalization) are bioequivalent to the co-administered individual components (Forxiga, Onglyza, and Glucophage XR) under both fasted and fed conditions. Thus, no adjustments for food intake are needed for the product.

Discontinuation due to adverse events

7-study pool

There was no remarkable difference between treatment groups in the proportion and patterns of AEs leading to discontinuation of study drug. In total, 114 (3.6%) subjects discontinued study treatment due to AEs. Of these, 38 (3.0%) subject were reported in the Dapa10mg/Saxa5mg/Met group. The overall most common AEs leading to discontinuation were within the SOC *Investigations* (48 subjects [1.5%]) with the most common PTs GFR decreased (27 subjects [0.9%]) and creatinine renal clearance decreased (15 subjects [0.5%]). The second most common SOC in the Dapa10mg/Saxa5mg/Met group was *Infections and infestations* with 11 subjects (0.9%), including 3 cases of vulvovaginal mycotic infection and 2 cases of UTI.

5-study pool

The frequency of subjects reporting discontinuations due to AEs was lower in the group of subjects treated with simultaneous add-on treatment (2.7%, n=26/950) compared with the subjects treated sequentially with Dapa10 and Saxa5 to metformin (3.8%, n=12/313). The pattern of AEs was similar between the two treatment groups (simultaneous vs sequential).

Study CV181369

DAEs were reported for 6 (1.9%) subjects in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin group ± SU group. The most frequent DAEs in Study CV181369 were blood creatinine increased and GFR decreased, each of which was reported by 2 (0.6%) subjects.

2.6.1. Discussion on clinical safety

The database is in general considered sufficient. Overall, 1263 subjects were treated with Dapa10mg/Saxa5 mg/Met (the 7-study pool) for a mean time of 364 days. The majority of subjects (87.9%) received their study treatment for duration >120 days. Among the subjects in the 7-study pool, 950 subjects were treated with concomitant add-on treatment of Dapa 10 mg and Saxa 5 mg to metformin. The remaining subjects (n=313) were treated sequentially (stepwise) with Dapa 10 mg and Saxa 5 mg to metformin. In addition, dapagliflozin 10 mg and saxagliptin 5 mg to metformin and SU were studied in 166 subjects with a median duration of 168 days (Study CV181369).

Overall, no new safety concern was identified in the safety assessment of the 7-study pool and the AE profile observed with the combined use of dapagliflozin + saxagliptin added to metformin was consistent with the known safety profiles of dapagliflozin and saxagliptin and the safety results in the 3-study pool which was

based on the three pivotal studies included in the Qtern (Dapa/Saxa FCMP) MAA. In the 7-study pool, in total and for the Dapa/Saxa/Met group, the SOCs with most common reported PTs were *Infections and infestations* (25.5% and 28.1% respectively) and *Gastrointestinal disorders* (9.9% and 11.2% respectively). In total 145 (4.6%) SAEs were reported in the 7-study pool. Of these, 61 SAEs were reported in the Dapa/Saxa/Met group (4.8%).

The AE profile observed with the combined use of dapagliflozin 10 mg + saxagliptin 5 mg added to metformin ± SU in Study CV181369 was in line with the results in the 7-study pool.

As the triple combination is to be initiated in patients already on the corresponding metformin dose, i.e. substitution therapy, there is no need to further evaluate the specific safety profile of the metformin dose to the combination. Considering the potential risk of increased frequency and severity of adverse events (especially gastrointestinal adverse events) by the metformin component in the FCMP compared with the metformin used in the RCTs, the applicant has presented safety data from study CV181206. This study was designed to show therapeutic equivalence (efficacy and safety) of 2000 mg metformin XR once daily (as in the FCMP) with 2000 mg metformin IR 1000 mg twice daily in subjects with T2DM. In this study a slightly higher incidence of GI events was reported for the subjects treated with metformin XR 2000 mg once daily (15.9%; 41.7 per 100 PYE) compared to metformin IR 1000 mg twice daily (13.7%; 34 per 100 PYE). This difference is not considered clinically significant. The most commonly reported gastrointestinal AEs in either the metformin XR or the metformin IR group, respectively, were diarrhoea (8.8% and 7.7%), nausea (4.6% and 2.8%), vomiting (2.5% and 1.4%), and abdominal pain (1.4% and 2.1%). The GI events were not reported with higher grades of severity or seriousness in the metformin XR compared to the metformin IR group.

