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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Forxiga

dapagliflozin

Procedure No.: EMEA/H/C/002322

Note

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

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List of abbreviations

ABP	Ambulatory blood pressure
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT/ALAT	Alanine transaminase
ANOVA	Analysis of variance
AST/ASAT	Aspartat transaminase
AUC	Area under the analyte plasma concentration-time curve
AUEC	Area under the effect curve
AUC_{inf}	Area under the analyte plasma concentration-time curve from time point zero extrapolated to infinity
$AUC_{ô,ss(,norm)}$	Area under the analyte plasma concentration-time curve over a dosing interval at steady-state (dose normalized)
AUC(tau)	Area under the analyte plasma concentration-time curve in one dosing interval
BA	Bioavailability
BCS	Biopharmaceutical Classification Syste
BE	Bioequivalence
BMS-512148	Dapagliflozin [DAPA]
BMS-511926	Minor, pharmacologically-active, hydroxylated metabolite of DAPA
BMS-801576	DAPA- 3-O-glucuronide (major but inactive metabolite towards the SGLT2 transporter)
BMI	Body mass index
BMS	Bristol-Myers Squibb
C	Concentration
C-G	Cockroft-Gault
CI	Confidence interval
CL	Clearance
CrCl	Creatinine clearance
$CL/F_{,(ss)}$	Apparent clearance of the analyte in plasma following extravascular administration
$Cl_{er\ /\ CLR}$	Renal clearance of the analyte
CLi	Iohexol plasma clearance
Cmax	Maxmum observed concentration
$C_{max,ss(,norm)}$	Maximum analyte plasma concentration at steady-state (dose-normalized)
$C_{pre,ss}$	Predose concentration at steady state
CV	Coefficient of variation
DAPA	Dapagliflozin
DDI	Drug-drug interaction

DPP-4	Dipeptidyl peptidase-4
$E_{24(,ss)}$	Effect at time point 24 hours after dosing (at steady state)
eCLR / e CLer	Estimated renal clearance
EC_{50}	Half maximal effective concentration
eCcr	Estimated creatinine clearance
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
$E_{max(,ss)}$	Maximum effect at steady state)
E-R	Exposure- response
ESRD	End-stage renal-disease
F	Absolute bioavailability factor
FPG	Fasting plasma glucose
gCV	Geometric coefficient of variation
GFR	Glomerular filtration rate
GIP	Glucose-dependent insulinotropic peptide
GLP-1 (-2)	Glucagon-like peptide-1 (-2)
gMean	Geometric mean
GMR	Geometric mean ratio
HbA_{1c}	Glycosylated haemoglobin A1
HOMA	Homeostasis Model Assessment
HPLC-MS/MS	High-performance liquid chromatography-tandem mass spectrometry
HPLC	High-performance liquid chromatography
IC_{50}	Half maximal inhibitory concentration
LLOQ	Lower limit of quantitation
Max	Maximum
MD	Multiple dose
MRD	Multiple rising dose
MTT	Meal tolerance test
N/A.	Not available; not applicable
OGTT	Oral glucose tolerance test
PD	Pharmacodynamics
p-gp	Permeability glycoprotein
PK	Pharmacokinetics
PPK	Population PK
QD	Once per day
QTcX	Population based frequency correctec QT interval
R_A	Accumulation ratio of the analyte in plasma after multiple dose administration over a uniform dosing interval

SD	Standard deviation
SD	Single dose
SGLT2	Sodium glucose co-transporter type 2
ss	Steady state
SRD	Single rising dose
SU	Sulfonylurea
T-HALF	Terminal elimination half-life
$t_{1/2(,ss)}$	Terminal elimination half-life (at steady-state)
T2DM	Type 2 diabetes mellitus
$T_{max(,ss)}$; tmax	Time of maximum analyte plasma concentration after administration (at steady-state)
T/R	Ratio test/reference
TRA	Total radioactivity
$t_{z(,ss)}$	Time of last measurable concentration of the analyte in plasma (at steady state)
U	Units
UGT1A9	uridine diphosphate glucuronosyltransferase
V	Volume of distribution
Vs.	Versus
V_{ss} / $V_{(ss)}$	Apparent volume of distribution under steady state conditions
$V_{z/F(,ss)}$	Apparent volume of distribution during the terminal phase z following an extravascular administration (at steady state)

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Bristol-Myers Squibb/AstraZeneca EEIG submitted on 16 December 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Forxiga, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 April 2010.

The applicant applied for the following indication:

Monotherapy

Forxiga is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control:

- when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.

Combination therapy

Add-on combination

Forxiga is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control:

- in combination with metformin, when metformin alone with diet and exercise does not provide adequate glycaemic control;
- in combination with a sulfonylurea, when the sulfonylurea alone with diet and exercise does not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance;
- in combination with a thiazolidinedione, when the thiazolidinedione alone with diet and exercise does not provide adequate glycaemic control in patients for whom use of a thiazolidinedione is considered appropriate;
- in combination with insulin (alone or with up to two oral glucose-lowering agents), when the underlying treatment regimen with diet and exercise does not provide adequate glycaemic control.

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/100/2010) on the agreement of a paediatric investigation plan (PIP).

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

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

Applicant's request(s) for consideration

New active Substance status

The applicant requested the active substance dapagliflozin contained in the above medicinal product to be considered as a new active substance in itself.

Scientific Advice / Protocol Assistance

The applicant received Scientific Advice from the CHMP on 18-21 February 2008. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

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

1.2. Manufacturers

Manufacturer responsible for batch release

Bristol-Myers Squibb S.r.l.

Loc. Fontana del Ceraso, 03012 Anagni (FR)

Italy

1.3. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: Martina Weise

- The application was received by the EMA on 16 December 2010.
- The procedure started on 19 January 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 8 April 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 18 April 2011.

- During the meeting on 16-19 May 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 May 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 August 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 September 2011.
- During the CHMP meeting on 17-20 October 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 29 November 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 4 January 2012.
- During a meeting of a SAG on 9 January 2012, experts were convened to address questions raised by the CHMP.
- During the CHMP meeting on 16-19 January 2012, the CHMP agreed on a second list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the second CHMP List of Outstanding Issues on 13 February 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's written responses to the second List of Outstanding Issues to all CHMP members on 29 February 2012 and 29 March 2012.
- During the meeting on 16-19 April 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Forxiga on 19 April 2012.
- On 7 May 2012, the European Commission sent a letter to the CHMP Chairman requesting clarifications on some aspects of the CHMP Assessment Report adopted on 19 April 2012.
- During the meeting on 21-24 May 2012, the CHMP provided the requested clarifications, issuing a revised positive opinion for granting a Martketing Authorisation to Forxiga on 24 May 2012.
- On 8 June 2012, the European Commission sent a letter to the CHMP Chairman requesting clarifications on the amendments made to the revised CHMP Assessment Report adopted on 24 May 2012 and considerations to further clarify the SmPC wording in section 4.8.
- During the meeting on 18-21 June 2012, the CHMP provided the requested clarifications, issuing a revised positive opinion for granting a Martketing Authorisation to Forxiga on 21 June 2012.
- Revised CHMP Assessment Report was finalised by written procedure on 5 July 2012.
- On 12 July 2012, the European Commission sent a letter to the CHMP Chairman requesting clarifications on the amendments made to the revised CHMP Assessment Repprt adopted on 5 July 2012 and considerations to further clarify the revised SmPC wording in section 4.8.
- During the meeting on 17-20 September 2012, the CHMP provided the requested clarifications, issuing a revised positive opinion for granting a Marketing Authorisation to Forxiga on 18 September 2012.

2. Scientific discussion

2.1. Introduction

Problem statement

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycaemia and an increased risk of microvascular and macrovascular complications. The number of adults with T2DM is approximately 285 million globally, 55 million in Europe, and 37 million in North America, and is expected to rise to 438 million, 67 million, and 53 million, respectively, by the year 2030.

Currently available therapy includes oral agents with different mechanisms of action such as insulin sensitizing agents (metformin and thiazolidinediones), agents promoting insulin secretion (sulphonylureas, GLP-1 analogues and DPP4-antagonists), as well as insulin.

Patients with T2DM are at risk for the development of microvascular complications and macrovascular complications. While improved glycaemic control results in reduced rates of complications, especially microvascular, at least 44% of patients continue to fall short of treatment goals.

Hypoglycaemia is a clinically important barrier to optimizing treatment with insulin and sulphonylureas (SUs), both of which are preferred second-line treatment options. Efforts by patients to lose weight as part of a therapeutic lifestyle program are undermined by therapies that lead to weight gain, such as thiazolidinediones (TZDs), insulin, and SUs.

There is a need for novel treatment options for T2DM, due to the increasing global prevalence of the disease, its progressive nature which eventually requires combination therapy in most patients as well as the undesirable side effects of currently available therapies.

About the product

Dapagliflozin (BMS-512148) is a potent, competitive, reversible, highly selective and orally active inhibitor of the human sodium-glucose co-transporter 2 (SGLT2), the major transporter responsible for the renal glucose reabsorption. It improves glycaemic control in patients with T2DM by reducing renal glucose reabsorption leading to urinary glucose excretion (glucuresis). Dapagliflozin's mechanism of action is different from and complementary to the mechanisms of currently available medicines, resulting in the direct, and insulin-independent, elimination of glucose by the kidney. SGLT2 is almost exclusively expressed in the kidney minimising the risk of off-target (i.e. non-kidney) effects.

The recommended starting dose is 10 mg once daily for monotherapy and add-on combination therapy with other glucose lowering drugs including insulin. In patients with severe hepatic impairment a starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg

Type of Application and aspects on development

This Marketing Authorisation application is a full, stand alone application in accordance with Directive 2001/83/EC Article 8 (3).

The dapagliflozin clinical development program was designed to demonstrate the safety and efficacy of dapagliflozin in a wide range of subjects with T2DM. The program included both placebo-controlled and active comparator studies (comparators were metformin XR and glipizide) in drug-naïve subjects at an early stage of disease and subjects who require additional therapy after failure to reach adequate glycaemic control with their current regimen, including oral anti-diabetic agents or insulin at a later stage of the disease. The clinical development program also examined the persistent loss of calories in the urine due to glucosuria and the resulting potential for weight loss with a reduction in total body fat. The clinical studies did not include subjects with severe renal impairment since glycaemic efficacy was not expected in the absence of adequate renal function.

The development programme of dapagliflozin complies with the CHMP guideline "Note for Guidance on the Clinical Investigation of Medicinal Products for the treatment of diabetes mellitus (CPMP/EWP/1080/00)". This guideline is currently under revision. This application is supported by an extensive clinical program including 11 Phase 3 studies whereof 7 are considered pivotal for the proposed indication.

Scientific advice was provided by the CHMP in February 2008 (EMEA/CHMP/SAWP/485029/2007) on the clinical aspects of the development program with main focus on the Phase 3 program. The importance of investigating the lower dose range in the Phase 3 studies was pointed out. Potential safety issues were also discussed such as the risk of electrolyte imbalances. The need to include sufficient numbers of patients from the EU was stressed as well as the need to include elderly patients. The design of study DC1690C00006 to support the add-on indication to insulin was discussed and points were made on the inclusion and exclusion criteria. The proposed investigation of changes in body weight/body composition was also discussed and the applicant's strategy was endorsed. Further, risk mitigation actions proposed by the applicant were discussed and the proposals were generally found acceptable. The advice given has been followed in all essential parts.

A Paediatric Investigation Plan (P/100/2010) and a waiver for children aged below 10 years of age have been agreed for dapagliflozin with the PDCO. A deferral to complete the PIP has been granted until September 2017.

2.2. Quality aspects

2.2.1. Introduction

The application relates to Forxiga, 5 and 10 mg film-coated tablets, containing the active substance dapagliflozin propanediol.

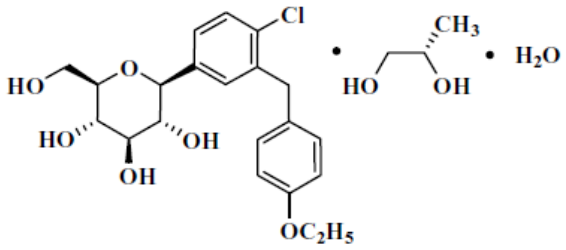
The excipients used in the formulation are common Ph. Eur. Excipients apart from the coating agent. The list of ingredients is described as follow: microcrystalline cellulose, crospovidone, lactose anhydrous, silicon dioxide, magnesium stearate for the core tablets, and opadry II yellow for the coating.

The tablets are kept in Aluminium- Aluminium (Alu/Alu) blisters.

2.2.2. Active Substance

An in-house monograph was submitted for dapagliflozin propanediol, since there is no monograph in the Ph. Eur. Complete scientific data was submitted in module 3.

The structure of dapagliflozin is depicted below:



The active substance is a white to off-white powder, and physico-chemical characteristics such as solubility (soluble in many polar solvents), pKa, partition coefficient, hygroscopicity (non-hygroscopic), specific optical rotation (five stereogenic centres), Xray diffraction (crystalline powder), polymorphism (single polymorphic form observed) and melting point were adequately described.

Manufacture

The manufacture of the final active substance was satisfactorily described including a flow-chart.

The commercial manufacturing process for the synthesis of the active substance was sufficiently detailed including quantities and operating conditions. The overall synthetic sequence has remained the essentially same throughout development; however in order to achieve a robust manufacturing process, some changes have been made mainly in relation to reagents, solvents, purification procedures. The information provided in the development history highlights the changes made in the individual manufacturing steps in order to either improve process efficiency, avoiding the generation of potential genotoxic impurities and improving the overall quality of the active substance. This indicated that the applicant seems to have a good understanding of the process and their product.

The starting materials, reagents and solvents used for the synthesis of the active substance were adequately characterised and justified. The starting materials mark the points in the synthesis beyond which cGMP and regulatory change control were applied.

Control of critical steps and intermediates were adequately presented as well as the analytical methods used.

Impurities including residual solvents have been well characterised and controlled during the manufacturing process.

To demonstrate process reproducibility and performance, the potential variables of input materials and process parameters that may have an impact on the quality of each intermediate and dapagliflozin propanediol were evaluated.

Based on the risk assessment and other development work, the applicant stated there were no critical process parameters (CPPs) identified for the manufacturing process.

Satisfactory In-process control (IPC) tests were applied throughout the manufacturing process to ensure the quality of dapagliflozin propanediol. The acceptance criteria established for reaction completion of each process step were based on development and manufacturing experience gained during the production of dapagliflozin propanediol to date.

According to the applicant batch analysis data demonstrated the consistency in the quality of batches of dapagliflozin propanediol. No data has been presented with regard to process validation. However, this was considered acceptable since dapagliflozin propanediol is a fully synthetic compound and a non-sterile active substance.

Discussion of Process Development Utilizing Quality by Design Concepts

The applicant provided the following general information about its development and control strategy:

- Appropriate critical quality attributes (CQAs) of the active substance were identified on the basis of their potential impact on the safety and efficacy of the drug product and thus the patient.
- A collective risk assessment was performed to define quality attributes of the starting materials and process intermediates which have the potential to impact the CQAs of the active substance. In summary, potential variability in the starting materials was understood and appropriate specifications have been established.
- Then individual risk assessment for each step of the process was carried out using a Failure Mode Analysis (FMEA) to identify process parameters that could impact the quality attribute of the intermediates and may directly or indirectly impact the CQAs of the active substance. These process parameters were designated as potential CPPs and were studied further using univariate and/or multivariate experiments, as appropriate, to ascertain interdependence of process parameters, if any, and to establish Proven Acceptable Ranges (PARs). PARs have been established for parameters which may impact the quality attributes with appropriate control strategies for the commercial manufacture of dapagliflozin propanediol.
- Impurities attributed to the starting materials were also controlled. The quality attributes of the intermediates from each step that could impact the next process step or intermediate were identified with defined control strategies.

Based on the control strategy for the active substance, it was concluded that no process parameters were identified as high risk. In conclusion, the predefined quality of dapagliflozin propanediol was achieved and assured by the design of a reproducible and robust manufacturing process with established controls. A set of active substance specifications has been established that verifies the CQAs and other quality attributes of dapagliflozin propanediol.

Elucidation of Structure and other Characteristics

The structure of dapagliflozin propanediol was confirmed by the route of synthesis and by the following analytical methods: elemental analysis, Ultra-violet (UV)-Vis spectroscopy, Infra-red (IR) spectroscopy, Raman spectroscopy, one- and two-dimensional Nuclear Magnetic Resonance ^{1}H-NMR and ^{13}C-NMR, Mass Spectrometry (MS electrospray), and by single-crystal X-ray crystallography. The physical characteristics have also been determined by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) studies.

The presence of a stable polymorphic form has been confirmed through analysis on numerous batches (>30), including four commercial batches. This crystalline form remains stable during manufacture and stability studies.

The non-hygroscopicity of dapagliflozin propanediol was also confirmed.

The particle size of the active substance was consistently produced by the manufacturing process.

Dapagliflozin is a chiral molecule with five stereogenic centers. An evaluation was carried out to assess the probability of epimerisation of the stereogenic centers during the synthesis. Results showed that epimerisation was highly unlikely.

Impurities

An extensive discussion on impurities including organic impurities, inorganic impurities, potential genotoxic impurities, and residual solvents was presented. Impurities were found below the limits authorised by the ICH Q3A guidelines and the residual level of solvents observed was well below the ICH limits (ICH Q3C (R4): *Impurities: Residual Solvents*).

Specification

Adequate specification was presented and the following parameters were evaluated: appearance (visual), colour (visual), identification (IR and HPLC), assay (HPLC), propylene glycol (GC), water content (Karl-Fisher), related substances (HPLC), residual solvents (GC) and particle size (Laser Light Scattering).

The analytical methods were described and satisfactory validated.

Analytical data for 25 batches manufactured with the proposed commercial process have been provided. Seven of these batches were of full production scale. Results were found satisfactory. The specification was adequately justified and in line with the corresponding ICH guidelines on impurities and residual solvents.

Container closure system

Dapagliflozin propanediol was packaged and stored in closed, double, antistatic-treated, low-density polyethylene bags (LDPE) placed in a high-density polyethylene (HDPE) drum with a secure fitting lid. A declaration of compliance with EU food contact directive 2002/72/EC and its subsequent amendments was provided for the PE bag primary packaging. Specification for the LDPE-bag, including requirements for identification (IR) and physical/dimensional characteristics was provided.

Stability

Stability studies were conducted on three primary batches of the active substance kept in a packaging similar to the commercial packaging under the following ICH conditions: 24 months under long term, 25 °C and 60% RH and intermediate 30 °C and 65% RH, 6 months under accelerated 40 °C and 75% RH and stress studies including photostability).

The parameters tested included: appearance, color, identity (HPLC), assay (HPLC), organic impurities (HPLC), polymorphic identity (X-ray powder diffraction), water content and propylene glycol content. The analytical methods used during stability studies were the same as the ones used for the control of the active substance apart from the X-ray method that was presented separately.

Results of the stability study were found well within the specification limits for all the conditions. Trends in the long-term, intermediate and accelerated stability data so far indicate no degradation of the active substance.

Based on the stability study data presented, the re-test period proposed by the applicant when stored in the primary packaging can be approved.

2.2.3. Finished Medicinal Product

Description and composition of the drug product

Dapagliflozin Film-Coated Tablets exist as two strengths 5 mg and 10 mg. The tablets are kept in aluminium/aluminium (Alu-Alu) blister packs.

The 5 mg tablets are yellow, biconvex round, film-coated tablet with “5” debossed on one side and “1427” on the other side. The 10 mg tablets are yellow biconvex diamond, film-coated tablet with “10” debossed on one side and “1428” on the other side. The tablets are dose proportional.

The excipients used for the core tablets are described in the Ph.Eur and commonly used for solid oral dosage forms: microcrystalline cellulose (diluent), anhydrous lactose (diluent), crospovidone (disintegrant), silicon dioxide (glidant), magnesium stearate (lubricant). For the film-coating: Opadry II yellow and purified water (solvent) were used. Opadry is not described in any Pharmacopoeia, but all the individual ingredients (Polyvinyl Alcohol-Part Hydrolyzed, Titanium Dioxide, Polyethylene Glycol 3350, Talc, and Iron Oxide Yellow, NF/E172) are either described in Ph.Eur or EC Food Directive.

Pharmaceutical Development

The pharmaceutical development of the dapagliflozin film-coated tablets included quality risk assessments and design of experiments (DoE) to understand the quality of the input raw materials required for a robust formulation and the impact of manufacturing process parameters on the critical quality attributes (CQAs) of the drug product. The purpose of the development studies was to gain knowledge about the product and the manufacturing process. But no design space approach was claimed and the control strategy of the finished product remained a conventional testing at the end of the manufacture.

Because the drug loading for dapagliflozin was low , uniform distribution of dapagliflozin in the pre-blend was important to attain reproducible tablet content.

A quality target product profile (QTPP) was presented comprising regular requirements for tablets such as tablet strengths, general types of packages, compliance with standard tablet requirements (e.g. dissolution, content uniformity), impurity level to be below the qualified level, target patient population (adults) and route of administration.

The key Development Challenges were:

Polymorphic form: Transformation from the crystalline form to amorphic anhydrate may occur upon long exposure to high temperature. This may affect assay, content uniformity, dissolution and impurity content and was avoided by environmental controls on storage and shipment of the active substance. Also comparative *in-vitro* dissolution and bioequivalence studies were performed comparing heat stressed versus non-heat stressed tablets where the tablets were demonstrated to be similar. These results showed that the changes of polymorphic form of the active substance had no impact on drug product performance and quality.

Control of particle size: Particle size distribution may affect content uniformity. Therefore, appropriate particle size control at the final manufacturing step of the active substance was established.

Poor flow, cohesive, and sticky nature of the active substance: Assay and content uniformity may be affected therefore all the properties above were controlled by the excipients used and the choice of the manufacturing process.

Targeted low dose: Content uniformity may be affected. Process was developed to ensure uniformity of both the preblend and the final blend.

Susceptibility of the active substance to oxidative degradation in the presence of excipients and moisture: Assay and degradation products may be affected. Compatible excipients were selected and water content was controlled to ensure acceptable drug product

stability. Moisture protective primary packages and/or the use of dessiccant were proposed for the commercial tablets.

Active Substance

Dapagliflozin propanediol is a solvate containing 1:1:1 ratio of the dapagliflozin, (S)-(+)-1,2-propanediol, and water. It is a white to off-white powder, non-hygroscopic. It is a BCS Class III drug. Stability and compatibility with the selected excipients were evaluated and found satisfactory.

The quality attributes of the active substance that have the potential to impact the drug product quality and manufacturing process were studied.

Excipients

The core tablet excipients chosen for the commercial formulation were conventional and the amounts per tablet were within their typical levels of usage in solid dosage forms.

Further assurance of excipient compatibility for the core tablet and film coating materials was confirmed by stability data at long-term and accelerated storage conditions.

Formulation Development

The formulation development was extensively presented including the choice and level of the excipients in the different clinical formulations and a dry granulation manufacturing process was used throughout the formulation development. Dissolution profiles of the clinical formulations and the final formulation were found comparable, and the changes to the formulation were not expected to affect the dissolution and the absorption of the drug product.

The target levels and acceptable ranges for the composition of dapagliflozin film-coated tablets proposed for commercial use were provided and satisfactorily justified. It consisted of a range of material levels that were demonstrated to have no impact on drug product quality and performance; thus, showing formulation robustness.

Manufacturing Process Development

A FMEA was performed to quantify the level of risk remaining in the dapagliflozin tablet manufacturing process and it was demonstrated that the process was well under control.

Container Closure System

Three container closure systems were evaluated together with bulk package:

- High density polyethylene (HDPE) bottle with a two-piece child resistant, continuous thread (CRCT) polypropylene closure having an aluminium-foil induction seal and a silica gel canister desiccant.
- Aluminium-Aluminium (Alu-Alu) blister packs
- Polyvinyl chloride (PVC)-Aclar blister packs
- For bulk packaging, the tablets were packaged using an inner low density polyethylene (LDPE) bag and an outer aluminium foil bag. Desiccants were placed between the two bags and then sealed.

Stability data for dapagliflozin film-coated tablets in all three container closure systems were found acceptable; however, only the Alu-Alu blister packs were evaluated for commercialization. The stability of the tablets in the bulk packaging was also acceptable.

Microbiological Attributes

The long-term stability data indicates the tablets were not susceptible to microbial growth as demonstrated by microbial test.

In conclusion, a thorough pharmaceutical development was made where the parameters affecting the quality of the final film-coated tablets were evaluated.

Adventitious agents

The magnesium stearate used was of vegetable origin. The anhydrous lactose used was sourced from bovine milk that was suitable for human consumption. Declaration from the supplier of anhydrous lactose was provided. Therefore no TSE risk was foreseen and the information was in line with the TSE guideline (EMA/410/01 rev 3).

Manufacture of the product

The manufacturing process consists of the manufacture of the final blend intermediate, tablet compression and film-coating with a coating suspension consisting of the Opadry II material in water. Adequate process controls for the critical steps and intermediates in the manufacture of dapagliflozin film-coated tablets were presented and justified.

Process Validation and/or Evaluation

A process validation protocol for three consecutive batches for each tablet strength was presented and was considered acceptable.

Product specification

Specification for the Dapagliflozin film-coated tablets included the following parameters: description (visual), identification (IR and HPLC), assay (HPLC), related substances (HPLC), uniformity of dosage units content uniformity (PhEur.), disintegration test (PhEur.) water content (Karl-Fisher),

Analytical methods were adequately described and where applicable validated.

Batch results for both tablet strengths (clinical, registrational/stability, and commercial scale batches) manufactured at the registered sites) were in line with the proposed specification.

Characterisation of Impurities

Impurities in the drug product that were carried over from the active substance were discussed as well as their structure, origin and degradation pathways. Limits of the impurities were below the ICH limits and did not raise any safety concern.

The proposed specification and their analytical procedures were satisfactory for the control of the drug product. The tests and limits were well justified.

Container closure system

The proposed commercial presentation for dapagliflozin film-coated tablets, 5 mg and 10 mg was an Aluminium/Aluminium (Alu/Alu) blister The blister components were in compliance with the EU directives for materials that are intended to come into contact with food. The PVC film which comes in contact with the drug product complies with the Ph.Eur.3.1.11. The specification for the package components comprised tests for appearance, identification (IR for the blister cavity) and area weight. Representative IR spectra were provided and acceptable.

Stability of the product

Stability studies were conducted on three batches of film-coated tablets (pilot or production size) for each strength kept in the alu/alu blisters intended for marketing. The batches were stored under ICH conditions (long term, intermediate, accelerated, stress-freeze thaw, photostability, open-dish conditions)

Matrix design used for dapagliflozin film-coated tablets stored under ICH conditions: 5°C, 25°C/60%RH and 30°C/75%RH included a one-third reduction at 3, 6, 9, 15, 18 and 30 months testing with full testing at annual time points (12, 24 and 36 months).

Samples were exposed to temperatures between -20°C ± 5°C and 40°C ± 2°C/75%RH ± 5% RH for 24 hours each, for a duration of two weeks (seven complete cycles)

Parameters tested at long-term (5°C, 25 °C and 30°C) and accelerated (40°C) conditions were appearance, potency, impurity, water, disintegration time, hardness, dissolution, microbiological quality, identity and uniformity of dosage units. Parameters tested under all other conditions were appearance, potency, impurity, disintegration, hardness and dissolution.

Analytical methods were described and validated, and identical to the ones used for the control of the finished product.

No out of specification results were seen under any storage condition. The results indicated that Dapagliflozin Film-Coated Tablet was stable under long-term conditions. There were little or no change observed in any attribute tested in the freeze/thaw study indicating that the tablets were not sensitive to brief low and high temperature excursions. In the open dish study essentially no significant change was observed. In the photostability study there were little to no change observed in any attribute tested indicating that the tablets were not sensitive to light.

In the bulk package study no major change could be observed.

Based on the stability data, the proposed shelf-life can be supported in line with the conditions of storage specified in the SmPC.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Quality Development

Dapagliflozin propanediol is a solvate containing a 1:1:1 ratio of dapagliflozin, propanediol and water. Characterisation of the active substance and its manufacture have been well detailed. This is a chiral molecule with five stereogenic centres, and only one polymorphic form was observed. Dapagliflozin is not light sensitive and the proposed re-test period can be approved.

Forxiga is formulated as immediate-release 5 mg and 10 mg film-coated tablets. The manufacture consists of a dry granulation process followed by compression and film-coating and has been adequately described. The applicant has provided extensive development studies for the active substance and the finished product employing Quality by Design strategies. However no Design space was claimed and the control strategy follows the traditional approach using end product testing. The drug product is well controlled. Stability has been studied under ICH conditions and the proposed shelf-life can be granted.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of the medicinal product has been adequately demonstrated (both for the active substance dapagliflozin propanediol and the drug product 5 mg and 10 mg film-coated tablets). There are no remaining issues from the quality point of view that could impact on the safety or the efficacy of the drug product.

2.3. Non-clinical aspects

2.3.1. Introduction

The Applicant conducted a comprehensive non-clinical development programme to support the chronic use of dapagliflozin in humans. This programme is in general agreement with the applicable scientific guidelines. All main non-clinical toxicity studies were conducted in compliance with GLP. In addition, non-GLP studies were conducted too but were not considered to compromise the scientific integrity or affect the experimental results.

2.3.2. Pharmacology

The pharmacology programme was considered to be adequate. The overall results of these studies are reported below.

Primary pharmacodynamic studies

Internal quantitative RT-PCR, Northern blot and in situ hybridization studies as well as some external reports showed SGLT2 to be selectively expressed in the kidney, although other external reports suggest a broader pattern of tissue distribution. Other sodium glucose co-transporters are present in the gut, heart, skeletal muscle and other tissues.

Studies in normal and diabetic animal models have demonstrated that parenteral delivery of the non-selective SGLT inhibitor Phlorizin leads to the excretion of glucose in the urine, and only in diabetic animal models lower blood glucose in a manner independent of insulin secretion or insulin action, without hypoglycaemia.

Primary pharmacodynamic *in vitro*

The Applicant demonstrated dapagliflozin's activity towards human, rat and mouse SGLT2 *in vitro* (artificial overexpression of the respective transporters in Chinese hamster ovary (CHO) cells) and thereby also verified the suitability of the rodent models used for further studies. The potency for human SGLT2 inhibition was around 0.2 nM; for the rat and mouse SGLT2 it was slightly lower (3.0 and 2.3 nM, respectively). High selectivity (around 1200 for humans, based on EC_{50}) of SGLT2 inhibition over SGLT1 inhibition was also demonstrated *in vitro*. The selectivity was markedly lower in rodents (around 200 in rats and 130 in mice) but still considered sufficiently high to allow meaningful extrapolation of animal findings to humans.

The Applicant also confirmed restricted expression in the kidney (renal proximal tubule) in studies using PCR and in situ hybridisation because individual reports suggested a wider expression.

The Applicant investigated metabolites of dapagliflozin for any action on SGLT2 or SGLT1. All metabolites were at least 300-fold less potent than dapagliflozin. No metabolite had a detectable activity towards SGLT1.

Primary pharmacodynamics *in vivo*

In vivo primary pharmacodynamic studies with dapagliflozin were carried out in single-dose, dose-ranging studies in non-diabetic and diabetic rats or mice in order to evaluate the potency, SGLT2-specificity and duration of action in stimulating urinary glucose excretion, and to describe the secondary consequences of urinary glucose excretion, such as changes in urine volume or blood or plasma glucose effects. Subsequently a multiple-dose study was carried out to evaluate the ability of dapagliflozin to have sustained effects on urinary glucose excretion, urine volume, and fasting plasma glucose in diabetic rats over a two-week dosing period.

Dapagliflozin increased renal glucose excretion in (healthy, non-diabetic) experimental animals. This was accompanied, by osmotic diuresis as measured by increased urine flow. An oral glucose tolerance test was also performed showing that dapagliflozin was able to significantly reduce glucose area under the curve (AUC), compared to vehicle treatment. A study in knock-out mice lacking the gene for SGLT2 revealed that SGLT2 is indeed the main target for dapagliflozin at least at lower doses. This study also demonstrated the reversibility of dapagliflozin's action towards SGLT2.

As in healthy animals, dapagliflozin led to increased renal glucose excretion and urine flow in ZDF rats. However, this renal glucose loss also led to a counter-regulatory endogenous glucose production and increased nutrient (i.e. food) intake. The advantage of these counter-regulatory mechanisms was that dapagliflozin decreased the blood glucose level but did not cause hypoglycaemia. The renal glucose loss was even over-compensated by increased food intake since weight gain was increased in ZDF rats after repeated doses of dapagliflozin as compared to controls. In another T2DM model, the DIO (diet-induced obese) rat, no weight gain in response to dapagliflozin was observed. As in healthy animals dapagliflozin did not cause hypoglycaemia in diabetic animals but could lower blood glucose level (starved and post-prandial) and HbA1c over a prolonged time when administered repeatedly.

Secondary pharmacodynamic studies

The secondary PD programme encompassed *in vitro* studies to investigate dapagliflozin's action on glucose carriers other than SGLT1 and SGLT2 and *in vivo* studies in special animal models to

investigate some mechanistic aspects of dapagliflozin's action in more detail, e.g. single nephron GFR in Wistar rats, body composition in DIO rats and glucose balance in ZDF rats.

Secondary pharmacodynamics *in vitro*

3 studies measured the action of dapagliflozin on the sodium myoinositol transporter (artificially overexpressed in CHO cells) and on the glucose transporters GLUT1, GLUT2 and GLUT4 (measured as glucose uptake in cultured 3T3-L1 mouse adipocytes, human adipocytes and HepG2 human hepatocarcinoma cells). These transporters were only influenced by dapagliflozin in the micromolar range, i.e. far beyond the nanomolar range needed to block SGLT2.

Secondary pharmacodynamics *in vivo*

A renal micropuncture study in diabetic rats was conducted to detect any potential beneficial effect of dapagliflozin on early diabetic nephropathy since proximal-tubular reabsorption of sodium and glucose and their feedback on GFR have been discussed to play a role in early diabetic nephropathy. Dapagliflozin corrected the enhanced single nephron GRF by limiting the reabsorption of glucose and sodium in the proximal tubule. Total GFR was not changed.

