EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 May 2017
EMA/CHMP/291920/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Onglyza	saxagliptin
Komboglyze	saxagliptin / metformin hydrochloride

Procedure No. EMEA/H/C/xxxx/WS/1078

Note

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

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List of abbreviations

Abbreviation or special term	Explanation
5-OH	5-hydroxy
AE	Adverse event
AEoSI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AR	Adverse reaction
AST	Aspartate aminotransferase
AUC	Area under the concentration vs. time curve
$AUC_{(0-T)}$	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration
$AUC_{(INF)}$	Area under the plasma concentration-time curve from time zero extrapolated to infinity
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CK	Creatine kinase
C_{max}	Maximum plasma concentration
CrCl	Creatinine clearance
CSP	Clinical study protocol
CSR	Clinical study report
CV	Cardiovascular
CYP	Cytochrome
DDI	Drug-drug interaction
DPP4	Dipeptidyl peptidase 4
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease
EU	European Union
FDA	Food and Drug Administration (US Department of Health and Human Services)
FDC	Fixed-dose combination
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic peptide
GLP-1	Glucagon-like peptide-1
GM	Geometric mean
GMP	Good Manufacturing Practice
HbA1c	Glycosylated haemoglobin
HDL-C	High density lipoprotein-cholesterol
ICH	International Conference on Harmonisation
IR	Immediate release
LDL-C	Low density lipoprotein-cholesterol

LOQ	List of Questions
LT	Long-term
MA	Marked abnormality
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MDRD	Modification in Diet and Renal Disease
MEB	Medicines and Evaluation Board
MI	Myocardial infarction
MOA	Mechanism of action
MTT	Meal tolerance test
NYHA	New York Heart Association
NLT	Not less than
OL	Open-label
OGTT	Oral glucose tolerance test
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PPG	Postprandial glucose
PT	Preferred term
RMP	Risk Management Plan
RVG #	Marketing Authorisation number in NL
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SGLT2	Sodium-glucose cotransporter 2
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA Query
SOC	System Organ Class
ST	Short-term
SU	Sulphonylurea
T2DM	Type 2 diabetes mellitus
TB	Total bilirubin
TC	Total cholesterol
TG	Triglycerides
TZD	Thiazolidinedione
ULN	Upper limit of normal
UTI	Urinary tract infection
XR	Extended-release

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 14 December 2016 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of indication to include the use of Onglyza and Komboglyze in combination with other diabetes medicines; as a consequence, sections 4.1 and 5.1 of the SmPC are updated. Editorial changes are made throughout the Summary Product Characteristics and Package Leaflets. Furthermore, the Product Information is brought in line with the latest QRD template version 10 for Onglyza.

In addition, the WSA took the opportunity to update the list of local representatives in the Package Leaflet.

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet.

Information on paediatric requirements

Onglyza

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0059/2016) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (P/0059/2016) was not yet completed as some measures were deferred.

Komboglyze

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/240/2009) 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

Timetable	Actual dates
Submission date	14 December 2016
Start of procedure:	18 February 2017
CHMP Rapporteur Assessment Report	12 April 2017
CHMP members comments	8 May 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	11 May 2017
Opinion	18 May 2017

2. Scientific discussion

2.1. Introduction

Saxagliptin is a DPP4-inhibitor, used in the treatment of Type 2 diabetes mellitus (T2DM). It was first approved for marketing in the European Union (EU) via the Centralised Procedure on 01 October 2009 as Onglyza and as fixed dose combination with metformin as Komboglyze on 24 November 2011. Currently saxagliptin is indicated as monotherapy, as dual therapy with metformin, SU or TZD, as triple therapy with metformin and SU, and as combination with insulin. In this type 2 variation the MAH seeks extension of the indication as triple oral therapy in combination with metformin plus dapagliflozin. The application is supported by data from three clinical trials (CV181168, CV181169, and MB102129). These trials were previously submitted in support of the QTERN (saxagliptin/dapagliflozin) marketing application (procedure number EMEA/H/C/004057, CHMP positive opinion dated 26 May 2016). Supportive safety information are presented from the ST + LT Pool (pooled data from Study CV181169) and the ST + LT treatment periods (from Studies CV181168 and MB102129).

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

- Tabular overview of clinical studies

Table 1 - Description of the clinical efficacy and safety studies

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

2.3.2. Pharmacokinetics

N/A

2.3.3. Pharmacodynamics

N/A

2.4. Clinical efficacy

2.4.1. Main studies

In support of the application three clinical trials were submitted: (CV181168, CV181169, and MB102129). Studies CV181169 and CV181168 will be used to support efficacy, and the integrated data from all 3 of these studies will be used to show safety and tolerability in the short-term plus long-term treatment periods (ie. ST + LT Pool) for up to 52 weeks.

Methods

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

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

Study participants

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

Objectives

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

Outcomes/endpoints

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

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

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

Statistical methods

The primary efficacy analysis was 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. For all three studies, in order to protect the overall type I error rate, the interpretation of the family-wise statistical significance of treatment comparisons for each secondary efficacy endpoint was done using a step-wise procedure (in CV181169, the test was simultaneously applied to the two treatment comparisons).

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

Results

Participant flow

Patient disposition is shown in Table 2. Data for Long-term treatment period of study CV181168 and MB102129 are shown in Table 3.

Table 2 - Disposition of subjects – Studies CV181169, CV181168, and MB102129 - ST treatment period

	Concomitant add-on study				Sequential add-on studies					
	Study CV181169				Study CV181168			Study MB102129		
	Saxa + Dapa + Met	Saxa + Met	Dapa + Met	Total	Saxa + Dapa + Met	Pla + Dapa + Met	Total	Saxa + Dapa + Met	Pla + Saxa + Met	Total
Subjects enrolled	1282				857			818		
Subjects not entering treatment period (%)	643 (50.2)				373 (43.5)			335 (40.9)		
Subjects entering treatment period (%)	639 (49.8)				484 (56.5)			483 (59.0)		
Subjects not randomised	105 (16.4)				169 (34.9)			163 (33.8)		
Subject no longer meets study criteria					127 (26.3)			130 (26.9)		
HbA1c < 7%					106 (22.0)			61 (17.5)		
HbA1c>10%					8 (1.7)			12 (3.4)		
Subjects randomised	179	176	179	534	153	162	315	160	160	320
Subjects completing the short-term treatment (%)	169 (94.4)	161 (91.5)	160 (89.4)	490 (91.8)	142 (92.8)	156 (96.3)	298 (94.6)	148 (92.5)	153 (95.6)	301 (94.1)
Subjects not completing the short-term treatment (%)	10 (5.6)	15 (8.5)	19 (10.6)	44 (8.2)	11 (7.2)	6 (3.7)	17 (5.4)	12 (7.5)	7 (4.4)	19 (5.9)
Reasons for not completing the short- term treatment (%)										
Lack of efficacy[a]	0	0	0	0	0	0	0	0	0	0
Adverse event	1 (0.6)	0	1 (0.6)	2 (0.4)	0	1 (0.6)	1 (0.3)	3 (1.9)	0	3 (0.9)
Subject request to discontinue study treatment	1 (0.6)	0	2 (1.1)	3 (0.6)	1 (0.7)	0	1 (0.3)	0	0	0
Subject withdrew consent	1 (0.6)	8 (4.5)	6 (3.4)	15 (2.8)	4 (2.6)	2 (1.2)	6 (1.9)	2 (1.3)	0	2 (0.6)
Death	0	0	0	0	0	0	0	0	0	0
Lost to follow-up	5 (2.8)	6 (3.4)	8 (4.5)	19 (3.6)	4 (2.6)	2 (1.2)	6 (1.9)	4 (2.5)	4 (2.5)	8 (2.5)
Poor/non-compliance	0	1 (0.6)	0	1 (0.2)	1 (0.7)	1 (0.6)	2 (0.6)	0	0	0
Pregnancy	1 (0.6)	0	1 (0.6)	2 (0.4)	0	0	0	0	0	0
Subject no longer meets study	0	0	0	0	1 (0.7)	0	1 (0.3)	0	1 (0.6)	1 (0.3)

criteria										
Administrative reason by sponsor	0	0	0	0	0	0	0	0	0	0
Other	1 (0.6)	0	1 (0.6)	2 (0.4)	0	0	0	1 (0.6)	0	1 (0.3)
Not reported	0	0	0	0	0	0	0	2 (1.3)	2 (1.3)	4 (1.3)