Hypoglycaemia

The incidence of overall hypoglycaemia in the Dapa10mg/Saxa5mg/Met group in the 7-study pool was significantly higher (7.5%) compared with the same group in the studies included in the 3-study pool (2.0%). These differences were driven by higher incidences of overall hypoglycaemia rates reported in the Dapa10mg/Saxa5mg/Met arm in study CV181365 (18.5%) and study CV181363 (12.9%). The higher rates of hypoglycaemia (also in the comparator arms) observed in these studies might be caused by cross-study confounders including different criteria for when to measure blood glucose. No study in the clinical program compared concomitant treatment to sequential treatment. To reflect a possible higher frequency of overall hypoglycaemia with concomitant treatment compared to sequential treatment, it was instead proposed to compare the Dapa10/Saxa5/Met treatment groups with comparator groups within the respective concomitant add-on studies. Such an analysis did not indicate any higher incidences of overall hypoglycaemia in the Dapa10/Saxa5/met concomitant add-on treatment groups compared with control groups. Further, to compare the two administration strategies (concomitant vs sequential add on treatment) side-by-side the applicant suggested to use the 3-study pool since these studies were conducted around the same time so the individual protocols for these studies were based on the same guidelines for defining hypoglycaemia. The results from this approach demonstrated that the incidence of overall hypoglycaemia was low and varied between 1-3% in the Dapa10/Saxa5/Met treatment arms without any apparent difference between control groups or administration strategy.

The overall incidence of severe hypoglycaemia was low across all studies (<1%).

Treatment with SU is known to cause hypoglycaemia. Thus, as expected, the overall incidence of hypoglycaemia was higher in subjects treated with SU (39.8%) compared to treatment without SU (10.8%) in the dapagliflozin 10 mg + saxagliptin 5 mg + metformin treatment group in study CV181369.

Use of dapagliflozin and saxagliptin simultaneous vs sequential added to metformin

In general, subjects treated with the Dapa/Saxa concomitantly added to metformin, had a similar pattern and percentages of AEs as was reported for subjects treated with the Dapa and Saxa sequentially added to metformin. However, initiation of concomitant treatment with dapagliflozin and saxagliptin may make judgements of causal relationship of the adverse events more difficult compared to a stepwise treatment. Furthermore, handling of dose reductions or temporary interruptions (temporarily or permanent) is considered more complicated if a FCMP is used compared with use of mono components.

2.6.2. Conclusions on the clinical safety

Overall, the safety profile for Dapa10mg/Saxa5mg/Met treatment was in accordance with use of the monocomponents and dual combinations of the substances. The SOC with most common adverse reactions were "Infections and infestations" and "Gastrointestinal disorders". The incidences of overall hypoglycaemia with Dapa10/Saxa5/Met treatment varied widely across the different studies (1.1%-18.5%). The higher rates of hypoglycaemia (also in the comparator arms) observed in two of the studies is probably caused by cross-study confounders including different criteria for when to measure blood glucose. Overall no new safety concern was identified in the extended safety-pool with 7 studies compared to earlier experience with dapagliflozin + saxagliptin treatment combined with metformin.

Treatment with the dapagliflozin 10 mg and saxagliptin 5 mg administered simultaneous (concomitant) added to metformin, had a similar pattern and percentages of AEs as was reported the group treated with dapagliflozin 10 mg and saxagliptin 5 mg administered sequential to metformin. However, it was considered that concomitant treatment with dapagliflozin and saxagliptin to metformin may make judgements of causal relationship to the events, compared to a sequential treatment, more difficult.

2.7. Risk Management Plan

Safety concerns

Important identified risks	Urinary tract infections (UTI) (dapagliflozin) Diabetic ketoacidosis (DKA) including events with atypical presentation (dapagliflozin) Renal impairment (dapagliflozin) Lactic acidosis (metformin)
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Important potential risks	<p>Severe cutaneous adverse reactions (saxagliptin)</p> <p>Pancreatic cancer (saxagliptin)</p> <p>Cardiac failure (saxagliptin)</p> <p>Serious hypersensitivity reactions (dapagliflozin)</p> <p>Volume depletion (dapagliflozin)</p> <p>Clinical consequences of increased haematocrit (dapagliflozin)</p> <p>Bone fracture (dapagliflozin)</p> <p>Liver injury (dapagliflozin)</p> <p>Bladder cancer (dapagliflozin)</p> <p>Breast cancer (dapagliflozin)</p> <p>Prostate cancer (dapagliflozin)</p> <p>Lower limb amputation (LLA) (dapagliflozin)</p> <p>Pancreatitis (dapagliflozin)</p>
Missing Information	Use in patients with CHF defined as New York Heart Association (NYHA) class III and IV (dapagliflozin)

Pharmacovigilance plan

There are no ongoing or planned additional pharmacovigilance activities which are specific for the triple combination Qtrilmet. However, there are ongoing or planned additional pharmacovigilance activities for the monocomponent products and these are also included in the pharmacovigilance plan of the Qtrilmet RMP as the results of these will potentially provide relevant information to the safety profile of Qtrilmet.