Body composition was studied in DIO (diet-induced obese) rats. In these animals, in contrast to the ZDF rats, body weight was reduced in dapagliflozin-treated (*ad libidum* fed) animals. This weight loss was not only due to water loss but body fat mass was also reduced by dapagliflozin treatment.

Furthermore, the Applicant conducted glucose clamp studies to measure insulin resistance and islet function in ZDF rats previously treated with dapagliflozin for 34 days. Dapagliflozin was absent during the clamp. Improvements in insulin sensitivity and beta cell function were observed in the dapagliflozin-treated animals, most likely due to improved glycaemic control in the dapagliflozin treated ZDF rats.

Safety pharmacology programme

Non-clinical studies on cardiovascular safety did not identify any concern for human safety. The *in vivo* studies were performed at high exposure multiples.

No specific safety pharmacology studies assessing effects on the CNS or the respiratory system were performed. The Applicant referred to the absence of any effects in toxicity studies with high exposure multiples. Toxicity studies in dogs included further endpoints addressing respiratory effect as well as neurophysiological functions. In addition, distribution studies in rats demonstrated low distribution of dapagliflozin to the brain. The absence of dedicated safety pharmacology studies addressing the CNS and the respiratory system was considered justified by the CHMP.

In parallel with testing of dapagliflozin, its 3-O-glucuronide metabolite was evaluated in a secondary pharmacology screen consisting of >300 *in vitro* radioligand binding and enzyme activity assays. Similar to dapagliflozin, the 3-O-glucuronide metabolite had no significant activity (all < 50% inhibition) at a free drug concentration of 10 µM in any of the >300 assays, indicating that there were no identified off-target liabilities for parent or its 3-O-glucuronide metabolite.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were performed in animals. The Applicant stated that PD interactions were studied during the clinical development program. This was considered acceptable by the CHMP.

2.3.3. Pharmacokinetics

Non-clinical pharmacokinetic studies were conducted in mice, rats, dogs, and monkeys. The *in vitro* biotransformation of dapagliflozin was investigated in mice, rats, monkeys and humans. The overall results of these investigations are reported below.

Methods of analysis

Validated LC-MS/MS methods were used to determine concentrations of either dapagliflozin or dapagliflozin and its metabolites, desethyl dapagliflozin and dapagliflozin 3-O-glucuronide, in rat liver homogenate and plasma from mouse, rat, rabbit, dog and monkey.

Absorption

Study ID	Species	Route	Dose (mg/kg)	Cmax (µg/ml)	Tmax (h)	AUC (µg•h/ml)	CLTp (ml/min/kg)	T½ (h)	Vss (l/kg)
930005141	Rat	IA	1	NA	NA	3.55	4.8	4.6	1.6
-"-		Oral	1	0.6	1.7	2.96	NA	NC	NA
-"-	Dog	IV	6.6	NA	NA	76.4	1.5	7.4	0.8
-"-		Oral	6.6	10.7	0.6	63.6	NA	NC	NA
-"-	Monkey	IV	6.0	NA	NA	17.1	6.4	3.5	0.8
-"-		Oral	6.0	1.54	1.9	4.27	NA	NC	NA

NA: Not applicable, NC: non calculated

Absorption of dapagliflozin after oral administration was rapid, with T_{max} values being 1.7 ± 2.0 hours, 0.6 ± 0.4 hours, and 1.9 ± 1.8 hours in rats, dogs, and monkeys, respectively. The absolute bioavailability of dapagliflozin was high in rats receiving a 1 mg/kg dose (84 ± 21%) and dogs receiving a 6.6 mg/kg dose (83 ± 2%), indicating that it is well-absorbed in these species. Bioavailability was lower in monkeys receiving a 6 mg/kg dose (25 ± 2%).

In a mass balance study with [^{14}C]dapagliflozin in human subjects receiving a single 50-mg oral dose, 75% of the radioactive dose was recovered in urine, indicating that oral absorption was at least 75% in humans. This is consistent with the high (~76%) oral absolute bioavailability observed in humans.

These data show a high oral bioavailability of dapagliflozin in humans and animals except monkeys, the reason for the low oral availability in monkeys is not clear.

In vitro data indicated that dapagliflozin is a substrate of P-gp. However, the membrane permeability of dapagliflozin was high and oral absorption was good in most species, indicating that the action of P-gp is unlikely to play a limiting role in the oral absorption of dapagliflozin.

Distribution

Distribution of dapagliflozin into red blood cells after a two-hour incubation was low, at 10 to 23% in rat, dog, and monkey and 37% in human. *In vitro* plasma protein binding of dapagliflozin was similar at 0.5 and 5 µg/mL; the overall mean binding was 93, 95, 94, 93 and 91% in mouse, rat, rabbit, dog, and human plasma, respectively.

The steady-state volume of distribution (Vss) for dapagliflozin was moderate in rats, dogs, and monkeys (1.6, 0.8, and 0.8 L/kg, respectively) following intra-arterial or IV doses of 1, 6.6, and 6 mg/kg, indicative of some extra vascular distribution.

The tissue distribution of radioactivity was initially studied in pigmented Long-Evans rats receiving a single oral dose of [^{14}C]dapagliflozin (25 mg/kg, 100 µCi/kg) using tissue combustion and liquid scintillation counting techniques. No retention of dapagliflozin in pigmented skin was observed. A more detailed tissue distribution study was conducted following a single oral dose of [^{14}C]dapagliflozin (~23 mg/kg, ~130 µCi/kg) to adult male and female albino Sprague Dawley rats using quantitative whole-body autoradiography. Tissue-to-blood AUC_{INF} ratios were highest for intestine and renal cortex, ranging from 6.21 to 15.2. The lowest concentrations were observed in the tissues of bone and the lens of the eye, with tissue-to-blood AUC_{INF} ratios of 0.075 and 0.158; the brain-to-blood ratio was 0.250 to 0.335.

In pregnant Sprague Dawley rats receiving [^{14}C]dapagliflozin, the distribution of radioactivity into maternal and fetal tissues, including placenta, was rapid. Fetal blood radioactivity AUC(INF) was 64% of the corresponding maternal blood radioactivity AUC(INF). Fetal tissue radioactivity AUC(INF) values were 80 to 129% of maternal blood radioactivity AUC(INF). These results indicate that dapagliflozin and/or its metabolites cross the placenta in rats resulting in fetal exposure. In nursing rats receiving dapagliflozin, the compound was detected in rat milk 2 hours after dosing at concentration around 50% of that in plasma.

Metabolism

The *in vitro* metabolic fate of [^{14}C]dapagliflozin was studied in liver microsomes and hepatocytes from mice, rats, dogs, monkeys, and humans, as well as in S9 fraction from Aroclor 1254-treated rat liver. *In vivo* biotransformation studies in mice, rats, dogs, and humans, as well as bile duct-cannulated (BDC) rats, were conducted after oral administration of [^{14}C]dapagliflozin followed by profiling and structural elucidation of metabolites in bile (in rat only), plasma, urine, and feces.

Primary biotransformation reactions of dapagliflozin included glucuronidation to form dapagliflozin 3-O-glucuronide (BMS-801576, m15, the overall most-abundant metabolite), dapagliflozin 2-O-glucuronide (BMS-805525, m10), and another dapagliflozin O-glucuronide (m13, the exact site of conjugation for m13 was not determined); oxidative dealkylation to form desethyl dapagliflozin (BMS-511926, m8); and oxidation at various positions of the molecule to form benzylic hydroxy-dapagliflozin (BMS-639432, m12), hydroxy-dapagliflozin-1, -2, and -3 (m4, m9, and m15a, respectively), oxo-dapagliflozin-1, -2, and -3 (m11, m14, and m16, respectively), and dapagliflozin carboxylic acid (m7). Combinations of these reactions produced desethyl dapagliflozin glucuronide-1, -2, and -3 (m2, m3, and m6a, respectively) and hydroxy-dapagliflozin O-glucuronide-1 and -2 (m5 and m6, respectively). There were no unique human metabolites.

There was a markedly different metabolism pattern in animals and humans. Although the nature of metabolites formed was similar, the amount of individual metabolites markedly differed. In particular, humans formed high amounts of directly glucuronidated dapagliflozin (dapagliflozin 3-O-glucuronide, i.e. glucuronidation without prior phase I reactions). This dapagliflozin glucuronidate was present in the plasma in approximately the same amount as native dapagliflozin. Other metabolites played a minor role. In animals, less than half of dapagliflozin was metabolized but the metabolites formed were much more heterogeneous than in humans. Most metabolites were oxidation products of dapagliflozin, and part of them was consecutively also glucuronidated. This means that the main human metabolite was formed only in small amounts in animal, making toxicological qualification difficult. The Applicant stated that in single dose toxicity studies in rats and dogs the exposure of the animals towards dapagliflozin 3-O-glucuronide was similar to the human exposure under therapeutic conditions. No information about repeated-dose toxicity of dapagliflozin 3-O-glucuronide is therefore available. However, mere glucuronidation of a given compound is not expected to increase its toxicity. Usually the glucuronidated product is no longer active on the target structure of the native compound (as it is the case here) and becomes rapidly excreted (via kidney in the present case) without further action in the organism. Therefore, this major human metabolite dapagliflozin 3-O-glucuronide is not considered posing a toxicological concern.

Excretion

Species	Dose (mg/kg)	Anal.	Time (h)	Urine (% dose)	Faeces (% dose)	Bile (% dose)	Recovery (% dose)
Mouse	200	^{14}C	0-120	39.2	41.0	NA	80.2
Rat	26	^{14}C	0-168	39.8	49.0	NA	88.8
Rat (bile duct cannulated)	20	^{14}C	0-24	46.4	3.8	27.0	77.2
Dog	24	^{14}C	0-168	21.6	72.3	NA	93.9
Human	50 mg	^{14}C	0-312	75	21	NA	96

In general, >90% of the administered dose were recovered in all species tested (mouse, rat, dog) including humans. In animals, dapagliflozin excretion was proximally equally distributed between urine and faeces; in humans urine was the predominant route (around 75%). This was due to the major human metabolite dapagliflozin 3-O-glucuronide that was excreted renally. In rats it was shown that biliary clearance and not unabsorbed drug was responsible for the recovery of dapagliflozin in the faeces.

The difference in metabolism of dapagliflozin between humans and animals leads also to differences in its excretion since the main human metabolite dapagliflozin 3-O-glucuronide is mainly excreted via urine. Hence, a higher proportion of dapagliflozin is finally excreted via the kidney than via the bile and in the feces in humans, but, as in animals, the main path of dapagliflozin's inactivation is by metabolism in the liver. Hence, liver insufficiency appears more likely to increase dapagliflozin exposure than kidney insufficiency.

Pharmacokinetic drug interactions

Dapagliflozin is a substrate for various CYP enzymes (highest turnover with CYP1A2, CYP2C9, CYP2D6, and CYP3A4). However, in humans, less than 10% of dapagliflozin's dose is eliminated via pathways involving oxidative metabolism. Dapagliflozin was also a substrate for various UGT enzymes (UGT1A9, UGT2B4, and UGT2B7). In humans, dapagliflozin's elimination is highly dependent on the formation of dapagliflozin 3-O-glucuronide, which is mediated by UGT1A9. *In vitro* data suggest that the inhibition of UGT1A9 can impact on dapagliflozin's elimination: Mefenamic acid (an inhibitor of UGT1A9 and UGT2B) and niflumic acid (a non-steroidal anti-inflammatory drug and a UGT1A9-specific inhibitor) inhibited the formation of dapagliflozin 3-O-glucuronide by human liver microsomes (IC_{50} = 1.17 and 0.091 µM, respectively) and by recombinant UGT1A9 (IC_{50} = 0.426 and 0.067 µM, respectively). In addition, the formation of dapagliflozin 3-O-glucuronide in human kidney microsomes was inhibited by niflumic acid and propofol (a high-affinity UGT1A9 substrate) (IC_{50} = 0.40 and 133 µM, respectively).

Dapagliflozin was a weak substrate for the P-gp transporter. The failure of dapagliflozin or dapagliflozin 3-O-glucuronide to inhibit P-gp suggests that co-administration of dapagliflozin will not affect the absorption or disposition of drugs that are P-gp substrates.

Data from *in vitro* studies with transfected MDCK and HEK-293 kidney cells indicate that, while not inhibitors of hOAT1 or hOCT2, dapagliflozin and dapagliflozin 3-O-glucuronide were inhibitors of hOAT3, with IC_{50} values of 33 and 100 µM, respectively; the metabolite was also a substrate of hOAT3.

2.3.4. Toxicology

The toxicity of dapagliflozin has been evaluated in an extensive non-clinical programme. The toxicology programme included single-dose and repeat dose toxicity studies in mice, rats and dogs, *in vivo* and *in vitro* genotoxicity studies, reproduction and developmental toxicity studies and carcinogenicity studies.

Single dose toxicity

Single-dose oral toxicity studies with dapagliflozin were conducted at doses of 375 to 3000 mg/kg in mice and rats and 200 to 1000 mg/kg (2 doses of 500 mg/kg) in dogs. Dapagliflozin was tolerated at doses up to 1500 mg/kg in mice, 375 mg/kg in rats, and 1000 mg/kg in dogs. Doses of 3000 mg/kg in mice and 750 mg/kg in rats were associated with mortality, while no lethality was observed in the single-dose dog study. No dapagliflozin related gross pathologic lesions were noted. Also no cause of death were noted in any of the mice or rats that died during the single-dose toxicity studies. Although exposures were not measured in these studies, exposure multiples are expected to be very large (> 1000× in mice and > 3000× in rats) based on comparisons to exposures in repeat dose studies at similar doses, and therefore, the lethality observed in mice and rats was not considered relevant to humans.

Repeat dose toxicity

Repeat-dose toxicity studies with dapagliflozin have been performed by oral administration for time intervals up to 3 months in mice, 6 months in rats, and 12 months in dogs. The pivotal GLP studies covered all required outcome measures (toxicokinetic, clinical observations, food and water consumption, haematology, ophthalmology, coagulation, serum chemistry, urianalysis, gross and histopathological examinations of tissues).

Mice

CD-1 mice were administered dapagliflozin at oral gavage doses of 4.1, 25, 43, or 75 mg/kg/day (18 males, 18 females per dose) for 1 week, doses of 0, 150, or 300 mg/kg/day (10 males per dose, 5 males for the highest dose) for 4 consecutive weeks, doses of 0, 50, 150, or 250 mg/kg/day (10 males, 10 females per dose) for 12 consecutive weeks. The NOAEL was considered to be 75 mg/kg/day in this study with an exposure of ≤ 298 µg.h/mL.

In a 1-month exploratory study, the administration of 150 mg/kg/day of dapagliflozin to male mice was associated with the death of one out of 10 mice. No dapagliflozin-related pathologic changes or cause of death were determined. There were no dapagliflozin-related deaths in the 300 mg/kg/day dose group dosed for 2 weeks in this study suggesting that the death at 150 mg/kg/day was not dapagliflozin-related. Clinical signs reported in this study were restricted to rough/urine-stained hair coats at 150 mg/kg/day and polyuria at 150 and 300 mg/kg/day.

In a 3-months mouse toxicity study, 76 mice were administered 50, 150, 250, and 400 mg/kg/day of dapagliflozin. The administration of dapagliflozin in the 250 and 400 mg/kg/day dose groups was not tolerated and was associated with dapagliflozin related deaths (4 males and 5 females for the 250 mg/kg/day dose and 7 males and 4 females in the 400 mg/kg/day dose). No cause of death was identified. Decreased activity, abdominal distention and hunched posture were observed at all doses in the 3-month mouse toxicity study starting on Day 3. The effects generally increased with dose and are most likely related to off target inhibition of intestinal SGLT1 and the decreased intestinal absorption of glucose. The clinical observations in the 3-month mouse toxicity study were not associated with decreases in body weights or food consumption. In fact, dapagliflozin-treated mice actually exhibited increased food consumption at all doses (26 to 44%) with an increase in end-of study body-weight gains relative to controls. Pathologic changes were limited to decreases in absolute prostate weight (20 to 23%) at 150 and 250 mg/kg/day. The NOAEL was considered to be 150 mg/kg/day in this study with an exposure of ≤ 492 µg.h/mL.

Rats

Sprague Dawley rats were administered dapagliflozin at oral gavage doses of 0, 5, 50, or 300 mg/kg/day (10 males, 10 females per dose) for 4 consecutive weeks, doses of 0, 5, 50, or 200 mg/kg/day (15 males, 15 females per dose) for 12 consecutive weeks, doses of 0, 5, 25, or 150 mg/kg/day (30 males, 30 females per dose) for 26 consecutive weeks. The NOAEL was considered to be 50 mg/kg/day in the 4 weeks study with an exposure ≤ 292 µg.h/mL, 50 mg/kg/day in the 12 weeks study with an exposure ≤ 438 µg.h/mL and 25 mg/kg/day in the 26 weeks study with an exposure ≤ 314 µg.h/mL. Dapagliflozin exhibited potent pharmacologic activity with increases in urinary glucose excretion at all doses examined. As in the mouse, the resulting loss of calories induced compensatory increases in food consumption in the rat. However, in most studies conducted in rats, increases in food consumption were associated with decreases in body weight and body weight gains. Dapagliflozin induced glucosuria was also associated with increases in urinary volume, decreases in urine osmolality, and compensatory increases in water consumption. The increase in urinary glucose will lead to an increased risk for urinary infections. A few cases were observed in rats. Increases in adrenal gland weights were noted in rats, most likely due to a compensatory increase in aldosterone production in response to the increased loss of sodium. The target organs for toxicity were kidney and bone. Kidney findings were reactive hyperplasia of collecting duct epithelium, dilation of cortical and/or medullary tubules, and mineralisation of the collection ducts and exacerbation of chronic progressive neuropathy (CPN). There were changes indicative of abnormal bone formation. The mineralisation and bone changes were related to increases in serum calcium. A mechanistic study in rats on a glucose-free diet suggested that these findings were related to off-target inhibition of intestinal SGLT1 at high doses. No changes in serum calcium, no renal effects and no mineralisation were observed in rats on glucose-free diet. Liver enzymes (ALT, AST) were increased with dapagliflozin in rats.

Dogs

Beagle dogs were administered dapagliflozin at oral gavage doses of 0, 5, 25, or 250 mg/kg/day (3 males, 3 females per dose) for 4 consecutive weeks, doses of 0, 5, 30, or 180 mg/kg/day (5 males, 5 females per dose) for 12 consecutive weeks, doses of 0, 5, 20, or 120 mg/kg/dose (11 males, 11 females per dose) for 52 consecutive weeks. The NOAEL was considered to be 25 mg/kg/day in the 4 weeks study with an exposure ≤ 394 µg.h/mL, 30 mg/kg/day in the 12 weeks study with an exposure ≤ 549 µg.h/mL and 120 mg/kg/day in the 52 weeks study with an exposure ≤ 1540 µg•h/mL. Similar to the rat, dapagliflozin exhibited potent pharmacologic activity with increases in urinary glucose excretion at all doses examined. The loss of calories from urinary glucose excretion induced decreases in body weight and body-weight gains in these studies despite compensatory increases in food consumption. High doses of dapagliflozin were also associated with increases in emesis and diarrhea in dog repeat dose toxicity studies. The increased incidence of diarrhea following dapagliflozin administration is most likely due to the off-target inhibition of SGLT1 in the intestines and the resulting decreases in intestinal glucose absorption. Administration of high doses of dapagliflozin was associated with slight increases in total serum cholesterol (≤ 1.6× relative to controls) in the 1, 3 and 12 months dapagliflozin dog studies. Increases in serum cholesterol are most likely due to the observed increased food consumption in dogs following dapagliflozin administration. There was no target organ toxicity observed in the repeat-dose dog toxicity studies even at very high doses of dapagliflozin (≤ 3312×). As in rats, increases in adrenal gland weights and a few cases of urinary infections were noted in dogs.

These *in vitro* screening results were further substantiated by results from a 12-month dog toxicity study, in which exposure to the 3-O-glucuronide metabolite at the no-observed adverse effect-level (NOAEL; 120 mg/kg/day) was estimated to be approximately 90× the human exposure to this metabolite at the maximum recommended human dose of 10 mg. Based on clinical and veterinary observations, clinical pathology and histopathology, there was no evidence of any estrogenic/androgenic effects or disruption of hormonal balance in dogs through 1 year of exposure. Thus, these data also support the conclusion that the 3-Oglucuronide metabolite does not induce toxicity or any signs of hormonal imbalance *in vivo* at relative large multiples of the human metabolite exposure.

Genotoxicity

In vitro

The *in vitro* reverse mutation assays in the *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and *E.Coli* strain WP2*uvr*A were negative with dapagliflozin in the presence of S9 activation. Chromosomal aberration tests in Chinese Hamster Ovary (CHO) cells were negative without metabolic activation but consistently positive with metabolic activation. In an *in vitro* micronucleus screening assay in CHO cells, dapagliflozin was clastogenic at concentrations ≥ 100 µg/mL in the presence of S9 metabolic activation.

In vivo

Due to the positive response in *in vitro* clastogenicity tests with metabolic activation, follow up *in vivo* tests were additionally performed. Unscheduled DNA Synthesis (UDS) assays in rat hepatocytes with dapagliflozin showed negative results. The micronucleus aberrations assays in the bone marrow of rats with dapagliflozin were negative. In the chromosomal aberrations assay in peripheral blood lymphocytes of rats, there was a small dose-dependent increase in the percentage of aberrations in male rats (from 0.4 to 2.2%). These differences were not statistically significant and the numbers are within the historical control range at the laboratory; the Applicant concluded that dapagliflozin was not clastogenic in this assay and this is supported by the CHMP.

Considering the clearly negative *in vivo* assays covering structural as well as numerical chromosome alterations and in addition the absence of induction of DNA repair *in vivo* the positive effects in *in vitro* tests with metabolic activation are regarded to be biologically irrelevant. In conclusion there is no evidence for any clinically relevant genotoxic potential of dapagliflozin.

Carcinogenicity

The carcinogenic potential of dapagliflozin was evaluated in 24-month oral carcinogenicity studies in mice and rats. No short-term carcinogenicity studies were performed; the dose selection for the long-term studies was based on the repeated-dose toxicity studies.

Table 1. Steady-state exposures and AUC multiples from the carcinogenicity studies in mice and rats

Species, Duration, Route [Study Number]	Dose (mg/kg/day)	AUC (0-T h)[a] (µg•h/mL)		AUC Multiples[b]	
		M	F	M	F
Mouse, 24-month, (oral gavage) [DN06072][38]	5M, 2F	2.00	5.09	4.3	10.9
	15M, 10F	6.41	24.0	13.8	51.6
	40M[c], 20F[c]	33.5	48.6	72.0	104.5
Rat, 24-month, (oral gavage) [DN06073][39]	0.5	3.12	4.04	6.7	8.7
	2	11.8	16.0	25.4	34.4
	10[c]	60.7	86.6	130.5	186.2

[a] AUC values at the end of the dosing period. T = 8 or 24 hours.

[b] At the MRHD of 10 mg, the dapagliflozin value is 0.465 µg•h/mL (Clinical pharmacology report MB-102027).[1] AUC multiple = animal AUC ÷ human AUC.

[c] Underlined doses are the no observed effect level (NOEL) for dapagliflozin-related tumors.

Mice (study DN06072)

Exposure of CD-1 mice towards dapagliflozin in this study was sufficiently high, and a sufficient number of animals survived to allow meaningful conclusions. In high-dose males' survival was markedly reduced compared to controls. The Applicant argued that the males spontaneously developed mouse urologic syndrome, a background condition commonly seen in CD-1 mice, leading to urogenital obstruction and mortality. Thus, the higher diuresis caused by dapagliflozin would deteriorate the sequels of urogenital obstruction and hence lead to higher mortality. This explanation was considered acceptable by the CHMP. Importantly, the number of neoplasms was not increased in response to dapagliflozin treatment so that it is unlikely that the increased mortality was linked to neoplastic processes. Hence, the mouse carcinogenesis study gave no hint for carcinogenic potential of dapagliflozin. The non-neoplastic findings are in line with the established action of dapagliflozin, increased (osmotic) diuresis in response to the desired increase in renal glucose excretion and do not raise further concern. In particular, dilation of the renal pelvis and distension of the urinary bladder were observed, most likely due to the high urine volumes to be handled.

Rats (study DN06073)

Exposure of Sprague Dawley rats towards dapagliflozin was sufficiently high, and a sufficient number of animals survived to allow meaningful conclusions. The number of neoplasms was not increased in response to dapagliflozin treatment. Hence, the rat carcinogenesis study gave no hint for carcinogenic potential of dapagliflozin. The non-neoplastic findings in rats are in line with the observations made in the repeated-dose toxicity studies and raise no further concern.

The carcinogenicity studies in mice and rats were performed at large exposure multiples in comparison to clinical exposure. It is agreed that no carcinogenic risk was identified in these studies.

Reproduction Toxicity

Fertility and early embryonic development

In male and female rats, dapagliflozin showed no effects on mating, fertility or early embryonic development at doses up to 75 mg/kg, representing AUC values 675x and 998x clinical exposure, respectively.

Embryo-foetal development

In the embryofoetal toxicity studies in rats, adverse foetal effects were only observed at very high exposure multiples in presence of maternal toxicity. The NOAEL for maternal and developmental toxicity was 75 mg/kg, representing an AUC value 141x clinical exposure.

In rabbits, there were no important findings of maternal or embryofetal toxicity at any dose up to 180 mg/kg, representing an AUC 1191x clinical exposure.

Prenatal and postnatal development, including maternal function

In the pre and post-natal study in rats there was an increased incidence and/or severity of renal pelvic dilation, in absence of maternal toxicity. The NOAEL for developmental toxicity was 1 mg/kg, representing and AUC 19x clinical exposure.

Studies in which the offspring (juvenile animals) were dosed and/or further evaluated

Juvenile rats (21/sex/group) were dosed once daily with dapagliflozin from postnatal day (PND) 21 until PND 90 at 0, 1, 15 or 75 mg/kg.

Table 2. Rat Juvenile Toxicokinetic Summary

Parameter	Day	Dapagliflozin 1 mg/kg/day Male	Female	15 mg/kg/day Male	Female	75 mg/kg/day Male	Female
Cmax (µg/mL)	21	0.935	0.921	14.1	14.3	56.4	67.1
	83	0.772	1.12	11.3	15.9	39.9	51.4
AUC(0-24 h) (µg•h/mL)	21	9.92	11.7	167	176	849	937
	83	6.97	9.63	97.0	135	505	779

Renal pelvic and tubular dilatations were reported at all dose levels; pup exposures at the lowest dose tested were ≥ 15 times the maximum recommended human dose. These findings were associated with dose-related increases in kidney weight and macroscopic kidney enlargement observed at all doses. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the approximate 1-month recovery period. The persistent renal findings might be due to the reduced ability of the developing rat kidney to handle dapagliflozin-increased urine volumes. The primary target organs at doses ≥ 1 mg/kg/day (mean AUC on PND 83 ≥ 6.97 µg*h/ml) were the kidney and adrenal gland. The findings unique to juvenile animals suggest a decreased capacity in juveniles to mount compensatory metabolic responses to dapagliflozin's pharmacology. The findings in the juvenile rat toxicity study are in line with the findings in the pre and post-natal toxicity study.

Local Tolerance

In vitro and *in vivo* studies were conducted in isolated bovine corneas, rabbits, mice, and dogs to determine the ocular irritation, dermal irritation, sensitization potential and vascular/perivascular irritation potential of dapagliflozin. These studies were conducted for the purpose of establishing occupational worker safety in the event of ocular or dermal exposure to dapagliflozin, and to support the intravascular administration of dapagliflozin to humans in an absolute bioavailability study.

In a Bovine Corneal Opacity and Permeability Assay, dapagliflozin exhibited moderate to severe ocular toxicity. Dapagliflozin was considered to be a non-sensitizer based on the results of a local lymph node assay in the mouse. In an acute dermal irritation study in rabbits, dapagliflozin was a non-irritant. Five days of repeated IV administration of an intravenous formulation of dapagliflozin did not cause any vascular effects. After subcutaneous injections, there was slight focal necrosis of subcutaneous muscle at the injection site.

2.3.5. Ecotoxicity/environmental risk assessment

The Environmental Risk Assessment (ERA) for dapagliflozin was provided in accordance with the CHMP guideline EMEA/CHMP/SWP/4447/00. A Phase I environmental risk assessment was performed to evaluate potential environmental risks of dapagliflozin. The log K_{ow} was determined according to study OECD 107 with a value of 2.34 at ph /7. Based on the log K_{ow} value being below 4.5, dapagliflozin is not expected to be a bio-accumulative substance. The refined $PEC_{surfacewater}$ of 9.15 ng/L did not exceed the action limit of 0.01 µg/L. However the use of market forecasts for Fpen refinement is not allowed in Phase I of the ERA. The applicant performed nevertheless a phase II – Tier A assessment. Based on the calculated PEC/PNEC ratios, it is predicted that dapagliflozin will not significantly partition into the solid phase waste water treatment in domestic sewage, which means that an ERA in the terrestrial compartment is needed. Based on the results of the water/sediment study (OECD study 308), a phase II - Tier B assessment was triggered for dapagliflozin.

Dapagliflozin – PEC/PNEC assessments			
	PEC (µg/L)	**PNEC (µg/L)**	**PEC/PNEC**
Microorganisms	0.00915	20000	4.58×10^{-6}
Surface water	0.00915	100	9.15×10^{-5}
Groundwater	0.00229	1000	2.29×10^{-6}

Based on the $PEC_{sediment}/PNEC_{sediment}$, dapagliflozin is considered unlikely to present a risk to sediment dwelling species and therefore no further testing is required. Dapagliflozin is not a PBT substance.

Table 3. Summary of main study results

Substance (INN/Invented Name): dapagliflozin					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	2.34 at pH 7			Potential PBT: NO
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.05 (default) 0.00915 (refined)	µg/L			> 0.01 threshold YES Refined PEC accepted for Phase II
Other concerns (e.g. chemical class)					No
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OPPTS 835.1110	K_{oc} =138 K_d = 51			
Ready Biodegradability Test	OECD 301	Not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 13.5 d (12°C) $DT_{50, sediment}$ = 240 d (12°C) Mineralisation: 37.5 and 67.5% on d 99 40.7 and 75.7% on d 148 Bound residues: 44 % on d 99 49.3 % on d 148			Dapagliflozin is persistent in sediments.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/	OECD 201	NOEC	37,000	µg/L	*Pseudokirchnella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	10,000	µg/L	
Fish, Early Life Stage Toxicity	OECD 210	NOEC	1,000	µg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	107,600	µg/L	
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC	150	mg/kg	*Chironomus sp.*

Considering the above data, dapagliflozin is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

The Applicant has extensively studied the pharmacology of dapagliflozin. These studies demonstrated the expected pharmacological response in mice and rats and in *in vitro* studies a similar activity on SGLT2 from mice, rats and humans was observed. The data also suggested a high selectivity versus SGLT1, a glucose transporter expressed predominantly in the gut. The selectivity was somewhat less in rats and mice, and this may explain some findings in the rat toxicology studies at high doses. The activity at SGLT2 from dogs and rabbits was not studied. However the pharmacological activity of SGLT2 in dogs was demonstrated in the toxicity studies. Considering the similar activity in mouse, rat and human SGLT2 it is considered unlikely that dapagliflozin would not be pharmacologically active in the rabbit. It is concluded that toxicity studies have been performed in pharmacologically relevant species.

Studies with a number of receptors, enzymes, ion channels and transporters, including several other members of the sodium-glucose co-transporter family, did not identify any risk for off-target effects.

No specific safety pharmacology studies addressing the CNS or the respiratory system were performed. Based on the available data from toxicity studies and the low distribution of dapagliflozin to the brain the absence of CNS studies is considered justified. In the absence of respiratory effects in the general toxicology studies and with no clinical concerns, the lack of formal respiratory safety pharmacology studies is acceptable.

No studies on pharmacodynamic interactions have been performed. This is considered acceptable.

The non-clinical pharmacokinetics of dapagliflozin is sufficiently characterised. There are major differences in the metabolite pattern in humans and the toxicology species. The main human metabolite dapagliflozin 3-O-glucuronide is present at much lower levels in rats and dogs. Studies were performed to evaluate the exposure to this metabolite in rats and dogs. Extrapolating from these data it was concluded that exposure to the glucuronide was equal to clinical exposure (rat) or higher (dog) at NOAEL levels in the toxicology studies. The 3-O-glucoronide is not pharmacologically active and glucuronides are generally considered of limited toxicological importance. The Applicant presented data from *in vitro* screening showing no relevant activity of the 3-O-glucuronlide metabolite of dapagliflozin. No toxicity was seen in the 12 month dog toxicity study with high exposure multiples. It is agreed that the data support the conclusion that the 3-O-glucucuronide metabolite does not induce toxicity or any signs of hormonal imbalance *in vivo* at relatively large multiples of the human metabolite exposure.

It is therefore agreed that based on metabolism, the toxicology studies in mice, rats and dogs are appropriate to judge on the toxicological profile of dapagliflozin.

Since dapagliflozin is a P-gp substrate it cannot be excluded that inhibition of P-gp by a concomitantly administered drug could lead to increased exposure in the brain. However, the distribution to the brain in rats was shown to be sufficiently high to ascertain that brain exposure in the toxicity studies was well above therapeutic plasma exposure.

Most of the effects in the repeat-dose toxicity studies were considered to be secondary to the pharmacologically mediated increase in urinary glucose and included decreases in body weights and/or body-weight gains, increases in urine volume and increases in urinary electrolytes. In rats, kidney and bone were identified as toxicological target organs. Mechanistic studies suggest that these effects were related to off-target effects on SGLT1 in the gut, and it maybe expected that those effects will not occur in humans at clinical doses.

While the pharmacological changes in the animals were not considered adverse, it should be borne in mind that the toxicology studies are performed in healthy animals. Type 2 diabetes is commonly associated with renal defects. The safety in patients with renal impairment needs to be carefully addressed clinically. It is not considered that vital information on safety could be gained by performing further toxicology studies in animal models of disease.

The increase in urinary glucose will lead to an increased risk for urinary infections. A few such cases were observed in the animal studies but this was only discussed briefly by the Applicant. The risk of urinary infections is included in the RMP and in the SmPC.

Dapagliflozin was shown to induce chromosomal aberrations in eukaryotic cells in presence of metabolic activation. However, *in vivo* studies on genotoxicity were negative and thus dapagliflozin is not considered to represent a genotoxic risk to humans.