[a] Does not include patients receiving rescue medication

Table 3 - Disposition of subjects – CV181168 and MB102129 - LT treatment period

	Sequential add-on studies					
	Study CV181168			Study MB102129		
	Saxa + Dapa + Met	Pla + Dapa + Met	Total	Saxa + Dapa + Met	Pla + Saxa + Met	Total
Subjects completing ST treatment period (%)	142 (92.8)	156 (96.3)	298 (94.6)	148 (92.5)	150 (93.8)	298 (93.1)
Subjects entering LT treatment period (%)	142 (92.8)	155 (95.7	297 (94.3)	147 (91.9)	147 (91.9)	294 (91.9)
Subjects completing LT treatment period (%)	133 (86.9)	147 (90.7)	280 (88.9)	141 (88.1)	140 (87.5)	281 (87.8)
Subjects not completing LT treatment period (%)	9 (5.9)	8 (4.9)	17 (5.4)	6 (3.8)	7 (4.4)	13 (4.1)
Reason for not completing LT treatment period (%)						
Lack of efficacy	1 (0.7)	0	1 (0.3)	0	1 (0.6)	1 (0.3)
Adverse event	3 (2.0)	2 (1.2)	5 (1.6)	4 (2.5)	2 (1.3)	6 (1.9)
Subj request to discontinue study trt	0	1 (0.6)	1 (0.3)	0	0	0
Subject withdrew consent	2 (1.3)	2 (1.2)	4 (1.3)	0	2 (1.3)	2 (0.6)
Death	0	1 (0.6)	1 (0.3)	0	0	0
Lost to follow-up	2 (1.3)	2 (1.2)	4 (1.3)	0	2 (1.3)	2 (0.6)
Subject no longer meets study criteria	1 (0.7)	0	1 (0.3)	2 (1.3)	0	2 (0.6)
Subjects entering follow-up (%)	5 (3.3)	2 (1.2)	7 (2.2)	6 (3.8)	8 (5.0)	14 (4.4)
Subjects completing follow-up (%)	4 (2.6)	2 (1.2)	6 (1.9)	4 (2.5)	7 (4.4)	11 (3.4)
Subjects not completing follow-up (%)	1 (0.7)	0	1 (0.3)	2 (1.3)	1 (0.6)	3 (0.9)

Recruitment

Recruitment periods for each of the studies were as follows:

Study CV181168 Study initiation date: 29-jun-2012, Study completion date: 12-Jan-2015. Database lock for the 24 week, Short-term, Double blind period was 27-aug-2014.

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

Study MB102129 : Study initiation date: 21-sep-2012, Study completion date: 19-Feb-2015. Database lock for the 24 week, short-term, double blind period was 25-sep-2014.

Conduct of the study

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

Baseline data

The demographics and disease characteristics of the subjects in study CV181169, CV181168, and MB102129 are summarized in Table 4. The treatment groups within the respective studies were well-balanced with regard to demographic and baseline characteristics, including diabetes-related medical history (hyperlipidaemia, dyslipidaemia, hypertension, and CV disease). The majority of subjects were White; mean age was 53.8-55.1 years. There were few subjects ≥75 years of age (1 to 5 subjects per study). The entrance criterion of HbA1c ≥8.0%, ≤12.0% (Study CV181169) and ≥8.0%, ≤11.5% (Studies CV181168 and MB102129) in subjects not controlled on metformin monotherapy was selected to be more representative of patient populations with T2DM encountered in clinical practice. In Study CV181169, the mean baseline HbA1c was 8.9%. In Studies CV181168 and MB102129, the mean baseline HbA1c values after the pre-randomisation OL treatment period were 7.9% and 8.2%, respectively. Across studies, subjects had a high mean weight ≥87 kg and body mass index (BMI) ≥31 kg/m^2. Mean duration of T2DM was at least 7.6 years. Along with high mean baseline HbA1c, these characteristics suggest more advanced disease in these subjects and are representative of T2DM patients that present in clinical practice who have not achieved their target goals.

Table 4 - Subject demographics and baseline characteristics – studies CV181169, CV181168, and MB102129

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

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

Numbers analysed

For all three studies, the primary data set for efficacy analysis was the respective Randomised Subjects data set. These consisted of data from all randomised subjects who took at least one dose of double-blind study drug during the ST double-blind periods. Numbers are shown in Table 2 (Disposition of subjects).

Outcomes and estimation

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

Summary of main studies

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 5 - Summary of efficacy for trial CV181169

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

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

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

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

Table 6 - Summary of efficacy for trial CV181168

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

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)			
	Secondary endpoints			
	2-hour PPG from a liquid MTT	Mean change from baseline in 2-hour post-prandial glucose during a MTT at Week 24.		
	FPG	Mean change from baseline in FPG at Week 24.		
	Responders	Percent of subjects achieving a therapeutic glycemic response, defined as a HbA1c < 7.0% at Week 24.		
	Glycemic rescue	The percent of subjects who required glycemic rescue or discontinuation of study treatment for lack of efficacy up to Week 24, and the time to glycemic rescue or discontinuation for lack of efficacy in the double-blind treatment period.		
	Glucose	Mean change from baseline in AUC glucose obtained during the MTT at Week 24.		
	Lipids	Mean percent change from baseline in fasting serum lipids (Total-C, LDL-C, HDL-C, TG) during the double-blind treatment period.		
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Longitudinal repeated measures analysis - change in HbA1c from baseline to Week 24			
Descriptive statistics, point estimate, and effect estimate	Primary endpoint	Treatment group	Saxa+Dapa+Met (N=153)	Pla+Dapa+Met (N=162)
	HbA1c (%)	n	139	149
		Baseline: Mean (SD)	7.95 (0.826)	7.85 (0.920)
		Change from baseline to endpoint (Week 24): Adj mean (SE) [95% CI]	-0.51 (0.0624) [-0.63, -0.39]	-0.16 (0.0605) [-0.28, -0.04]
		Change from baseline to endpoint (Week 24): difference Saxa+Dapa+Met vs Pla+Dapa+Met [95% CI]		-0.35 (-0.52, -0.18) P<0.0001
Analysis description	**Secondary Analysis**			
	120-min PPG (mmol/L)	n	135	144
		Baseline: Mean (SD)	11.53 (2.811)	11.31 (2.887)
		Change from baseline to endpoint (Week 24): Adj mean (SE) [95% CI]	-2.06 (0.1824) [-2.42, -1.71]	-1.74 (0.1766) [-2.09, -1.39]
		Change from baseline to endpoint (Week 24): difference (SE) Saxa+Dapa+Met vs Pla+Dapa+Met [95% CI]		-0.32 (0.2539) (-0.82, 0.18) P=0.2054
	FPG (mmol/L)	n	139	146

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)			
		Baseline: Mean (SD)	9.07 (1.905)	8.71 (1.879)
		Change from baseline to endpoint (Week 24): Adj mean (SE) [95% CI]	-0.50 (0.1468) [-0.79, -0.21]	-0.30 (0.1438) [-0.58, -0.02]
		Change from baseline to endpoint (Week 24): difference (SE) Saxa+Dapa+Met vs Pla+Dapa+Met [95% CI]		-0.20 (0.2061) [-0.61, 0.20]
	Number (%) of patients at endpoint	n	150	160
		HbA1c<7%	51 (34)	39 (24.4)
		Difference (SE) Saxa+Dapa+Met vs Pla+Dapa+Met		12.2 (4.504) [3.4, 21.0]