Additional Pharmacovigilance Activities for the monocomponent products (i.e. saxagliptin and dapagliflozin)

Study status	Summary of objectives	Safety concerns	Milestones	Due dates
Saxagliptin RMP				
Category 3				
D1680C00016 MEASURE-HF, Mechanistic evaluation of glucose-lowering strategies in patients with heart failure (HF). Ongoing	To investigate the effects of saxagliptin and sitagliptin on cardiac dimensions and function in patients with T2DM mellitus and HF.	Cardiac failure	Final clinical study report (CSR)	2020

Additional Pharmacovigilance Activities for the monocomponent products (i.e. saxagliptin and dapagliflozin)

Study status	Summary of objectives	Safety concerns	Milestones	Due dates
Dapagliflozin RMP				
Category 3				
MB102103 (D1690R00008) - Observational study: Complications of UTI in Patients on Dapagliflozin Ongoing	Assess the incidence of hospitalisation or emergency department visit for severe complications of UTI among new users of dapagliflozin compared to those who are new users of certain other antidiabetic drugs.	Severe complications of UTI	Submission of Interim Data	2016, 2019
			Submission of Final Data	2020
MB102104 (D1690R00005) - Observational study: Acute Liver Injury (ALI) in Patients on Dapagliflozin Ongoing	To assess the incidence of hospitalisation for ALI among new users of dapagliflozin compared to those who are new users of certain other antidiabetic drugs.	Risk of acute hepatic failure	Submission of Interim Data	2016, 2019
			Submission of Final Data	2020
MB102110 (D1690R00004) - Observational study: Acute Kidney Injury in Patients on Dapagliflozin and Other Antidiabetic Medications Ongoing	To assess the incidence of hospitalisation for AKI among new users of dapagliflozin compared to those who are new users of certain other antidiabetic drugs.	Risk of acute kidney injury	Submission of Interim Data	2016, 2019
			Submission of Final Data	2020
MB102118 (D1690R00007) - Observational study: Cancer in Patients on Dapagliflozin and Other Antidiabetic Treatment Ongoing	To assess the incidence of breast and bladder cancer among new users of dapagliflozin compared to those who are new users of certain other antidiabetic drugs.	Risk of cancer	Submission of Interim Data	2016, 2019, 2021, 2023
			Submission of Final Data	2025

Additional Pharmacovigilance Activities for the monocomponent products (i.e. saxagliptin and dapagliflozin)

Study status	Summary of objectives	Safety concerns	Milestones	Due dates
D1693C00001 (DECLARE) - Interventional: Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events Ongoing	To assess the estimated risk ratio of the composite endpoint of CV death, myocardial infarction or ischaemic stroke, in patients with T2DM with either established CV disease or at least 2 CV risk factors in addition to T2DM, treated with dapagliflozin compared to placebo.	Clinical consequences of increased haematocrit, Renal impairment, Bone fracture, Liver injury, Serious hypersensitivity reactions, Bladder cancer, Breast cancer, Prostate cancer	Submission of Final Data	2020
Nonclinical mechanistic model studies - postdoc project Ongoing	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	Submission of final data	When available
Meta-analysis across studies D1690C00018, D1690C00019, and D1693C00001 (DECLARE) Planned	Determine the incidence of amputation and relevant preceding AEs over time by showing the cumulative proportion of subjects with events and numbers of subjects at risk at relevant time points.	LLA	Protocol Submission Submission of Final Data	Q1 2018 Q3 2020

Risk minimisation measures

Safety concern	Risk minimisation measures
Urinary tract infections (UTI) (Important identified risk)	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. Patients with signs and symptoms of UTI should be evaluated and promptly treated, if indicated (SmPC section 4.4). PL sections 2 and 4.
Diabetic ketoacidosis (DKA) including events with atypical presentation (Important identified risk)	Routine risk minimisation measures: SmPC section 4.3, 4.4 and 4.8. Qtrilmet should be discontinued if DKA is suspected or diagnosed (SmPC section 4.4). PL sections 2 and 4.
Renal impairment (Important identified risk)	Routine risk minimisation measures: SmPC section 4.3, 4.4 and 4.8. Advice is given on monitoring renal function (SmPC section 4.4). Qtrilmet should not be used in patients with moderate to severe renal impairment (SmPC section 4.2). Use in severe renal failure (eGFR < 30 mL/min/1.73 m ²) is contraindicated (SmPC section 4.3). PL sections 2 and 4.