The carcinogenicity studies in mice and rats did not indicate any carcinogenic risk. The studies were performed with very high exposure multiples.

Reproductive and developmental toxicity studies with dapagliflozin did not indicate a risk for effects on fertility, early embryonic development or embryofoetal development.

In the pre- and postnatal development study in rats, there were findings on renal pelvic dilatation in the offspring in absence of maternal toxicity. Similar findings were seen in a juvenile toxicity study in rats. The Applicant argued that these effects are due to a reduced ability of the developing rat kidney to handle dapagliflozin-increased urine volumes. Although there was a reasonable exposure margin at the developmental NOAEL in the pre- and postnatal study (19x clinical exposure), these effects are reflected in the SmPC.

An Environmental Risk Assessment (ERA) for dapagliflozin was provided in accordance with the CHMP guideline EMEA/CHMP/SWP/4447/00 including a phase I, phase II- Tier A and phase II-Tier B assessment. Based on these data, the CHMP considers that dapagliflozin is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The overall non-clinical development programme was considered adequate to support the marketing authorisation application for dapagliflozin and the concerns identified by the CHMP during its evaluation are considered resolved.

2.4. Clinical aspects

2.4.1. Introduction

The Applicant is seeking a Marketing Authorisation for dapagliflozin film-coated tablets (5 and 10 mg) for the once-daily treatment of T2DM in adults, either as monotherapy in patients intolerant to metformin or as add-on combination therapy with other glucose lowering drugs including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control. The recommended starting dose is 10 mg taken once daily. In patients with severe hepatic impairment a starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg.

This application is supported by an extensive clinical program to establish the therapeutic dose and to assess the efficacy and safety of dapagliflozin Three phase IIB and eleven phase III studies investigating dapagliflozin doses of 2.5 mg, 5 mg and 10 mg in the treatment of T2DM in adult patients as monotherapy, as add-on combination (to metformin, SU, TZD and insulin), and as initial combination therapy with metformin.

Scientific advice was provided by the CHMP in February 2008 (EMEA/CHMP/SAWP/485029/2007) on the clinical aspects of the development program with main focus on the Phase 3 program. The importance of investigating the lower dose range in the Phase 3 studies was pointed out. Potential safety issues were also discussed such as the risk of electrolyte imbalances. The need to include sufficient numbers of patients from the EU was stressed as well as the need to include elderly patients. The design of study DC1690C00006 to support the add-on indication to insulin was discussed and points were made on the inclusion and exclusion criteria. The proposed investigation of changes in body weight/body composition was also discussed and the Applicant's strategy was endorsed. Further, risk mitigation actions proposed by the Applicant were discussed and the proposals were generally found acceptable. The advice given has been followed in all essential parts.

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC. The table below lists only the main phase II dose-finding and the main phase III studies submitted as part of this Marketing Authorisation Application.

Table 4. Dapagliflozin Phase IIb and Phase III clinical development program

Study number/ Duration	Subject population	Treatment groups N per group/N treated with dapagliflozin/Total
Phase 2b studies		
MB102008 12 weeks	Drug-naïve subjects with HbA1c ≥7.0% and ≤10.0%	Dapa 2.5, 5, 10, 20, and 50 mg, placebo and metformin XR 750/1500 mg 47-59/279/389
MB102009 12 weeks	Insulin-dependent subjects with HbA1c ≥7.5% and ≤10.0%	Dapa 10 or 20 mg and placebo 23-24/48/71
D1692C00005 12 weeks	Japanese subjects with HbA1c ≥7.0% and ≤10.0%	Dapa 1, 2.5, 5, and 10 mg and placebo 54-59/225/279
Phase 3 studies		
Monotherapy		
MB102013 24 plus 78 weeks	Drug-naïve subjects with HbA1c ≥7.0% and ≤10.0% Open treatment group with HbA1c ≥10.1% and ≤12.0%	Dapa 2.5, 5, and 10 mg and placebo 64-76/410/485 Dapa 5, 10 mg 34-39/73/73
MB102032 24 weeks	Drug-naive subjects with HbA1c ≥7.0% and ≤10.0%	Dapa 1, 2.5, and 5 mg and placebo 68-74/214/282
Add-on combination therapy with metformin		
MB102014 24 plus 78 weeks	Subjects on metformin ≥1500 mg/day with HbA1c ≥7.0% and ≤10.0%	Dapa 2.5, 5, and 10 mg and placebo 135-137/409/546
D1690C00012 24 plus 78 weeks	Subjects on metformin ≥ 1500 mg/day with HbA1c ≥6.5% and ≤8.5%	Dapa 10 mg and placebo 91/91/182
Add-on combination therapy with insulin		
D1690C00006 24 plus 24 plus 56 weeks	Subjects on insulin ≥30 IU/day ± maximum 2 OAD with HbA1c ≥7.5% and ≤10.5%	Dapa 2.5, 5, and 10 mg and placebo 196-212/610/807
Add-on combination therapy with TZD		
MB102030 24 plus 24 weeks	Subjects on pioglitazone with HbA1c ≥7.0% and ≤10.5%	Dapa 5, and 10 mg and placebo 139-141/281/420
Add-on combination therapy with SU		
D1690C00005 24 plus 24 weeks	Subjects on SU with HbA1c ≥7.0% and ≤10.0%	Dapa 2.5, 5, and 10 mg and placebo 146-154/450/596
Initial combination therapy with metformin		
MB102021 24 weeks	Treatment- naïve subjects with HbA1c ≥7.5% and ≤12.0%	Dapa 5 mg + metformin extended release (XR) up to 2000 mg, dapa 5 mg, and metformin XR up to 2000 mg 194-203/397/598
MB102034 24 weeks	Treatment- naïve subjects with HbA1c ≥7.5% and ≤12.0%	Dapa 10 mg + metformin XR up to 2000 mg, dapa 10 mg, and metformin XR up to 2000 mg 208-219/430/638

Study number/ Duration	Subject population	Treatment groups N per group/N treated with dapagliflozin/Total
Active comparator		
D1690C00004 52 plus 156 weeks	Subjects on metformin >1500 mg/day with HbA1c >6.5% and ≤10.0% Non-inferiority vs glipizide	Dapa titrated to 2.5, 5, and 10 mg and glipizide titrated to 5, 10, and 20 mg 406-408/406/814
Special populations		
MB102029 24 plus 28 plus 52 weeks	Subjects with moderate renal impairment (GFR >30 to <60 mL/min/1.73m^2 on a stable anti-diabetic regimen with HbA1c ≥7% and ≤11%	Dapa 5 and 10 mg and placebo 83-85/168/252

2.4.2. Pharmacokinetics

The clinical pharmacology programme for dapagliflozin included 28 studies conducted in 688 subjects (635 of these subjects were exposed to dapagliflozin) (Table 5). These studies included healthy subjects as well as subjects with T2DM (118 subjects, 101 exposed to dapagliflozin) and subjects with renal or hepatic impairment (20 and 18 subjects respectively, all exposed to dapagliflozin).

Aqueous solutions of dapagliflozin were used for oral doses <10 mg in the single ascending dose study, for oral doses <1 mg in the low dose study, for the ADME study and for the microtracer dose administered intravenously in the absolute oral bioavailability study. Capsule formulations were used in the Phase 1 ascending dose studies and the Phase 2a study. Tablet formulations were used in the Phase 2b studies. Film-coated tablet formulations were subsequently developed for the Phase 3 program (1, 2.5, 5, and 10 mg dose strengths). A common granulation was used for the 5 and 10 mg strengths of the Phase 3 tablets, and the tablets proposed for commercialisation. Clinical Pharmacology studies generally used the Phase 3 tablet formulation.

Plasma dapagliflozin concentrations were measured using validated liquid chromatography tandem mass spectrometry (LC-MS/MS) bioanalytical methods. Pharmacokinetic parameters in clinical pharmacology studies were generally calculated by non-compartmental methods. Nonlinear mixed effects modelling (population pharmacokinetic analysis) was used to evaluate pharmacokinetics in phase III patients.

Table 5. Dapagliflozin Clinical Pharmacology Studies

Study Description [Dapagliflozin Dose(s) Used in the Study]	Study Number
Safety/Pharmacokinetics/Pharmacodynamics	
Single ascending doses in healthy subjects [2.5 - 500 mg]	MB102001
Multiple ascending doses in healthy subjects [2.5 to 100 mg]	MB102002
Multiple doses in subjects with T2DM [5 - 100 mg]	MB102003
Low dose pharmacokinetics/pharmacodynamics in healthy subjects [0.001 to 2.5 mg]	MB102088
^{14}C-ADME and Mass Balance [50 mg/~12 μCi]	MB102006
Absolute Oral Bioavailability [Intravenous: 80 μg/~160 μCi. Oral: 10 mg]	MB102059
Thorough QTc study [20 and 150 mg]	D1690C00001
Specific Populations	
Renal impairment [20 mg and 50 mg]	MB102007
Hepatic impairment [10 mg]	MB102027
Single ascending doses in healthy Japanese subjects [2.5 - 50 mg]	MB102010
Multiple ascending doses in Japanese subjects with T2DM [2.5 - 20 mg]	MB102025
Drug-Drug Interactions	
Antidiabetic Agents	
Pioglitazone (45 mg QD) + Dapagliflozin [50 mg]	MB102017
Metformin (1000 mg) + Dapagliflozin [20 mg]	MB102026
Glimepiride (4 mg) + Dapagliflozin [20 mg]	MB102037
Sitagliptin (100 mg) + Dapagliflozin [20 mg]	MB102037
Voglibose (0.2 mg TID) + Dapagliflozin [10 mg]	D1692C00002
Potentially Co-Prescribed Cardiovascular Disease Agents	
Hydrochlorothiazide (25 mg)) + Dapagliflozin [50 mg]	MB102004
Valsartan (320 mg) + Dapagliflozin [20 mg]	MB102036
Simvastatin (40 mg) + Dapagliflozin [20 mg]	MB102036
Bumetanide (1 mg) + Dapagliflozin [10 mg]	MB102057
Digoxin (0.25 mg) + Dapagliflozin [10 mg]	MB102058
Warfarin (25 mg) + Dapagliflozin [10 mg]	MB102058
Metabolic Enzyme Inducer	
Rifampin (600 mg) + Dapagliflozin [10 mg]	MB102074
Metabolic Enzyme Inhibitor (UGT1A9 inhibitor)	
Mefenamic acid (250 mg) + Dapagliflozin [10 mg]	MB102093
Biopharmaceutics	
Relative bioavailability (capsules *vs* tablets) [50 mg]	MB102005
Food effect study [10 mg, crystalline form]	MB102019
Bioequivalence of crystalline and amorphous forms in tablets and food effect on the amorphous form [10 mg]	MB102062
Bioequivalence & food effect of crystalline and amorphous forms in tablets [2.5 mg]	MB102090

Absorption

Dapagliflozin was rapidly absorbed after oral administration in the fasted state, with C_{max} usually observed about 1h after administration. The Caco-2 cell data suggest that dapagliflozin is a weak P-gp substrate. As absolute bioavailability is high, potential interaction with P-gp inhibitors is not expected to result in clinically relevant interactions *in vivo*. Absolute bioavailability (78%) and mass balance data (about 75% of dose excreted in urine as parent compound and in urine and faeces as phase I and II metabolites) suggest that dapagliflozin is a BCS Class III compound.

Bioavailability

The absolute bioavailability was determined in study MB102059 in 7 healthy fasted subjects (Caucasian males with a mean age of 26 years). Subjects received a 10 mg oral dose of dapagliflozin first followed an hour later, at approximately the time of the oral dapagliflozin tmax, by an 80 μg micro-tracer dose of [^{14}C]dapagliflozin infused intravenously over 1 minute. PK samples were collected at selected time points up to 49 h post oral dose. Plasma concentrations of dapagliflozin were determined by LC-MS/MS, while the plasma concentrations of [^{14}C]dapagliflozin were determined using an accelerator mass spectrometry (AMS) method, thereby allowing the individual quantification of the simultaneously administered oral and intravenous doses. The geometric mean absolute bioavailability was 77.8% (CV 9%), with individual values ranging from 70 to 90%.

Bioequivalence

The differences between the Phase 3 and the proposed commercial formulations are minor (colour, shape, debossing and grade of microcrystalline cellulose) and their *in vitro* dissolution characteristics possess a high degree of similarity. As such, comparable *in vivo* performance of the commercial tablet formulations compared to the Phase 3 tablet formulations is anticipated. Since the 5 and 10 mg formulations share the same granulation, the biopharmaceutics program has studied the 10 mg formulations, where appropriate, and these data are considered applicable to the 5 mg formulations.

Comparison between capsule and tablet

Study MB102005 was conducted to bridge the early clinical capsule formulation of dapagliflozin with the Phase 2b clinical tablets. Fourteen subjects received dapagliflozin as either 5 x 10 mg capsule or 1 x 50 mg clinical tablet. Bioequivalence was demonstrated for AUC_{inf}, AUC_{0-t} (90% confidence interval 1.00-1.08) and C_{max} (90% confidence interval 0.82-1.09).

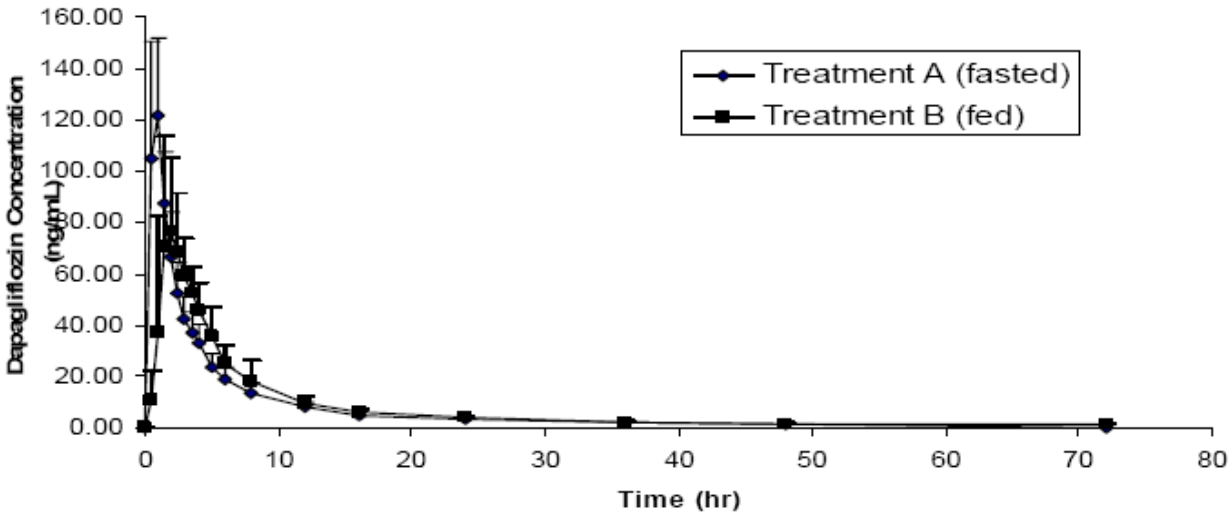
Influence of heat-stress on the tablet formulation

The drug substance converts to an amorphous desolvate upon exposure to high temperature for extended period (heat-stress). To assess the *in vivo* impact of the potential physical form change in tablets after heat stress (crystalline to amorphous), two bioequivalence studies using the proposed commercial tablets (heat-stressed and non heat-stressed) were conducted with the 2.5 mg (study MB102090) and 10 mg (study MB102062) tablet strengths. Bioequivalence was demonstrated for both AUC and C_{max} when comparing heat-stressed versus non-heat stressed conditions. For the 10 mg tablet the point estimates (90%CI) were 0.99 (0.969, 1.021) for AUC and 1.01 (0.925, 1.122) for C_{max}. Similar results were observed for the 2.5 mg tablet.

Influence of food

Study MB102019 was conducted to evaluate the effect of a high-fat meal on the single-dose pharmacokinetics of dapagliflozin. Fourteen subjects received a single, oral 10 mg dose of dapagliflozin (Phase 3 tablet formulation) administered while fasting or after a high-fat meal. The meal contained 985 kcal with 52% of calories from fat, 34% from carbohydrates and 14% from proteins. The mean dapagliflozin plasma concentration time profile is displayed in the figure below.

Figure 1. Mean (+SD) Plasma Concentration-Time Profiles of Dapagliflozin after administration of 10 mg in fasting and fed state



Administration of dapagliflozin with a high-fat meal reduced the rate but not the extent of absorption resulting in a 1 h delay of t_{max} and a 30-45% decrease in C_{max} but no change in AUC. In the Phase 3 program dapagliflozin was administered before breakfast or dinner. The cumulative urinary excretion data, with similar glucose excretion over the first 8 h for the 2.5 and 10 mg doses, suggest that glucose excretion seems to become saturated at higher concentrations and that a 30-50% reduction in C_{max} is not clinically relevant. Hence, dapagliflozin may be taken with or without food.

Distribution

The *in vitro* plasma protein binding of dapagliflozin was determined by equilibrium dialysis at dapagliflozin concentrations 500 and 5000 ng/ml. The *in vitro* plasma protein binding was 91%. The *ex vivo* plasma protein binding of dapagliflozin in healthy human subjects was ~92%, and was similar to that in diabetic subjects with or without renal impairment and in subjects with hepatic impairment. The *in vitro* protein binding of dapagliflozin 3-O-glucuronide in human plasma was similar to parent dapagliflozin at 89% bound. In the massbalance study the ratio between blood and plasma in AUC of radioactivity was 0.58, suggesting no distribution to blood cells. The mean Vss for dapagliflozin following intravenous administration was 118L (study MB102059). Vss was greater than plasma volume, indicative of extravascular distribution.

Study 930045130 was conducted to determine if dapagliflozin 3-O-glucuronide is a substrate of renal uptake transporters and whether dapagliflozin and dapagliflozin 3-O-glucuronide have the potential to inhibit renal uptake transporters. The substrate studies on dapagliflozin 3-O-glucuronide were performed using stably transfected HEK-293 or MDCK cells that singly expressed each of the following transporters, hOCT2, hOAT1, and hOAT3. The studies indicate that dapagliflozin 3-O-glucuronide is a substrate of hOAT3, but not hOCT2 and hOAT1 in vitro. The Km value of dapagliflozin 3-O-glucuronide for transport by hOAT3 was 115 µM.

To conclude, dapagliflozin is relatively highly bound to proteins, with a fraction bound of 92%. Volume of distribution is 118 L, suggesting extravascular distribution. The main (inactive) metabolite dapagliflozin 3-O-glucuronide was found to be a substrate of hOAT3.

Elimination

Dapagliflozin is mainly eliminated by metabolism. The geometric mean clearance of dapagliflozin following i.v. administration was 207 mL/min. The clearance is substantially less than the plasma flow to either liver or kidney, indicating low hepatic and renal extraction. The terminal half-life after intravenous administration was 12.2 h.

Excretion

In study MB102006, [^{14}C]dapagliflozin 50 mg oral solution was administered as a single dose to 6 healthy male subjects under fasting conditions. About 96% of the radioactive dose administered was recovered in the excreta within 13 days following administration, with 75% of the dose recovered in urine and 21% in faeces. 76% of the total recovery was within 24 h after dosing and 89% of the total recovery was within 48 h after dosing. Only 1.6% of the dose was recovered in urine as parent drug.

Metabolism

The *in vitro* metabolism was evaluated in human liver microsomes (HLM) and recombinant human enzymes expressing CYP450 (CYP1A1, CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, CYP3A4, and CYP3A5) and UGT (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B15, and UGT2B17) enzymes.

Based on inhibition and correlation studies UGT1A9 was identified as the main enzyme metabolising dapagliflozin. The formation rate for dapagliflozin 3-O-glucuronide (m15), the predominant human *in vivo* metabolite, by human recombinant UGT1A9 was ~100-times greater than that observed with any other UGT tested, and the formation of dapagliflozin 3-O-glucuronide correlated with UGT1A9 activity in a panel of human liver microsomes (study DCN 930034845). Niflumic acid (potent UGT1A9 inhibitor), mefenamic acid (UGT1A9 and 2B7 inhibitor), propofol (UGT1A9 substrate) inhibited m15 formation in both recombinant UGT1A9 and pooled HLM. In experiments with a bank of microsomes isolated from 15 individual donors, significant correlation was observed between m15 formation and glucuronidation of the UGT1A9 substrate propofol. No significant correlation was found between m15 formation and formation of conjugates of known UGT1A1 substrates, such as estradiol, EE and bilirubin, which further confirms that the formation of m15 is not catalyzed by UGT1A1. UGT2B7 and UGT2B4 exhibited catalytic activity with respect to the formation of a second minor glucuronide, dapagliflozin 2-O-glucuronide (m10).

The rate of dapagliflozin metabolism was investigated in human liver, kidney, and intestine microsomes supplemented with UDPGA. The formation of dapagliflozin 3-O-glucuronide was more rapid in microsomes from kidney than in microsomes from either liver or intestine (formation rates of 184, 60.8, and 1.69 pmol/minute/mg protein, respectively). In human kidney microsomes, the intrinsic clearance (Vmax/Km) resulting from formation of dapagliflozin 3-O-glucuronide (1.66 μL/minute/mg protein) was much more rapid than that resulting from formation of dapagliflozin 2-O-glucuronide (0.0173 μL/minute/mg). The formation of dapagliflozin 2-O-glucuronide was more rapid in liver microsomes than in either kidney or intestine microsomes (formation rates of 2.80, 1.34, and 0.81 pmol/minute/mg protein, respectively). These tissue differences are consistent with the higher expression of UGT1A9 (the enzyme principally responsible for the formation of dapagliflozin 3-O-glucuronide) in human kidney relative to human liver, and the higher expression of UGT2B7 (the enzyme principally responsible for the formation of dapagliflozin 2-O-glucuronide) in human liver relative to human kidney.

The metabolism of dapagliflozin was investigated in 6 healthy male human subjects following a single oral dose of [^{14}C]dapagliflozin 50 mg in solution (study MB102006). Plasma prepared from blood collected at 1, 4, and 12 hours after dosing and urine and faeces collected from 0 to 312 hours after dosing were analyzed for metabolites.

Dapagliflozin 3-O-glucuronide was the predominant drug-related component in human plasma, accounting for 42% [based on AUC(0-12 h)] of total plasma radioactivity, similar to the 39% contribution by parent drug. No other metabolite detected in human plasma constituted >5% of plasma radioactivity.

Dapagliflozin was extensively metabolized in humans with 73.7% of the dose being recovered as metabolites (72.0 and 1.65% in urine and faeces, respectively) and 16.6% of the dose being recovered as unchanged parent compound (1.2 and 15.4% in urine and faeces, respectively). The metabolic routes included glucuronidation (m15, m10, m13), dealkylation (m8), and oxidation at various positions of the molecule (m12). Combinations of these reactions produced desethyl dapagliflozin glucuronides. Approximately 9% of the dose underwent oxidative metabolism (~ 29% of the oxidative metabolites were also glucuronidated) and ~ 66% of the dose underwent direct glucuronidation. Dapagliflozin 3-O-glucuronide (m15) constituted 60.7% of the dose (all recovered in urine); the only other metabolite representing > 5% of the dose was dapagliflozin 2-O-glucuronide (5.4%) (m10).

Hence, based on *in vitro* and *in vivo* data, glucuronidation is the main elimination pathway with dapagliflozin 3-O-glucuronide being the main human metabolite and UGT1A9 the main metabolising enzyme.

UGT1A9 is preferentially expressed in human kidney, and *in vitro* data indicate that dapagliflozin 3-O-glucuronide is formed in both kidney and liver. Hence, formation of dapagliflozin 3-O-glucuronide in the kidney may play an important role in the disposition of dapagliflozin. While the precise relative contribution of renal versus hepatic glucuronidation of dapagliflozin in humans is not known, the impact of severe hepatic impairment and severe renal impairment (67 and 87% higher AUC parameters compared to the reference populations, respectively) on the exposure of dapagliflozin are similar which is indicative of both the liver and the kidney being substantially involved in the metabolic clearance of dapagliflozin.

PK of metabolites

The main metabolite, dapagliflozin 3-O-glucuronide, has a slightly higher exposure than dapagliflozin (1.3-fold higher exposure on a molar basis) in healthy volunteers and about 2-fold higher exposure in subjects with T2DM. The *in vitro* effect is very low compared to dapagliflozin, and the metabolite will thus not contribute to efficacy. Other metabolites accounted for less than 12% of parent plasma exposure. The pharmacologically active metabolite BMS-511926 has very low plasma exposure, AUC <1% of dapagliflozin AUC and will thus not contribute to the in vivo activity of the drug.

Possible genetic polymorphism

In order to study the effects of UGT1A9 single-nucleotide polymorphisms (SNPs) on dapagliflozin clearance, a sub-study was conducted to explore the association between dapagliflozin clearance and SNP genotypes from the UGT1A9 gene. The Applicant concludes that the UGT1A9 genotyping results and the distribution of dapagliflozin clearance values suggest that UGT1A9 polymorphism does not impact the PK of dapagliflozin to any meaningful extent. The genotypes evaluated had only a small influence on dapagliflozin clearance, with differences up to 31%.

Dose proportionality and time dependencies

Dose proportionality has been evaluated over the dose range 0.1 to 500 mg after single dose administration and 2.5 to 100 mg multiple dose administration in healthy volunteers and type 2 diabetes patients. To assess the proportionality of dapagliflozin fasted doses, linear regression of log[Cmax] on log(dose) and of log(AUC) on log(dose) were performed for dapagliflozin, using a power model. The slope for Cmax was estimated to be 0.975 and for AUC 1.017 supporting dose proportional increase in exposure over the dose range 0.1-500 mg. It can be concluded that dapagliflozin displays linear pharmacokinetics. Pharmacokinetic parameters were similar on Day 7 and 14. Time of day of dosing (in the morning (AM) or in the evening (PM)) was tested as a covariate on CL/F in the population PK model development but was found not to be significant. There are no indications of time dependency in dapagliflozin pharmacokinetics.

Special populations

Pharmacokinetics in target population

MB102003 was a double-blind, placebo-controlled, randomized, parallel-group, multiple-dose study designed to provide an initial assessment of the safety, tolerability, PD, and PK of dapagliflozin in 47 diabetic subjects following once-daily administration of 5, 25, and 100-mg dapagliflozin for 14 days. Subjects taking stable doses of metformin for at least 4 weeks were maintained at that dose throughout the study. Cmax and AUC increased approximately in proportion to dose in the dose range 5 to 25 mg but slightly more than dose proportional at 100 mg.

Comparison of the exposure in study MB1002003 in T2DM patients and MB1002002 in healthy volunteers suggest similar dapagliflozin exposure in T2DM patients and healthy volunteers. This is also supported by the population PK analysis, where subject type was not statistically significant in the final model whereas other factors (renal function, body weight and gender) explained the inter-individual variability. The exposure to the main metabolite was about 40% higher in type 2 diabetes patients than in healthy volunteers.

Renal impairment

The effects of renal impairment on the PD and/or PK of dapagliflozin have been evaluated in a Clinical Pharmacology renal impairment study, in a pooled analysis of Clinical Pharmacology studies (normal renal function and mild renal impairment), and in a PPK analysis (patients with T2DM with normal renal function and mild or moderate renal impairment).

The effect of renal impairment on dapagliflozin pharmacokinetics was evaluated in T2DM patients after single (50 mg) and multiple (20 mg for 7 days) dose administration. Patients with normal renal function (GFR > 80 ml/min, n=12) or mild (GFR 50 – 80 ml/min n=8), moderate (GFR 30-50 ml/min, n=8) or severe (GFR <30 ml/min, n=4) renal impairment were included in the study. A group of healthy subjects with normal renal function (GFR > 80 ml/min, n=8) was included in the single dose part of the study. Iohexol clearance was used to determine GFR. In addition measured urinary creatinine clearance was assessed using urinary creatinine excretion (Ucr) over 24 hours and serum creatinine (Scr) measured at the 12 hour timepoint. Also creatinine clearance was estimated using the Cockroft Gault formula.

Table 6. Summary Statistics for Dapagliflozin Pharmacokinetic Parameters (20 mg Dapagliflozin Once-Daily)

Diabetic Status, Renal Function Group	Study Day	Dapagliflozin Pharmacokinetic Parameters				
		Cmax (ng/mL) Geom. Mean (CV%)	Tmax (h) Median (Min, Max)	AUC(TAU) (ng·h/mL) Geom. Mean (CV%)	CLR (mL/min) Geom. Mean (CV%)	%UR (%) Mean (SD)
Diabetic Normal	Day 4 (n=4)	249 (21)	1.00 (0.50, 1.50)	864 (11)	5.22 (38)	1.4 (0.51)
	Day 10 (n=4)	310 (22)	1.00 (0.50, 1.00)	853 (8)	6.51 (34)	1.7 (0.52)
Diabetic Mild	Day 4 (n=4)	410 (23)	1.00 (1.00, 6.00)	1428 (38)	2.37 (54)	1.1 (0.38)
	Day 10 (n=4)	358 (25)	1.00 (1.00, 1.50)	1443 (21)	2.52 (51)	1.2 (0.54)
Diabetic Moderate	Day 4 (n=6)	466 (21)	1.00 (0.50, 1.00)	1807 (31)	2.54 (71)	2.0 (2.15)
	Day 10 (n=5[a])	512 (23)	1.00 (0.50, 1.50)	2467 (37)	2.06 (77)	1.8 (1.11)
Diabetic Severe	Day 4 (n=3)	330 (6)	1.00 (0.50, 2.00)	1920 (26)	1.42 (30)	0.9 (0.43)
	Day 10 (n=3)	338 (16)	1.00 (0.50, 1.00)	2207 (27)	1.13 (19)	0.8 (0.31)

Dapagliflozin exposure is increased in patients with reduced renal impairment. Based on linear regressions of logarithmically transformed AUCtau and iohexol clearance (GFR) an about 1.3, 1.5 and 1.8-fold increase in exposure was estimated in mild, moderate and severe renal impairment, respectively. Metabolite exposure was increased about 2- and 3-fold in moderate and severe renal impairment respectively. These data support the claim that dapagliflozin metabolism via UGT1A9 to a large extent takes place in the kidney.

Compared to subjects with T2DM and normal renal function, renal glucose clearance was decreased in subjects with impaired renal function. On Day 10 renal glucose clearance was decreased by 43 %, 84% and 84%, respectively in subjects with T2DM and mild, moderate and severe renal impairment. The urinary glucose excretion over 24 h was similarly reduced. Daily 24 hour urinary glucose excretion was 85 g of glucose/day from subjects with T2DM and normal renal function and was 51, 18 and 11 g of glucose/day from subjects with T2DM and mild, moderate or severe renal impairment, respectively. Higher systemic exposures to dapagliflozin in subjects with T2DM and moderate or severe renal impairment did thus not result in a correspondingly higher renal glucose clearance or total cumulative glucose excretion in urine.

The efficacy of dapagliflozin is dependent on renal function. Forxiga is not recommended for use in patients with moderate to severe renal impairment (patients with creatinine clearance [CrCl] < 60 ml/min or estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m^2. No dosage adjustment is indicated in patients with mild renal impairment.

Hepatic impairment

The influence of hepatic impairment on dapagliflozin's PK was evaluated in a study including subjects with a wide range of hepatic impairment and a fair number of subjects with severe hepatic impairment with Child Pugh score 10 and 11. In patients with mild hepatic impairment dapagliflozin's PK was similar to the control group. Moderate hepatic impairment had only a small effect on dapagliflozin's pharmacokinetics, 36% increase in AUC. In patients with severe hepatic impairment with Child Pugh score 10-11, the mean increase in dapagliflozin exposure was 67%. Patients at the higher end of Child Pugh class C (score 12-15) were not included in the study and it cannot be excluded that they may have a larger increase in dapagliflozin exposure. No dose adjustment in patients with mild or moderate hepatic impairment is necessary. However in patients with severe hepatic impairment, a lower starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg.

Gender and race

The estimates of difference in exposure between male and female patients were consistent between the pooled analysis of Clinical Pharmacology studies and the population PK analysis. AUC is about 22% higher in females than in males. The difference in AUC between White, Blacks and Asians were <11%. No dose adjustment is therefore necessary.

Weight

In the pooled analysis of clinical pharmacology studies weight had an influence on dapagliflozin exposure resulting in lower exposure in heavy patients and higher exposure in low-weight patients. Based on this analysis, a subject weighing 140 kg is expected to have 25% lower AUC than a subject weighing 90 kg (mean weight in phase 3 population) and a subject weighing 50 kg 20% higher AUC and 40% higher Cmax. The differences in exposure over the weight range 50-140 kg are not large enough to warrant a dose adjustment.

Elderly population

There is no clinically meaningful increase in exposure based on age alone in subjects up to 70 years old. However, an increased exposure due to age-related decrease in renal function can be expected. There are insufficient data to draw conclusions regarding exposure in patients > 70 years old.

Paediatric population

Pharmacokinetics in the paediatric population have not been studied.

Pharmacokinetic interaction studies

In vitro

Studies to evaluate the potential of dapagliflozin and the main metabolite to inhibit P-gp and the renal uptake transporters hOCT2, hOAT1 and hOAT3 and the potential for dapagliflozin to inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 and induce CYP1A2, CYP2B6 and CYP3A4 were conducted *in vitro*.

There were no sign for competitive inhibition of CYP isoenzymes or P-gp or mechanism-based inhibitor of CYP450 isoenzymes or induction of CYP1A2, CYP2B6 or CYP3A4 and only weak inhibition of hOAT3 (IC_{50} 33 µM). This is however not likely to be clinically relevant at therapeutic concentrations (Cmax of dapagliflozin and dapagliflozin 3-O-glucuronide at 10-mg dapagliflozin daily 0.49 and 0.56 µM, respectively). The potential for dapagliflozin to affect the metabolism of other UGT1A9 substrates has not been specifically investigated. The applicant claimed that an interaction is unlikely given the low affinity of dapagliflozin to UGT1A9. Additional *in vitro* studies were submitted with the responses to the D120 LOQ. These showed that dapagliflozin is not a substrate for OCT2, OAT1, OATP1B1 and OATP1B3 and had a Km value for transport via OAT3 of >100 µM. Hence clinically relevant drug interactions via inhibition of these transporters are not expected.