Table 7 - Summary of efficacy for trial MB1021293

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
Statistical methods	With 133 subjects per treatment group, there was 90% power to detect a difference in means of 0.4% between the dapagliflozin + saxagliptin + metformin treatment group and the placebo + saxagliptin + metformin treatment group, assuming a standard deviation of 1.0%. Assuming that 5% of subjects would not have a post-baseline assessment, a total of approximately 280 subjects (140 subjects per treatment group) were to be randomized. The mean change from baseline in HbA1c at Week 24 was assessed comparing the dapagliflozin + saxagliptin + metformin treatment group with the placebo + saxagliptin + metformin treatment group. The primary efficacy analysis was performed using a longitudinal repeated measures analysis with terms for baseline value, treatment group, time, stratum, the interaction of treatment group and time, and the interaction of baseline value and time, including observations prior to rescue.	
Treatments groups	Saxa+Dapa+Met 160 patients randomised	5mg+10mg+≥1500mg
	Pla+Saxa+Met 160 patients randomised	Pla+5mg+≥1500mg

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)			
	During the open-label, pre-randomisation treatment period of the study, subjects were divided into two strata (Stratum A and Stratum B), depending on whether or not they had been on DPP4 inhibitor therapy prior to the screening visit. Subjects in Stratum B had been on the maximum approved dose of a DPP4 inhibitor for at least 8 weeks prior to the screening visit.			
Endpoints and definitions	Primary endpoint			
	Change in HbA1c (%)	Change from baseline to week 24		
	Secondary endpoints			
	FPG	Mean change from baseline in FPG at Week 24.		
	2-hour PPG from a liquid MTT	Mean change from baseline in 2-hour post-prandial glucose during a MTT at Week 24.		
	Body weight	Change from baseline to Week 24 in body weight		
	Responders	Percent of subjects achieving a therapeutic glycemic response, defined as a HbA1c < 7.0% at Week 24.		
	Glycemic rescue	The percent of subjects who required glycemic rescue or discontinuation of study treatment for lack of efficacy up to Week 24, and the time to glycemic rescue or discontinuation for lack of efficacy in the double-blind treatment period.		
	Glucose	Mean change from baseline in AUC glucose obtained during the MTT at Week 24.		
	Lipids	Mean percent change from baseline in fasting serum lipids (Total-C, LDL-C, HDL-C, TG) during the double-blind treatment period.		
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Longitudinal repeated measures analysis - change in HbA1c from baseline to Week 24			
Descriptive statistics, point estimate, and effect estimate	Primary endpoint	Treatment group	Saxa+Dapa+Met (N=153)	Pla+Saxa+Met (N=162)
	HbA1c (%)	n	146	129
		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)

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): Adj mean (SE) [95% CI]	-4.08 (0.2252) [-4.53, -3.64]	-2.11 (0.2279) [-2.56, -1.66]
		Change from baseline to endpoint (Week 24): difference (SE) Saxa+Dapa+Met vs Pla+Saxa+Met [95% CI]		-1.97 (0.3050) (-2.57, -1.37) P<0.0001
	FPG (mmol/L)	n	146	129
		Baseline: Mean (SD)	9.91 (2.700)	9.80 (2.599)
		Change from baseline to endpoint (Week 24): Adj mean (SE) [95% CI]	-1.81 (0.1567 [-2.12, -1.50]	-0.29 (0.1649) [-0.62, 0.03]
		Change from baseline to endpoint (Week 24): difference (SE) Saxa+Dapa+Met vs Pla+Saxa+Met [95% CI]		-1.52 (0.2230) [-1.96, -1.08]
	Number (%) of patients at endpoint	n	158	158
		HbA1c<7%	58 (36.7)	21 (13.3)
		Difference (SE) Saxa+Dapa+Met vs Pla+Saxa+Met		25.5 (4.5) [16.7, 34.4] P<0.0001

Clinical studies in special populations

No separate studies were conducted specifically to address the efficacy of dapagliflozin + saxagliptin in special populations. In all three studies, treatment-by-subgroup interaction testing was used to evaluate treatment effects on the primary endpoint (adjusted mean change in HbA1c) in subgroups where the effect might vary (from the primary endpoint analysis). Subgroups analysed were Baseline HbA1c, Race, Gender, Age, Female/Age and Region.

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

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

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

Potential treatment interactions were detected for female age in Studies CV181169 (p=0.0082) and MB102129 (p=0.0154). In Studies CV181169 and MB102129, the reduction of HbA1c in saxagliptin-

containing treatment groups was diminished in women ≤50 years of age. Results are shown in Table 8. However, as the studies were not designed to detect such subgroup differences, and due to the small sample size in the female ≤50 groups, these results should be interpreted with caution.

Table 8 - HbA1c Subgroup Analysis by Age and Gender at 24 Weeks, study CV181169

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

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

Primary efficacy endpoint: HbA1c change from baseline at Week 24

The primary efficacy endpoint was met for both studies (Table 9). Repeated measures analysis of the primary endpoint (excluding data after rescue) demonstrated a clinically relevant effect of saxagliptin + dapagliflozin + metformin treatment in lowering HbA1c at Week 24 which was statistically significant versus the addition of dapagliflozin to metformin (studies CV181169 and CV181168) and versus the addition of saxagliptin to metformin (studies CV181169).

In Study CV181168, the adjusted mean changes from baseline in HbA1c at Week 24 in the saxagliptin + dapagliflozin + metformin and placebo + dapagliflozin + metformin groups were 0.51% and 0.16%, respectively. The difference with saxagliptin + dapagliflozin + metformin treatment was -0.35% ($p<0.0001$) vs placebo + dapagliflozin + metformin.

In study CV 181169, adjusted mean change from baseline in HbA1c at Week 24 was -1.47% for the saxagliptin + dapagliflozin + metformin treatment group, -0.88% for the saxagliptin + metformin group and -1.20% for the dapagliflozin + metformin group. The difference with saxagliptin + dapagliflozin + metformin treatment was -0.27 versus dapagliflozin + metformin.

The treatment effect observed at the end of the 24-week period was durable to the end of the 52-week ST + LT treatment period of Study CV181168. At week 52 changes from baseline in HbA1c 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, with a mean difference of -0.42% [(5% CI: -0.64, -0.20).

Secondary endpoints

120-minute PPG change from baseline at week 24

Repeated measures analysis of 120-minute PPG at Week 24 (excluding data after rescue) did not show a statistically significant effect of saxagliptin + dapagliflozin + metformin in lowering PPG at Week 24 (LOCF) when tested against placebo + dapagliflozin + metformin in Study CV181168 or when tested simultaneously against both saxagliptin + metformin and dapagliflozin + metformin in Study CV181169. The difference between the saxagliptin + dapagliflozin + metformin group and the dapagliflozin + metformin was -0.51 and -0.32 mmol/L in study CV181169 and CV181168, respectively.

FPG change from baseline at week 24

The adjusted mean change in FPG from baseline at Week 24 (excluding data after rescue) for the saxagliptin + dapagliflozin + metformin group was larger than that of the saxagliptin + metformin group and similar to that of the dapagliflozin + metformin group. Differences between the triple therapy and dapagliflozin + metformin treated group were -0.34 and -0.20 mmol/L, respectively in trial CV181169 and CV181168 (non-significant). In study CV181168 changes were maintained up to week 52, with a difference between triple therapy and dapagliflozin + metformin group of -0.45 mmol/L.

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

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

In study CV181168, the proportion of subjects achieving HbA1c <7.0% at Week 24 was greater in the saxagliptin + dapagliflozin + metformin group (35.3%) than in the placebo + dapagliflozin + metformin group (23.1%). The difference between the two groups was 12.2%. At Week 52 the adjusted percent of subjects with HbA1c <7.0% was 29.3% in the saxagliptin + dapagliflozin + metformin group and 13.1% in the placebo + dapagliflozin + metformin group; the adjusted percent difference between the two treatment groups at Week 52 was 16.2% (95% CI: 8.1, 24.2).

Body weight change from baseline at Week 24

In both studies, the dapagliflozin-containing treatment groups showed a decrease from baseline in mean adjusted body weight at Week 24 (-0.51 kg to -2.39 kg). The weight reduction observed in groups treated with both saxagliptin and dapagliflozin suggests that the dapagliflozin-induced weight loss is maintained in the presence of saxagliptin.
Over 52-weeks of treatment, there were modest body weight decreases in both treatment groups in Study CV181168: -1.13 kg in the saxagliptin + dapagliflozin + metformin group, and -1.50 kg in the placebo + dapagliflozin + metformin group. Dapagliflozin results in the consistent reduction of body weight. Saxagliptin has been shown to be weight neutral. The combination of saxagliptin + dapagliflozin + metformin provides significant glycaemic control with the potential for moderate weight loss.