Safety concern	Risk minimisation measures
Lactic acidosis (Important identified risk)	<p>Routine risk minimisation measures:</p> <p>SmPC sections 4.3, 4.4, and 4.8.</p> <p>Routine risk minimisation activities recommending specific clinical measures to address the risk:</p> <p>Information included on the need to assess risk factors for lactic acidosis, such as inadequately controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency, dehydration, any acute conditions associated with hypoxia or impacting renal function. Symptoms of lactic acidosis included and information that Qtrilmet should be stopped and patient seek immediate medical attention if lactic acidosis is suspected. (SmPC section 4.4).</p> <p>Qtrilmet is contraindicated in patients with metabolic acidosis (SmPC section 4.3).</p>
Severe cutaneous adverse reactions (Important potential risk)	<p>Routine risk minimisation measures:</p> <p>Monitoring for skin disorders, such as blistering, ulceration or rash, is recommended (SmPC section 4.4).</p> <p>Recommendation to follow instructions from healthcare provider (HCP) regarding skin care (PL section 2).</p>
Pancreatic cancer (Important potential risk)	No risk minimisation measures

Safety concern	Risk minimisation measures
Cardiac failure (Important potential risk)	<p>Routine risk minimisation measures:</p> <p>Information on findings of increased rate of hospitalisation for heart failure in the SAVOR study. Caution is warranted if Qtrilmet is used in patients who have known risk factors for hospitalisation for heart failure, and that patients should be advised of the characteristic symptoms of heart failure, and to immediately report such symptoms (SmPC section 4.4).</p> <p>PL section 2.</p>
Serious hypersensitivity reactions (Important potential risk)	<p>Routine risk minimisation measures:</p> <p>SmPC section 4.8.</p> <p>Contraindicated in hypersensitive patients (SmPC section 4.3).</p> <p>Qtrilmet must not be used in patients who have had any serious hypersensitivity reaction to a DPP-4 inhibitor or a SGLT-2 inhibitor (SmPC section 4.4).</p> <p>PL sections 2 and 4.</p>
Volume depletion (Important potential risk)	<p>Routine risk minimisation measures:</p> <p>SmPC sections 4.2 and 4.8</p> <p>In SmPC section 4.4, it is stated that:</p> <p>Monitoring of volume status in at-risk patients is recommended.</p> <p>Not recommended in patients on loop diuretics or volume depleted.</p> <p>Use caution in patients for whom dapagliflozin-induced reduction in blood pressure could pose a risk.</p> <p>PL sections 2 and 4.</p>

Safety concern	Risk minimisation measures
Clinical consequences of increased haematocrit (Important potential risk)	Routine risk minimisation measures: SmPC section 4.8. It is recommended to use Qtrilmet with caution in patients with already elevated haematocrit (SmPC section 4.4). PL section 4.
Bone fracture (Important potential risk)	No risk minimisation measures.
Liver injury (Important potential risk)	No risk minimisation measures.
Bladder cancer (Important potential risk)	Routine risk minimisation measures: SmPC section 4.8 Qtrilmet is not recommended for patients on concomitant pioglitazone (SmPC section 4.4).
Breast cancer (Important potential risk)	Routine risk minimisation measures: SmPC section 4.8
Prostate cancer (Important potential risk)	Routine risk minimisation measures: SmPC section 4.8
Lower limb amputation (LLA) (Important potential risk)	Routine risk minimisation measures: An increase in cases of LLA (primarily of the toe) has been observed in ongoing long-term, clinical studies with another SGLT-2 inhibitor. Recommendation on counselling patients on routine preventive foot care (SmPC section 4.4) and guidance for patients on routine/directed foot care (PL section 2).

Safety concern	Risk minimisation measures
Pancreatitis (Important potential risk)	No risk minimisation measures.
Use in patients with congestive heart failure (CHF) defined as New York Heart Association (NYHA) class III and IV (Missing information)	Routine risk minimisation measures: There is no experience in clinical trials with dapagliflozin and limited with saxagliptin (SmPC section 4.4). PL section 2.

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 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.

Periodic Safety Update Reports submission requirements

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 applicant did request the alignment of the new PSUR cycle with the current yearly reporting cycle for Qtern (saxagliptin/dapagliflozin). The new EURD list entry will therefore use the DLP of Qtern (saxagliptin/dapagliflozin) to determine the forthcoming Data Lock Points.

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*.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The indication proposed for Qtrilmet (final wording) is:

"Qtrilmet is indicated in adults aged 18 years and older with type 2 diabetes mellitus:

- to improve glycaemic control when metformin with or without sulphonylurea (SU) and either saxagliptin or dapagliflozin does not provide adequate glycaemic control.
- when already being treated with metformin and saxagliptin and dapagliflozin."