In vivo

In vivo interaction studies were conducted with metformin, pioglitazone, sitagliptin, glimepriride, voglibose, hydrochlorothiazide, bumetanide, valsartan, simvastatin, digoxin, warfarin and rifampicin. No clinically relevant interactions were observed. Rifampicin decreased dapagliflozin AUC by 22%. Dapagliflozin increased AUC of simvastatin by 19% and simvastatin acid by 31%.

Based on the dapagliflozin PK characteristics, there is a potential for clinically relevant interactions with inhibitors and inducers of UGT1A9. Potent *in vivo* inhibitors of UGT1A9 seem to be rare. The Applicant submitted during the evaluation an *in vivo* interaction study with an inhibitor of UGT1A9. Co-administration of the UGT1A9 inhibitor mefenamic acid under steady state conditions with a single dose of dapagliflozin resulted in a 55% increase in dapagliflozin AUCt, 22% reduction in dapagliflozin 3-O-glucuronide AUC and an increase in urine excretion of glucose.

2.4.3. Pharmacodynamics

The pharmacodynamics of dapagliflozin was evaluated in 8 phase-I studies. Potential PD interactions were evaluated in 4 additional studies. A further study aimed at investigating dapagliflozin's effect on QT interval.

Mechanism of action

Dapagliflozin is a selective and orally-active inhibitor of the human renal sodium glucose co-transporter type 2 (SGLT2), the major transporter responsible for renal glucose re-absorption. Dapagliflozin lowers plasma glucose by inhibiting the renal re-absorption of glucose in the proximal tubule, thereby promoting its urinary excretion. Dapagliflozin's mechanism of action is dependent on glomerular filtration rate. The absence of complete inhibition of renal glucose re-absorption may be the result of the action of uninhibited SGLT2 or other tubular transport mechanisms such as SGLT1. When SGLT2 is inhibited by dapagliflozin, the amount of glucose excreted in the urine is dependent on the filtered glucose load, which is the product of glomerular filtration rate and serum glucose concentration. As a consequence, even if glomerular filtration rates are comparable, higher amounts of glucose are excreted in the urine by subjects with T2DM compared to healthy subjects.

Primary and Secondary pharmacology

Primary pharmacology

In healthy subjects and in subjects with T2DM, an increase in the amount of glucose excreted in the urine was observed following the administration of dapagliflozin doses ≥ 0.3 mg.

The change from baseline in the amount of glucose excreted over 24 hours post dapagliflozin dosing was higher for a given dapagliflozin dose in subjects with T2DM compared to healthy subjects. This finding was expected since subjects with T2DM with normal renal function have a higher amount of glucose filtered by the kidney due to their higher systemic glucose concentrations. Dapagliflozin exhibited similar PD properties in Japanese and US- based subjects.

In subjects with T2DM, dapagliflozin treatment at 10 mg/day for 12 weeks was associated with a mean urinary glucose excretion of 68 g/day and maximal increase in excretion was observed at doses ≥ 20 mg/day (85 g of glucose/day). Doses of dapagliflozin higher than 20 mg resulted in an increase in the duration of glucose excretion into the urine without further increase in the 24 hour post-dose period. At a dose of 10 mg dapagliflozin QD, the rate of urinary glucose excretion at steady-state was constant over 24 h indicating that the proposed dose of 10 mg is equally effective over the entire dosing interval and that once daily dosing of 10 mg dapagliflozin is appropriate. The 10 mg dose is also supported by population-based integrated modelling and simulation analysis. The modelling approach is considered adequate and allows successful assessment of efficacy, estimated as effect on FPG and HbA1c for different doses. The selected dose was found to maximize the efficacy of dapagliflozin and is supported by the modelling outcomes.

The steady-state 24 h urinary glucose excretion was highly dependent on renal function (e.g. 85, 51, 18 and 11 g of glucose/day were excreted in T2DM subjects with normal, mildly, moderately or severely impaired renal function, respectively).

Findings from the PD studies suggest that SGLT2 activity is not up regulated in response to dapagliflozin treatment in subjects with T2DM over the course of 2 weeks and indicate that an increase in glucose excretion leads to reduced filtered glucose loads in hyperglycaemic subjects following improved short-term glycaemic control, which in turn may result in lower amounts of glycosuria over time.

By promoting urinary glucose excretion, dapagliflozin results in osmotic diuresis and an increase in urinary volume. In subjects with T2DM, urinary volume increases were sustained at 12 weeks (approximately 375 mL/day). The increase in urinary volume was associated with a small and transient (2-3 days) increase in urinary sodium excretion that was not associated with changes in serum sodium concentrations. In addition, following administration of 10 mg dapagliflozin/day for 7 days to healthy subjects, urinary uric acid excretion was increased transiently (3-7 days) accompanied by a slight reduction in mean serum uric acid concentration (up to a 2 mg/dL, reduction after 7 days). No apparent increase in urinary calcium excretion after SD or MD of dapagliflozin was observed but day-to day variability of daily Ca excretion was high. No relevant effects of dapagliflozin on serum chemistries (sodium, potassium, chloride, calcium, magnesium, phosphorus, bicarbonate, creatinine, BUN) and osmolality was observed in healthy volunteers.

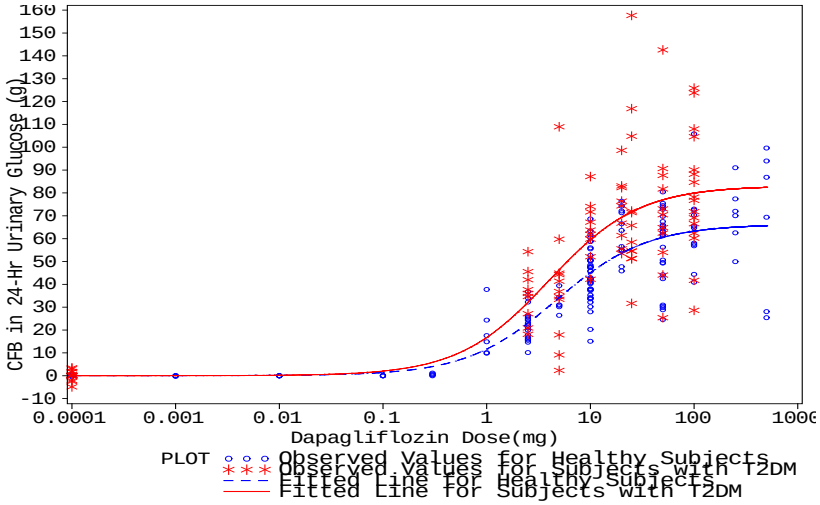
Secondary pharmacology

Exposure response

The exposure response was evaluated before phase III using data from phase I and II studies in healthy volunteers and T2DM patients covering a wide range of doses evaluating the relationship between different exposure measures (dose, AUC, Cmax) and PD (change from baseline in 24 hr urinary glucose amount excreted and renal glucose clearance). Moreover, a population-based exposure response analysis was conducted using data from the two phase III monotherapy studies, where the relationship between the estimated steady state AUCss (obtained using the final PPK model by calculating from the individual maximum a posterior (MAP) Bayesian estimates) after dapagliflozin or placebo administration and FPG or HbA1c response up to Week 24 was evaluated.

The relationship between exposure and change from baseline in 24-hr urinary glucose amount excreted was described by an E_{max} model where E_{max} was estimated to be 83 (95% CI 72-89) g in T2DM patients. ED_{50} was estimated to be 3.97 (95% CI 2.3-5.6) g in the model using dose and 198 (95%CI 102-294) ng*h/ml in the model using AUC as exposure measure. Based on this model, the 10 mg dose is expected to result in about 75% of the maximum effect of dapagliflozin on 24 h urinary glucose excretion.

Figure 2. Scatter Plot and Fitted Line of Change from Baseline in 24-hr Urinary Glucose Amount vs Dapagliflozin Dose in Healthy Subjects and Subjects with T2DM



The population exposure response model for FPG over time comprised in an additive manner a placebo model and a drug effect model. The placebo effect was approximated by a model that assumed a linear decrease of FPG from baseline as a function of baseline FPG and time within the 24 week treatment period. An indirect response model in which dapagliflozin AUCss was assumed to increase the elimination rate of FPG from the plasma pool via an Emax model described the FPG concentration-time profile over the 24 week treatment period. The maximal effect (Emax) and the dapagliflozin AUC achieving half maximal response (EC50) were estimated. An indirect response model described the effect of FPG on HbA1c over time. The model assumes that changes in baseline HbA1c response from the placebo effect or dapagliflozin exposure are due to changes in FPG response, given individual baseline HbA1c. The formation and elimination rates of HbA1c were estimated. For a typical subject with baseline FPG of 160 mg/dL and baseline HbA1c of 8.2% receiving dapagliflozin 10 mg QD, the model predicts about 25.0 mg/dL [5th, 95th percentiles: 11.4 mg/dL, 69.0 mg/dL] decrease of FPG and 1.26% [5th, 95th percentiles: 1.06%, 1.41%] decrease of HbA1c from baseline at the end of 24 week treatment period with 10 mg QD dapagliflozin. For the effect on FPG, the estimated EC_{50} in AUCss in a typical population is 147 ng.hr/mL [95% CI: 72.1 ng.hr/mL, 222 ng.hr/mL], corresponding to the AUCss level of a 3.37 mg [95% CI: 1.65 mg, 5.08 mg] dose QD. Dose levels of 1-, 2.5-, 5- and 10-mg QD were predicted to give dapagliflozin exposure equivalent to EC24.6, EC43.4, EC60.0, and EC74.7, assuming an Emax model at steady state and no placebo effect. Hence, the results from this analysis are consistent with the previous analysis of the relationship between exposure and 24 h urinary glucose excretion. The model predicts that efficacy at the 10 mg qd dose is about 75% of the theoretical maximum effect of dapagliflozin on FPG, which from an efficacy point supports the selected dose.

The relationship between dapagliflozin exposure and an increase in haematocrit (HCT) was described by an empirical indirect response model in which dapagliflozin exposure was assumed to increase the formation rate of HCT in the blood pool via an Emax model. The increase over baseline in haematocrit at the 10 mg QD dose level was predicted to be 2.44% [5th and 95th percentiles: 0.432%, 3.38%].

Pharmacodynamic interactions

In healthy subjects 7 days of dapagliflozin administration increased 24-h urinary sodium by about 35%. Bumetanide alone had a larger effect (increasing by 108%). The combination of dapagliflozin and bumetanide had a transient (about 3 days) additive effect (maximum increase by 122%). However, renal sodium loss may be even higher in patients with T2DM than in healthy volunteers due to the expected more pronounced dapagliflozin-induced diuresis. The combined administration of dapagliflozin and a loop diuretic such as bumetanide may present a certain risk for clinically-meaningful electrolyte disturbances. In addition, the combination of dapagliflozin and bumetanide led to more pronounced (increase by 1.164 l on the first day) and prolonged (9 days) renal fluid loss than either drug alone. This increase is considered substantial and the effect is maybe even more pronounced in patients with T2DM due to higher glucose load and consequently more pronounced osmotic diuresis. Particularly elderly patients with an already physiologically decreased sense of thirst may be at increased risk for dehydration. Bumetanide transiently (10 days) decreased dapagliflozin-induced urinary glucose excretion which is not considered clinically relevant. The results also suggested that dapagliflozin may have modest effects upon systolic BP (up to 12 mm Hg reduction) alone or in combination with bumetanide in normotensive subjects.

There was a greater than additive increase in 24-h urinary Na+ excretion when single doses of dapagliflozin and hydrochlorothiazide (HCTZ) were co-administered, compared to either treatment administered alone. This may trigger/cause dehydration by leading to increased sodium loss and hyponatraemia with sequelae such as insufficient water intake, increase in haematocrit and potentially increased risk of thrombosis, particularly in elderly patients with an already decreased sense of thirst. Hypotension / hypovolaemia / dehydration were numerically higher in subjects that received a diuretic (either loop or thiazide) in combination with an ACE-inhibitor or ARB and received dapagliflozin compared with those that received placebo. A respective special warning has been introduced in the product information (i.e. section 4.4 of the SmPC), as well as a respective information in sections "Interactions" (i.e. section 4.5 of the SmPC) and "Undesirable effects" (i.e. section 4.8. of the SmPC).

The mean amount of glucose excreted in the urine over 24 h following administration of dapagliflozin alone was not markedly affected (-10 to 16%) by rifampicin co-administration and, based on this PD endpoint and modest PK effects of rifampicin on dapagliflozin (decrease of 22% in exposure), no dose adjustment of dapagliflozin is proposed when it is co-administered with potent CYP inducers.

The PD effect of warfarin (the prothrombin time-International Nomalized) was not affected by co-administration of dapagliflozin.

Thorough QT/TQc study

The effect of dapagliflozin (SD of 20 mg and 150 mg) on the QTcX interval of healthy subjects was investigated in a study primarily aiming at the population corrected QTc-interval [QTcX]. Moxifloxacin (SD of 400 mg=) and placebo were the controls. The results of this adequately conducted study indicate that dapagliflozin, and in particularly the proposed dose for marketing (i.e. 10 mg qd), has no clinically relevant influence on human cardiac repolarisation.

2.4.4. Discussion on clinical pharmacology

A comprehensive clinical pharmacology programme was submitted to characterise the PK and PD profile of dapagliflozin.

Overall, the pharmacokinetics of dapagliflozin have been well documented. The absorption, distribution, metabolism and elimination of dapagliflozin have been adequately characterised. The effects of intrinsic factors on dapagliflozin PK have been sufficiently characterised.

The Applicant considered that only a ≥ 50% lower mean dapagliflozin systemic exposure and a > 100% higher (i.e., 2-fold) dapagliflozin exposure is potentially clinically meaningful, and that differences in exposure in different sub-populations within this range should not warrant a dose adjustment. The proposed 2-fold limit was further justified by the Applicant during the evaluation. The exposure response modelling suggests that a 50% reduction in exposure would result in a decrease in efficacy relative to maximum efficacy from 75% at the 10 mg dose level to 60% at the 5 mg dose level. Hence, gender, race, weight, age up to 70 years, mild renal impairment and mild to moderate hepatic impairment as well as the potential for UGT1A9 polymorphism seem not to have a clinically relevant influence on dapagliflozin's exposure. In patients with severe hepatic impairment with Child Pugh score 10-11, the mean increase in dapagliflozin exposure was 67%. Patients at the higher end of Child Pugh class C (score 12-15) were not included and it cannot be excluded that they may have a larger increase in dapagliflozin exposure. Given the remaining uncertainty that some patients may have even higher exposure increase than the 67% observed on average in patients with severe hepatic impairment, a starting dose of 5 mg is recommended in patients with severe hepatic impairment.

A number of *in vivo* interaction studies have been conducted (with metformin, pioglitazone, sitagliptin, glimepriride, voglibose, hydrochlorothiazide, bumetanide, valsartan, simvastatin, digoxin, warfarin and rifampicin). The interaction programme was based mainly on drugs likely to be co-administered in the target patient population and not on a mechanistic basis with regard to dapagliflozin's PK characteristics and *in vitro* inhibition potential. From a mechanistic perspective, *in vitro* studies did not reveal any potential for clinically relevant interaction *in vivo* with CYP450 isoenzymes, or the transport proteins OCT2, OAT1, OAT3, OATP1B1 and OATP1B3.

Based on dapagliflozin's PK characteristics, there is a potential for clinically relevant interactions with inhibitors and inducers of UGT1A9. Potent *in vivo* inhibitors of UGT1A9 seem to be rare. The UGT1A9 inhibitor mefenamic acid caused partial inhibition of UGT1A9 resulting in a 55% mean increase in dapagliflozin AUC. This interaction is not considered clinically relevant. Theoretically a larger effect could be expected by a more potent inhibition of UGT1A9. However, more potent clinically used UGT1A9 inhibitors are not known. Hence, clinically relevant interactions with UGT1A9 inhibitors are not expected.

There are few examples of induction of UGT1A9 in the literature and the mechanism for induction is not fully clear. It therefore seems difficult to predict or evaluate the potential for clinically relevant interactions with UGT1A9 inducers. Concomitant administration of rifampicin, a metabolizing enzyme inducer, for 6 days resulted in a weak reduction in dapagliflozin AUC, which is not considered clinically relevant. The effect may be slightly larger upon longer co-administration (as maximum induction probably has not been reached by Day 6). However, a clinically relevant interaction seems unlikely.

The pharmacodynamics of dapagliflozin was evaluated in 8 phase-I studies. Potential PD interactions were evaluated in 4 additional studies. A further study aimed at investigating dapagliflozin's effect on QT interval.

The steady-state 24-h urinary glucose excretion is highly dependent on renal function and serum glucose concentrations. The minimal effective dose was determined to be 0.3 mg qd and maximal urinary glucose excretion was observed at doses ≥ 20 mg/day in subjects with T2DM and normal renal function. At a dose of 10 mg qd, the rate of urinary glucose excretion at steady-state was constant over 24 h, indicating that this dose is equally effective over the entire dosing interval and that once daily dosing of 10 mg dapagliflozin is appropriate. The 10 mg dose is also supported by population-based integrated modelling and simulation analysis.

Concerns arose from the finding of increased renal sodium and fluid loss, particularly when dapagliflozin is co-administered with diuretics. Elderly patients may be especially vulnerable to relevant dehydration and potential sequelae. Adequate warnings have been included in the SmPC in addition to the recommendation to reduce the dose when dapagliflozin is given in combination with loop diuretics. No significant effect on urinary calcium was observed in the phase I and phase II studies but variability in daily calcium excretion was rather high.

Dapagliflozin did not show a clinically relevant influence on human cardiac repolarisation.

Dapagliflozin with or without co-administered loop diuretics may be associated with modest BP-reducing effects, which would be interesting to evaluate in hypertensive patients.

2.4.5. Conclusions on clinical pharmacology

Overall, the pharmacokinetics of dapagliflozin has been well documented. Dapagliflozin has a pharmacokinetic profile with low potential for interactions and moderate influence of intrinsic factors on its PK. Exposure differences based on gender, age (up to 70 years), weight, race, mild renal impairment, mild and moderate hepatic impairment, UGT1A9 genotype, concomitant administration of UGT1A9 inhibitor were estimated to be on average less than 40% and were not considered clinically relevant. In severe hepatic impairment dapagliflozin's exposure was on average increased by 67%, and it cannot be excluded that some patients may have more than a 2-fold increase in exposure. Hence, an (initial) dose reduction to 5 mg is recommended in patients with severe hepatic impairment.

The pharmacodynamics of dapagliflozin indicates that this compound is potentially efficient in the treatment of diabetes. The pharmacodynamics of dapagliflozin is considered to be adequately characterised by the studies performed in phase I, particularly for white/black American subjects (healthy and with T2DM). The results of these studies are appropriately reflected in the SmPC. The dependence on sufficient GFR to obtain an effect of dapagliflozin has implications on the target population.

Pharmacodynamic interactions with diuretics have been identified with an increased risk of hypotension/hypovolaemia and adequate warnings have been included in the SmPC.

2.5. Clinical efficacy

2.5.1. Dose response studies

Dose selection for the phase III clinical program was based primarily on the results of two pivotal dose response trials. In addition, 1 supportive trial was conducted. The primary endpoint was HbA1c at 12 weeks.

Study Description/ Current Status	Subject population	N per Group/ N treated with dapagliflozin/ Total	Duration	Treatment Groups/ Background therapy	Rescue Treatment	Primary efficacy assessment
MB102008 Monotherapy vs placebo/ Completed	Drug-naïve subjects with HbA1c ≥ 7.0% - ≤ 10.0%	47-59/279/389	12 weeks	7 groups: dapagliflozin 2.5, 5, 10, 20 or 50 mg vs placebo Additional group: metformin XR 750/1500 mg	None	Superiority: Change in HbA1c at 12 weeks vs placebo
D1692C00005 Monotherapy vs placebo/Completed	Japanese subjects with inadequate glycemic control with HbA1c ≥7.0% - ≤10.0%)	52-59/225/279	12 weeks	5 groups: dapagliflozin 1, 2.5, 5, or 10 mg or placebo	None	Superiority: Change in HbA1c at 12 weeks vs placebo
MB102009 Add-on to insulin vs placebo Completed	Subjects on insulin sensitizer (metformin and/or TZD) and insulin with HbA1c ≥ 7.5% - ≤10.0%)	Cohort 1: single blind, unrandomized 4/4/4 Cohort 2: double-blind: 23-24/48/71	12 weeks	dapagliflozin 20 mg (to determine insulin dose level for Cohort 2) 3 groups: dapagliflozin 10 or 20 mg in morning vs placebo Background therapy: 50% original insulin dose +metformin or TZD	Insulin up-titration	Superiority (Exploratory) : Change in HbA1c at 12 weeks vs placebo

The dapagliflozin doses for the Phase IIb studies MB102008 and MB102009 were selected based on findings from the Phase I and IIa program. Doses with acceptable safety margins were selected (2.5 mg to 50 mg) based on results from nonclinical and clinical data: in MB102008, dapagliflozin doses 2.5 mg, 5 mg, 10 mg, 20 mg, and 50 mg were included, whereas in study MB102009 the 10 mg and 20 mg doses were included. Based on a 12.5 hour half life, dapagliflozin was dosed once-daily.

The dapagliflozin doses 1 mg, 2.5 mg, 5 mg and 10 mg were chosen for the study D1692C00005, the Japanese Phase IIb study. PK and PD results were comparable between US and Japanese subjects in Phase I studies. The dose range of 2.5 to 10 mg was included to match the global Phase III doses. In addition, the 1 mg dose was included in this study to evaluate the lower end of the dose interval. The Applicant's justification for the selection of doses brought on to the phase III program is acceptable and supported by the results of the Phase I and II studies.

Study populations differed somewhat between the Phase II studies with patients in study MB102008 being more obese and with diabetes of shorter duration than in study D1692C00005. Subjects included in study MB102009 had more advanced diabetes.

Study MB102008

There was a significant reduction in HbA1C from baseline to Week 12 in all dapagliflozin groups as compared with placebo. All dapagliflozin doses were effective at lowering HbA1C, but no log-linear dose response relationship (secondary objective) was demonstrated within the dose range of 2.5 mg to 50 mg (p-value for trend = 0.4139).

There was a significantly greater reduction from baseline to Week 12 in FPG in all dapagliflozin treatment groups as compared with placebo, except for the dapagliflozin 2.5 mg group. The decrease in FPG appeared to be dose related. A reduction in postprandial glucose AUC (exploratory objective) was also achieved in the dapagliflozin treatment groups compared with the placebo group, but did not show dose dependence.

Change in total body weight was assessed as an exploratory variable. Reductions in total body weight at Week 12 were observed across all treatment groups; the reduction was larger in the dapagliflozin-treated groups than in the placebo group and was greatest in the dapagliflozin 20 mg and 50 mg treatment groups. The placebo-corrected mean body weight reductions were -1.52 kg, -1.38 kg, -1.54 kg, -2.25 kg and -2.24 kg in the dapagliflozin 2.5 mg, 5 mg, 10 mg, 20 mg and 50 mg treatment groups, respectively.

Study D1692C00005

Statistically significant greater mean reductions in HbA1c from baseline to Week 12 were achieved in all dapagliflozin groups compared with the placebo group. The greatest reductions were observed in the dapagliflozin 5 mg and 10 mg groups (at least 0.5% placebo-corrected reduction).

Statistically significant greater reductions in FPG were also achieved in all dapagliflozin groups compared with placebo and the effect appeared to be dose-dependent.

Numerically greater proportions of subjects achieved therapeutic glycaemic response, defined as HbA1c <7%, in the dapagliflozin 2.5 mg, 5 mg and 10 mg treatment groups, though the differences versus placebo were not statistically significant.

Study MB102009

This study explored the feasibility of lowering the insulin dose before starting dapagliflozin treatment in subjects with T2DM treated aggressively but not controlled on combination antihyperglycaemic therapy with metformin and/or TZD and insulin. No formal statistical hypothesis testing was performed. As per protocol, TDDI was reduced by 50% prior to treatment but could be up-titrated to achieve glycaemic control according to pre-specified criteria. Up-titration of TDDI occurred in 4/23 subjects in the placebo group and in 4/48 subjects in the dapagliflozin groups.

Dapagliflozin 10 mg and 20 mg appeared to be effective in lowering HbA1c. In spite of a reduction in the insulin dose by 50% at baseline, subjects in the placebo arm experienced little change in HbA1c, an outcome that likely reflects the relatively severe insulin resistance in these subjects and perhaps improved compliance with diet and lifestyle as a result of study participation. An apparent dose-dependent mean reduction from baseline in FPG from baseline at Week 12 versus placebo was observed.

Numerically greater mean reductions from baseline in body weight at Week 12 were observed in each dapagliflozin-treated group compared to the placebo group. Mean weight reduction in the dapagliflozin treatment groups appeared to be progressive and continuous through Week 12.

The strategy tested was not used in the pivotal add-on to insulin study.

Rationale for dose selection in the Phase III program

Doses ranging from 1 mg to 10 mg were selected for the phase III program. Higher doses were associated with more adverse events, i.e. hyperphosphataemia and genitourinary infections, and thus the benefit risk for these doses was considered negative. This strategy was considered acceptable by the CHMP and is also in line with the Scientific Advice recommendations.

2.5.2. Main studies

General issues applying to all studies

Methods

Study Participants

Males and females ≥18 years of age were eligible, and there was no upper age limit unless metformin was a background therapy, in which case the upper age limit was 77 years (due to the increased risk of renal impairment). In study D1690C00012, which included assessments of bone mineral density, post-menopausal women aged ≥55 and ≤75 years and men aged ≥30 and ≤75 years were eligible to avoid factors that could confound bone mineral density assessments.

Subjects with BMI ≥45 kg/m2 were excluded from the majority of Phase III studies because of the potential for pathological causes of obesity in this population.

Subjects with mild and moderate renal impairment were included in the Phase III studies; because the efficacy of dapagliflozin was expected to be reduced in subjects with severe renal impairment (eGFR <30mL/min/1.73m2), these patients were excluded. One study (MB102029) exclusively enrolled subjects with moderate renal impairment.

Subjects at advanced stages of T2DM, such as those with chronic complications of T2DM (retinopathy, neuropathy, mild nephropathy, or chronic CV disease) were generally not excluded. Subjects with significant hepatic disease, unstable cardiovascular disease including Class III and IV heart failure, pregnant and breastfeeding women and paediatric subjects were excluded.

Eligibility criteria for the Phase III studies were selected to include inadequately controlled T2DM subjects with a wide range of baseline HbA1c values. Studies MB102021 and MB102034, the initial combination therapy studies, enrolled subjects with HbA1c ≥7.5 % and ≤12.0%. Additionally, study MB102013 included open label dapagliflozin treatment arms (without a placebo control) enrolling subjects with baseline HbA1c ≥10.1 and < 12.0%.

The inclusion and exclusion criteria were considered appropriate. Due to expected lack of efficacy, patients with severe renal impairment have been excluded from the phase III studies. In one study (MB 102029) specifically patients with moderate renal impairment were investigated. Patients with more severe cardiovascular disease were excluded from the studies. Furthermore, patients were to have normal calcium levels at inclusion. Due to the use of metformin in many of the studies, the possibility to include elderly patients was limited.

Treatments

The dapagliflozin doses administered in all of the Phase III studies are summarized in the table below. The dapagliflozin 2.5 mg, 5 mg, and 10 mg doses were administered as fixed daily doses in four of the 11 Phase III studies (MB102013 [Group 1], MB102014, D1690C00005, and D1690C00006). Study MB102013 compared once-daily dosing of dapagliflozin with either the morning (AM) or evening (PM) meal. Other studies specified either morning or evening administration of study drug, or did not specify the timing of drug administration.

Table 7. Summary of dapagliflozin doses studies in the Phase IIb and Phase III studies in subject with T2DM

Therapeutic setting	Study number	Study description	Dapagliflozin doses (mg)					
			1	2.5	5	10	20	50
Phase 2b								
Monotherapy	MB102008	Monotherapy vs placebo		X	X	X	X	X
	D1692C00005	Monotherapy vs placebo	X	X	X	X		
Add-on combination	MB102009	Add-on to insulin (pilot study)				X	X	
Phase 3								
Monotherapy	MB102013	Monotherapy vs placebo		X	X	X		
	MB102032	Low-dose monotherapy vs placebo	X	X	X			
Add-on Combination	MB102014	Add-on to metformin IR vs placebo		X	X	X		
	D1690C00005	Add-on to SU vs placebo		X	X	X		
	MB102030	Add-on to TZD vs placebo			X	X		
	D1690C00006	Add-on to insulin vs placebo		X	X	X		
Active Comparator Add-on Combination	D1690C00004	Add-on to metformin IR vs active comparator		X →	X →	X		
Active Comparator Initial Combination	MB102021	Initial combination with metformin XR vs control and monotherapy			X			
	MB102034	Initial combination with metformin XR vs control and monotherapy				X		
Body Weight and Body Composition	D1690C00012	Add-on to metformin IR vs placebo				X		
Diabetes and Moderate Renal Impairment	MB102029	Monotherapy or add-on combination therapy (any combination except metformin) vs placebo			X	X		

SU = sulfonylurea; TZD = thiazolidinedione
Arrows indicate dose titration.

Study D1690C00004, the active comparator study, was the only study to implement a dose-titration procedure (2.5 mg ->5 mg -> 10 mg) to match the practice of gradual up-titration recommended for the active comparator, glipizide.

Subjects who failed to meet pre-specified glycaemic targets (which became more stringent as the trials progressed) received rescue medication, which varied from study to study, and included metformin, pioglitazone, rosiglitazone, sitagliptin, acarbose, and SU. In study D1690C00006, the add-on to insulin study, and partially in study MB102029 (in subjects with moderate renal impairment) rescue consisted of insulin up titration. In study D1690C00004, the active comparator study, there was no rescue medication.

The Phase III program thus explored a range of doses. The choice of doses in the different settings has been adequately justified.

Objectives

All Phase 3 studies, except the active comparator study (study D1690C00004) and the body composition study (study D1690C00012), were aimed at showing superiority with regards to HbA1c for dapagliflozin compared to placebo at 24 weeks. The active comparator study aimed at showing non-inferiority with regards to HbA1c for dapagliflozin compared to glipizide at 52 weeks. A predefined delta of 0.35 % was chosen. The body composition study had the primary objective of showing superiority with regards to weight reduction for dapagliflozin compared to placebo at 24 weeks.

The primary objectives were endorsed by the CHMP. The chosen delta could be considered somewhat generous; however, this delta has been accepted in previous studies and was therefore considered acceptable by the CHMP.

Outcomes/endpoints

The primary efficacy endpoint in 9 of the 11 Phase 3 studies was change from baseline in HbA1c to Week 24. For Study D1690C00004, the primary efficacy endpoint was change from baseline in HbA1c to Week 52, and for Study D1690C00012, change in total body weight to Week 24.

Other efficacy endpoints evaluated include but were not limited to FPG, PPG, the proportion of subjects achieving a therapeutic response of HbA1c<7.0% (and < 6.5), and change from baseline in body weight.

D1690C00012 evaluated changes in weight as the primary endpoint, as well as changes in body composition (by DXA and magnetic resonance imaging) in overweight subjects with T2DM.

Sample size

Sample size calculations were made for all studies. The calculations are considered adequate.

Randomisation

Different randomisation procedures were used in the studies. In some of the studies a web based response system was used.

Several Phase III studies included stratified randomization to ensure adequate representation of certain patient characteristics, such as gender and background medication, and to ensure even distribution of subjects across treatment groups.

Stratification at randomization for background therapy was included in 3 Phase III studies: MB102030, D1690C00006, and MB102029. In study MB102030, the add-on to TZD study, randomization was stratified by pre-enrolment anti-hyperglycaemic therapy (Group 1: pioglitazone 30 or 45 mg/day; Group 2: other eligible therapies including diet and exercise). Randomization of subjects from Group 2 was limited to approximately 67% of the total number of subjects. In study D1690C00006, the add-on to insulin study, randomization was stratified into two groups: subjects taking OADs, and subjects not taking OADs at baseline. Subjects taking insulin plus OAD were not to exceed 60% of the total number of subjects. The following four strata were defined for study MB102029, the "renal impairment study", based on pre-enrolment therapy: insulin-based regimen, SU-based regimen, TZD-based regimen, or other regimen.

Study D1690C00012, the body weight/composition study, was stratified by gender, and neither gender was to exceed 60% of the total number of randomized subjects. Subject randomization was stratified by site in studies MB102013 and MB102032 (monotherapy studies), MB102014 (add-on to metformin study) and MB102021 and MB102034 (initial combination studies).

The randomisation procedures were considered acceptable.

Blinding (masking)

The short-term period of all studies was double-blinded. The long-term extension treatment period was site- and subject-blinded, with the exception of study MB102029, where both the short term treatment period (24 weeks) and the first long-term extension treatment period (28 weeks) were double blinded.

The blinding procedures were considered acceptable.

Statistical methods

Analysis of Covariance (ANCOVA) was used to analyze the primary and all continuous secondary endpoints. A modified logistic regression was used for dichotomous secondary endpoints (e.g. proportion of responders). The primary endpoint in each study was evaluated by comparing the difference in the adjusted mean change from baseline between the dapagliflozin treatment group(s) and the comparator group(s), adjusting for multiple treatment comparisons in most cases with Dunnett's method.

Statistical testing of secondary efficacy endpoints proceeded in a sequential manner using alpha=0.05 tests for only those treatment groups found to be statistically significant in the primary efficacy analysis (an exception to this rule is study D1690C00012 where Hochberg's method was used). For each study, the number and order of secondary endpoints was specified prior to breaking of the blind.

Missing data from the short term period were handled in main analyses using LOCF methodology, excluding data obtained after rescue (except study D1690C00004 where no rescue was used and study D1690C00012 where the primary efficacy variable was weight change). Robustness of study conclusions was evaluated with respect to the primary endpoint through sensitivity analyses by (i) including versus excluding data after rescue, (ii) using observed values versus LOCF values, (iii) employing a longitudinal model versus visit specific analyses, and/or (iv) excluding major protocol violators versus including all randomized and treated subjects. Generally, confirmatory analyses for the short-term period of studies were based on LOCF values while exploratory analyses from the short-term plus long-term periods were based on observed values.