Table 9 - HbA1c change from baseline at Week 24 and Week 52 excluding data after rescue for randomised subjects – studies CV181169 and CV181168

	Concomitant add-on study			Sequential add-on study	
	Study CV181169			Study CV181168	
	Saxa+Dapa+ Met (N=179)	Saxa+Met (N=176)	Dapa+Met (N=179)	Saxa+Dapa+ Met (N=153)	Pla+Dapa+ Met (N=162)
HbA1c (%) at Week 24					
N#	176	175	172	150	160
Baseline	8.93	9.03	8.87	7.95	7.85
Mean (SD)	(1.186)	(1.053)	(1.174)	(0.826)	(0.920)
N##	158	143	151	139	149
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)
95% CI	(-1.62, -1.31)	(-1.03, -0.72)	(-1.35, -1.04)	(-0.63, -0.39)	(-0.28, -0.04)
HbA1c (%) at week 52					
N##				105	103
Adj. mean change from baseline (SE)	-	-	-	-0.38 (0.0786)	0.05 (0.0785)
95% CI				(-0.53, -0.22)	(-0.11, 0.20)
Comparison of adjusted mean change from baseline at week 24					
Saxa + Dapa+ Met vs Saxa + Met					
Difference	-0.59%				
95%CI for difference	(-0.81, -0.37)	-	-	-	-
p-value	P<0.0001				
Saxa + Dapa+ Met vs Dapa + Met				**Saxa + Dapa+ Met vs Pla + Dapa + Met**	
Difference	-0.27			-0.35	
95%CI for difference	(-0.48, -0.05)	-	-	(-0.52, -0.18)	-
p-value	P=0.0166			p<0.0001	
Comparison of adjusted mean change from baseline at week 52					
				Saxa + Dapa+ Met vs Pla + Dapa + Met	
Difference	-	-	-	-0.42	-
95%CI for difference				(-0.64, -0.20)	

Discontinuation for lack of glycaemic control or rescue for failing to achieve prespecified glycaemic targets

In Study CV181168, the saxagliptin + dapagliflozin + metformin group had fewer subjects discontinued for lack of glycaemic control or rescued for failing to achieve prespecified glycaemic targets than the placebo + dapagliflozin + metformin group (2.5% and 4.4%, respectively). Discontinuation or rescue began at Week 14.

In Study CV181169, the saxagliptin + metformin group had the greatest proportion of subjects discontinued for lack of glycaemic control or rescued for failing to achieve prespecified glycaemic targets: 9.4%, compared with 5.5% in the saxagliptin + dapagliflozin + metformin group and 3.4% in the dapagliflozin + metformin group. Discontinuation or rescue began at Week 8.

In the ST + LT period, lower proportions of subjects discontinued study treatment for lack of glycaemic control or were rescued for failing to achieve pre-specified glycaemic targets in the saxagliptin + dapagliflozin + metformin treatment group (18.6%) compared to the placebo + dapagliflozin + metformin group (28.4%) through Week 52.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

In support of the Application, data from three clinical Phase 3 studies were submitted. All three were multicentre, randomised, double-blind, active (CV181169) or placebo-controlled (CV181168 and MB102129), parallel-group studies. Study CV181169 consisted of a screening period, followed by a lead-in period (4-weeks), and then a 24-week double-blind treatment period. Study CV181168 and MB102129 had a screening period, followed by an OL treatment period (16 weeks), and then a 24-week double-blind treatment period.
Studies CV181169 and CV181168 were used to support efficacy, and the integrated data from all 3 of these studies were used to show safety and tolerability in the short-term plus long-term treatment periods (ie, ST + LT Pool) for up to 52-weeks.

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

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

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

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

The design and conduct of the studies were appropriate to establish the efficacy and safety of saxagliptin + dapagliflozin + metformin vs dapagliflozin + metformin.

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

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

Efficacy data and additional analyses

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

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

Primary endpoint

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

The difference of Saxa + Dapa + metformin vs Dapa + Met was small: only -0.27% in study CV181169. This is below the accepted delta for non-inferiority trials in diabetes. Apparently, the additional value of Saxagliptin on top of Dapagliflozin and Metformin is small. The clinical relevance is debatable, although one could argue that the response rate is different (22% Dapa + Met vs 41% Dapa/Saxa +Met). The finding observed in Study CV181169 is confirmed in Study CV181168: the additional efficacy of Saxagliptin on top of Dapa + Met is limited (HbA1c = -0.35%). This figure is very close to the delta of 0.30% used in non-inferiority trials. Although this difference is statistically significant, the clinical relevance is doubtful. Even the response rate Saxa + Dapa + Met is not convincingly superior to Dapa + Met (35% vs 23%).
The Applicant has shown that, when given together, the contribution of both components depends on baseline HbA1c. Saxagliptin is contributing a larger proportion to the total combination effect at lower baseline HbA1c levels than at higher ones, and conversely, dapagliflozin is contributing a larger

proportion to the total combination effect at higher baseline HbA1c levels than at lower ones. Furthermore, the difference measured between the combination and the monocomponents is not quite representative for the actual contribution of each component. Although there is no direct pharmacodynamic interaction, when combined, both the effect of saxagliptin and dapagliflozin seems to be reduced, as the total effect of the combination is not the sum of the individual effects. This is because both components for their action are dependent on plasma glucose levels.

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

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

Secondary endpoints

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

FPG
Reductions in FPG were seen in all dapagliflozin-treated groups. Numerically, these decreases were largest in the saxagliptin + dapagliflozin +metformin groups, but the differences with dapagliflozin + metformin treated groups were not statistically significant. Significance was reached for the comparison between saxagliptin + dapagliflozin +metformin and saxagliptin + metformin groups. For FPG too, results suggest that dapagliflozin has more effect than saxagliptin.

Responders

In study CV181169, treatment with saxagliptin + dapagliflozin + metformin resulted in 41% responders (HbA1c < 7%) after 24 weeks, compared to 18% for the saxagliptin + metformin group and 22% for the dapagliflozin + metformin group. In the sequential add-on study percentage responders after the OL treatment period was 22% for the dapagliflozin + metformin group. Adding saxagliptin in the 24 week treatment period resulted in an increase in responders (35%) that was larger than in the placebo group (23%).

Body weight

Treatment with saxagliptin was weight neutral.

Subgroups

The total number of elderly patients is limited in the three trials, and especially the number of subjects of 75 years and above: total number of 9.

In female subjects < 50 year, saxagliptin was virtually ineffective. Although the numbers of females < 50 was limited, the contrast with older females and males is large. Reduction in HbA1c was only -0.13 in the younger female group in study CV181169, and there was no statistical significant difference between the saxagliptin + dapagliflozin + metformin group vs dapagliflozin + metformin group, suggesting that the effect in the triple therapy group was due to the addition of dapagliflozin and not by saxagliptin. In Study MB102129, HbA1c increased in females < 50 years treated with saxagliptin + metformin. The Applicant has conducted a number of exploratory analyses to investigate

if evidence exists for a smaller treatment effect in younger females. There were no indications that baseline characteristics C-peptide, T2DM duration, BMI, FPG, PPG, and eGFR could explain the difference in study CV181169. Individual effects in younger females showed large variability. An analysis of 10 pooled studies did not reveal a treatment-by-female age for saxagliptin 5 mg. However, for saxagliptin 2.5 mg, the possibility of female age interaction cannot be excluded. But the clinical consequences, if any, are limited.

Long-term results

Results of the 52-week ST + LT treatment period of Study CV181168 indicate that glucose control was sustained at week 52. At week 52 change from baseline in HbA1c in the saxagliptin + dapagliflozin + metformin was -0.38% (compared to -0.51 at week 24); in the dapagliflozin + metformin group change was +0.05 (compared to -0.16 at week 24). Mean treatment difference at week 52 was -0.42% (compared to -0.35% at week 24).
Similar results were seen for percentage responders: a slight decrease in percentage responders was observed at week 52 compared to week 24 (from 35.3% to 29.3% in the saxa + dapa + met group, and from 23.1% to 13.1% in the dapa + met group), but the difference between treatment groups was sustained (12.2% at week 24 and 16.2% at week 52).