3.1.2. Available therapies and unmet medical need

An important goal of diabetes care is to achieve and maintain adequate glycaemic control as HbA1c levels over 7% are associated with an increased risk of microvascular and macrovascular complications in T2DM patients. According to current treatment guidelines T2DM treatment should be initiated with lifestyle modifications and metformin monotherapy. If treatment goals have not been reached, diabetes treatment should be intensified after 3 months by introducing a second antidiabetic agent and later a third agent could be introduced in a stepwise treatment approach. The treatment guidelines also recommend a more intensive approach with initial dual combination therapy for some patients, although no explicit HbA1c threshold has been defined. The need for individualised treatment where factors such as lifestyle, age, and comorbidities guide treatment plans is highlighted. Patient attributes and preferences are also important in therapeutic decisions.

Nearly half of all T2DM patients require combinations of 2 or more classes of non-insulin, oral antidiabetic agents. Among different countries in the EU, the percentage of patients with T2DM who fail to achieve HbA1c <7% range from 25.9% in the Netherlands to 68% in the United Kingdom (Adelphi Real World Diabetes DSP XII, 2015, de Pablos-Velasco et al 2014).

Because of the pathophysiologic complexity of T2DM, using a combination of antidiabetes agents, which can correct multiple pathophysiological disturbances through complementary MOAs is more likely to result in sustainable glycaemic control (De Fronzo et al 2013).

Apart from glycaemic control, treatment of T2DM is associated with the use of multiple medications for accompanying disorders such as dyslipidaemia, hypertension, and depression. As a result, taking multiple drugs simultaneously is common in patients with T2DM. In this context, FCMPs should be considered for improving medication adherence by reducing pill burden, which could translate into better clinical outcomes.

3.1.3. Main clinical studies

Three pivotal studies were submitted. The same studies also supported the MAA for QTERN (EMA/H/C/4057):

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 dapagliflozin and saxagliptin 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.

Study CV181168 was a multicentre, randomised, double-blind, placebo-controlled, parallel-group, 24-week Phase 3 trial in 315 subjects 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 compared with the addition of placebo to dapagliflozin and metformin in subjects with T2DM with inadequate glycaemic control on metformin and dapagliflozin. Eligible subjects could enter the long-term (LT) extension for an additional 28 weeks.

Study MB102129 was a multicentre, randomised, double-blind, placebo-controlled, parallel-group, 24-week Phase 3 trial designed to evaluate the safety and efficacy (primary endpoint: mean change from baseline in HbA1c) of the sequential addition of dapagliflozin to saxagliptin and metformin compared with the addition of placebo to saxagliptin and metformin in subjects with T2DM who had inadequate glycaemic control on metformin and saxagliptin. Eligible subjects could enter the LT extension for an additional 28 weeks.

In addition, three supportive studies, not previously assessed, were submitted:

Study CV181365 was a 52-week international, multicentre, randomised, double-blind, active-controlled, parallel group, Phase 3b trial with a blinded 104-week long-term extension period to evaluate the efficacy and safety co-administered dapagliflozin 10 mg and saxagliptin 5 mg added to metformin compared with glimepiride (1 mg to 6 mg) added to metformin in adult subjects with T2DM who had inadequate glycaemic control on metformin monotherapy. Study data from the first 52-week period is submitted.

Study D1689C00014 was a 52-week, multicentre, randomised, parallel-group, double-blind, double-dummy, active-controlled, Phase 4 study to evaluate the efficacy and safety of dapagliflozin added to metformin and dapagliflozin and saxagliptin added to metformin compared with SU (glimepiride) added to metformin in adult subjects with T2DM who had inadequate glycaemic control on a maximum tolerated dose of ≥ 1500 mg of metformin monotherapy and with individual need for therapy escalation.

Study CV181369 was a multicentre, randomised, open-label, 2-arm, parallel-group, active controlled, Phase 3b study to evaluate the efficacy and safety of saxagliptin co administered with dapagliflozin compared to insulin glargine in adult subjects with T2DM who had inadequate glycaemic control on metformin with or without SU therapy. The study included a 24-week short-term (ST) treatment period followed by a 28-week LT extension period. The subjects continued on the same open-label randomised medication and the stable dose of metformin with or without SU during the LT extension period. Only the data up to 24 weeks are included in this submission.