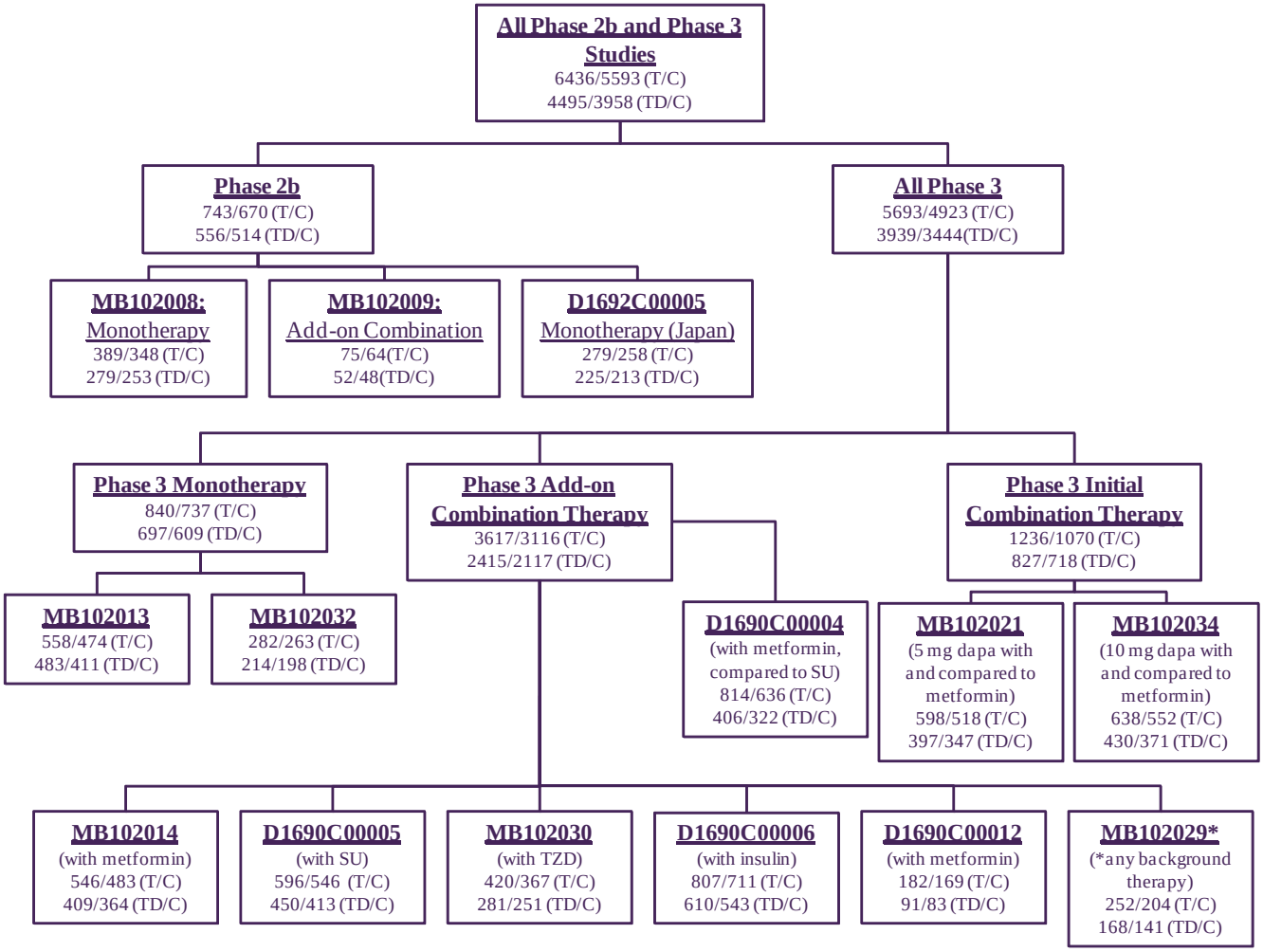
Long-term efficacy and safety of dapagliflozin was evaluated over the entire duration of the short-term combined with the long-term treatment period (and extension period if applicable). No p-values were calculated for long-term efficacy analyses as they were considered exploratory. Analyses were based on observed data without application of LOCF, to avoid carrying forward data over long periods of time. For continuous endpoints, a longitudinal repeated measures model was used.

The statistical methods used for sample size calculations and data analyses were considered adequate.

Results

Participant flow

Figure 3. Summary of subjects disposition in dapagliflozin Phase 2b and Phase 3 studies



T: treated; C: completed, TD: treated with dapagliflozin

Specific issues applying to studies MB102013 and MB102032: monotherapy studies

Studies MB102013 and MB102032 are two multicenter, double-blind, randomized, placebo-controlled, parallel group studies with the primary objective to evaluate the safety and efficacy of 3 different doses (2.5 mg, 5 mg and 10 mg for study MB102013 and 1 mg, 2.5 mg and 5 mg for study MB102032) of dapagliflozin as monotherapy in patients with T2DM who have inadequate glycaemic control with diet and exercise.

Methods

Study Participants

85 sites for study MB102013 enrolled subjects in the United States, in Canada, Mexico and Russia. Males and females with T2DM, ≥ 18 to ≤ 77 years old, who were drug naive and had inadequate glycaemic control, defined as HbA1c ≥ 7% and ≤ 10% for Group 1 and ≥ 10.1% and ≤ 12.0% for Group 2, BMI ≤ 45.0 kg/m2 at enrolment.

80 sites for study MB102032 enrolled subjects in the United States, in Canada and Latin America. Males and females with T2DM, ≥ 18 to ≤ 77 years old, who were drug naive (defined as subjects who never or < 24 weeks received antidiabetics since diagnosis) and had inadequate glycaemic control, defined as HbA1c ≥ 7% and ≤ 10, BMI ≤ 45.0 kg/m2 at enrolment.

Treatments

Study MB102013 consists of 4 periods: a qualification period (up to 14 days), a lead-in period (7 to 14 days), a short-term double blind treatment period (24 weeks) and a long-term period as follow-up (78 weeks.

Group 1: Eligible subjects were randomized to on of 3 doses of dapagliflozin (2.5 mg, 5 mg. 10 mg), administered either QAM or QPM, or to placebo treatment.

Group 2: Eligible subjects were randomized to either dapagliflozin 5 mg QAM or dapagliflozin 10 mg QAM.

Eligible subjects who completed the 24-week short-term treatment period could continue in the long-term treatment period for 78 weeks on the same blinded study medication. Subjects fulfilling the pre-defined rescue criteria were eligible to receive open-label rescue medication with metformin.

Study MB102032 consists of 4 periods: a qualification period (up to 14 days), a lead-in period (14 days ± 5 days), a short-term double blind treatment period (24 weeks ± 5 days) and a follow-up period (4 weeks ± 5 days). Eligible subjects received 1, 2.5, or 5 mg of dapagliflozin or dapagliflozin matching placebo administered daily with the morning meal during the 24-week treatment period. Subjects fulfilling the pre-defined rescue criteria were eligible to receive open-label rescue medication with metformin.

Objectives

The primary objective of studies MB102013 and MB102032 was to compare the change from baseline in HbA1c achieved with each dose of dapagliflozin (2.5 mg, 5 mg or 10 mg in study MB102013 and 1 mg, 2.5 mg or 5 mg in study MB102032, administered once daily) versus placebo after 24 weeks of oral administration of double-blind treatment.

Sample size

For study MB102013, with 67 subjects per treatment group with post-baseline measurements, there was 90% power to detect a difference in means of 0.7% between each dapagliflozin QAM dosing treatment group and the placebo group, assuming a standard deviation (SD) of 1.1%. Assuming that 5% of subjects would not have a post-baseline assessment, a total of 490 subjects (70 subjects per treatment group), with enrollment HbA1c between 7.0% to 10.0% inclusive, needed to be randomized to dapagliflozin AM dosing, dapagliflozin PM dosing or placebo.

For study MB102032, with 67 subjects per treatment group with post-baseline measurements, there was 90% power to detect a difference in means of 0.7% between each dapagliflozin treatment group (1 mg, 2.5 mg and 5 mg) and placebo, assuming a standard deviation (SD) of 1.1%. Assuming that 5% of subjects did not have a post-baseline assessment, a total of 280 subjects (70 subjects per treatment group) needed to be randomized.

Results

Participant flow

Table 8. Study MB102013: Subject disposition, short-term blind period, Group 1 AM and PM doses

	DAPA 2.5MG QPM	DAPA 5MG QPM	DAPA 10MG QPM	Total
SUBJECTS	67	68	76	485
SUBJECTS COMPLETING THE PERIOD (%)	58 (86.6)	57 (83.8)	65 (85.5)	412 (84.9)
SUBJECTS NOT COMPLETING THE PERIOD (%)	9 (13.4)	11 (16.2)	11 (14.5)	73 (15.1)
REASON FOR NOT COMPLETING THE PERIOD (%)				
LACK OF EFFICACY	0	0	0	2 (0.4)
ADVERSE EVENT	0	3 (4.4)	3 (3.9)	16 (3.3)
SUBJECT WITHDREW CONSENT	6 (9.0)	4 (5.9)	6 (7.9)	27 (5.6)
LOST TO FOLLOW-UP	3 (4.5)	2 (2.9)	2 (2.6)	18 (3.7)
POOR/NON-COMPLIANCE	0	1 (1.5)	0	3 (0.6)
ADMINISTRATIVE REASON BY SPONSOR	0	1 (1.5)	0	3 (0.6)
OTHER	0	0	0	4 (0.8)
SUBJECTS CONTINUING IN THE STUDY (%)	58 (86.6)	57 (83.8)	65 (85.5)	408 (84.1)
SUBJECTS NOT CONTINUING IN THE STUDY (%)	9 (13.4)	11 (16.2)	11 (14.5)	77 (15.9)
REASON FOR NOT CONTINUING IN THE STUDY (%)				
LACK OF EFFICACY	0	0	0	2 (0.4)
ADVERSE EVENT	0	3 (4.4)	3 (3.9)	17 (3.5)
SUBJECT WITHDREW CONSENT	6 (9.0)	4 (5.9)	6 (7.9)	29 (6.0)
LOST TO FOLLOW-UP	3 (4.5)	2 (2.9)	2 (2.6)	18 (3.7)
POOR/NON-COMPLIANCE	0	1 (1.5)	0	3 (0.6)
ADMINISTRATIVE REASON BY SPONSOR	0	1 (1.5)	0	3 (0.6)
OTHER	0	0	0	5 (1.0)

This table includes all randomized subjects who took at least one dose of double-blind study medication.
Percentages reported are based on the total number of subjects in each treatment group.
Subjects continuing in the study refers to subjects entering the long-term treatment period.

Table 9. Study MB102032: Subjects disposition, double-blind treatment period

	Number (%) of Subjects				
	PLA N = 68	DAPA 1MG N = 72	DAPA 2.5MG N = 74	DAPA 5MG N = 68	Total N = 282
Subjects completing the study	65 (95.6)	68 (94.4)	67 (90.5)	63 (92.6)	263 (93.3)
Subjects not completing the study	3 (4.4)	4 (5.6)	7 (9.5)	5 (7.4)	19 (6.7)
Reason for not completing the study					
Lack of efficacy	1 (1.5)	0	0	0	1 (0.4)
Adverse event	0	1 (1.4)	1 (1.4)	0	2 (0.7)
Subject withdrew consent	2 (2.9)	1 (1.4)	3 (4.1)	3 (4.4)	9 (3.2)
Lost to follow-up	0	0	2 (2.7)	1 (1.5)	3 (1.1)
Poor/non-compliance	0	0	1 (1.4)	1 (1.5)	2 (0.7)
Subject no longer met study criteria	0	1 (1.4)	0	0	1 (0.4)
Other	0	1 (1.4)	0	0	1 (0.4)
Subjects continuing in the study	66 (97.1)	71 (98.6)	67 (90.5)	63 (92.6)	267 (94.7)
Subjects not continuing in the study	2 (2.9)	1 (1.4)	7 (9.5)	5 (7.4)	15 (5.3)

This table includes all randomized subjects who took at least 1 dose of double-blind study medication.
Percentages reported are based on the total number of subjects in each treatment group.
Subjects continuing in the study refers to subjects entering the follow-up period.
DAPA = dapagliflozin; PLA = placebo; N = number of randomized and treated subjects

Recruitment

Study MB102013 was conducted from 19 September 2007 until 10 February 2009 until 30 July 2010. Study MB102032 was conducted from 22 September 2008 until 06 January 2010.

Conduct of the study

There were 4 amendments to the original protocol for study MB102013 and 3 for study MB102032 which were considered acceptable.

Baseline data

For study MB102013, the mean age was 52.6 years, 86% were less than 65 years old, 52.8% were female, 52.9% were from North America, 34.3% from Latin America and 12.9% from Europe; More subjects in both dapagliflozin 10 mg groups (QAM and QPM) were < 65 years old than in the other groups. Mean weight was 90.19 kg. The overall mean duration of T2DM was 1.73 years (median < 6 months). The overall mean baseline HbA1c was 7.9% (Min 6.2%/ Max 12.2%). The baseline mean FPG was 162.7 mg/dL. Overall, the mean baseline estimated GFR in the placebo group (86.4 mL/min/1.73 m2) and dapagliflozin groups (83.3 to 89.0 mL/min/1.73 m2) were similar. More than half of the subjects (55.7%) had mild renal impairment at baseline.

In study MB102032, more than 80% of subjects were less than 65 years of age and were White, 50% were male. Overall 90.8% had a BMI of ≥ 25 kg/m2, 77.7% had a BMI ≥ 27 kg/m2 and 60.6% of ≥ 30 kg/m2. Mean baseline weight was 86.90 kg, it was slightly lower for subjects in the dapagliflozin 2.5 and 5 mg treatment groups than in the dapagliflozin 1 mg and placebo treatment groups. The geographic distribution of the subjects was North America (33.3%/N=94), Latin America (28.0%/N=79), and Europe (27.7%/N=78), while 11.0% (N=31) of the subjects were from Asia/Pacific region. The mean duration of T2DM was 1.38 years (range 0.0 to 22.5 years). Most subjects had been diagnosed with T2DM for < 3 years. The overall mean baseline HbA1c was 7.9% (ranking between 7.80% for both PLA and Dapa 1mg and 8.11% for Dapa 2.5mg). Baseline mean FPG (158.5 mg/dL) was similar across the treatment groups. Baseline renal function was similar across all treatment groups. More than half (54.3%) the subjects had glomerular filtration rates (GFRs) in the range of 60 to 89 mL/min/1.73 m2.

Numbers analysed

Table 10. Disposition of subjects in the short-term period of studies MB102013 and MB102032, randomised subjects

Study	Treatment Group	No. Randomized and Treated	Completed n (%)	D/C for lack of efficacy[a] n (%)	Rescued n (%)
Phase 3 placebo-controlled studies					
MB102013					
Group 1 QAM dosing					
Monotherapy	Placebo	75	63 (84.0)	1 (1.3)	9 (12.0)
	Dapa 2.5 mg	65	60 (92.3)	0 (0.0)	7 (10.8)
	Dapa 5 mg	64	52 (81.3)	0 (0.0)	1 (1.6)
	Dapa 10 mg	70	57 (81.4)	0 (0.0)	0 (0.0)
Group 1: QPM dosing					
	Dapa 2.5 mg	67	58 (86.6)	0 (0.0)	2 (3.0)
	Dapa 5 mg	68	57 (83.8)	0 (0.0)	2 (2.9)
	Dapa 10 mg	76	65 (85.5)	0 (0.0)	0 (0.0)
Group 2 QAM dosing					
	Dapa 5 mg	34	28 (82.4)	0 (0.0)	3 (8.8)
	Dapa 10 mg	39	34 (87.2)	0 (0.0)	3 (7.7)
MB102032					
Monotherapy	Placebo	68	65 (95.6)	1 (1.5)	13 (19.1)
	Dapa 1 mg	72	68 (94.4)	1 (1.4)	4 (5.6)
	Dapa 2.5 mg	74	67 (90.5)	0 (0.0)	3 (4.1)
	Dapa 5 mg	68	63 (92.6)	1 (1.5)	3 (4.4)

a Discontinuation due to lack of efficacy is determined from the glycemic control page of the CRF, or study termination page for study D1690C00005

Outcomes and estimation

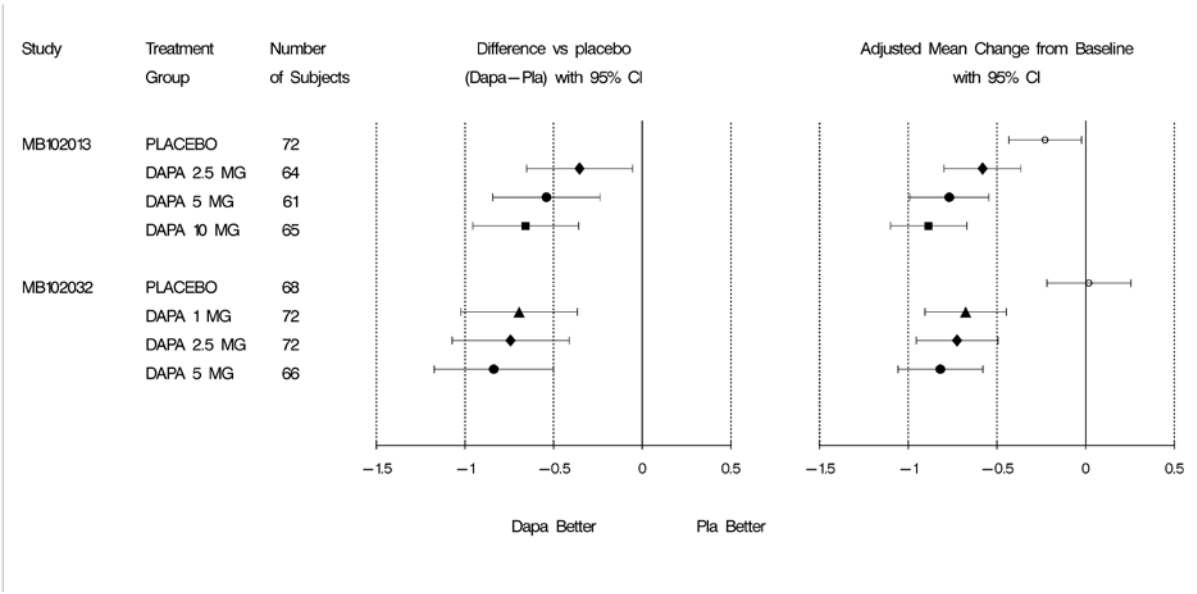
HbA1c change from baseline in drug naïve subjects

Table 11. HbA1c (%) change from baseline at Week 24 (LOCF), excluding data after rescue - Phase III placebo-controlled monotherapy studies (MB102013 and MB102032), Efficacy Analysis Data Set

Treatment	MB102013 QAM dosing[a]	QPM dosing[b]	MB102032 QAM dosing
Placebo	(N=75)	-	(N=68)
N#	72	-	68
Baseline mean (SD)	7.79 (0.831)	-	7.80 (1.117)
Mean at Week 24 (SD)	7.60 (1.434)	-	7.84 (1.787)
Adj. mean change (SE)	-0.23 (0.1044)	-	0.02 (0.1200)
Dapagliflozin 1 mg/day	-	-	(N=72)
N#	-	-	72
Baseline mean (SD)	-	-	7.80 (0.984)
Mean at Week 24 (SD)	-	-	7.15 (1.115)
Adj. mean change (SE)	-	-	-0.68 (0.1166)
Difference vs PLA (95% CI)	-	-	-0.69 (-1.02,-0.37)
p-value vs PLA	-	-	<0.0001 *
Dapagliflozin 2.5 mg/day	(N=65)	(N=67)	(N=74)
N#	64	62	72
Baseline mean (SD)	7.91 (0.892)	7.97 (0.997)	8.07 (1.032)
Mean at Week 24 (SD)	7.32 (1.178)	7.10 (1.086)	7.30 (1.100)
Adj. mean change (SE)	-0.58 (0.1107)	-0.83 (0.1125)	-0.72 (0.1169)
Difference vs PLA (95% CI)	-0.35 (-0.65,-0.05)	-0.61 (-0.91,-0.30)	-0.74 (-1.07,-0.41)
p-value vs PLA	0.0207	NA	<0.0001 *
Dapagliflozin 5 mg/day	(N=64)	(N=68)	(N=68)
N#	61	63	66
Baseline mean (SD)	7.83 (0.916)	7.74 (0.835)	7.92 (1.035)
Mean at Week 24 (SD)	7.09 (0.775)	7.01 (0.907)	7.10 (0.882)
Adj. mean change (SE)	-0.77 (0.1134)	-0.79 (0.1117)	-0.82 (0.1217)
Difference vs PLA (95% CI)	-0.54 (-0.84,-0.24)	-0.56 (-0.86,-0.26)	-0.84 (-1.17,-0.50)
p-value vs PLA	0.0005 *	NA	<0.0001 *
Dapagliflozin 10 mg/day	(N=70)	(N=76)	-
N#	65	73	-
Baseline mean (SD)	8.01 (0.952)	8.02 (1.061)	-
Mean at Week 24 (SD)	7.08 (0.751)	7.18 (0.994)	-
Adj. mean change (SE)	-0.89 (0.1099)	-0.79 (0.1037)	-
Difference vs PLA (95% CI)	-0.66 (-0.96,-0.36)	-0.56 (-0.85,-0.27)	-
p-value vs PLA	<0.001 *	NA	-

a In Study MB102013, the primary efficacy objective was assessed using data from Group 1, AM dosing.
b In Study MB102013, data from Group 1, PM dosing group was used to assess an exploratory efficacy objective related to dosing time of day.
(*) Significant p-value compared to placebo: the primary endpoint was tested at alpha=0.019 applying the Dunnett's adjustment. In Study MB102013, both AM and PM treatment groups were included in the same ANCOVA model.
N is the number of subjects in the Efficacy Analysis Data Set (randomized subjects in BMS studies, Full Analysis Set in AZ studies).
N# is the number of subjects in the efficacy data set with non-missing baseline and Week 24 (LOCF) values.
NA P-value is not available because this endpoint or exploratory dose group was not included in the sequential testing procedure for this study (BMS sponsored studies only).

Figure 4. HbA1c (%), adjusted mean change from baseline at Week 24 (LOCF), excluding data after rescue - Phase III placebo-controlled monotherapy studies (MB102013 and MB102032), Efficacy Analysis Data Set



A moderate but clinically relevant placebo-corrected decrease in HbA1c was observed in the 5 and 10 mg treated groups in study MB102013, whereas clinically relevant changes was seen for all doses tested in study MB102032. Baseline HbA1c was essentially similar between the two studies; however, patients in study MB102032 had somewhat lower body weight than patients in study MB102013. A dose-dependent decrease in HbA1c was observed in both studies.

Other glycaemic variables

The secondary endpoints all supported the outcome of the primary endpoint.

FPG change from baseline

In both monotherapy studies, treatment with dapagliflozin resulted in significant reductions in FPG change from baseline at Week 24 compared to placebo. The effect of dapagliflozin treatment on FPG appeared to be dose dependent and was consistent with the effect on the primary endpoint, HbA1c.

PPG (liquid meal) change from baseline

Change from baseline in 2-hour PPG after MTT at 24 weeks was a secondary endpoint in study MB102032. There was a statistically significant difference versus placebo for all three dapagliflozin dose groups, with the greatest reduction observed in the 5 mg group; this dose effect is in contrast to 2-hour PPG after OGTT results in the add-on combination therapy studies D1690C00005 and MB102030, where a dose-dependent effect was not observed.

Proportion of subjects achieving therapeutic glycaemic response

The proportions of subjects achieving therapeutic glycaemic response, defined as HbA1c<7% were numerically higher in all dapagliflozin treatment groups compared to placebo at Week 24 (LOCF) in both monotherapy studies.

Table 12. Proportion of subjects achieving Therapeutic Glycaemic Response (HbA1c <7.0%) at Week 24 (LOCF) , excluding data after rescue - Phase III placebo-controlled monotherapy studies (MB102013 and MB102032), Efficacy Analysis Data Set

Treatment	MB102013 AM dosing[a]	PM dosing[b]	MB102032 AM dosing
Placebo	(N=75)	-	(N=68)
N#	72	-	68
N achieving HbA1c <7.0%	24	-	26
Proportion of subjects[c] (95% CI)	31.6% (21.8, 41.5)	-	34.6% (24.3, 45.0)
Dapagliflozin 1 mg/day	-	-	(N=72)
N#	-	-	72
N achieving HbA1c <7.0%	-	-	40
Proportion of subjects[c] (95% CI)	-	-	53.6% (42.8, 64.3)
Difference[d] vs PLA (95% CI)	-	-	18.9% (3.6, 34.3)
p-value vs PLA	-	-	0.0157 *
Dapagliflozin 2.5 mg/day	(N=65)	(N=67)	(N=74)
N#	64	62	72
N achieving HbA1c <7.0%	26	31	28
Proportion of subjects[c] (95% CI)	41.3% (30.4, 52.3)	51.4% (40.8, 62.0)	43.4% (33.4, 53.5)
Difference[d] vs PLA (95% CI)	9.7% (-5.3, 24.7)	19.8% (4.9, 34.7)	8.8% (-6.2, 23.8)
p-value vs PLA	ND	NA	0.2512
Dapagliflozin 5 mg/day	(N=64)	(N=68)	(N=68)
N#	61	63	66
N achieving HbA1c <7.0%	28	30	32
Proportion of subjects[c] (95% CI)	44.2% (32.6, 55.8)	44.0% (33.3, 54.7)	49.1% (37.7, 60.6)
Difference[d] vs PLA (95% CI)	12.6% (-2.9, 28.1)	12.4% (-2.5, 27.3)	14.5% (-1.3, 30.3)
p-value vs PLA	ND	NA	0.0726
Dapagliflozin 10 mg/day	(N=70)	(N=76)	-
N#	65	73	-
N achieving HbA1c <7.0%	31	36	-
Proportion of subjects[c] (95% CI)	50.8% (39.8, 61.8)	51.6% (41.2, 61.9)	-
Difference[d] vs PLA (95% CI)	19.2% (4.1, 34.2)	19.9% (5.3, 34.5)	-
p-value vs PLA	ND	NA	-

a In Study MB102013, the primary efficacy objective was assessed using data from Group 1, AM dosing.
b In Study MB102013, data from Group 1, PM dosing group was used to assess an exploratory efficacy objective related to dosing time of day
c Proportion adjusted for baseline HbA1c, unadjusted proportions are available in CSR source tables.
d Difference in adjusted proportions.
N is the number of subjects in the Efficacy Analysis Data Set (randomized subjects in BMS studies, Full Analysis Set in AZ studies).
N# is the number of subjects in the efficacy data set with non-missing baseline and Week 24 (LOCF) values.
(*) Significant p-value compared to placebo: secondary endpoints were tested in each study following a sequential testing procedure at alpha=0.05. In Study MB102013, both AM and PM treatment groups were included in the same logistic regression model.
NA P-value is not available because this endpoint or exploratory dose group was not included in the sequential testing procedure for this study (BMS sponsored studies only).
ND P-value is not calculated because a test of a previous endpoint in the sequential testing procedure was not statistically significant (defined as $p \leq 0.05$) for this treatment group (BMS sponsored studies only).

Discontinuations or rescue for failing to achieve pre-specified glycaemic targets

Analyses of subjects who required rescue or were discontinued due to failure to achieve glycaemic control were performed as additional supportive measures of efficacy. According to the study protocols, rescue for failing to meet glycaemic targets preceded discontinuation for lack of glycaemic control. As a result, most subjects were rescued and few required discontinuation.

In study MB102013, by 24 weeks, the cumulative proportion of subjects in Group 1 rescued was greatest in the placebo and dapagliflozin 2.5 mg groups. No subjects in the dapagliflozin 10 mg group were rescued. Results were similar for the overall proportion of subjects discontinued or rescued for failing to achieve pre-specified glycaemic targets by Week 24 when adjusted for baseline HbA1c. By 24 weeks, the cumulative proportion of subjects in Group 2 rescued was similar between the 5 mg and 10 mg QAM groups.

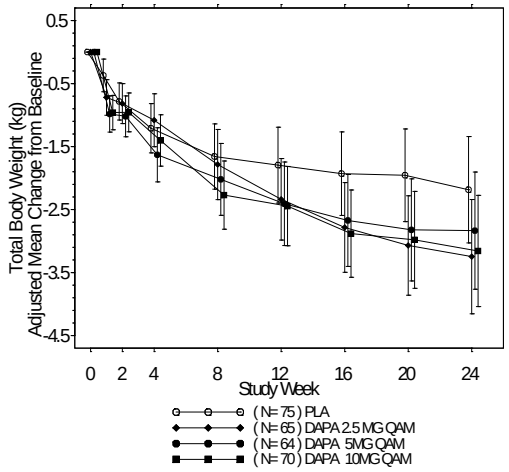
In study MB102032, at Week 24, the cumulative proportion of subjects rescued over time was greater in the placebo group than those in the dapagliflozin 1 mg, 2.5, and 5 mg groups. Results were similar for the overall proportion of subjects discontinued or rescued for failing to achieve pre-specified glycaemic targets by Week 24.

Variables related to body weight and body composition in treatment naïve subjects

Change in total body weight at 24 weeks was a secondary efficacy variable in studies MB102013 and MB102032. In study MB102013, treatment with dapagliflozin 2.5 mg, 5 mg and 10 mg resulted in numerical, but not statistically significant, decreases in body weight compared to placebo. The placebo effect was greater than expected in this study based on results in other dapagliflozin monotherapy studies. The data suggest that the patients included in this study were less well compliant with the diet and exercise regimen as a larger decrease in HbA1c was also observed in this group. In study MB102032 there was a significant decrease in body weight in subjects treated with dapagliflozin 1 mg, 2.5 mg and 5 mg compared to placebo. In neither of the studies was there any apparent dose relationship.

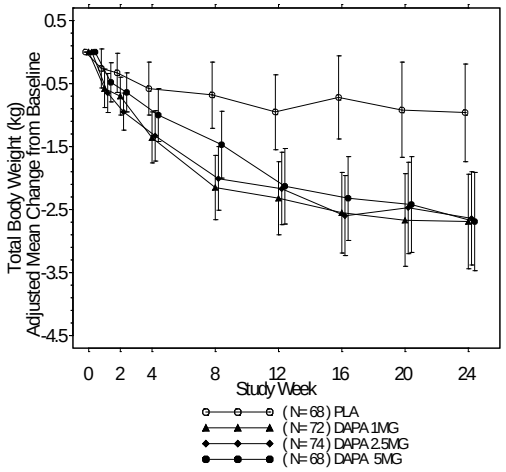
Figure 5. Weight (kg) adjusted mean change from baseline over time to Week 24 (LOCF), excluding data after rescue - Phase III placebo-controlled monotherapy studies (MB102013 and MB102032), Efficacy Analysis Data Set

Study MB102013 – Group 1, AM dosing



Randomized subjects who took at least one dose of double-blind study medication.
Mean value based on an ANCOVA model with treatment group as an effect and baseline value as a covariate.
Error bars represent 95% confidence intervals for the adjusted mean.
Treatment symbols shifted horizontally to prevent error bar overlapping.

Study MB102032



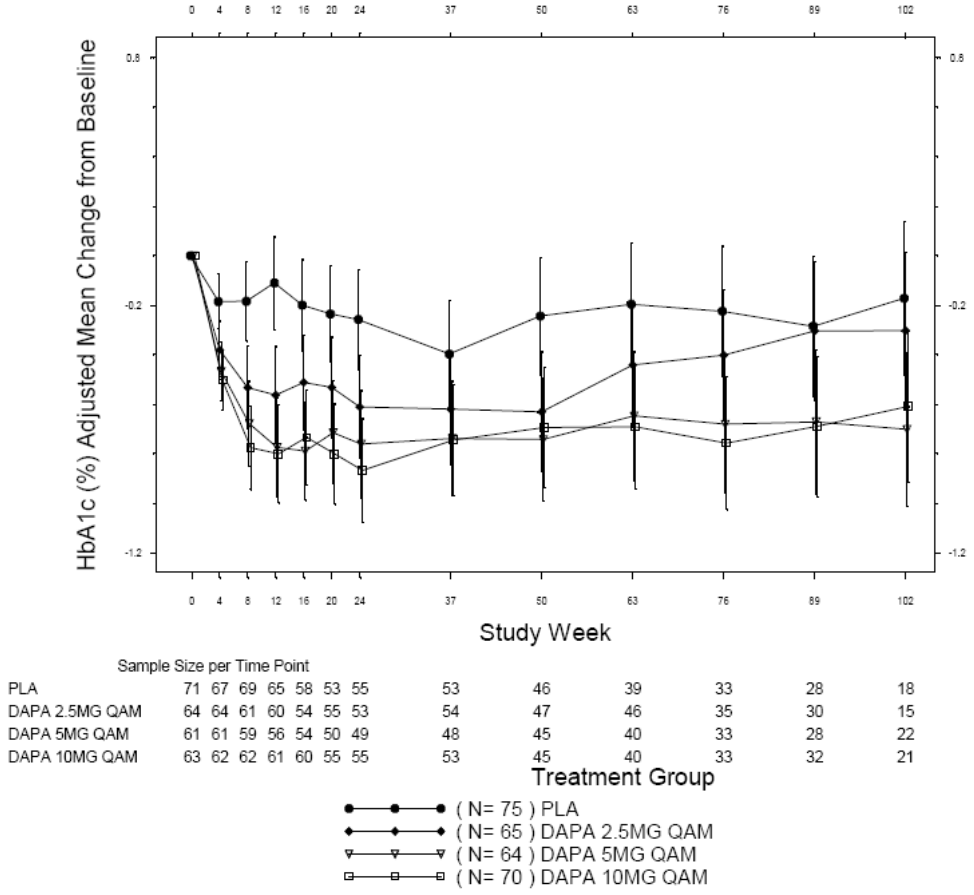
Randomized subjects who took at least one dose of double-blind study medication.
Mean value based on an ANCOVA model with treatment group as an effect and baseline value as a covariate.
Error bars represent 95% confidence intervals for the adjusted mean.
Treatment symbols shifted horizontally to prevent error bar overlapping.

However, relevant changes in body weight were seen in both studies.

Ancillary analyses

Data from the long-term extension of the monotherapy study MB102013 was submitted during the procedure. Out of 408 originally included patients 294 completed the study. The data indicate a maintained effect over the 102 week study period in patients not needing rescue therapy. At 102 weeks the number of drop-outs was comparable between all groups.