2.4.3. Conclusions on the clinical efficacy

Studies indicate that adding saxagliptin to metformin and dapagliflozin in subjects insufficiently controlled by these treatments can result in improved glycaemic control, although the additional effects are modest. Nevertheless, there might be patients who can benefit from this combination.

2.5. Clinical safety

Introduction

Saxagliptin was approved as Onglyza for marketing in the European Union (EU) via the Centralised Procedure on 01 October 2009 and has now been approved in more than 90 countries.
The most commonly reported adverse reactions in placebo-controlled trials reported in ≥5% of patients treated with Onglyza 5 mg and more commonly than in patients treated with placebo are upper respiratory tract infection (7.7%), urinary tract infection (6.8%) and headache (6.5%).

The safety and tolerability of the combined use of saxagliptin and dapagliflozin is based on 3 Phase 3 studies (CV181168, CV181169, and MB102129) and a Phase 1 study (CV181191) conducted in the clinical development programme. For the purpose of summarising the safety experience, the safety data from the 3 Phase 3 studies (ie, 52-week ST + LT treatment period in Studies CV181168 and MB102129 and 24-week ST treatment period in Study CV181169) were pooled. The integrated safety population is referenced as the ST + LT Pool. The rationale for pooling the safety data from the 3 Phase 3 studies is based on the overall similarity in their study design, and the availability of a larger subject population that is sufficient to establish the safety profile of the combined use of saxagliptin and dapagliflozin. The pooled population included all randomised and treated subjects from the 3 studies.

Patient exposure

A total of 1169 subjects were included in the safety analysis population of the ST + LT Pool. Of these, 492 received saxagliptin + dapagliflozin + metformin, 336 received saxagliptin + metformin, and 341

received dapagliflozin + metformin. The median exposure to study treatment was 359 days in the saxagliptin + dapagliflozin + metformin group and approximately 176 days each in the saxagliptin + metformin and the dapagliflozin + metformin group. The median exposure to study treatment in the saxagliptin + dapagliflozin + metformin group was nearly double that of the saxagliptin + metformin and dapagliflozin + metformin groups. This difference is due to the duration of Studies CV181168 and MB102129 in the ST + LT Pool that included a 28-week LT extension period. All 3 studies had a saxagliptin + dapagliflozin + metformin treatment arm. The saxagliptin + metformin and dapagliflozin + metformin groups were each included in only 2 studies, with 1 study each having a LT extension with the respective treatment arm. This results in the longer median exposure in the saxagliptin + dapagliflozin + metformin group. Because of this imbalance in exposure time among the groups in the ST + LT Pool, there are additional tables which adjust for exposure to allow for cross comparison of incidence rates for AEs.

At least 235 subjects in the saxagliptin + dapagliflozin + metformin group received saxagliptin and dapagliflozin for >360 days.

Adverse events

Adverse events reported in the ST + LT Pool are summarised in Table 10.

Of the 1169 subjects in the Integrated ST Pool, 670 reported at least 1 AE. The proportion of subjects who reported at least 1 AE was 282 subjects (57.3%) in the saxagliptin + dapagliflozin + metformin group, 207 subjects (61.6%) in the saxagliptin + metformin group, and 181 subjects (53.1%) in the dapagliflozin + metformin group. There were no differences in hypoglycaemia, SAEs, related AEs or SAEs. There were two deaths during the studies (in the saxa + dapa + met group and in the dapa + met group).

Overall, no new safety findings were identified in any treatment group, and the combined use of saxagliptin and dapagliflozin was consistent with the known safety profiles of the individual agents.

Table 10: Overall adverse event summary – ST + LT Pool

	Treatment groups		
	Saxa + Dapa + Met	**Saxa + Met**	**Dapa + Met**
	N=492	**N=336**	**N=341**
At least 1 AE	282 (57.3)	207 (61.6)	181 (53.1)
At least 1 hypoglycaemia	8 (1.6)	4 (1.2)	7 (2.1)
At least 1 AE or hypoglycaemia	282 (57.3)	208 (61.9)	184 (54.0)
At least 1 related AE	38 (7.7)	26 (7.7)	27 (7.9)
Deaths	1 (0.2)	0	1 (0.3)
At least 1 SAE	16 (3.3)	10 (3.0)	13 (3.8)
At least 1 related SAE	2 (0.4)	1 (0.3)	0
SAE leading to discontinuation of study medication	5 (1.0)	2 (0.6)	1 (0.3)
AE leading to discontinuation of study medication	13 (2.6)	3 (0.9)	6 (1.8)
Hypoglycaemia leading to discontinuation of study medication	0	0	0

Common adverse events

Common AEs (reported in ≥2.0% of subjects in any treatment group) in the ST + LT Pool are summarised by PT in Table 11.
The most common AEs by preferred term (PT) in the saxagliptin + dapagliflozin + metformin treatment group were urinary tract infection (UTI) (5.5%), headache (4.3%), and nasopharyngitis (4.3%). The most common AEs by PT in the saxagliptin + metformin treatment group were UTI (7.1%), influenza (5.7%), and headache (5.4%). The most common AEs by PT in the dapagliflozin + metformin treatment group were UTI (5.3%), nasopharyngitis (4.4%), and headache (4.1%). Taken together, the common AE profile observed with the combined use of saxagliptin and dapagliflozin in the ST + LT Pool is consistent with the established safety profiles of saxagliptin and dapagliflozin when used individually.

Table 11: Most common adverse events (reported in ≥2.0% of subjects in any treatment group) during ST + LT period – ST + LT Pool

Preferred term	Treatment groups		
	Saxa + Dapa + Met	Saxa + Met	Dapa + Met
	N=492	N=336	N=341
Total subjects with an event	**282 (57.3)**	**207 (61.6)**	**181 (53.1)**
Urinary tract infection	27 (5.5)	24 (7.1)	18 (5.3)
Headache	21 (4.3)	18 (5.4)	14 (4.1)
Nasopharyngitis	21 (4.3)	16 (4.8)	15 (4.4)
Diarrhoea	18 (3.7)	12 (3.6)	8 (2.3)
Influenza	18 (3.7)	19 (5.7)	12 (3.5)
Back pain	16 (3.3)	12 (3.6)	8 (2.3)
Hypertriglyceridaemia	13 (2.6)	14 (4.2)	9 (2.6)
Arthralgia	12 (2.4)	4 (1.2)	3 (0.9)
Dyslipidaemia	12 (2.4)	8 (2.4)	7 (2.1)
Upper respiratory tract infection	11 (2.2)	8 (2.4)	11 (3.2)
Vulvovaginal mycotic infection	10 (2.0)	1 (0.3)	9 (2.6)
Cough	8 (1.6)	7 (2.1)	6 (1.8)
Nausea	8 (1.6)	11 (3.3)	6 (1.8)
Pain in extremity	5 (1.0)	7 (2.1)	6 (1.8)
Dyspepsia	4 (0.8)	8 (2.4)	5 (1.5)
Depression	3 (0.6)	7 (2.1)	2 (0.6)
Muscle spasms	3 (0.6)	7 (2.1)	2 (0.6)
Hyperuricaemia	1 (0.2)	7 (2.1)	2 (0.6)

Serious adverse event / deaths / discontinuations due to adverse events

Deaths

Two subject deaths were reported in the ST + LT Pool: 1 subject in the saxagliptin + dapagliflozin + metformin group (Study MB102129) died of acute myocardial infarction (MI) and acute heart failure; and 1 subject in the dapagliflozin + metformin group (Study CV181168) died of MI. Both of these deaths were considered by the Investigator to not be related to study treatment.

In Study CV181168, 1 subject died prior to receiving study treatment (rectal adenocarcinoma), and 1 subject died during the OL treatment period (dapagliflozin + metformin)(pulmonary embolism). In Study CV181169, 1 subject died 6 months after the final treatment and post database lock (gastric neoplasm).