To support safety two additional studies were submitted:

Study CV181363 was a 26-week, 2-arm, randomised, double-blind, placebo-controlled, parallel-group Phase 3b study followed by a 26-week, site- and subject-blind LT extension treatment period to evaluate the efficacy and safety of the concomitant addition of dapagliflozin 10 mg and saxagliptin 5 mg compared with sitagliptin in adult patients with T2DM who had inadequate glycaemic control (screening HbA1c $\geq 8.0\%$ and $\leq 10.5\%$) on a stable metformin therapy at a dose of ≥ 1500 mg per day.

Study D1683C00005 study was initiated to confirm efficacy and safety of a low dose of Qtern. This was a 24-week, 3-arm, randomised, double-blind, placebo-controlled, parallel-group Phase 3 study that evaluated the

efficacy and safety of the concomitant addition of dapagliflozin 5 mg and saxagliptin 5 mg compared with dapagliflozin 5 mg or saxagliptin 5 mg in T2DM patients who had inadequate glycaemic control (screening HbA1c $\geq 7.5\%$ and $\leq 10.0\%$) on a stable metformin therapy at a dose of ≥ 1500 mg per day.

3.2. Favourable effects

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

The estimated treatment difference compared to placebo when dapagliflozin was added to saxagliptin+metformin ranged between -0.59 to -0.72% , whereas when saxagliptin was added to dapagliflozin+metformin the estimated treatment difference ranged between -0.27 to -0.35% . 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 Dapa+Saxa+Met group (41.4%) compared with the Saxa+Met group (18.3%) and the Dapa+Met group (22.2%).

In study CV181168, the proportions were 35.5% in the Dapa+Saxa+Met group and 23.1% in the Dapa+Met 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 Dapa+Saxa+Met group (38.0%) compared with the Saxa+Met 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.

Supportive studies

The primary endpoint was met in all three supportive studies. In study CV181365, Dapa+Saxa+Met was superior to Glim+Met, treatment difference -0.37% . Non-inferiority was shown for both Dapa+Saxa+Met and Dapa+Met vs Glim+Met in study D1689C00014, and a subsequent analysis showed that triple therapy was superior to Glim+Met, treatment difference -0.21% . In study CV181369, non-inferiority for Dapa+Saxa+Met vs Insulin+Met was shown and an analysis by SU treatment indicates that the outcome was driven by a larger treatment effect in the group on concomitant SU treatment. About 50% of subjects were treated with SU in both groups.

The change in HbA1c from baseline for Dapa+Saxa+Met in studies CV181365 and D1689C00014 was comparable to that observed in study CV181169. A larger reduction was observed in Study CV181369, where the baseline HbA1c was higher.

The secondary endpoints supported the primary endpoint. In studies CV181365 and D1689C00014, a greater effect on FPG was observed with the triple combination compared to Glim+Met. Numerically higher proportions of subjects achieved the target of HbA1c $< 7.0\%$ with Dapa+Saxa+Met (44.3% and 40.3%, respectively) compared to Glim+Met (34.3% and 33.9%, respectively). The proportion of responders with Dapa+Met treatment was 20.3%. No difference was observed with Dapa+Saxa+Met compared to Insulin+Met (33.2% and 33.5%, respectively).

In the two studies of 52 weeks duration, Dapa+Saxa+Met and Dapa+Met treatment resulted in a body weight reduction of about 4-5 kg whereas Glim+Met resulted in a slight weight gain. In study CV181369, which was of shorter duration (24 weeks), the body weight reduction was -1.50 kg with Dapa+Saxa+Met whereas the body weight increased by 2.14 kg in the Insulin+Met treated group.

Confirmed hypoglycaemia (defined as blood glucose <2.8 mmol/L in study D1689C00014 and as blood glucose <3.9 mmol/L in study CV181369) was more common with Glim+Met (4%) or Insulin+Met (40%) than with Dapa+Saxa+Met (0.3% in study D1689C00014 and 24% in study CV181369) or Dapa+Met (0%). It should be noted that about 50% of subjects in study CV181369 also used SU.

The proportion of subjects achieving therapeutic glycaemic response without any hypoglycaemia was significantly higher for Dapa+Saxa+Met (20.9%) than for Insulin+Met (13.1%) in study CV181369. The same pattern with regards to responders without confirmed hypoglycaemias was observed when comparing Dapa+Saxa+Met with Glim+Met in studies D1689C00014 and CV181365.

The mean change in SBP from baseline was a secondary endpoint in studies CV181365 and D1689C00014. The treatment difference between Dapa+Saxa+Met and Glim+Met was 4-5 mmHg in both studies.

3.3. Uncertainties and limitations about favourable effects

The number of elderly subjects (>75 years) was limited. Data from these subjects and data from the individual monocomponent clinical programmes in elderly patients are reassuring. However, section 4.2 of the SmPC adequately reflects the limited experience.