Figure 6. HbA1c (%)Adjusted Mean Change from Baseline Over Time, Short-term Plus Long-term Treatment Period, Excluding Data After Rescue, Randomized Subjects (MB102013 ST + LT)

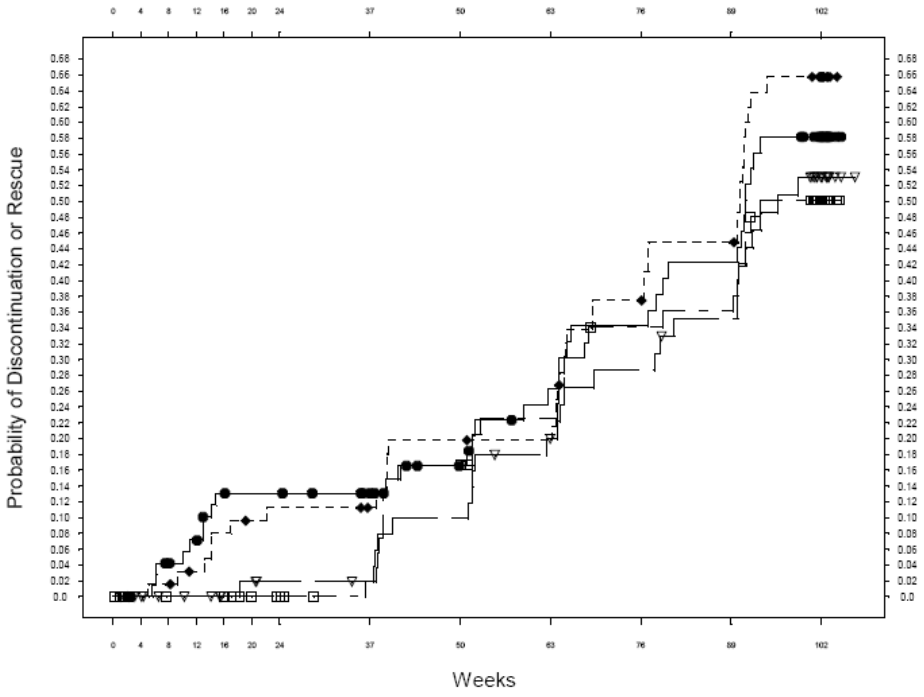


Randomized subjects who took at least one dose of double-blind study medication
Mean value based on a longitudinal repeated measures model with fixed categorical effects of treatment,week, strata and treatment-by-week interaction as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction.
Error bars represent 95% confidence intervals for the adjusted mean change from baseline.
Treatment symbols shifted horizontally to prevent error bar overlapping.

In the time to rescue analysis in patients on monotherapy, a difference was observed between dapagliflozin 5 and 10 mg compared to placebo and dapagliflozin 2.5 mg during the first 36 weeks of the study with a lower risk of failure in the 5 and 10 mg treated groups. After 36 weeks there appears to be an increase in the risk of failure in the higher dose groups.

The available overall controlled data up to 102 weeks on dapagliflozin are deemed sufficient to support the proposed first-line indication.

Figure 7. Time to Discontinuation for Lack of Glycaemic Control or Rescue for Failing to Achieve Pre-specified Glycaemic Targets, Randomized Subjects (MB102013 ST + LT)



Number of Subjects at Risk

PLA	75	71	67	64	58	57	57	53	44	37	33	29	16
DAPA 2.5MG QAM	65	64	63	60	57	55	54	52	47	46	35	30	13
DAPA 5MG QAM	64	61	58	57	53	52	50	49	45	39	33	29	14
DAPA 10MG QAM	70	63	62	62	62	59	57	53	45	40	33	32	18

PLA
DAPA 2.5MG QAM
DAPA 5MG QAM
DAPA 10MG QAM

Symbols represent censored observations
Week is not the scheduled visit week but the actual number of days from the first dose of double-blind study medication divided by 7.
Number of subjects at risk is the number of subjects at risk at the beginning of the period.
The results beyond Week 102 should be interpreted with caution as the number of subjects at risk might be limited.

Specific issues applying to studies MB102014, D1690C00005, MB102030 and D1690C00006: add-on combination studies

Study MB102014 is a multicenter, randomized, double-blind, placebo-controlled, parallel group study with the primary objective to evaluate the safety and efficacy of 3 different doses (2.5 mg, 5 mg and 10 mg) of dapagliflozin in combination with metformin in patients with T2DM who have inadequate glycaemic control on metformin alone.

Study D1690C00005 is a multicenter, randomized, double-blind, placebo-controlled, parallel group study with the primary objective to evaluate the safety and efficacy of 3 different doses (2.5 mg, 5 mg and 10 mg) of dapagliflozin in combination with glimepiride in patients with T2DM who have inadequate glycaemic control on glimepiride alone.

Study MB102030 is a multicenter, randomized, double-blind, placebo-controlled, parallel group study with the primary objective to evaluate the safety and efficacy of 2 different doses (5 mg and 10 mg) of dapagliflozin in combination with thiazolidinedione therapy in patients with T2DM who have inadequate glycaemic control on thiazolidinedione therapy alone.

Study D1690C00006 is a multicenter, randomized, double-blind, placebo-controlled, parallel group study with the primary objective to evaluate the efficacy and safety of 3 different doses (2.5 mg, 5 mg and 10 mg) of dapagliflozin therapy when added to the therapy of patients with T2DM with inadequate glycaemic control on insulin.

Methods

Study Participants

80 sites for study MB102014 enrolled subjects in the United States, in Canada and in Latin America. Males and females with T2DM, ≥ 18 to ≤ 77 years old, BMI ≤ 45.0 kg/m2 with HbA1c ≥ 7.0% and ≤ 10%, who had been on a stable dose of ≥ 1500 mg per day of metformin for at least 8 weeks prior to the enrolment.

84 sites for study D1690C00005 enrolled subjects in the EU, Ukraine, Korea, the Philippines and Thailand. Male or female subjects ≥18 years of age, with T2DM and HbA1c ≥7% and ≤10.0% on current sulphonylurea monotherapy of at least half maximal recommended dose for at least 8 weeks prior to enrolment were eligible to enter the study. Besides the general exclusion criteria pre-defined for all Phase III studies performed with dapagliflozin: Subjects on glimepiride dose higher than 4 mg/day were not eligible for the study.

105 sites for study MB102030 enrolled subjects in the United States, in Canada, Latin America, India, the Philippines, Taiwan and Puerto Rico. Patients with T2DM, ≥ 18 years old, HbA1C ≥ 7.0 and ≤ 10.0%, BMI ≤ 45.0 kg/m2 were eligible.

- Group 1: Subjects on a stable dose of pioglitazone 30 or 45 mg/day for at least 12 weeks prior to enrolment
- Group 2: Patients on different or no pre-treatment(s) were eligible:
    - Drug naive subjects defined as no exposure to antidiabetic medications for 10 weeks with HbA1c≥ 8.0 and ≤ 11.0%
    - Subjects on a stable dose of TZD (pioglitazone 15 mg/day or rosiglitazone at any dose) for at least 12 weeks prior to enrolment
    - Subjects on stable monotherapy with metformin ≤ 1700 mg/day or sulfonylurea ≤ half the maximum dose for at least 8 weeks prior to enrolment.

1131 sites for study D1690C00006 enrolled subjects in the United States, Canada, EU and Russia. Patients with T2DM, ≥18 and ≤80 years of age, with HbA1c ≥7.5% and ≤10.5%, BMI ≤45 kg/m2, who were on a stable insulin regimen, with a mean daily dose of at least 30 IU, for a period of at least 8 weeks prior to enrolment, were eligible. Subjects could also be treated with maximally two additional OADs at a stable dose for a period of at least 8 weeks. Doses were to be at least 1500 mg/day of metformin or at least half maximum daily recommended dose of other OADs. Subjects were stratified according to whether their treatment regimen included OADs or not. No more than 60% of enrolled subjects were allowed to take insulin plus OADs. Subjects treated with more than two additional OADs were excluded.

Treatments

Study MB102014 consists of 4 periods: a qualification period (up to 14 days), a lead-in period (14 days), a short-term double blind treatment period (24 weeks) and a long-term treatment period (78 weeks). Eligible subjects received treatment with 2.5, 5 or 10 mg of dapagliflozin daily or placebo. Open-label metformin background therapy had to remain unchanged. Subjects were to take study drug in the morning, 1 hour (or at least 30 minutes) prior to the morning meal. Open-label metformin could be split between AM and PM as required. Eligible subjects who completed the 24-week short-term treatment period could continue in the long-term treatment period for 78 weeks on the same blinded study medication. The rescue medication for this study was pioglitazone 15 mg and was to be taken with the morning meal. Alternatively, acarbose could have been used.

Study D1690C0005 consists of 6 periods: a one week enrolment period, an 8 weeks open-label glimepiride lead-in period, a one week qualification period, a 24 weeks double-blind treatment period, a 24 weeks double-blind extension period and a 3 weeks follow-up period. Eligible patients were randomized to receive either 2.5 mg, 5 mg, and 10 mg of dapagliflozin or placebo, to be taken once daily in the morning immediately before or with a meal. Background therapy with glimepiride had to remain stable except for down titration (to 2 or even 0 mg) due to hypoglycaemia. Rescue therapy (metformin, pioglitazone or rosiglitazone) could be administered to subjects fulfilling rescue criteria during the 24-week double-blind treatment period and the 24-week double-blind extension period.

Study MB102030 consists of 5 periods: a qualification period (up to 14 days), a 10 weeks TZD dose optimization period, followed by a 14 days single-blind lead-in period, a 24 weeks double-blind short-term period and a 24 weeks single-blind long-term period.

Dose optimization period (only subjects of Group2): Subjects in Group 2 discontinued their original antidiabetic therapy, if applicable, and started on pioglitazone at 30 mg/d for 6 weeks with a subsequent increase to 45 mg/d (if tolerated) for the next 4 weeks before entering the lead-in phase. Patients of group 1 directly entered the lead-in phase.

Short-term treatment period (24 weeks): Eligible patients (pre-randomisation HbA1c ≥ 7.0 and ≤ 10.5%) were randomized to receive 5 mg or 10 mg of dapagliflozin or placebo. Subjects were to take study drug daily with the morning meal. Open-label pioglitazone was to be taken daily at an unchanged dose.

Long-term treatment period (24 weeks): Subjects who completed the 24-week short-term treatment period could continue in the long-term treatment period on their randomized blinded study medication.

Rescue medication: Subjects meeting rescue criteria could receive open-label rescue medication with metformin or sulfonylurea.

Study D1690C00006 consists of 3 periods: a 24 weeks short-term treatment period followed by 2 extension periods of 24 weeks and 56 weeks respectively.

Subjects were randomized to receive dapagliflozin 2.5 mg, 5 mg, 10 mg or placebo as add-on therapy to insulin with or without additional use of 1 or 2 OADs for the 24-week double-blind treatment period and the 24-week long-term double-blind extension period I. Subsequently, subjects randomized to placebo, dapagliflozin 2.5 or 10 mg continued their treatment without change in the 56-weeks extension period II, while subjects randomized to dapagliflozin 5 mg switched to dapagliflozin 10 mg.

Subjects meeting pre-defined FPG criteria could have up-titration of insulin, defined as an increase in mean daily insulin dose that meets both of the following criteria: the increase in insulin dose is more than 5 IU (i.e. 6 IU or greater) and the increase in insulin dose is greater that 10% of the baseline insulin dose (baseline insulin dose is calculated daily mean insulin dose documented at visit 2, week 0).

Objectives

The primary objective of study MB102014 was to compare the change from baseline in HbA1c achieved with each dose of dapagliflozin plus metformin versus placebo plus metformin after 24 weeks of oral administration of double-blind treatment.

The primary objective of study D1690C00005 was to compare the change from baseline in HbA1c achieved with each dose of dapagliflozin plus glimepiride versus placebo plus glimepiride after 24 weeks of oral administration of double-blind treatment.

The primary objective of study MB102030 was to compare the change from baseline in HbA1c achieved with each dose of dapagliflozin plus pioglitazone versus placebo plus pioglitazone after 24 weeks of oral administration of double-blind treatment.

The primary objective of study D1690C00006 was to compare the change from baseline in HbA1C achieved with each dose of dapagliflozin plus insulin versus placebo plus insulin after 24 weeks of oral administration of double-blind treatment.

Sample size

For study MB102014, with 129 subjects per treatment group with post-baseline measurements, there was 90% power to detect a difference in means of 0.5% between each dapagliflozin plus metformin treatment group and the placebo plus metformin group, assuming a standard deviation (SD) of 1.1%. Assuming that 5% of subjects did not have a post-baseline assessment, a total of 544 subjects (136 subjects per treatment group) needed to be randomized.

For study D1690C00005, each pair-wise treatment group comparison was tested at a significance level of approximately 0.019, according to Dunnett's method, in order to maintain an overall type I error rate ≤0.050 for the primary objective. To detect a difference of 0.5% between each dapagliflozin group versus placebo for changes in HbA1c from baseline to Week 24, assuming a SD =1.1%, and at a two-sided significance level of 0.019, 129 evaluable subjects were needed in each treatment group to provide 90% power. Assuming that 5% of the subjects would not be evaluable in the Full Analysis Set, 136 subjects per treatment group (544 subjects total) were planned for randomization.

For study MB102030, with 132 subjects per treatment group with post-baseline measurements, there is at least 92% power to detect a difference in means of 0.5% between each of the dapagliflozin plus pioglitazone treatment groups vs. the placebo plus pioglitazone treatment group at a two-sided significance level of 0.027, using Dunnett's adjustment and assuming a standard deviation (SD) of 1.1%. Assuming that 5% of subjects do not have a post baseline assessment, a total of 417 subjects (139 subjects per treatment group) needed to be randomized. With a total of 278 subjects randomized to dapagliflozin (5 mg and 10 mg) plus pioglitazone, 200 subjects will have 48 weeks of exposure to dapagliflozin (5 mg and 10 mg) plus pioglitazone, assuming a dropout rate of 15% every 6 months.

Each pair-wise treatment group comparison was to be tested at a significance level of approximately 0.019, according to Dunnett's method, in order to maintain an overall type I error rate <0.050 for the primary objective. To detect a difference of 0.5% between each dapagliflozin group versus placebo for changes from baseline to week 24 in HbA1c, assuming a SD = 1.2%, and at a two-sided significance level of 0.019, 153 evaluable subjects were needed in each treatment group to provide 90% power. Assuming that 5% of the subjects were not evaluable in the full analysis set, 161 subjects per treatment group (644 subjects total) were planned for randomization (808 were randomized). Originally, around 1600 subjects were planned to be enrolled but the number was decreased due to a lower screening failure rate than anticipated.

Results

Participant flow

Table 13. Study MB102014: Subjects disposition – Short-term double-blind period

	Number (%) of Subjects				
	PLA + MET N = 137	DAPA 2.5 mg + MET N = 137	DAPA 5 mg + MET N = 137	DAPA 10 mg + MET N = 135	Total N = 546
Subjects completing the period	119 (86.9)	121 (88.3)	122 (89.1)	121 (89.6)	483 (88.5)
Subjects not completing the period	18 (13.1)	16 (11.7)	15 (10.9)	14 (10.4)	63 (11.5)
Reason not completing the period					
Lack of efficacy	2 (1.5)	0	1 (0.7)	0	3 (0.5)
Adverse event	4 (2.9)	3 (2.2)	2 (1.5)	3 (2.2)	12 (2.2)
Subject withdrew consent	6 (4.4)	4 (2.9)	5 (3.7)	2 (1.5)	17 (3.1)
Lost to follow-up	5 (3.7)	4 (2.9)	4 (2.9)	5 (3.7)	18 (3.3)
Poor/non-compliance	0	0	2 (1.5)	0	2 (0.4)
No longer meets study criteria	0	3 (2.2)	0	2 (1.5)	5 (0.9)
Sponsor administrative reason	1 (0.7)	1 (0.7)	0	1 (0.7)	3 (0.5)
Other	0	1 (0.7)	1 (0.7)	1 (0.7)	3 (0.5)
Subjects continuing in the study	115 (83.9)	120 (87.6)	122 (89.1)	119 (88.1)	476 (87.2)
Subjects not continuing in the study	22 (16.1)	172 (12.4)	22 (10.9)	16 (11.9)	70 (12.8)
Reason not continuing in the study					
Lack of efficacy	3 (2.2)	0	1 (0.7)	0	4 (0.7)
Adverse event	4 (2.9)	4 (2.9)	2 (1.5)	4 (3.0)	14 (2.6)
Subject withdrew consent	7 (5.1)	5 (3.7)	5 (3.7)	3 (2.2)	20 (3.7)
Lost to follow-up	5 (3.7)	4 (2.9)	4 (2.9)	5 (3.7)	18 (3.3)
Poor/non-compliance	0	0	2 (1.5)	0	2 (0.4)
No longer meets study criteria	2 (1.5)	3 (2.2)	0	2 (1.5)	7 (1.3)
Sponsor administrative reason	1 (0.7)	1 (0.7)	0	1 (0.7)	3 (0.5)
Other	0	0	1 (0.7)	1 (0.7)	2 (0.4)

All randomized subjects who took at least one dose of double-blind study medication. Percentages reported are based on the total number of subjects in each treatment group. Subjects continuing in the study = subjects entering the long-term treatment period.
DAPA = dapagliflozin; MET = metformin; N = number of treated subjects

Table 14. Study D1690C00005: Subjects status at end of 24-week short-term double-blind treatment period

Table 10 Subject status at end of 24-week short-term double-blind treatment period (Safety Analysis Set)

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End of 24-Week Short-term Double-blind Treatment Period Subject Status Summary
Safety Analysis Set

	PLA + GLI	DAPA 2.5MG + GLI	DAPA 5MG + GLI	DAPA 10MG + GLI	Total
SUBJECTS	146	154	145	151	596
SUBJECTS COMPLETING THE PERIOD (%)	133 (91.1)	140 (90.9)	132 (91.0)	141 (93.4)	546 (91.6)
SUBJECTS NOT COMPLETING THE PERIOD (%)	13 (8.9)	14 (9.1)	13 (9.0)	10 (6.6)	50 (8.4)
REASON FOR NOT COMPLETING THE PERIOD (%)					
ADVERSE EVENT	3 (2.1)	5 (3.2)	3 (2.1)	3 (2.0)	14 (2.3)
SUBJECT NO LONGER MEETS STUDY CRITERIA	2 (1.4)	0	2 (1.4)	0	4 (0.7)
SUBJECT WITHDREW CONSENT	8 (5.5)	8 (5.2)	3 (2.1)	2 (1.3)	21 (3.5)
LOST TO FOLLOW-UP	0	0	1 (0.7)	1 (0.7)	2 (0.3)
POOR/NON-COMPLIANCE	0	0	3 (2.1)	0	3 (0.5)
DEATH	0	1 (0.6)	0	1 (0.7)	2 (0.3)
OTHER	0	0	1 (0.7)	3 (2.0)	4 (0.7)
SUBJECTS CONTINUING IN THE STUDY (%)	133 (91.1)	140 (90.9)	131 (90.3)	141 (93.4)	545 (91.4)
SUBJECTS NOT CONTINUING IN THE STUDY (%)	13 (8.9)	14 (9.1)	14 (9.7)	10 (6.6)	51 (8.6)
REASON FOR NOT CONTINUING IN THE STUDY (%)					
ADVERSE EVENT	3 (2.1)	5 (3.2)	3 (2.1)	3 (2.0)	14 (2.3)
SUBJECT NO LONGER MEETS STUDY CRITERIA	2 (1.4)	0	2 (1.4)	0	4 (0.7)
SUBJECT WITHDREW CONSENT	8 (5.5)	8 (5.2)	3 (2.1)	2 (1.3)	21 (3.5)
LOST TO FOLLOW-UP	0	0	1 (0.7)	1 (0.7)	2 (0.3)
POOR/NON-COMPLIANCE	0	0	3 (2.1)	0	3 (0.5)
DEATH	0	1 (0.6)	0	1 (0.7)	2 (0.3)
OTHER	0	0	1 (0.7)	3 (2.0)	4 (0.7)
NOT REPORTED	0	0	1 (0.7)	0	1 (0.2)

Percentages reported are based on the total number of subjects in each treatment group.
Subjects continuing in the study refers to subjects entering the long-term treatment period.
Program Source: /gbs/prod/clin/programs/mb/102/020/stcsr01/rpt/rt_ds_dispsts_v01.sas 08FEB2010: 5:33:41

Table 15. Study MB102030: Subjects disposition – 24 week double-blind treatment period

	Number (%) of Subjects			
	PLA + PIO N = 139	DAPA 5 mg + PIO N = 141	DAPA 10 mg + PIO N = 140	Total N = 420
Subjects completing the study	116 (83.5)	125 (88.7%)	126 (90.0)	367 (87.4)
Subjects not completing the study	23 (16.5)	16 (11.3)	14 (10.0)	53 (12.6)
Reason for not completing the study				
Lack of efficacy	3 (2.2)	0	1 (0.7)	4 (1.0)
Adverse event	4 (2.9)	3 (2.1)	3 (2.1)	10 (2.4)
Subject withdrew consent	9 (6.5)	8 (5.7)	6 (4.3)	23 (5.5)
Death	0	1 (0.7)	0	1 (0.2)
Lost to follow-up	4 (2.9)	2 (1.4)	4 (2.9)	10 (2.4)
Poor/non-compliance	1 (0.7)	1 (0.7)	0	2 (0.5)
Subject no longer met study criteria	0	1 (0.7)	0	1 (0.2)
Other	1 (0.7)	0	0	1 (0.2)

This table includes all randomized subjects who took at least 1 dose of double-blind study medication.
Percentages reported are based on the total number of subjects in each treatment group.
DAPA = dapagliflozin; PIO = pioglitazone; PLA = placebo; N = number of randomized subjects

Study D1690C00006

In total, 1240 subjects were enrolled out of which 808 were randomized. The most common reason for not being randomized was not fulfilling all the inclusion criteria and fulfilling at least one exclusion criterion (396 subjects). More than 85% of the subjects completed the short-term treatment period and more than 80% of the subjects completed the long-term extension period I. The most common reasons for not completing the periods were withdrawal of consent and occurrence of an AE.

Recruitment

Study MB102014 was conducted from 18 September 2007 until 13 May 2010. Study D1690C00005 was conducted from 30 April 2008 until 19 November 2009. Study MB10203 was conducted from 29

July 2008 until 11 January 2010. Study D1690C00006 was conducted from 30 April 2008 until 19 May 2009.

Conduct of the study

There were 6 amendments to the original protocol for study MB102014, 1 for study D1690C00005, 3 for study MB10203 and 2 for study D1690C0006 which were considered acceptable.

Baseline data

For study MB102014, the mean age was 53.9 years, most subjects (85.5%) were less than 65 years of age and only 0.7% 75 years or older. Overall, 87.9% were White and 93.2% had a BMI of ≥ 25 kg/m2 and 53.5% were male. Almost two-thirds of the subjects were from Latin America (63.7%, N= 348) and the remaining 36.3 % (N=198) from North America. Overall, the mean baseline weight was 85.9 kg. Baseline diabetes characteristics were similar across treatment groups. Mean duration of T2DM was 6.09 years (range 0.2 to 42.6 years). Mean HbA1c was 8. 06 % (range 5.6% to 10.9%) and mean FPG was 163.27 mg/dL. Overall, 46.2% of subjects had diabetes > 3 years and ≤ 10 years and 17.9% had diabetes >10 years. Half of the subjects mild and 11% had moderate renal impairment. Baseline renal function was similar across all treatment groups.

For study D1690C00005, the mean age was 59.8 years. Overall, 67.4% were less than 65 years old and 5.1% over 75 years. A higher proportion of 75.5% of patients was less than 65 years old in the dapagliflozin 10 mg plus Gli group. The proportion of males was 48.1%. Gender distribution was similar in all treatment groups. Overall, 69.4% were White (Europeans) and 30.6% were Asian; all subjects were of non-Hispanic/Latino ethnicity. Overall, 82.6% of subjects had BMI ≥25 kg/m2) and almost 47.5% BMI ≥30 kg/m2. Mean weight at baseline amounted to 80.56 kg. Mean HbA1c was 8.11% (range 5.4 % to 10.2 %), mean duration of diabetes was 7.4 years (range 0.2 to 35.7 years), most of the patients (50.5%) had a duration of diabetes ≥3 years and ≤ 10 years, and 25.5% of more than 10 years. Mean FPG was 172.85 mg /dL. Upon entry in the study, 57.8% of the subjects had eGFRs corresponding to mild and 10.6% had moderate renal impairment. In the placebo group the rate of subjects with Stage 3 was higher (16.6%) compared to the overall study population (10.6%).

For study MB102030, of the subjects included, 51.1%, 55.3% and 42.1% were male in the PLA, dapagliflozin 5 mg and dapagliflozin 10 mg group, respectively. Mean age was 53.5 years. Overall 84% of subjects were less than 65 years old, 13.6% between 65 and 75 years and 2.4% were aged 75 or older. Overall 72.6% of patients were White, 16.9% Asian and 5.2 % Black or of “other” race. Of the subjects included there were 44.8 % (N=188), 41.0% (N=172) and 14.3 % (N=60) from North and Latin America and Asia respectively. Overall 89% of subjects had a BMI of ≥25 kg/m2. Mean duration of T2DM was 5.49 years, mean HbA1c 8.38%, mean FPG 164.75 mg/dl. Baseline renal function was similar across all treatment groups. Mean eGFR was 87.2 to 89.1 mL/min/1.73 among treatment groups; half of the subjects had mild and 5.7% had moderate renal impairment.

For study D1690C0006, the mean age was 59.3 years with 75% aged below 65 years and less than 3% aged over 75 years. Overall, 47.8% were male. About 78.9 % of patients were from Europe and 21.1% from USA and Canada. 95% of the subjects were white and 98.6% were of non-Hispanic/Latino ethnicity. Overall 94.6% of the subjects had BMI ≥25 kg/m2 and 70.3% BMI ≥30 kg/m2, mean weight was 93.8 kg. Mean duration of T2DM was 13.6 years (range 0.3-46.3 years) with 66.1% of the subjects with T2DM over 10 years. Overall, mean insulin treatment duration was 6 years. Mean HbA1c was 8.53% and mean FPG 178 mg/dl. The calculated mean daily insulin dose was 77.11 IU/day with 20.6 % of the subjects on a dose ≥100 IU/day, 37.5% on ≥60 and <100 IU/day and 41.9% < 60 IU insulin daily. Only 17% of the subjects were on basal insulin only, the rest received sliding scale insulin plus basal insulin (47.8% of the subjects) or without basal insulin (35.3% of the subjects). Overall, 42.6% of the subjects used 1 OAD and 7.2 % were treated with 2 OADs in addition to insulin treatment, 39.9% of patients received metformin alone as additional OAD, 5.8% received Met plus SU and 3.3% other drugs or drug combinations, less than 1% received Met plus SU or TZD each. Overall, 56.4% of patients had an eGFR ≥60 and< 90 and 27.4% ≥ 90 (ml/Min /1.73 m2).

Numbers analysed

Table 16. Disposition of subjects in the short-term treatment period of the add-on combination studies, randomized subjects

Study	Treatment Group	No. Randomized and Treated	Completed n (%)	D/C for lack of efficacy[a] n (%)	Rescued n (%)
Phase 3 placebo-controlled studies					
MB102014					
Metformin	Placebo	137	119 (86.9)	3 (2.2)	22 (16.1)
	Dapa 2.5 mg	137	121 (88.3)	0 (0.0)	5 (3.6)
	Dapa 5 mg	137	122 (89.1)	1 (0.7)	5 (3.6)
	Dapa 10 mg	135	121 (89.6)	0 (0.0)	5 (3.7)
D1692C00005					
SU	Placebo	146	133 (91.1)	2 (1.4)	23 (15.8)
	Dapa 2.5 mg	154	140 (90.9)	0 (0.0)	9 (5.8)
	Dapa 5 mg	145	132 (91.0)	1 (0.7)	8 (5.5)
	Dapa 10 mg	151	141 (93.4)	0 (0.0)	3 (2.0)
MB102030					
TZD	Placebo	139	116 (83.5)	3 (2.2)	16 (11.5)
	Dapa 5 mg	141	125 (88.7)	0 (0.0)	2 (1.4)
	Dapa 10 mg	140	126 (90.0)	1 (0.7)	5 (3.6)
D1690C00006					
Insulin	Placebo	197	168 (85.3)	1 (0.5)	54 (27.4)
	Dapa 2.5 mg	202	179 (88.6)	1 (0.5)	20 (9.9)
	Dapa 5 mg	212	186 (87.7)	0 (0.0)	24 (11.3)
	Dapa 10 mg	196	178 (90.8)	0 (0.0)	19 (9.7)

a Discontinuation due to lack of efficacy is determined from the glycemic control page of the CRF, or study termination page for study D1690C00005

Outcomes and estimation

HbA1c change from baseline

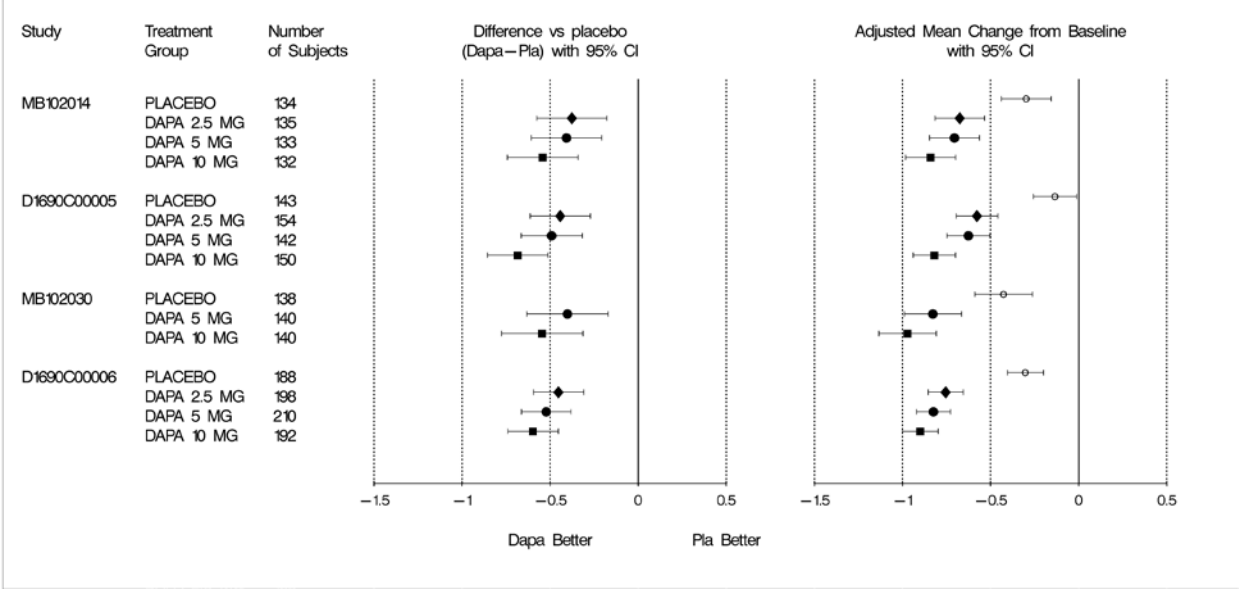
The Phase III placebo-controlled add-on combination therapy studies included MB102014 (add-on to metformin study), D1690C00005 (add-on to SU study), MB102030 (add-on to TZD study), and D1690C00006 (add-on to insulin ± OAD study). The 5 mg and 10 mg dapagliflozin doses were included in all four studies, while the 2.5 mg dapagliflozin dose was included in all studies with the exception of MB102030. In the four studies, treatment with dapagliflozin resulted in significant reductions in HbA1c at Week 24 versus placebo that appeared to be dose dependent. Treatment with dapagliflozin 10 mg consistently demonstrated HbA1c reductions of at least 0.5% in each of the four studies; the 2.5 mg and 5 mg doses provided statistically significant but lesser degrees of HbA1c reduction.

Table 17. HbA1c (%) change from baseline at Week 24 (LOCF), excluding data after rescue - Phase III placebo-controlled add-on combination therapy studies (MB102014, D1690C00005, MB102030, and D1690C00006), Efficacy Analysis Data Set

	MB102014	**D1690C00005**	**MB102030**	**D1690C00006**
Treatment	Metformin	SU	TZD	Insulin
Placebo	(N=137)	(N=145)	(N=139)	(N=193)
N#	134	143	138	188
Baseline mean (SD)	8.11 (0.959)	8.15 (0.741)	8.34 (1.003)	8.46 (0.764)
Mean at Week 24 (SD)	7.79 (1.184)	8.00 (0.928)	7.93 (1.375)	8.19 (0.972)
Adj. mean change (SE)	-0.30 (0.0718)	-0.13 (0.0625)	-0.42 (0.0834)	-0.30 (0.0521)
Dapagliflozin 2.5 mg/day	(N=137)	(N=154)	-	(N=202)
N#	135	154	-	198
Baseline mean (SD)	7.99 (0.897)	8.11 (0.749)	-	8.47 (0.776)
Mean at Week 24 (SD)	7.34 (0.934)	7.54 (0.871)	-	7.74 (0.815)
Adj. mean change (SE)	-0.67 (0.0715)	-0.58 (0.0602)	-	-0.75 (0.0507)
Difference vs PLA (95% CI)	-0.38 (-0.58,-0.18)	-0.44 (-0.61,-0.27)	-	-0.45 (-0.59,-0.31)
p-value vs PLA	0.0002 *	<0.0001 *	-	<0.0001 *
Dapagliflozin 5 mg/day	(N=137)	(N=142)	(N=141)	(N=211)
N#	133	142	140	210
Baseline mean (SD)	8.17 (0.964)	8.12 (0.781)	8.40 (1.026)	8.61 (0.893)
Mean at Week 24 (SD)	7.42 (0.937)	7.49 (0.924)	7.56 (1.068)	7.76 (0.898)
Adj. mean change (SE)	-0.70 (0.0722)	-0.63 (0.0627)	-0.82 (0.0828)	-0.82 (0.0493)
Difference vs PLA (95% CI)	-0.41 (-0.61,-0.21)	-0.49 (-0.67,-0.32)	-0.40 (-0.63, -0.17)	-0.52 (-0.66,-0.38)
p-value vs PLA	<0.0001 *	<0.0001 *	0.0007 *	<0.0001 *
Dapagliflozin 10 mg/day	(N=135)	(N=151)	(N=140)	(N=194)
N#	132	150	140	192
Baseline mean (SD)	7.92 (0.818)	8.07 (0.792)	8.37 (0.963)	8.58 (0.818)
Mean at Week 24 (SD)	7.13 (0.941)	7.27 (0.843)	7.40 (1.216)	7.66 (0.823)
Adj. mean change (SE)	-0.84 (0.0724)	-0.82 (0.0610)	-0.97 (0.0828)	-0.90 (0.0515)
Difference vs PLA (95% CI)	-0.54 (-0.74,-0.34)	-0.68 (-0.86,-0.51)	-0.55 (-0.78, -0.31)	-0.60 (-0.74,-0.45)
p-value vs PLA	<0.0001 *	<0.0001 *	<0.0001 *	<0.0001 *

(*) Significant p-value compared to placebo: the primary endpoint was tested at alpha=0.019 (alpha=0.027 in study MB102030) applying Dunnett's adjustment.
N is the number of subjects in the Efficacy Analysis Data Set (randomized subjects in BMS studies, Full Analysis Set in AZ studies).
N# is the number of subjects in the efficacy data set with non-missing baseline and Week 24 (LOCF) values.