Serious adverse events

Overall, the incidence of SAEs was low and balanced across the 3 treatment groups. A total of 39 subjects experienced at least 1 SAE: 16 subjects (3.3%) in the saxagliptin + dapagliflozin + metformin group, 10 subjects (3.0%) in the saxagliptin + metformin group, and 13 subjects (3.8%) in the dapagliflozin + metformin group. In the saxagliptin +dapagliflozin + metformin group, 2 SAEs were considered by the Investigator to be related to the study treatment: pyelonephritis in Study CV181168 and thrombocytopaenia in Study MB102129. In the saxagliptin + metformin group, 1 SAE was considered treatment-elated by the Investigator: hyperkalaemia in Study CV181169.
Eight subjects discontinued study treatment due to an SAE: 5 subjects (1.0%) in the saxagliptin + dapagliflozin + metformin group (pyelonephritis, cardiac failure, thrombocytopenia, unstable angina and invasive ductal breast carcinoma, respectively), 2 subjects (0.6%) in the saxagliptin + metformin group (ankle fracture and gangrene, respectively), and 1 subject (0.3%) in the dapagliflozin + metformin group (MI).

Discontinuations due to adverse events

A total of 22 subjects discontinued the study treatment due to an AE: 13 subjects (2.6%) in the saxagliptin + dapagliflozin + metformin group, 3 subjects (0.9%) in the saxagliptin + metformin group, and 6 subjects (1.8%) in the dapagliflozin + metformin group. Subjects who discontinued the study treatment due to an AE were numerically greater in the saxagliptin + dapagliflozin + metformin group; however, PTs of the AE that led to discontinuation were dispersed across various SOCs in this group and did not occur in more than 2 subjects.

Adverse events of special interest

Hypoglycaemia

Overall, the incidence of hypoglycaemia was low (≤1.8% in any treatment group). Hypoglycaemia events, excluding data after rescue, were reported in a total of 14 subjects: 7 subjects (1.4%) in the saxagliptin + dapagliflozin + metformin group, 1 subject (0.3%) in the saxagliptin + metformin group, and 6 subjects (1.8%) in the dapagliflozin + metformin group. None of the reported hypoglycaemia events was a major episode of hypoglycaemia, and no subject discontinued the study treatment due to hypoglycaemia. Confirmed hypoglycaemia, defined as fingerstick glucose value ≤50 mg/dL with

associated symptoms, was reported in 1 subject in the saxagliptin + dapagliflozin + metformin group The event was considered a minor episode.

Renal impairment/failure

In the ST + LT Pool, the incidence of AEs of renal impairment/failure was balanced, with an AE of renal impairment/failure reported in 18 subjects: 10 (2.0%) in the saxagliptin + dapagliflozin + metformin group, 6 (1.8%) in the saxagliptin + metformin group, and 2 (0.6%) in the dapagliflozin + metformin group. These included AEs of the PT GFR decrease, renal impairment, renal failure, renal failure acute, renal failure chronic, blood creatinine increased, urine output decreased. None of the subjects had a serious AE of renal impairment. Five subjects (3 subjects in the saxagliptin + dapagliflozin + metformin group and 2 subjects in the dapagliflozin + metformin group) discontinued study treatment due to an AE of renal impairment/failure. Four of the 5 subjects discontinued study treatment due to a decrease in GFR, which was below protocol-specified criteria.

Infections

In the ST + LT Pool, the incidence of AEs of the SOC Infections and infestations was generally balanced across the 3 treatment groups, with at least 1 AE reported in 130 subjects (26.4%) in the saxagliptin + dapagliflozin + metformin group, 102 subjects (30.1%) in the saxagliptin + metformin group, and 100 subjects (29.3%) in the dapagliflozin + metformin group. The most common PTs in the SOC were UTIs, nasopharyngitis, and influenza. This was consistent across the treatment groups and across the safety profile for the mono-components.

Genital infections were reported in 38 subjects. The proportion of subjects who reported an AE of genital infection in the ST + LT Pool was higher in the 2 dapagliflozin-containing treatment groups: 15 (3.0%) subjects in the saxagliptin + dapagliflozin + metformin group and 20 (5.9%) subjects in the dapagliflozin + metformin group compared to 3 (0.9%) subjects in the saxagliptin + metformin group.

UTI was the most commonly reported AE in the ST + LT Pool. UTIs were balanced across the 3 treatment groups (72 subjects total): 28 subjects (5.7%) in the saxagliptin + dapagliflozin + metformin group, 25 subjects (7.4%) in the saxagliptin + metformin group, and 19 subjects (5.6%) in the dapagliflozin + metformin group. More females in each treatment group reported PTs of UTI compared to males (8.3% vs 2.6% in the saxagliptin + dapagliflozin + metformin group, 12.0% vs 2.9% in the saxagliptin + metformin group, and 9.1% vs 1.8% in the dapagliflozin + metformin group, respectively).

Malignancies

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

The malignancies that are defined as AEoSI in the saxagliptin/dapagliflozin FDC clinical programme include bladder neoplasm, breast neoplasm, and pancreatic cancer. No case of bladder neoplasm was reported in the Integrated ST Pool. One case of invasive ductal breast carcinoma was reported in 1 subject in the saxagliptin + dapagliflozin + metformin group. No AE of the PT pancreatic cancer was

reported in the Integrated ST Pool; however, the malignancy of hepatic cancer reported at Week 16 in 1 subject in the saxagliptin + dapagliflozin + metformin group during the double-blind treatment period was, upon adjudication, determined to be pancreatic cancer that metastasised to the liver.

Fractures

AEs of fractures were reported in a total of 9 subjects: 3 subject (0.6%) in the saxagliptin + dapagliflozin + metformin group, 4 subjects (1.2%) in the saxagliptin + metformin group, and 2 subjects (0.6%) in the dapagliflozin + metformin group.

Cardiovascular events and Cardiac Failure

CV events that were adjudicated and confirmed as CV events were reported in a total of 10 subjects: 5 subjects (1.0%) in the saxagliptin + dapagliflozin + metformin group, 2 subjects (0.6%) in the saxagliptin + metformin group, and 3 subjects (0.9%) in the dapagliflozin + metformin group.

AEs suggestive of heart failure were reported in a total of 18 subjects: 6 subjects (1.2%) in the saxagliptin + dapagliflozin + metformin group, 8 subjects (2.4%) in the saxagliptin + metformin group, and 4 subjects (1.2%) in the dapagliflozin + metformin group. Two subjects in the saxagliptin + dapagliflozin + metformin group discontinued study treatment due to SAEs. One subject discontinued due to a SAE of cardiac failure. The other subject died due to SAEs of acute MI and cardiac failure acute. A subject in the dapagliflozin + metformin group discontinued from study treatment; this subject had non-serious AEs of cardiac failure and hepatocellular injury, but discontinued due to ascites.

Other AEs of special interest

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

Laboratory findings

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

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

Clinical chemistry values generally remained within the normal range. Small mean increases from baseline in creatinine were observed in the saxagliptin + dapagliflozin + metformin and dapagliflozin + metformin groups. These changes started at Week 6 and shifted towards baseline by Week 52. There were also small decreases in eGFR observed across the treatment groups. There were no clinically meaningful changes from baseline in electrolytes, creatine kinase (CK), and total protein.

Mean values in hepatic laboratory values in the ST + LT Pool were small, stable, consistent over time, and generally stayed within normal range.

Microscopic haematuria was reported in similar proportion of subjects across the 3 treatment groups: 7.5%, 6.1%, and 7.9% of subjects in the saxagliptin + dapagliflozin + metformin, saxagliptin + metformin, and dapagliflozin + metformin groups, respectively. Across all treatment groups, mean baseline values of the albumin/creatinine ratio were consistently above normal (>30 mg/g) through

Week 52. Generally, there was a slight decrease in mean change from baseline over time in the saxagliptin + dapagliflozin + metformin treatment group, an increase in the saxagliptin + metformin group, and a slight increase in the dapagliflozin + metformin group. The mean changes over time in these parameters were not considered to be clinically relevant.

The frequency of Marked Abnormalities (MAs) in laboratory test results in the ST + LT Pool was generally low and similar across the 3 treatment groups.