3.4. Unfavourable effects

Safety data were pooled (comprised of short-term + long-term data) from the three pivotal studies that supported safety in the Qtern MAA (CV181169, CV181168, and MB102129). Another four studies (CV181365, CV181363, D1689C00014 and D1683C00005), completed after the Qtern MAA has been added to support safety for Dapa/Saxa/Met XR FCMP. In addition, safety data from the Dapa/Saxa/Met ± SU study (CV181369) were submitted.

Safety data was mainly presented as two different pools:

- 3-study pool (CV181169, CV181168, and MB102129) which served as a reference to the 7-study pool
- 7-study pool which included all studies except study CV181369.

A total of 3134 subjects were included in the 7-study pool, of these 1263 subjects were treated with Dapa/Saxa/Met. The median exposure to treatment in this group was 364 days. Study (CV181369) contributes with safety data on 324 patients treated with Dapa/Saxa/Met. Thus, overall the exposure of treatment with Dapa/Saxa/Met is considered sufficient for safety assessment.

Overall, no new safety concern was identified in the safety assessment of the 7-study pool and the AE profile observed with the combined use of Dapa+Saxa added to metformin was consistent with the known safety profiles of the three monocomponents as well as with the safety data from the 3-study pool. A higher proportion of subjects experienced at least one AE in groups treated with dapagliflozin 10 mg (56.7% in the Dapa/Saxa/Met group and 56.4% in the Dapa/Met group) compared to groups not on dapagliflozin (51.2% in the Saxa/Met group) or groups with dapagliflozin in low dose i.e 5 mg (41.6%; 244/586).

In the 7-study pool, in total and for the Dapa/Saxa/Met group, the SOCs with most common reported PTs were *Infections and infestations* (25.5% and 28.1% respectively) and *Gastrointestinal disorders* (9.9% and 11.2% respectively). In total 145 (4.6%) SAEs were reported in the 7-study pool. Of these, 61 SAEs were reported in the Dapa/Saxa/Met group (4.8%).

The incidence of *overall hypoglycaemia* in the Dapa10mg/Saxa5mg/Met group in the 7-study pool was significant higher (7.5%) compared with the same group in the studies included in the 3-study pool (2.0%). These differences were driven by higher incidences of overall hypoglycaemia rates reported in the Dapa10mg/Saxa5mg/Met arm in study CV181365 (18.5%) and study CV181363 (12.9%) and most possible explained by cross-study confounders (including varying frequency of B-glucose testing). No study in the clinical program compared concomitant treatment to sequential treatment. The incidence of overall hypoglycaemia in the 3-study pool varied between 1-3% in the Dapa10/Saxa5/Met treatment arms without any difference of clinical significance between concomitant and sequential administration of dapa10 and saxa5 to metformin. The overall incidence of severe hypoglycaemia was low across all studies (<1%).

Regarding the adverse events of other special interest there were no unexpected findings in the Dapa/Saxa/Met group in the 7-study pool compared with the other treatment groups in this pool or the 3 study-pool.

Dapa and Saxa administered concomitantly vs as sequential add-on to metformin

In general, subjects treated with the Dapa/Saxa concomitantly added to metformin, had a similar pattern and percentages of AEs as was reported for subjects treated with the Dapa and Saxa sequentially added to metformin.

Dapa/Saxa/Met ± SU (study CV181369)

The AE profile observed with the combined use of Dapa + Saxa added to metformin ± SU in Study CV181369 was in line with the results in the 7-study pool. However, as expected higher frequencies of hypoglycaemia were noted in the Dapa/Saxa/Met group treated with SU (39.8%) compared to the group treated with Dapa/Saxa/Met without SU (10.8%).

3.5. Uncertainties and limitations about unfavourable effects

Exposure in subjects above 75 years was very low (n=9). Safety data from these subjects (and the age group 65-74 years) as well as data from the individual monocomponent clinical programmes in elderly patients are reassuring. The SmPC adequately reflects both the limited experience in this age group (> 75 years) and precautions to be taken in elderly.