Figure 8. HbA1c (%) adjusted mean change from baseline at Week 24 (LOCF), excluding data after rescue - Phase III add-on combination therapy studies (MB102014, D1690C00005, MB102030, and D1690C000006), Efficacy Analysis Data Set



Studies MB102030 and D1690C00006 included stratification of subpopulations at randomization. Study MB102030 was stratified according to baseline OAD use; no signal for potential treatment interaction for the primary efficacy variable was observed in a subgroup analysis based on enrolment strata. In study D1690C00006, which was stratified according to background OAD therapy, the effect of dapagliflozin was similar in subjects who were treated with insulin alone and in subjects who were treated with both insulin and an OAD.

The results of longitudinal repeated measures analyses of HbA1c at Week 24, either excluding or including data after rescue, were consistent with the results of the primary efficacy analysis. In studies MB102014, D1690C00005 and MB102030, slightly smaller differences were generally seen between dapagliflozin doses and placebo when data after rescue were included, whereas in study D1690C00006, results were similar whether data after rescue were included or excluded.

Thus a clinically relevant add-on effect of the 10 mg dose on HbA1c was observed in all add-on studies.

Other glycaemic variables

The secondary endpoints all supported the outcome of the primary endpoint.

FPG change from baseline

FPG change from baseline at Week 24 was a secondary variable in all add-on combination therapy studies. Reductions in FPG from baseline to Week 24 compared to placebo were observed for all dapagliflozin treatment groups across the add-on combination studies. Comparisons with placebo were statistically significant except for the 2.5 mg group in study D1690C00005 and the 5 mg group in study D1690C00006 for which formal statistical testing was not performed based on the hierarchical closed testing procedure; however, nominal p-values were generated. The reductions were numerically similar at each dose across all studies and appeared to be dose ordered.

PPG change from baseline

Change in 2-hour PPG levels as a response to an OGTT from baseline to Week 24 was a secondary variable in studies D1690C00005 and MB102030.

Dapagliflozin lowered 2-hour PPG levels as a response to an OGTT from baseline to Week 24 (LOCF), compared to placebo, across all dapagliflozin groups in both studies. This effect was more pronounced in study MB102030, likely due to a higher baseline mean PPG in this study (293.6 mg/dL) compared to study D1690C00005 (158.6 mg/dL). For the 2.5 mg group in study D1690C00005, formal statistical testing was not performed based on the hierarchical closed testing procedure (nominal p-value calculated). There was no clear dose relationship for the dapagliflozin effect on PPG within either study, in contrast to PPG after MTT results in study MB102032, where a dose-dependent effect was observed.

Proportion of subjects achieving therapeutic glycaemic response

The proportion of subjects achieving a therapeutic glycaemic response defined as HbA1c <7.0% was a secondary endpoint in studies MB102014, D1690C00005 and MB102030 and an exploratory endpoint in study D1690C00006.

Treatment with dapagliflozin 5 mg and 10 mg led to a statistically significantly greater proportion of subjects achieving a therapeutic glycaemic response defined as HbA1c <7.0% in studies MB102014, D1690C00005 and MB102030, in which this was a pre-specified secondary variable. Statistical significance was not reached for the 2.5 mg dose in any of the studies. In study D1690C00005, formal statistical testing was not performed for the 2.5 mg dose based on the hierarchical closed testing procedure. Similar results were observed for study D1690C00006; only nominal p-values were calculated for this exploratory endpoint. The effect was consistent across all four studies and appeared to be dose-dependent, with the greatest proportion of subjects achieving HbA1c < 7.0% in the dapagliflozin 10 mg groups in each study.

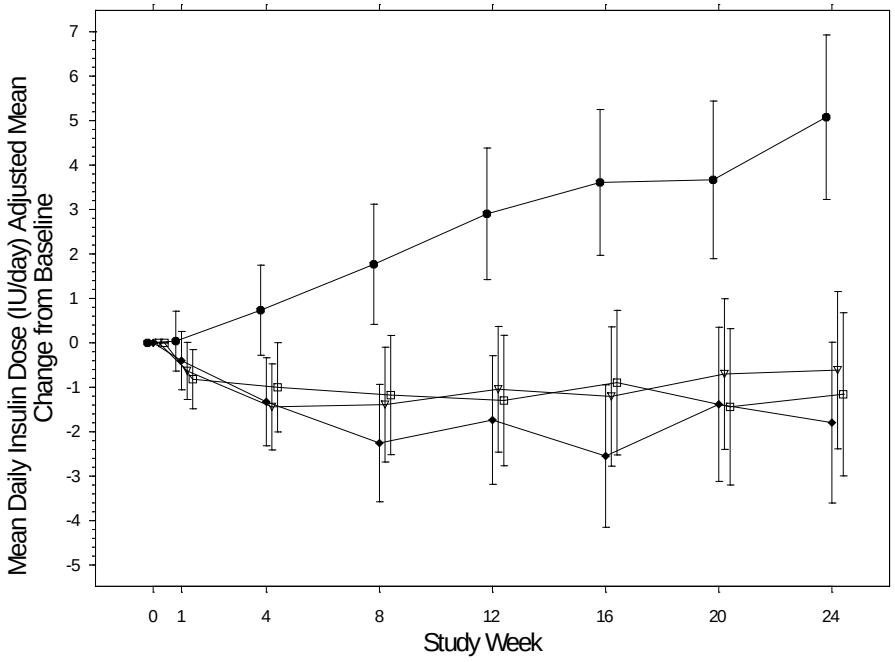
Insulin dose

Mean daily insulin dose (adjusted mean change from baseline at Week 24 (LOCF), including data after insulin up-titration) and the proportion of subjects with a decrease of at least 10% in daily insulin dose were assessed as secondary endpoints in study D1690C00006.

Treatment with dapagliflozin resulted in a lower calculated mean daily insulin dose from baseline to Week 24 compared to placebo. The change in dose from baseline to 24 weeks (LOCF), compared to placebo, was statistically significant for all dapagliflozin groups.

Most of the reduction in insulin dose in the dapagliflozin groups occurred over the first 8 weeks, while a gradual increase in dose over the duration of the 24 weeks was observed in the placebo group. The effect was maintained up to 48 weeks as shown by exploratory analyses in the long-term extension treatment period. The data show that dapagliflozin appears to have an “insulin saving” effect.

Figure 9. Mean daily insulin dose (IU/day) adjusted mean change from baseline over time to Week 24 (LOCF), including data after insulin up-titration - Phase III add-on combination study with insulin as background therapy (Study D1690C00006), Efficacy Analysis Data Set



LOCF Sample Size per Time Point

PLA + INS	193	190	191	191	191	191	191	191
DAPA 2.5MG + INS	202	200	200	200	200	200	200	200
DAPA 5MG + INS	211	209	209	209	209	209	209	209
DAPA 10MG + INS	194	194	194	194	194	194	194	194

(N= 193) PLA + INS
(N= 202) DAPA 2.5MG + INS
(N= 211) DAPA 5MG + INS
(N= 194) DAPA 10MG + INS

Subjects in the full analysis set
Mean value based on an ANCOVA model with treatment group and stratum as effects and baseline value as a covariate
Error bars represent 95% confidence intervals for the adjusted mean change from baseline
Treatment symbols shifted horizontally to prevent error bar overlapping
Program Path: /dbs/prod/clin/programs/mb/102/033/stcsr01/rpt/graph

Variables related to body weight and body composition

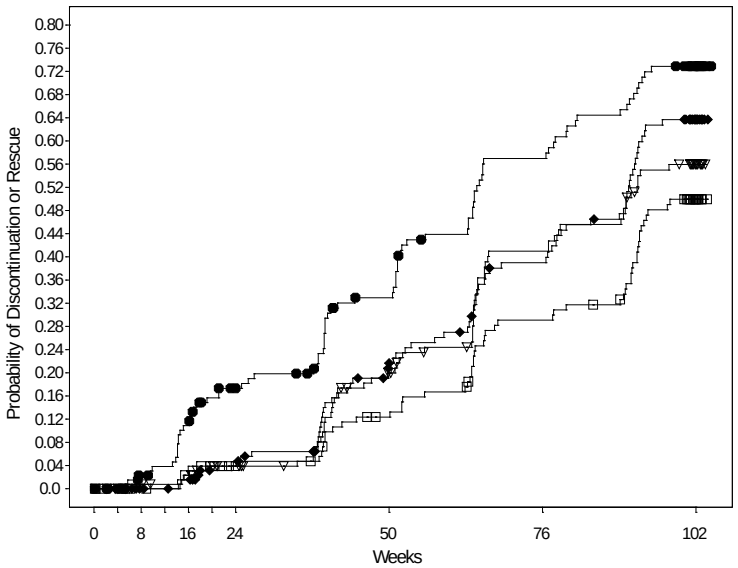
Change in total body weight at 24 weeks was a secondary variable in all four placebo-controlled add-on combination therapy studies. Across the four add-on combination studies, treatment with dapagliflozin 2.5 mg, 5 mg, and 10 mg overall resulted in statistically significant reductions in body weight compared to placebo except for the 2.5 mg dose in study D1690C00005 (add-on to SU), where the reductions were not statistically different from placebo. A dose dependent effect was for the most part observed in these four studies.

Ancillary analyses

Study MB102014

When dapagliflozin was given in combination with metformin the risk of treatment failure was lower for all dapagliflozin doses compared to placebo.

Figure 10. Time to rescue or discontinuation for failing to achieve pre-specified glycaemic targets to Week 102 - Phase III placebo-controlled add-on combination study with metformin as background therapy (MB102014) ST+LT treatment, Efficacy Analysis Data Set



Number of Subjects at Risk

PLA + MET	137	134	126	123	114	103	99	74	46	20
DAPA 2.5 MG + MET	137	136	131	130	127	119	118	91	65	26
DAPA 5MG + MET	137	135	130	128	126	121	118	92	64	28
DAPA 10MG + MET	135	132	130	129	125	120	116	101	80	32

Symbols represent censored observations.
Week is not the scheduled visit week but the actual number of days from the first dose of double-blind study medication divided by 7.
Number of subjects at risk is the number of subjects at risk at the beginning of the period.
The results beyond Week 102 should be interpreted with caution as the number of subjects at risk might be limited.
Program Path: /gbs/prod/clin/programs/mb/102/014/ltcsr01/rpt/graphs

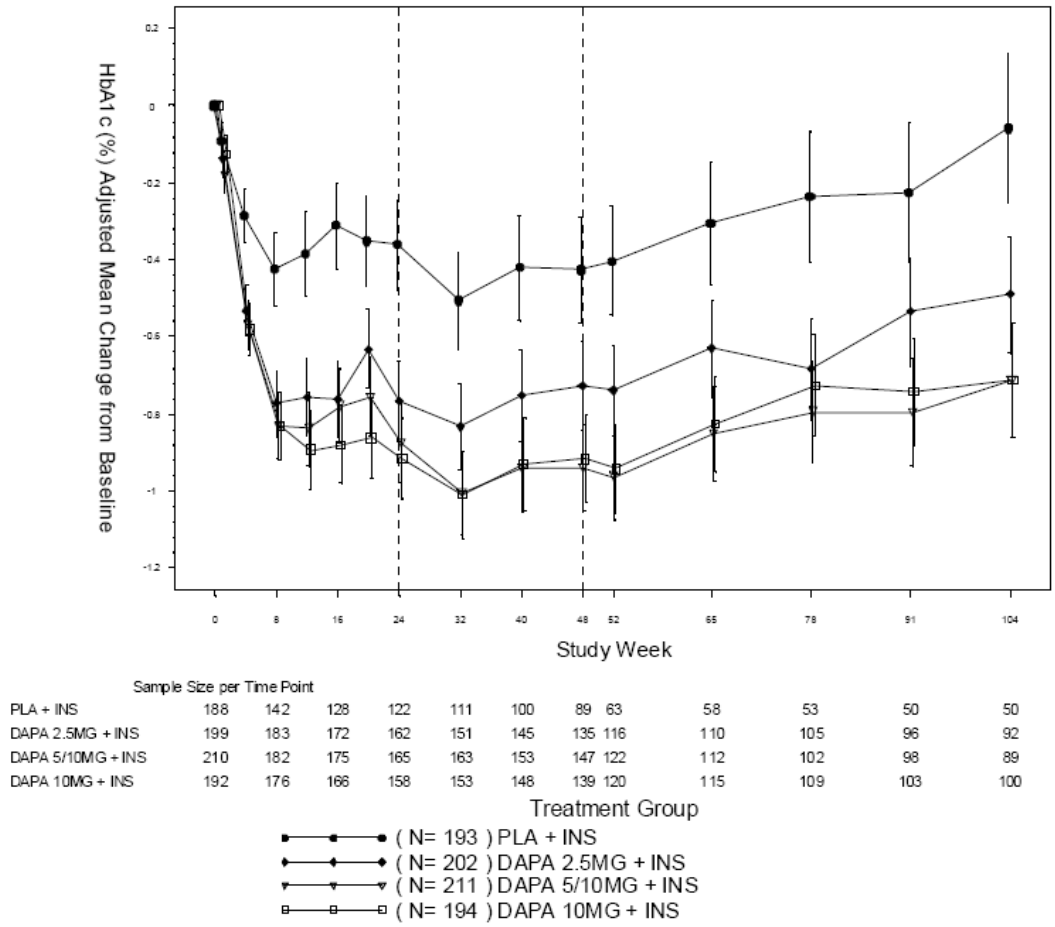
Study D1690C00006

This study had a 24-week short-term treatment period with a 24-week double-blind extension period I and a 56-week double-blind extension period II incorporating a switch of dapagliflozin 5 to 10 mg during extension period II to evaluate the efficacy and safety of dapagliflozin 2.5 mg, 5/10 mg, and 10 mg as add-on therapy to insulin in adult subjects with type 2 diabetes mellitus (T2DM) with inadequate glycaemic control. Subjects were randomized to one of the dapagliflozin groups or placebo at a 1:1:1:1 ratio.

In total 1240 subjects were enrolled in the extension period out of which 808 were randomized. Overall, approximately 64% of the subjects completed LT2 and 63% of subjects completed the study. One subject in the dapagliflozin 2.5 mg group did not complete the study after completing LT2. The number of subjects completing the study was higher in the dapagliflozin groups than in the placebo group. The most frequent reason for not completing the study was withdrawal of informed consent and 'other'.

At week 104, a mean reduction in HbA1c compared to baseline was observed in all dapagliflozin treatment groups using repeated measures analyses and excluding data after insulin up-titration. The reductions were clinically significant (differences compared to placebo of more than 0.5%) in the dapagliflozin 5/10 and 10 mg groups. The HbA1c reductions from baseline observed in the dapagliflozin groups at week 104 were similar to those at week 48, whereas in the placebo group the initial reductions in HbA1c observed at weeks 24 and 48 were not observable any longer.

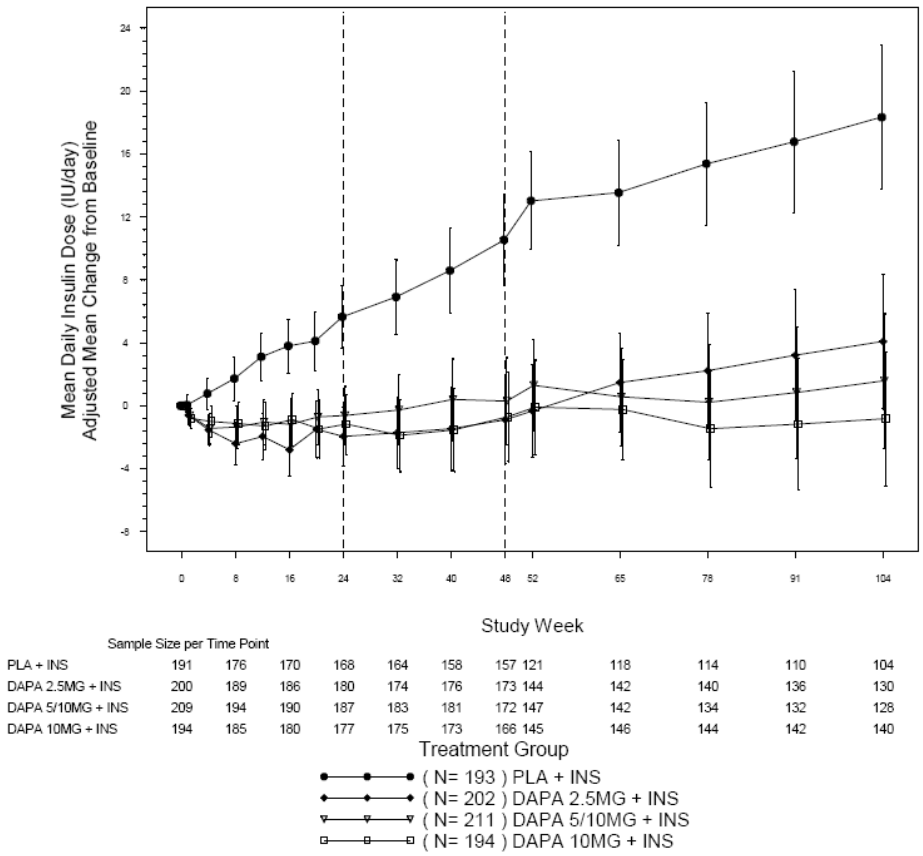
Figure 11. Adjusted mean change from baseline over time in HbA1c (%) for the 24-week short-term treatment period + the 24-week long-term extension period I + 56-week long-term extension period II, excluding data after insulin up-titration (full analysis set) (D1690C00006)



The proportion of subjects who discontinued or received insulin up-titration due to lack of glycaemic control prior to or at week 104 was higher in the placebo group (50.4%) than in the dapagliflozin groups (29.1% in the 2.5 mg, 26.5% in the 5/10 mg, and 25.5% in the 10 mg groups, percent adjusted).

There was no meaningful change in calculated mean daily insulin dose at week 48 compared to baseline in the dapagliflozin groups, while in the placebo group, an increase by around 10 IU was observed. At week 104, the increase of the calculated mean daily insulin dose in the placebo group observed at week 48 had almost doubled, whereas there was only a slight increase in dapagliflozin 2.5 mg group and the mean insulin dose in the dapagliflozin 5/10 mg and 10 mg groups remained stable.

Figure 12. Adjusted mean change from baseline over time in calculated mean daily insulin dose (IU/day) for the 24-week ST treatment period + the 24-week long-term extension period I + 56-week long-term extension period II , including data after insulin up-titration (full analysis set) (D1690C00006)



The modest weight loss compared to baseline observed in the dapagliflozin groups at week 48 improved further at week 104, while subjects in the placebo group did not show a meaningful mean change in body weight at week 48, and showed a slight increase at week 104. The effect was most pronounced in the dapagliflozin 10 mg group. Analysis in subjects completing ST + LT1 confirmed that weight loss in the dapagliflozin groups observed at week 48 remained stable over the 56-week second extension period (-0.02, -0.10, and -0.01 kg in the 2.5, 5/10, and 10 mg groups, respectively) whereas in the placebo group there was a small increase (0.56 kg).

Seated SBP showed a mean decrease from baseline to week 104 in all treatment groups. Decreases were slightly more pronounced in the dapagliflozin 2.5, 5, and 10 mg groups (-5.12, -4.70, and -5.92 mmHg, respectively) than in the placebo group (-2.05 mmHg) (analyses excluding data after insulin up-titration). The effect was maintained from week 48 to week 104 in all dapagliflozin treatment groups.

Seated DBP showed a small mean decrease from baseline to week 104 in all treatment groups. Decreases were slightly more pronounced in the dapagliflozin 2.5 and 10 mg groups (-3.42 and -3.74 mmHg) than in the placebo and dapagliflozin 5/10 mg group (-2.36 and -2.30 mmHg) (analyses excluding data after insulin up-titration,). There was no meaningful change in seated DBP from week 48 to week 104 in any treatment group.

Specific issues applying to study D1690C00004: active comparator study

Study D1690C00004 is a multicenter, randomized, double-blind, active-controlled, parallel group study with the primary objective to evaluate the safety and efficacy of dapagliflozin in combination with metformin compared with a sulphonylurea in combination with metformin in patients with T2DM who have inadequate glycaemic control on metformin therapy alone.

Methods

Study Participants

95 sites enrolled subjects in 10 countries.

Treatments

Study D1690C00004 consists of 4 periods: a metformin dose stabilization period (8 weeks), a 2 week placebo lead-in, a study drug titration period (18 weeks) after randomization and a maintenance period (34 weeks). Eligible patients were randomized to receiving Dapagliflozin or Glipizide or matching placebo. In addition, all patients received open-label metformin at a dose of 1500, 2000 or 2500 mg/day based on his/her metformin dose and other OAD therapy during the last 8 weeks prior to enrolment. Study drug was taken orally, 30 minutes before a meal. Dapagliflozin or matching placebo had to be taken once daily and glipizide or placebo had to be taken once (dose levels 1 and 2) or twice daily (dose level 3) depending on the dose directed by the investigator.

During the titration phase, subjects were up-titrated to the optimal effect (FPG <110 mg/dL, <6.1 mmol/L,) or the highest tolerable dose. All subjects started with the investigational product at dose level 1 (dapagliflozin 2.5 mg or glipizide 5 mg). They could be up-titrated in 3 week intervals to dose level 2 (dapagliflozin 5 mg or glipizide 10 mg) and 3 (dapagliflozin 10 mg or glipizide 20 mg). During the maintenance phase, subjects continued on the dose level they have reached at the end of the titration period. At any time during the study, the investigational product could be down-titrated to mitigate recurrent hypoglycaemic events. Rescue was not allowed for the 52-week study period.

Objectives

The primary objective of study D1690C00004 was to examine whether, after 52 weeks of oral administration of double-blind treatment, the absolute change from baseline in HbA1c level with dapagliflozin plus metformin was non-inferior to glipizide (sulphonylurea) plus metformin in subjects with T2DM who had inadequate glycaemic control on 1500 mg/day or higher doses of metformin therapy alone.

Sample size

To demonstrate non-inferiority of dapagliflozin in comparison with glipizide as add-on therapy to metformin for changes from baseline to week 52 in HbA1c within a non-inferiority margin of 0.35%, assuming a standard deviation SD = 1.25%, and at a one-sided significance level of 0.025, 280 evaluable subjects were needed in each treatment group to provide approximately 90% power (given a true difference of zero between the two treatment groups). Assuming a 5% exclusion rate from the full analysis set, 295 subjects per treatment group were needed for the full analysis set. Additionally, to have 90% power for the per-protocol population, assuming a 25% exclusion rate from the per-protocol population, 373 subjects per treatment group (746 subjects total) were planned for randomization.

In 6-month dapagliflozin studies, a standard deviation (SD) of 1.1% was selected based upon the Phase II dapagliflozin study as well as historical data from other diabetes programs. A slightly larger SD, 1.25%, was chosen for this study because of the titration regimen for dapagliflozin and the longer duration of the trial.

Results

Participant flow

Table 18. Study D1690C00004: subjects status at end of 52 week short-term treatment period

Table 8 Subject status at end of 52-week short-term treatment period (safety analysis set)

Protocol: D1690C00004 Page 1 of 1

End of 52-Week Short-term Double-blind Treatment Period Subject Status Summary
Safety Analysis Set

	DAPA + MET	GLIP + MET	Total
SUBJECTS	406	408	814
SUBJECTS COMPLETING THE PERIOD (%)	322 (79.3)	314 (77.0)	636 (78.1)
SUBJECTS NOT COMPLETING THE PERIOD (%)	84 (20.7)	94 (23.0)	178 (21.9)
REASON FOR NOT COMPLETING THE PERIOD (%)			
INCORRECT ENROLMENT	1 (0.2)	1 (0.2)	2 (0.2)
ADVERSE EVENT	33 (8.1)	19 (4.7)	52 (6.4)
SUBJECT NO LONGER MEETS STUDY CRITERIA	6 (1.5)	27 (6.6)	33 (4.1)
SUBJECT WITHDREW CONSENT	23 (5.7)	32 (7.8)	55 (6.8)
LOST TO FOLLOW-UP	3 (0.7)	3 (0.7)	6 (0.7)
POOR/NON-COMPLIANCE	5 (1.2)	1 (0.2)	6 (0.7)
SAFETY	1 (0.2)	0	1 (0.1)
DEATH	1 (0.2)	3 (0.7)	4 (0.5)
OTHER	11 (2.7)	8 (2.0)	19 (2.3)
SUBJECTS CONTINUING IN THE STUDY (%)	315 (77.6)	309 (75.7)	624 (76.7)
SUBJECTS NOT CONTINUING IN THE STUDY (%)	91 (22.4)	99 (24.3)	190 (23.3)
REASON FOR NOT CONTINUING IN THE STUDY (%)			
INCORRECT ENROLMENT	1 (0.2)	1 (0.2)	2 (0.2)
ADVERSE EVENT	33 (8.1)	21 (5.1)	54 (6.6)
SUBJECT NO LONGER MEETS STUDY CRITERIA	6 (1.5)	27 (6.6)	33 (4.1)
SUBJECT WITHDREW CONSENT	29 (7.1)	34 (8.3)	63 (7.7)
LOST TO FOLLOW-UP	3 (0.7)	3 (0.7)	6 (0.7)
POOR/NON-COMPLIANCE	5 (1.2)	1 (0.2)	6 (0.7)
SAFETY	1 (0.2)	0	1 (0.1)
DEATH	1 (0.2)	3 (0.7)	4 (0.5)
OTHER	12 (3.0)	9 (2.2)	21 (2.6)

Percentages reported are based on the total number of subjects in each treatment group.
Subjects continuing in the study refers to subjects entering the long-term treatment period.

Recruitment

The short-term phase of study D1690C0004 was conducted from 31 March 2008 until 15 December 2009, the long-term extension period is currently ongoing.

Conduct of the study

There were 3 amendments to the original protocol which were considered acceptable.

Baseline data

At study start, main demographic characteristics were as follows [mean (range)] or proportion:

Gender*:44.9% female, 55.1% male,

Age*: 58.4y (24-80), 27.5% of patients were ≥ 65 y, 3.5% of patients were ≥ 75 y,

BMI*: 31.47 kg/m^2 (19.9- 45.5)*, 95 % had an BMI ≥ 25 kg/$m^2$and 56.2% and had a BMI ≥ 30 kg/m^2

Race*: white 81.1%, Asian 7.6%, Black/African American 6.2%,

Ethnicity*: Hispanic/Latino 25.3%,

Geographic region: Europe: 74.4%, Latin America: 25.6%

*: Full analysis set

In general the treatment groups were balanced with respect to demographic and baseline characteristics.

Numbers analysed

Table 19. Disposition of subjects in the short-term treatment period of the active comparator study, randomized subjects

Study	Treatment Group	No. Randomized and Treated	Completed n (%)	D/C for lack of efficacy[a] n (%)	Rescued n (%)
Phase 3 placebo-controlled studies					
Phase 3 active comparator Add-on combination Study					
D1690C00004[b]					
	SU (titrated dosing)	408	314 (77.0)	15 (3.7)	NA
	Dapa (titrated dosing)	406	322 (79.3)	1 (0.2)	NA

Outcomes and estimation

HbA1c change from baseline

D1690C00004, the active comparator study, was the only Phase 3 study to include a dose-titration scheme due to dosing recommendations for the active comparator, glipizide. The titration dosing strategy also provided an opportunity to assess percentage of subjects reaching the top dose of dapagliflozin 10 mg based on FPG measurements and tolerability, when dosing was started at the 2.5 mg dose level. Subjects who had failed treatment with metformin IR monotherapy were randomized 1:1 to glipizide or dapagliflozin (5 mg or 2.5 mg starting dose, respectively), and were up-titrated over 18 weeks to optimal glycaemic effect (FPG <110 mg/dL) or to the highest dose level (up to 20 mg glipizide and 10 mg dapagliflozin) as tolerated. Thereafter, doses were kept constant, except for down-titration in the event of hypoglycaemia. At the end of the titration period, 87% of subjects in the dapagliflozin group had been titrated to the maximum study dose (10 mg), versus 73% in the glipizide group (20 mg). Of those subjects receiving dapagliflozin, 0.5% subsequently required down-titration, versus 5.1% of subjects receiving glipizide.

Treatment with either dapagliflozin or glipizide resulted in a mean reduction of 0.52% in HbA1c compared to baseline at Week 52. The effect observed for glipizide is acceptable and confirms the validity of the study. Dapagliflozin was non-inferior to glipizide for change in HbA1c at Week 52 according to statistical criteria (non-inferiority margin = 0.35%, with 95% confidence interval completely below margin). Although the non-inferiority margin may be considered to be somewhat generous, the outcome supports the conclusion that dapagliflozin is non-inferior to glipizide.

In the dapagliflozin group, most of the HbA1c effect occurred by Week 12, followed by a further slight mean decrease until Week 52. In the glipizide group, there was a rapid decrease in HbA1c from baseline to Week 18 followed by a reversal in direction until Week 52; this pattern is consistent with the glycaemic effect of sulphonylureas in other long-term studies. At Week 52, the mean change from baseline in HbA1c was identical in both treatment groups.

The per-protocol analysis resulted in slightly larger estimated reductions than the primary analysis, with mean HbA1c reduction at Week 52 in the dapagliflozin group of -0.55% and -0.56% for the glipizide group. The results of longitudinal repeated measures analyses of HbA1c at Week 52 were consistent with the results of the primary efficacy analysis. The data on the per-protocol population further support that non-inferiority has been shown.

Table 20. HbA1c (%) adjusted mean change from baseline at Week 52 (LOCF), excluding data after rescue -Phase III active comparator study (D1690C00004), Efficacy Analysis Data Set

	Dapa + metformin	Glip + metformin
Primary: HbA1c (%)		
N	(N=400)	(N=401)
N#	400	401
Baseline mean (SD)	7.69 (0.855)	7.74 (0.886)
Mean at Week 52 (SD)	7.19 (0.760)	7.21 (1.090)
Adj. mean change (SE)	-0.52 (0.0403)	-0.52 (0.0402)
Difference vs glip + met (95% CI)	0.00 (-0.11, 0.11)	-
Non-inferiority p-value vs glip + metformin	<0.0001 *	-

N is the number of subjects in the Efficacy Analysis Data Set (randomized subjects in BMS studies, Full Analysis Set in AZ studies).
N# is the number of subjects in the efficacy data set with non-missing baseline and Week 52 (LOCF) values.
(*) Significant p-value: Primary endpoint is significantly non-inferior (alpha=0.025 one-sided) if upper limit of 95% confidence interval is <0.35%,

Other glycaemic variables

Hypoglycaemic events

A comparison of hypoglycaemic events between dapagliflozin and glipizide was a secondary efficacy endpoint in study D1690C00004. There were less than one-tenth as many subjects in the dapagliflozin group (3.5%; n=14), compared to the glipizide group (40.8%; n=162), who experienced at least one event of hypoglycaemia over 52 weeks of treatment ($p < 0.0001$).

Glycaemic response

The proportion of subjects achieving glycaemic response (defined as HbA1c ≤6.5% at Week 52) was lower in the dapagliflozin (16.5%) than in the glipizide group (27.5%) as was the proportion of subjects who had an HbA1c ≥7% at baseline and <7% at Week 52 (27.4% in the dapagliflozin group and 32% in the glipizide group).

Although a higher percentage of subjects treated with glipizide achieved a therapeutic glycaemic response, discontinuations due to lack of glycaemic control were numerically more frequent in the glipizide comparator group. One subject in the dapagliflozin group (0.3%) and 15 subjects in the glipizide group (3.7%) were discontinued from the study due to lack of glycaemic control.

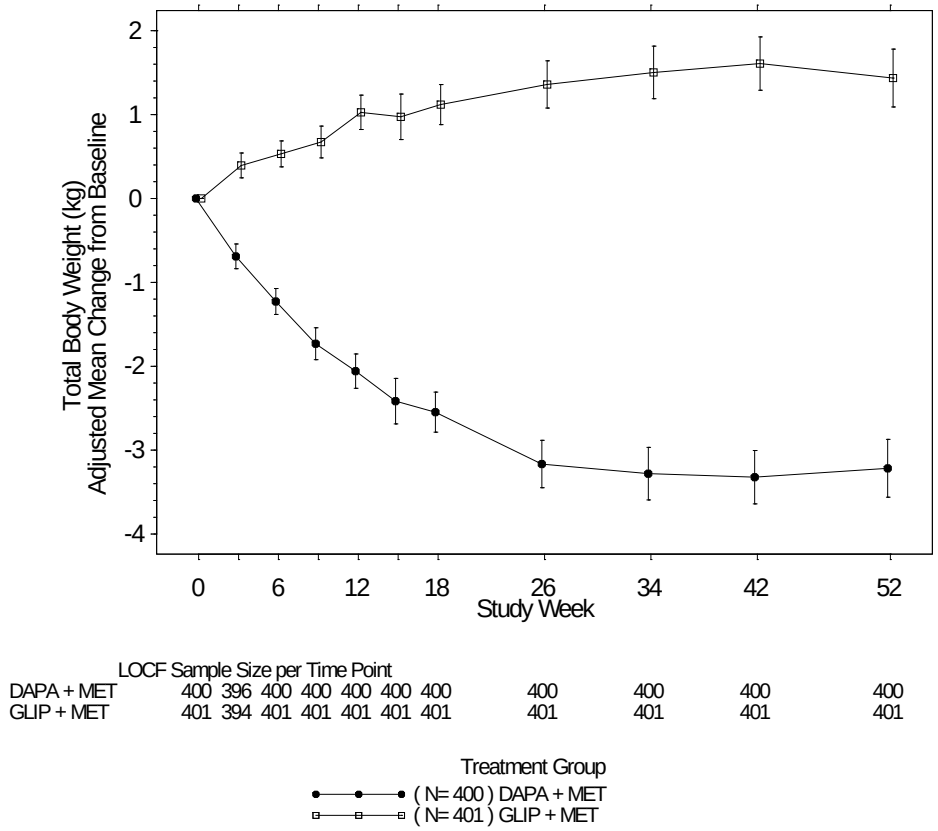
Variables related to body weight

The short term treatment period in study D1690C00004 was 52 weeks. A statistically significant mean reduction in body-weight-related variables from baseline to Week 52 compared to glipizide was observed in the dapagliflozin treatment group.