Marked abnormalities (elevations) in CK were observed in a higher proportion of subjects in the saxagliptin + dapagliflozin + metformin group (7 subjects) compared with the saxagliptin + metformin (no subject) and dapagliflozin + metformin (1 subject) groups. These elevations were transient in nature, with levels normalising to baseline values within an average of 2 weeks, while subjects continued on treatment without interruption (except for 1 subject). None of the subjects had study treatment permanently discontinued due to CK elevation. In most subjects (7 of 8), the CK elevation was asymptomatic and observed at a single time point (isolated finding). Only 1 subject had an associated AE of myalgia, which was related to increased physical activity. None of the subjects had associated changes in renal function or CV events. Most subjects (7 of 8) had alternative plausible explanations, including concomitant use of medications known to elevate CK levels (eg. statins or fibrates), increased physical activity, syncope with possible fall, CK elevations observed prior to randomisation, and acute illness. Overall, review of the data revealed that most of the CK increases were asymptomatic, resolved without interruption of medication and had alternative plausible explanations suggesting that a causal relationship with saxagliptin + dapagliflozin + metformin treatment is unlikely.

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

Safety in special populations

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

Age

Of the 1169 subjects in the Integrated ST Pool, 1007 subjects (86.1%) were aged <65 years, 162 subjects (13.9%) were aged ≥65 years, and 9 subjects (0.8%) were aged ≥75 years. The distribution of subjects by age was balanced across the treatment groups. No clinically meaningful difference in the AE incidence was observed in the age subgroup <65 years and ≥65 years. There were too few subjects (0.8%) in the ≥75 year age group to evaluate the AE reporting in this group. The proportion of subjects who had AEs of SOC cardiac disorders was higher in the age category ≥ 65 years (8.0%, 13 out of 162 subjects) when compared with that in age category <65 years (2.2%, 22 out of 1007 subjects). However, within the age category ≥ 65 years, the proportion of subjects who had AEs of cardiac disorders was comparable across the 3 treatment groups (6.3% in the saxagliptin + dapagliflozin + metformin group, 8.9% in the saxagliptin + metformin group, and 9.3% in the dapagliflozin + metformin group.

Gender

There were 563 males and 606 females in the ST + LT Pool. Overall, a slightly higher proportion of female subjects reported AEs as compared with males. In males, 125 (54.8%) subjects in the saxagliptin + dapagliflozin + metformin group, 93 (54.7%) subjects in the saxagliptin + metformin

group and 83 (50.3%) subjects in the dapagliflozin + metformin group reported an AE. In females 157 (59.5%) subjects in the saxagliptin + dapagliflozin + metformin group, 114 (68.7%) subjects in the saxagliptin + metformin group and 98 (55.7%) subjects in the dapagliflozin + metformin group reported an AE. The increased proportion of females reporting AEs is in part because of an increased frequency of UTI and vulvovaginal mycotic infection in the female subgroup. For both females and males, the most frequently reported AEs were in the SOC Infections and infestations.

Race

The majority of subjects in the ST + LT Pool were White (946 subjects, 80.9%); 98 subjects were black.. The most common AEs were similar in both the White and Black subgroups and were consistent with the overall AEs in the ST + LT Pool. Because of the low numbers of subjects who were of Asian (48) or Other racial origin (77), no conclusions could be drawn based on an analysis of AEs.

Safety related to drug-drug interactions and other interactions

The pharmacokinetic drug-drug interaction between saxagliptin and dapagliflozin was evaluated in healthy subjects in Study CV181191. The coadministration of saxagliptin and dapagliflozin did not affect the pharmacokinetics of either drug and that of the active metabolite (5-hydroxy saxagliptin). No dose adjustment of either saxagliptin or dapagliflozin is needed when the 2 drugs are coadministered.

Discontinuation due to adverse events

A total of 22 subjects discontinued the study treatment due to an AE: 13 subjects (2.6%) in the saxagliptin + dapagliflozin + metformin group, 3 subjects (0.9%) in the saxagliptin + metformin group, and 6 subjects (1.8%) in the dapagliflozin + metformin group. Subjects who discontinued the study treatment due to an AE were numerically greater in the saxagliptin + dapagliflozin + metformin group; however, PTs of the AE that led to discontinuation were dispersed across various SOCs in this group and did not occur in more than 2 subjects.

Phase 1 safety experience

A total of 42 healthy volunteers were dosed in this study. All treatments were well tolerated. There were no deaths, SAEs, or DAEs. A total of 16 subjects (38.1%) reported at least 1 AE; of these, 10 subjects (23.8%) reported an AE that was considered by the Investigator to be related to the study treatment. All AEs were reported as mild; and headache was the most commonly reported AE (6 of 42 subjects).

2.5.1. Discussion on clinical safety

For the purpose of summarising the safety experience, the safety data from the 3 Phase 3 studies (ie, 52-week ST + LT treatment period in Studies CV181168 and MB102129 and 24-week ST treatment period in Study CV181169) were pooled. The rationale for pooling the safety data from the 3 Phase 3 studies is based on the overall similarity in their study design, and the availability of a larger subject population that is sufficient to establish the safety profile of the combined use of saxagliptin and dapagliflozin. The pooled population included all randomised and treated subjects from the 3 studies.

A total of 1169 subjects were included in the safety analysis population of the ST + LT Pool. Of these, 492 received saxagliptin + dapagliflozin + metformin, 336 received saxagliptin + metformin, and 341 received dapagliflozin + metformin. The median exposure to study treatment was 359 days in the saxagliptin + dapagliflozin + metformin group and approximately 176 days each in the saxagliptin + metformin and the dapagliflozin + metformin group. The median exposure to study treatment in the saxagliptin + dapagliflozin + metformin group was nearly double that of the saxagliptin + metformin and dapagliflozin + metformin groups, because triple therapy was included in both LT extensions, while dual therapy was only included in one of the LT extensions.

Numerically more patients in the saxagliptin + metformin group (61.6%) reported at least 1 AE compared to the dapagliflozin + metformin group (53.1%) and the saxagliptin + dapagliflozin + metformin group (57.3%). The difference consisted primarily in slight differences in percentage of infections and headache. The triple combination was not associated with more AEs. No new safety concerns were noted.

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

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

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

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

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

No efficacy/safety trials were executed in special populations.

2.5.2. Conclusions on clinical safety

As expected, specific side effects related to the monocomponents, such as UTI for dapagliflozin and GI events for saxagliptin may occur when the two products are given together, but in general the combination was tolerated reasonably well.

The number of elderly subjects, and especially subjects >75 years was limited in the three studies.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

For this procedure, no new safety concerns have been identified and updated RMPs for Onglyza and Komboglyze were not submitted and therefore not assessed.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1and 5.1 of the SmPC have been updated.

3. Benefit-Risk Balance

3.1. Therapeutic context

3.1.1. Disease or condition

Saxagliptin (Onglyza) is a DPP4-inhibitor, used in the treatment of Type 2 diabetes mellitus (T2DM). The MAH seeks to extend the indication for saxagliptin with triple therapy with metformin plus dapagliflozin, when metformin together with dapagliflozin plus diet and exercise, does not provide adequate glycaemic control.

3.1.2. Available therapies and unmet medical need

There are several classes of medicinal products for the treatment of T2DM, with different mechanism of action. All products have been shown to reduce blood glucose level, and to improve HbA1c. Combination treatment is a generally accepted therapy to improve glycaemic control in subjects failing on one or more treatments.

Based on the extensive therapeutic experience including a well-understood safety profile, metformin is currently recommended as first-line treatment for all patients with T2DM, unless contraindications apply (most notably, GFR < 30 ml/min).

3.1.3. Main clinical studies

The application is supported by data from three clinical trials (CV181168, CV181169, and MB102129). These trials were previously submitted in support of the QTERN (saxagliptin/dapagliflozin) marketing application (procedure number EMEA/H/C/004057, CHMP positive opinion dated 26 May 2016). Supportive safety information is presented from the ST + LT Pool (pooled data from Study CV181169) and the ST + LT treatment periods (from Studies CV181168 and MB102129).