3.6. Effects Table

Table 23 Effects Table for Qtrilmet in the treatment of T2DM

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
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Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
HbA1c	Change from Baseline	%	Dapa10/ Saxa 5/Met -1.47	Saxa/Met -0.88 Dapa/Met -1.20	Difference (95%CI) -0.59 (-0.81, -0.37) -0.27 (-0.48, -0.05)	Study CV181169
HbA1c	Change from Baseline	%	Dapa10/ Saxa 5/Met -0.51	Pla/Dapa/Met -0.16	Difference (95%CI) -0.35 (-0.52, -0.18)	Study CV181168
HbA1c	Change from Baseline	%	Dapa10/ Saxa 5/Met -0.82	Pla/Saxa/Met -0.10	Difference (95%CI) -0.72(-0.91, -0.53)	Study MB102129
Unfavourable Effects						
			Dapa10/ Saxa 5/Met	Dapa10/Met and Saxa5/Met		
Infections (mainly UTI and genital infection)	Known common identified riskfactors for both Saxa Dapa	%	28.1	31.0 and 23.1	None	7-study pool
Gastrointestinal reactions	Know common adverse reactions for saxa	%	11.2	10.9 and 11.3	None	7 study pool
Overall Hypoglycemia	Hypoglycemia is reflected in SmPC section 4.4 and 4.8	%	2.0* respectively 3.1**	Dapa10+Met: 3.7* and Saxa5+Met 0.6**	The frequency of hypoglycemia differs among studies due to cross-study confounders	*study CV181168 **study MB102129

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The data submitted has shown that triple combination with Dapa+Saxa+Met provides a clinically relevant lowering of HbA1c and that all components contribute to the effect. The use of the combination of Dapa+Saxa+Met is already approved since it is covered by the indication for QTERN (Dapa+Saxa) which is indicated for sequential add-on of saxagliptin or dapagliflozin to either dapagliflozin and metformin +/- SU or saxagliptin and metformin +/- SU respectively, or as substitution therapy.

However, the initial claim for concomitant add-on with dapagliflozin + saxagliptin in patients not adequately controlled on metformin, as was proposed at initial submission of this application, is not accepted. As was concluded in the MAA for QTERN, the only benefit of this strategy compared to sequential addition of the

components, is a faster achievement of a lower HbA1c. The clinical relevance of this benefit is uncertain. Taking the limitations of comparisons between studies into account, it should be noted that HbA1c at the end of the sequential add-on studies CV181168 and MB102129 was comparable to that achieved in the concomitant add-on study CV181169, as all groups had a mean HbA1c of about 7.5% at week 24. The applicant proposed that concomitant add-on with dapagliflozin + saxagliptin should be indicated in patients who require $\geq 1.5\%$ reduction in HbA1c to reach glycaemic target, in line with the EASD/ADA treatment guidelines published in 2018. However, the main objections of the CHMP against an indication allowing concomitant add-on are the lack of data supporting a benefit of reaching HbA1c target faster compared to sequential add on of one product at the time, and the disadvantage of risking adverse events from two products instead of just one. Since no new data has been submitted that could alleviate these concerns, the indication as initially proposed is not acceptable.

Furthermore, adding saxagliptin to dapagliflozin showed modest effect depending on HbA1c baseline. Although the difference measured between the FCMP 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 are likely patients who can benefit from the addition of saxagliptin. However, as it is not known which patient will benefit from concomitant addition of dapagliflozin and saxagliptin to metformin, treatment effects should be evaluated in individual patients. This also argues in favour of sequential add-on treatment.

In general, subjects treated with the Dapa/Saxa concomitantly added to metformin, had a similar pattern and percentages of AEs as was reported for subjects treated with the Dapa and Saxa sequentially added to metformin. However, initiation of concomitant treatment with dapagliflozin and saxagliptin may make judgements of causal relationship of the adverse events more difficult compared to a stepwise treatment. Furthermore, handling of dose reductions or interruptions (temporarily or permanent) is considered more complicated if a FCMP is used compared with use of monocomponents.

Limited data on the combination with SUs has been provided for the FCMP, and it has also been investigated for the individual components. No additional safety concerns other than increased incidences of hypoglycaemia were expected, based on the knowledge on the MOAs. This was supported by the data submitted on the use of Qtrilmet together with SU. Therefore, the combination with SU is acceptable.

3.7.2. Balance of benefits and risks

The overall B/R of Qtrilmet as sequential add-on treatment or substitution in patients already being treated with the free combination of dapagliflozin + saxagliptin + metformin is considered positive. The FCMP may improve medication adherence by reducing pill burden, which could translate into better clinical outcomes.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall B/R of Qtrilmet is positive in the indications:

- to improve glycaemic control when metformin with or without sulphonylurea (SU) and either saxagliptin or dapagliflozin does not provide adequate glycaemic control.
- when already being treated with metformin and saxagliptin and dapagliflozin.

4. Recommendations

Outcome

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

Qtrilmet is indicated in adults aged 18 years and older with type 2 diabetes mellitus:

- to improve glycaemic control when metformin with or without sulphonylurea (SU) and either saxagliptin or dapagliflozin does not provide adequate glycaemic control.
- when already being treated with metformin and saxagliptin and dapagliflozin.

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

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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.

Medicinal product no longer authorised