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

Study CV181168 and *Study MB102129* were multicentre, randomised, double-blind, placebo-controlled, parallel-group, 24-week Phase 3 trials in 315 and 320 subjects, respectively, designed to evaluate the safety and efficacy (primary endpoint: mean change from baseline in HbA1c) of the sequential addition of saxagliptin to dapagliflozin and metformin (CV118168) or dapagliflozin to saxagliptin and metformin (MB102129) compared with the addition of placebo in subjects with T2DM with inadequate glycaemic control on metformin and dapagliflozin or saxagliptin. The studies had a screening period, followed by an OL treatment period (16 weeks), and then a 24-week double blind treatment period. Eligible subjects could enter the long-term (LT) extension for an additional 28 weeks.

3.2. Favourable effects

Repeated measures analysis of the primary endpoint demonstrated a clinically relevant effect of saxagliptin + dapagliflozin + metformin treatment (added concomitantly or sequentially) in lowering HbA1c at Week 24 which was statistically significant versus the combination of dapagliflozin and metformin (studies CV181169 and CV181168). Difference versus dapagliflozin + metformin was -0.27% in study CV181169 and -0.35% in study CV181168.

Results of secondary endpoints were in line with the primary analysis, although not all comparisons reached statistical significance. In study CV181169, the proportion of subjects achieving HbA1c <7% at Week 24 was nearly 2-fold higher in the saxagliptin + dapagliflozin + metformin group (41.4%) compared with the dapagliflozin + metformin group (22.2%). The difference in responders depended on baseline HbA1c with the largest difference for subjects with baseline HbA1c of 8 – 9% (± 30%), and smallest for subjects with HbA1c <8% (7% vs saxagliptin + metformin) or >9% (9% vs dapagliflozin + metformin).

In study CV181168, the proportions were 35.5% in the saxagliptin + dapagliflozin + metformin group and 23.1% in the dapagliflozin + metformin group. Treatment with saxagliptin was weight neutral. Effects on HbA1c were sustained at week 52.

Incidence of hypoglycaemia was low. Numerically, there were more events of hypoglycaemia in the saxagliptin + dapagliflozin + metformin group and dapagliflozin + metformin group as compared to the saxagliptin + metformin group, but differences were small.

3.3. Uncertainties and limitations about favourable effects

Only study CV181168 had the right design for the claimed indication, i.e. addition of saxagliptin to patients failing on dapagliflozin and metformin. In study CV181169, saxagliptin was added concomitantly with dapagliflozin to subjects inadequately controlled by metformin only.

The number of elderly subjects (>65 years) was limited: 162. Number of subjects > 75 was only 9. Data from these subjects and data from the individual monocomponent clinical programmes in elderly patients are reassuring.

Benefit in female subjects < 50 year was uncertain. In the studies saxagliptin showed very little effect in this patient group. Additional analyses did not reveal a treatment-by-female age interaction for saxagliptin 5 mg, but for saxagliptin 2.5 mg an interaction could not be excluded.

In study CV181169, metformin XR tablets were used. These tablets are not registered in all EU countries. In the other two studies metformin IR tablets were used. Two thirds of subjects used metformin XR in a dose between 1700 and 2500 mg daily, and one third used 1500-1700 mg daily. Maximum recommended dose of metformin XR is 2000 mg, while maximum daily dose for metformin

IR is 2550 to 3000 mg. That is probably the reason why more patients in the two sequential studies used metformin in higher doses (above 2500 mg) as in these studies metformin IR was used. This makes a comparison between studies in terms of background therapy more complicated.

Addition to other SGLT-2 inhibitors than dapagliflozin has not been studied.

3.4. Unfavourable effects

For the purpose of summarising the safety experience, the safety data from the 3 Phase 3 studies (ie, 52-week ST + LT treatment period in Studies CV181168 and MB102129 and 24-week ST treatment period in Study CV181169) were pooled. A total of 1169 subjects were included in the safety analysis population of the ST + LT Pool. Of these, 492 received saxagliptin + dapagliflozin + metformin, 336 received saxagliptin + metformin, and 341 received dapagliflozin + metformin. The median exposure to study treatment was 359 days in the saxagliptin + dapagliflozin + metformin group and approximately 176 days each in the saxagliptin + metformin and the dapagliflozin + metformin group. The median exposure to study treatment in the saxagliptin + dapagliflozin + metformin group was nearly double that of the saxagliptin + metformin and dapagliflozin + metformin groups, because triple therapy was included in both LT extensions, while dual therapy was only included in one of the LT extensions.

Numerically more patients in the saxagliptin + metformin group (61.6%) reported at least 1 AE compared to the dapagliflozin + metformin group (53.1%) and the saxagliptin + dapagliflozin + metformin group (57.3%). The difference consisted primarily in slight differences in percentage of infections and headache. The triple combination was not associated with more AEs. No new safety concerns were noted.

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

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

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

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

3.5. Uncertainties and limitations about unfavourable effects

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

No efficacy/safety trials were executed in special populations.

3.6. Benefit-Risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effect

The most important effect is the reduction in HbA1c of around -0.30% when saxagliptin is added to dapagliflozin and metformin. This is just near the accepted delta for non-inferiority in clinical trials for diabetes. Apparently, the additional value of saxagliptin on top of dapagliflozin and metformin is small. However, as for Qtern, there might be patients who can benefit from the addition of saxagliptin.

An important benefit is the low incidence of hypoglycaemia. Fear of hypoglycaemia might be an obstacle when trying to achieve good metabolic control, and therefore, a treatment with low risk for hypoglycaemia has a clear benefit.

Secondary endpoints were in line with the primary endpoint.

In general, the combination treatment was well tolerated, and no unexpected safety issues were observed.

Only study CV181168 had the right design for the claimed indication, i.e. addition of saxagliptin to patients failing on dapagliflozin and metformin. In study CV181169, saxagliptin was added concomitantly with dapagliflozin to subjects inadequately controlled by metformin only. However, this is considered less important, as the additive value of saxagliptin could be assessed.

3.6.2. Balance of benefits and risks

Adding saxagliptin to patients failing on metformin and dapagliflozin can result in a modest improvement of glycaemic control. The additional risk for hypoglycaemia is low, and no new or unexpected safety issues have been observed.

Therefore the benefit risk balance is considered positive.

Since the initial authorisation of saxagliptin-containing products, the general wording of the indication for medicinal products for the treatment of diabetes has evolved, and in addition more data has been accumulated regarding the combined use of saxagliptin with other products for the treatment of diabetes representing the standard of care. Therefore, it was suggested to the MAH to amend the wording of the indication in section 4.1 of the SmPC to refer in more general terms to the combined use of saxagliptin and saxagliptin/metformin with other products for the treatment of diabetes, including insulin. Although this wording of the indication is relatively broad, the combinations studied are described in section 5.1 of the SmPC. The MAH agreed, and the following indications are proposed and accepted:

Onglyza

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

- as monotherapy when metformin is inappropriate due to intolerance or contraindications
- in combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 for available data on different combinations).

Komboglyze

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

- in patients inadequately controlled on their maximally tolerated dose of metformin alone
- in combination with other medicinal products for the treatment of diabetes, including insulin, in patients inadequately controlled with metformin and these medicinal products (see sections 4.4, 4.5 and 5.1 for available data on different combinations).
- in patients already being treated with the combination of saxagliptin and metformin as separate tablets.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of indication to include the use of Onglyza and Komboglyze in combination with other diabetes medicines; as a consequence, sections 4.1 and 5.1 of the SmPC are updated. Editorial changes are made throughout the Summary Products Characteristics and Package Leaflets. Furthermore, the Product Information is brought in line with the latest QRD template version 10 for Onglyza.

In addition, the Worksharing applicant (WSA) took the opportunity to update the list of local representatives in the Package Leaflet.

The worksharing procedure leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet.

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and 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.

In addition, 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.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to include the use of Onglyza and Komboglyze in combination with other diabetes medicines; as a consequence, sections 4.1 and 5.1 of the SmPC are updated. Editorial changes are made throughout the Summary Products Characteristics and Package Leaflets. Furthermore, the Product Information is brought in line with the latest QRD template version 10 for Onglyza.

In addition, the Worksharing applicant (WSA) took the opportunity to update the list of local representatives in the Package Leaflet.

Summary

Please refer to the Scientific Discussion WS1078.

Attachments

1. SmPC, Labelling, Package Leaflet (changes highlighted) of Onglyza 2.5 film-coated tablets, as a relevant example with changes highlighted as adopted by the CHMP on 18 May 2017.