A statistically significant and clinically relevant higher proportion of subjects in the dapagliflozin group (33.3%), compared to glipizide (2.5%), had body weight reductions of at least 5% from baseline to Week 52.

Subjects in the dapagliflozin group showed a mean decrease in body weight from baseline to Week 26 which was sustained through Week 52, while subjects in the glipizide group displayed a mean increase in body weight.

Figure 13. Weight (kg) adjusted mean change from baseline over time to Week 52 week (LOCF) - Phase III active comparator study (D1690C00004), Efficacy Analysis Data Set



Subjects in the full analysis set.
Mean value based on an ANCOVA model with treatment group as an effect and baseline value as a covariate.
Error bars represent 95% confidence intervals for the adjusted mean change from baseline.
Treatment symbols shifted horizontally to prevent error bar overlapping.
Program Path: /ghs/prod/glip/programs/mb/102/022/stcsr01/rpt/graphs

A mean body weight decrease of -3.35 kg was observed in subjects with a BMI ≥27 kg/m2 in the dapagliflozin group, and a mean increase of 1.41 kg was observed in the glipizide group (nominal p-value for the difference between dapagliflozin and glipizide <0.0001). These findings were similar to the mean weight changes seen in the overall study population.

This is the only pivotal study where a direct comparison between an established therapy and dapagliflozin on body weight is made. The data support a beneficial effect of dapagliflozin on body weight.

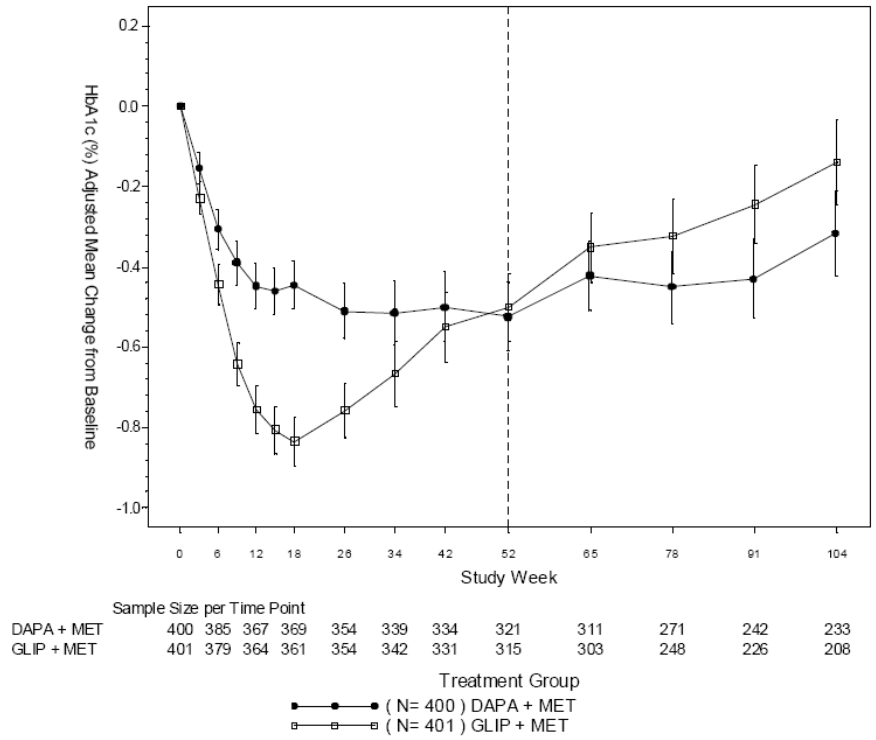
Ancillary analyses

This study had a 52-week short-term treatment period (ST) followed by a 52-week extension period I (LT1) and a 104-week extension period II to evaluate the efficacy and safety of dapagliflozin as add-on therapy to metformin compared with glipizide as add-on therapy to metformin in adult subjects with T2DM. Data from the initial 52 week period was initially provided and final data from 52 week extension period I were submitted during the evaluation.

In total, 1217 subjects were enrolled and 816 subjects were randomized. A total of 56.2% and 50.0% of subjects in the dapagliflozin and glipizide group, respectively, completed LT1. Most common reasons for not completing LT1 were failure to meet the study criteria and withdrawal of consent.

At week 104, HbA1c showed a larger mean reduction compared to baseline in the dapagliflozin group (-0.32%) than in the glipizide group (-0.14%), whereas the mean decrease in HbA1c from baseline to week 52 was comparable in both groups when non-inferiority of efficacy of dapagliflozin compared to glipizide as add-on therapy to metformin was demonstrated (-0.52% vs. -0.50% in the dapagliflozin and glipizide groups, respectively).

Figure 14. Adjusted mean change from baseline over time in HbA1c (%) for ST +LT1 (full analysis set)



A total of 56/400 subjects in the dapagliflozin group (14.5%) and 89/401 subjects in the glipizide group (21.6%) were discontinued from the study due to lack of glycaemic control.

Subjects in the dapagliflozin group showed a mean decrease of 3.31 kg in body weight from baseline to week 26 after which body weight remained almost stable until week 104. In the glipizide group, a mean increase of 1.55 kg in body weight was observed from baseline to week 52, followed by a slight mean decrease until week 104. At week 104, the mean change from baseline in body weight was -3.70 kg in the dapagliflozin group and 1.36 kg in the glipizide group.

Seated SBP showed a mean decrease from baseline to week 52 in the dapagliflozin group (-3.79 mmHg) compared to a slight mean increase in the glipizide group (0.93 mmHg). At week 104, the group difference was maintained but on a slightly higher level than at week 52 (-2.69 mmHg vs. 1.20 mmHg change compared to baseline in the dapagliflozin and glipizide groups, respectively).

Seated DBP showed a slight mean decrease from baseline to week 52 in both treatment groups (-1.30 mmHg in the dapagliflozin group and -0.43 mmHg in the glipizide group). At week 104, both groups showed a comparable reduction in DBP (-1.95 mmHg vs. -1.51 mmHg change compared to baseline in the dapagliflozin and glipizide groups, respectively).

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 respective sections in the overview).

Table 21. Summary of Efficacy for trial MB102013

Title: A multicenter, randomized, double-blind, placebo-controlled, parallel group, phase 3 trial to evaluate the safety and efficacy of dapagliflozin as monotherapy in subjects with type 2 diabetes who have inadequate glycemic control with diet and exercise					
Study identifier	Study code: MB102013 (Monotherapy) ClinicalTrials.gov identifier: NCT00528372				
Design	Multicenter, randomized, double-blind, placebo-controlled, parallel group				
	Duration of main phase:	24 weeks			
	Duration of Run-in phase:	7 to 14 day lead-in period			
	Duration of Extension phase:	78 weeks			
Hypothesis	Superiority after 24 weeks (Group 1 QAM)				
Treatments groups	Dapa 2.5 mg (Group 1 QAM)	Dapagliflozin 2.5 mg, QAM, 24 weeks, 65 randomized (Group 1)			
	Dapa 5 mg (Group 1 QAM)	Dapagliflozin 5 mg, QAM, 24 weeks, 64 randomized (Group 1)			
	Dapa 10 mg (Group 1 QAM)	Dapagliflozin 10 mg, QAM, 24 weeks, 70 randomized (Group 1)			
	Placebo	Placebo, 24 weeks, 75 randomized (Group 1)			
	Dapa 2.5 mg (Group 1 QPM)	Dapagliflozin 2.5 mg, QPM, 24 weeks, 67 randomized (Group 1)			
	Dapa 5 mg (Group 1 QPM)	Dapagliflozin 5 mg, QPM, 24 weeks, 68 randomized (Group 1)			
	Dapa 10 mg (Group 1 QPM)	Dapagliflozin 10 mg, QPM, 24 weeks, 76 randomized (Group 1)			
	Dapa 5 mg (Group 2)	Dapagliflozin 5 mg, 24 weeks, 34 randomized (Group 2)			
	Dapa 10 mg (Group 2)	Dapagliflozin 10 mg, 24 weeks, 39 randomized (Group 2)			
Endpoints and definitions	Primary endpoint	HbA1c	Change from baseline in HbA1c at 24 weeks (Group 1 QAM)		
	Secondary endpoint	FPG	Change from baseline in FPG at 24 weeks (Group 1 QAM)		
	Secondary endpoint	TBW	Change from baseline in total body weight at 24 weeks (Group 1 QAM)		
Database lock	24 April 2009				
Results and Analysis					
Analysis description	Primary Analysis				
Analysis population and time point description	Randomized subjects data set, consisting of all randomized subjects who took at least one dose of double-blind study medication during the short-term (24 week) double-blind period				
Descriptive statistics and estimate variability	Treatment group	Placebo	Dapa 2.5 mg (Group 1 QAM)	Dapa 5 mg (Group 1 QAM)	Dapa 10 mg (Group 1 QAM)
	Number of subjects (randomized subjects data set)	75	65	64	70

	HbA1c (%) (adjusted mean change)	-0.23	-0.58	-0.77	-0.89
	Standard error	0.1044	0.1107	0.1134	0.1099
	FPG (mg/dL) (adjusted mean change)	-4.1	-15.2	-24.1	-28.8
	Standard error	3.906	4.196	4.298	4.046
	TBW (kg) (adjusted mean change)	-2.19	-3.25	-2.83	-3.16
	Standard error	0.4297	0.4615	0.4731	0.4493
Effect estimate per comparison	Primary endpoint: HbA1c (%)	Comparison groups		Dapagliflozin 2.5, 5 and 10 mg vs placebo	
		Difference from placebo		-0.35, -0.54 and -0.66	
		Standard error		0.1522, 0.1541 and 0.1518	
		P-value (ANCOVA)		0.0207, 0.0005, <.0001	
	Secondary endpoint: FPG (mg/dL)	Comparison groups		Dapagliflozin 2.5, 5 and 10 mg vs placebo	
		Difference from placebo		-11.1, -19.9 and -24.7	
		Standard error		5.734, 5.806 and 5.626	
		P-value (ANCOVA)		N/A, 0.0007, <.0001	
	Secondary endpoint: TBW (kg)	Comparison groups		Dapagliflozin 2.5, 5 and 10 mg vs placebo	
		Difference from placebo		-1.06, -0.65, -0.97	
		Standard error		0.6307, 0.6388, 0.6223	
		P-value (ANCOVA)		N/A, 0.3101, 0.1189	
		Difference from placebo		-0.4, -13.9, -13.6	
		Standard error		4.324, 4.342, 4.176	
		P-value (ANCOVA)		N/A	
Notes					

Table 22. Summary of Efficacy for trial MB102032

Title: A multicenter, randomized, double-blind, placebo-controlled, parallel group, phase 3 trial to evaluate the safety and efficacy of dapagliflozin as monotherapy in subjects with type 2 diabetes who have inadequate glycaemic control with diet and exercise					
Study identifier	Study code: MB102032 (Monotherapy) ClinicalTrials.gov identifier: NCT00736879				
Design	Multicenter, randomized, double-blind, placebo-controlled, parallel group				
	Duration of main phase:	24 weeks			
	Duration of Run-in phase:	14 day lead-in period			
	Duration of Extension phase:	N/A			
Hypothesis	Superiority after 24 weeks				
Treatments groups	Dapa 1 mg	Dapagliflozin 1 mg, 24 weeks, 72 randomized			
	Dapa 2.5 mg	Dapagliflozin 2.5 mg, 24 weeks, 74 randomized			
	Dapa 5 mg	Dapagliflozin 5 mg, 24 weeks, 68 randomized			
	Placebo	Placebo, 24 weeks, 68 randomized			
Endpoints and definitions	Primary endpoint	HbA1c	Change from baseline in HbA1c at 24 weeks		
	Secondary endpoint	TBW	Change from baseline in total body weight at 24 weeks		
	Secondary endpoint	FPG	Change from baseline in FPG at 24 weeks		
Database lock	18 February 2010				
Results and Analysis					
Analysis description	Primary Analysis				
Analysis population and time point description	Randomized subjects data set, consisting of all randomized subjects who took at least one dose of double-blind study medication during the short-term (24 week) double-blind period				
Descriptive statistics and estimate variability	Treatment group	Placebo	Dapa 1 mg	Dapa 2.5 mg	Dapa 5 mg
	Number of subjects (randomized subjects data set)	68	72	74	68
	HbA1c (%) (adjusted mean change)	0.02	-0.68	-0.72	-0.82
	Standard error	0.1200	0.1166	0.1169	0.1217
	TBW (kg) (adjusted mean change)	-0.96	-2.69	-2.64	-2.69
	Standard error	0.3942	0.3820	0.3776	0.3961
	FPG (mg/dL) (adjusted mean change)	4.1	-11.0	-21.6	-28.5
	Standard error	4.200	4.082	4.025	4.230
Effect estimate per comparison	Primary endpoint: HbA1c (%)	Comparison groups		Dapa 1, 2.5 and 5 mg vs placebo	
		Difference from placebo		-0.69, -0.74, -0.84	
		Standard error		0.1672, 0.1679, 0.1710	
		P-value (ANCOVA)		<.0001, <.0001*, <.0001	

	Secondary endpoint: TBW (kg)	Comparison groups	Dapa 1, 2.5 and 5 mg vs placebo
		Difference from placebo	-1.73, -1.68, -1.73
		Standard error	0.5481, 0.5474, 0.5598
		P-value (ANCOVA)	0.0018, 0.0024, 0.0022
	Secondary endpoint: FPG (mg/dL)	Comparison groups	Dapa 1, 2.5 and 5 mg vs placebo
		Difference from placebo	-15.1, -25.7, -32.6
		Standard error	5.859, 5.816, 5.962
		P-value (ANCOVA)	0.0103, <.0001 <.0001
Notes			

Table 23. Summary of Efficacy for trial MB102014

Title: A multicenter, randomized, double-blind, placebo-controlled, parallel group, phase 3 trial to evaluate the safety and efficacy of dapagliflozin in combination with metformin in subjects with type 2 diabetes who have inadequate glycemic control on metformin alone					
Study identifier	Study code: MB102014 (Add-on to metformin) ClinicalTrials.gov identifier: NCT00528879				
Design	Multicenter, randomized, double-blind, placebo-controlled, parallel group				
	Duration of main phase:	24 weeks			
	Duration of Run-in phase:	14 day lead-in period			
	Duration of Extension phase:	78 weeks			
Hypothesis	Superiority after 24 weeks				
Treatments groups	Dapa 2.5 mg	Dapagliflozin 2.5 mg on a background therapy of metformin ≥ 1500 mg/day, 24 weeks, 137 randomized			
	Dapa 5 mg	Dapagliflozin 5 mg on a background therapy of metformin ≥ 1500 mg/day, 24 weeks, 137 randomized			
	Dapa 10 mg	Dapagliflozin 10 mg on a background therapy of metformin ≥ 1500 mg/day, 24 weeks, 135 randomized			
	Placebo	Placebo on a background therapy of metformin ≥ 1500 mg/day, 24 weeks, 137 randomized			
Endpoints and definitions	Primary endpoint	HbA1c	Change from baseline in HbA1c at 24 weeks		
	Secondary endpoint	FPG	Change from baseline in FPG at 24 weeks		
	Secondary endpoint	TBW	Change from baseline in total body weight at 24 weeks		
Database lock	29 January 2009				
Results and Analysis					
Analysis description	Primary Analysis				
Analysis population and time point description	Randomized subjects data set, consisting of all randomized subjects who took at least one dose of double-blind study medication during the short-term (24 week) double-blind period				
Descriptive statistics and estimate variability	Treatment group	Placebo	Dapa 2.5 mg	Dapa 5 mg	Dapa 10 mg
	Number of subjects (randomized subjects data set)	137	137	137	135
	HbA1c (%) (adjusted mean change)	-0.30	-0.67	-0.70	-0.84
	Standard error	0.0718	0.0715	0.0722	0.0724
	FPG (mg/dL) (adjusted mean change)	-6.0	-17.8	-21.5	-23.5
	Standard error	2.673	2.663	2.679	2.721
	TBW (kg) (adjusted mean change)	-0.89	-2.21	-3.04	-2.86
	Standard error	0.2368	0.2357	0.2358	0.2392

Effect estimate per comparison	Primary endpoint: HbA1c (%)	Comparison groups	Dapagliflozin 2.5, 5 and 10 mg vs placebo
		Difference from placebo	-0.38, -0.41, -0.54
		Standard error	0.1014, 0.1016, 0.1021
		P-value (ANCOVA)	0.0002, <.0001, <.0001
	Secondary endpoint: FPG (mg/dL)	Comparison groups	Dapagliflozin 2.5, 5 and 10 mg vs placebo
		Difference from placebo	-11.8, -15.5, -17.5
		Standard error	3.774, 3.781, 3.819
		P-value (ANCOVA)	0.0019, <.0001, <.0001
	Secondary endpoint: TBW (kg)	Comparison groups	Dapagliflozin 2.5, 5 and 10 mg vs placebo
		Difference from placebo	-1.32, -2.16, -1.97
		Standard error	0.3344, 0.3344, 0.3365
		P-value (ANCOVA)	<.0001, <.0001, <.0001
		P-value (ANCOVA)	N/A, <.0001, <.0001
Notes			

Table 24. Summary of Efficacy for trial MB102030

Title: A multicenter, randomized, double-blind, placebo-controlled, parallel group, phase 3 trial to evaluate the safety and efficacy of dapagliflozin in combination with thiazolidinedione therapy in subjects with type 2 diabetes who have inadequate glycemic control on thiazolidinedione therapy alone				
Study identifier	Study code: MB102030 (Add-on to TZD) ClinicalTrials.gov identifier: NCT00683878			
Design	Multicenter, randomized, double-blind, placebo-controlled, parallel group			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks 14 day lead-in period 24 weeks		
Hypothesis	Superiority after 24 weeks			
Treatments groups	Dapa 5 mg	Dapagliflozin 5 mg on a background of pioglitazone ≥30 mg/day, 24 weeks, 141 randomized		
	Dapa 10 mg	Dapagliflozin 10 mg on a background of pioglitazone ≥30 mg/day, 24 weeks, 140 randomized		
	Placebo	Placebo on a background of pioglitazone, 24 weeks, 139 randomized		
Endpoints and definitions	Primary endpoint	HbA1c	Change from baseline in HbA1c at 24 weeks	
	Secondary endpoint	TBW	Change in total body weight from baseline at 24 weeks	
	Secondary endpoint	FPG	Change from baseline in FPG at 24 weeks	
Database lock	16 March 2010			
Results and Analysis				
Analysis description	Primary Analysis			
Analysis population and time point description	Randomized subjects data set, consisting of all randomized subjects who took at least one dose of double-blind study medication during the short-term (24 week) double-blind period			
Descriptive statistics and estimate variability	Treatment group	Placebo	Dapa 5 mg	Dapa 10 mg
	Number of subjects (randomized subjects data set)	139	141	140
	HbA1c (%) (adjusted mean change)	-0.42	-0.82	-0.97
	Standard error	0.0834	0.0828	0.0828
	TBW (kg) (adjusted mean change)	1.64	0.09	-0.14
	Standard error	0.2760	0.2752	0.2753
	FPG (mg/dL) (adjusted mean change)	-5.5	-24.9	-29.6
	Standard error	2.893	2.884	2.880
Effect estimate per comparison	Primary endpoint: HbA1c (%)	Comparison groups	Dapa 5 and 10 mg vs placebo	

		Difference from placebo	-0.40, -0.55
		Standard error	0.1175, 0.1175
		P-value (ANCOVA)	0.0007, <.0001
	Secondary endpoint: TBW (kg)	Comparison groups	Dapa 5 and 10 mg vs placebo
		Difference from placebo	-1.55, -1.78
		Standard error	0.3896, 0.3896
		P-value (ANCOVA)	<.0001, <.0001
	Secondary endpoint: FPG (mg/dL)	Comparison groups	Dapa 5 and 10 mg vs placebo
		Difference from placebo	-19.5, -24.1
		Standard error	4.088, 4.082
		P-value (ANCOVA)	<.0001, <.0001
Notes			

Table 25. Summary of Efficacy for trial D1690C00004

Title: A 52-week international, multi-centre, randomized, parallel-group, double-blind, active-controlled, phase III study with a 156-week extension period to evaluate the efficacy and safety of dapagliflozin in combination with metformin compared with sulphonylurea in combination with metformin in adult patients with type 2 diabetes who have inadequate glycemic control on metformin therapy alone			
Study identifier	Study Code: D1690C00004 (Add-on to metformin) EudraCT No.: 2007-005220-33 ClinicalTrials.gov identifier: NCT00660907		
Design	Multicenter, randomized, double-blind, active-controlled, parallel group		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	52 weeks 14 day lead-in period 156 weeks	
Hypothesis	Non-inferiority after 52 weeks		
Treatments groups	Dapagliflozin	Dapagliflozin titrated to 2.5, 5 or 10 mg on a background of open label metformin ≥1500 mg/day, 52 weeks, 406 randomized [a]	
	Glipizide	Glipizide titrated to 5, 10 or 20 mg on a background of open label metformin ≥1500 mg/day, 52 weeks, 408 randomized [a]	
Endpoints and definitions	Primary endpoint	HbA1c	Change from baseline in HbA1c at 52 weeks
	Key secondary endpoint	TBW	Change from baseline in total body weight at 52 weeks
Database lock	23 February 2010		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Full analysis set, consisting of all randomized subjects who received at least one dose of investigational product during the double-blind treatment period, who had a non-missing baseline value and at least one post-baseline efficacy value for at least one efficacy variable.		
Descriptive statistics and estimate variability	Treatment group	Dapagliflozin	Glipizide
	Number of subjects (full analysis set)	400	401
	HbA1c (%) (adjusted mean change)	-0.52	-0.52
	Standard error	0.0403	0.0402
	TBW (kg) (adjusted mean change)	-3.22	1.44
	Standard error	0.1756	0.1754
Effect estimate per comparison	Primary endpoint: HbA1c (%)	Comparison groups	Dapagliflozin vs glipizide
		Difference from active comparator	0.00
		Standard error	0.0569
		P-value (ANCOVA)	<.0001
	Secondary endpoint: TBW (kg)	Comparison groups	Dapagliflozin vs glipizide
		Difference from active comparator	-4.65
		Standard error	0.2483

		P-value (ANCOVA)	<.0001
Notes			

Table 26. Summary of Efficacy for trial D1690C00005

Title: A 24-week, international, randomized, double-blind, parallel-group, multi-center, placebo-controlled phase III study with a 24-week extension period to evaluate the efficacy and safety of dapagliflozin in combination with glimepiride (a sulphonylurea) in subjects with type 2 diabetes who have inadequate glycaemic control on glimepiride therapy alone					
Study identifier	Study code: D1690C00005 (Add-on to SU) EudraCT No.: 2007-005931-27 ClinicalTrials.gov identifier: NCT00680745				
Design	Multicenter, randomized, double-blind, placebo-controlled, parallel group				
	Duration of main phase:	24 weeks			
	Duration of Run-in phase:	8 week lead-in period			
	Duration of Extension phase:	24 weeks			
Hypothesis	Superiority after 24 weeks				
Treatments groups	Dapa 2.5 mg	Dapagliflozin 2.5 mg on a background of glimepiride 4 mg/day, 24 weeks, 154 randomized			
	Dapa 5 mg	Dapagliflozin 5 mg on a background of glimepiride 4 mg/day, 24 weeks, 146 randomized			
	Dapa 10 mg	Dapagliflozin 10 mg on a background of glimepiride 4 mg/day, 24 weeks, 151 randomized			
	Placebo	Placebo on a background of glimepiride 4 mg/day, 24 weeks, 146 randomized			
Endpoints and definitions	Primary endpoint	HbA1c	Change from baseline in HbA1c at 24 weeks		
	Key secondary endpoint	TBW	Change from baseline in total body weight at 24 weeks		
	Key secondary endpoint	FPG	Change from baseline in FPG at 24 weeks		
Database lock	28 January 2010				
Results and Analysis					
Analysis description	Primary Analysis				
Analysis population and time point description	Full analysis set, consisting of all randomized subjects who received at least one dose of investigational product during the double-blind treatment period, who had a non-missing baseline value and at least one post-baseline efficacy value for at least one efficacy variable.				
Descriptive statistics and estimate variability	Treatment group	Placebo	Dapa 2.5mg	Dapa 5 mg	Dapa 10 mg
	Number of subjects (full analysis set)	145	154	142	151
	HbA1c (%) (adjusted mean change)	-0.13	-0.58	-0.63	-0.82
	Standard error	0.0625	0.0602	0.0627	0.0610
	TBW (kg) (adjusted mean change)	-0.72	-1.18	-1.56	-2.26
	Standard error	0.2263	0.2196	0.2286	0.2217

	FPG (mg/dL) (adjusted mean change)	-2.0	-16.8	-21.2	-28.5
	Standard error	2.528	2.453	2.555	2.485
Effect estimate per comparison	Primary endpoint: HbA1c (%)	Comparison groups		Dapagliflozin 2.5, 5 and 10 mg vs placebo	
		Difference from placebo		-0.44, -0.49, -0.68	
		Standard error		0.0867, 0.0885, 0.0873	
		P-value (ANCOVA)		<.0001, <.0001, <.0001	
	Secondary endpoint: TBW (kg)	Comparison groups		Dapagliflozin 2.5, 5 and 10 mg vs placebo	
		Difference from placebo		-0.46, -0.84,-1.54	
		Standard error		0.3153, 0.3217, 0.3168	
		P-value (ANCOVA)		0.1410, 0.0091, <.0001	
	Secondary endpoint: FPG (mg/dL)	Comparison groups		Dapagliflozin 2.5, 5 and 10 mg vs placebo	
		Difference from placebo		-14.9, -19.3, -26.5	
		Standard error		3.522, 3.594, 3.545	
		P-value (ANCOVA)		<.0001, <.0001, <.0001	
Notes					

Table 27. Summary of Efficacy for trial D1690C00006

Title: A 24-week international, randomized, parallel-group, double-blind, placebo-controlled phase III study with an 80-week extension period to evaluate the efficacy and safety of dapagliflozin therapy when added to the therapy of patients with type 2 diabetes with inadequate glycaemic control on insulin					
Study identifier	Study code: D1690C00006 (Add on to insulin) EudraCT No.: 2007-007540-10 ClinicalTrials.gov identifier: NCT00673231				
Design	Multicenter, randomized, double-blind, placebo-controlled, parallel group				
	Duration of main phase:	24 weeks			
	Duration of Run-in phase:	No lead-in period (14 day enrollment period)			
	Duration of Extension phase:	80 weeks			
Hypothesis	Superiority after 24 weeks				
Treatments groups	Dapa 2.5 mg	Dapagliflozin 2.5 mg on a background of insulin ≥30 IU/day ± maximum 2 oral anti-diabetic drugs, 24 weeks, 202 randomized			
	Dapa 5 mg	Dapagliflozin 5 mg on a background of insulin ≥30 IU/day ± maximum 2 oral anti-diabetic drugs, 24 weeks, 212 randomized			
	Dapa 10 mg	Dapagliflozin 10 mg on a background of insulin ≥30 IU/day ± maximum 2 oral anti-diabetic drugs, 24 weeks, 196 randomized			
	Placebo	Placebo on a background of insulin ≥30 IU/day ± maximum 2 oral anti-diabetic drugs, 24 weeks, 197 randomized			
Endpoints and definitions	Primary endpoint	HbA1c	Change from baseline in HbA1c at 24 weeks		
	Key secondary endpoint	TBW	Change from baseline in total body weight at 24 weeks		
	Key secondary endpoint	FPG	Change from baseline in FPG at 24 weeks		
Database lock	8 August 2009				
Results and Analysis					
Analysis description	Primary Analysis				
Analysis population and time point description	Full analysis set, consisting of all randomized subjects who received at least one dose of investigational product during the double-blind treatment period, who had a non-missing baseline value and at least one post-baseline efficacy value for at least one efficacy variable.				
Descriptive statistics and estimate variability	Treatment group	Placebo	Dapa 2.5mg	Dapa 5 mg	Dapa 10 mg
	Number of subjects (full analysis set)	193	202	211	194
	HbA1c (%) (adjusted mean change)	-0.30	-0.75	-0.82	-0.90
	Standard error	0.0521	0.0507	0.0493	0.0515
	TBW (kg) (adjusted mean change)	0.02	-0.98	-0.98	-1.67
	Standard error	0.1833	0.1786	0.1734	0.1814

	FPG (mg/dL) (adjusted mean change)	3.3	-12.5	-18.8	-21.7
	Standard error	3.370	3.247	3.140	3.309
Effect estimate per comparison	Primary endpoint: HbA1c (%)	Comparison groups		Dapagliflozin 2.5, 5 and 10 mg vs placebo	
		Difference from placebo		-0.45, -0.52, -0.60	
		Standard error		0.0726, 0.0718, 0.0733	
		P-value (ANCOVA)		<.0001, <.0001, <.0001	
	Secondary endpoint: TBW (kg)	Comparison groups		Dapagliflozin 2.5, 5 and 10 mg vs placebo	
		Difference from placebo		-1.00, -1.00, -1.68	
		Standard error		0.2560, 0.252,3, 0.2578	
		P-value (ANCOVA)		0.0001, <.0001, <.0001	
	Secondary endpoint: FPG (mg/dL)	Comparison groups		Dapagliflozin 2.5, 5 and 10 mg vs placebo	
		Difference from placebo		-15.8, -22.1, -25.0	
		Standard error		4.684, 4.616, 4.718	
		P-value (ANCOVA)		0.0008, <.0001, <.0001	
Notes					

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

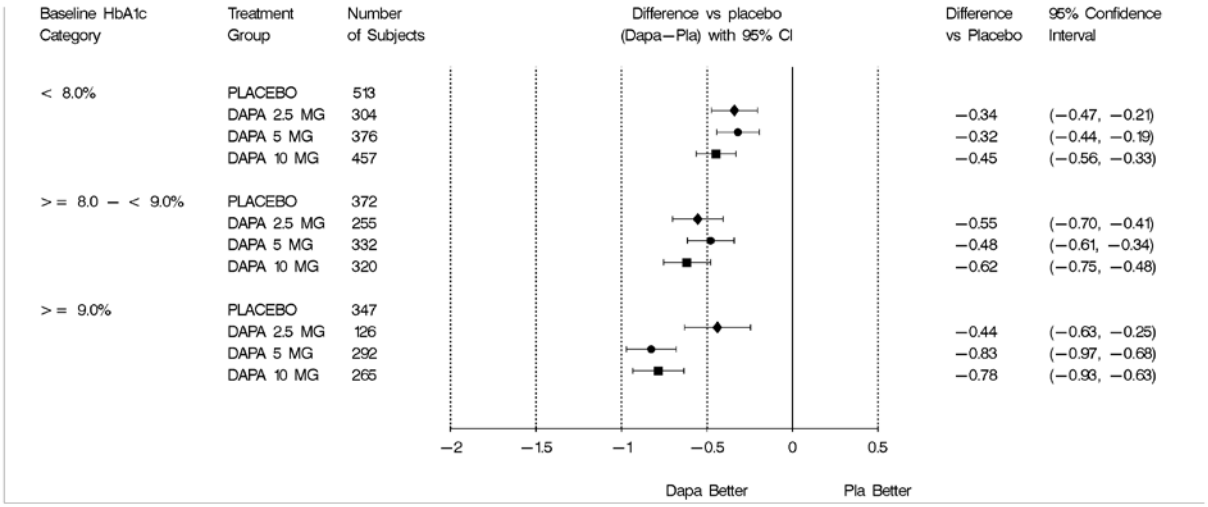
Summaries were prepared of demographics and baseline characteristics for the pooled monotherapy / combination therapy group (MB102013 [QAM and QPM doses combined, excluding Group 2], MB102032 [excluding 1 mg], MB102014, MB102030, D1690C00005, D1690C00006, D1690C00012, MB102021, and MB102034 [excluding dapagliflozin arm]). The demographic and baseline characteristics were generally balanced across the pooled dapagliflozin 2.5 mg, 5 mg, 10 mg and placebo groups. Overall there were slightly more females than males (pooled total 48.8% males and 51.2% females) and the mean age ranged between 55.0 and 57.1 years across the pooled treatment groups. Mean duration of T2DM ranged from 5.28 years in the pooled placebo group to 7.27 years in the pooled dapagliflozin 2.5 mg group; mean HbA1c was lowest in the pooled dapagliflozin 2.5 mg group (8.16%) and highest in the pooled dapagliflozin 5 mg group (8.43%).

In the All Phase 3 studies population, the mean age was 56 years; 1212 (21.3%) subjects were ≥65 years old and 157 (2.8%) subjects were ≥75 years old. The proportion of males (50.5%) was similar to the proportion of females (49.5%). Across all Phase 3 studies 83.7% were white, 3.4% were black or African American and 10.2% were Asian.

Subgroup analyses

A number of subgroup analyses were performed on the pooled monotherapy / combination therapy group. Below is shown the analysis based on HbA1c at baseline. As would be expected, the most prominent effect was seen in patients with high baseline values.

Figure 15. Difference versus placebo in adjusted mean change from baseline in HbA1c (percent) at Week 24 (LOCF) excluding data after rescue by baseline HbA1c category (Pooled Monotherapy/Combination therapy Studies) Randomized Subjects/Full Analysis Set

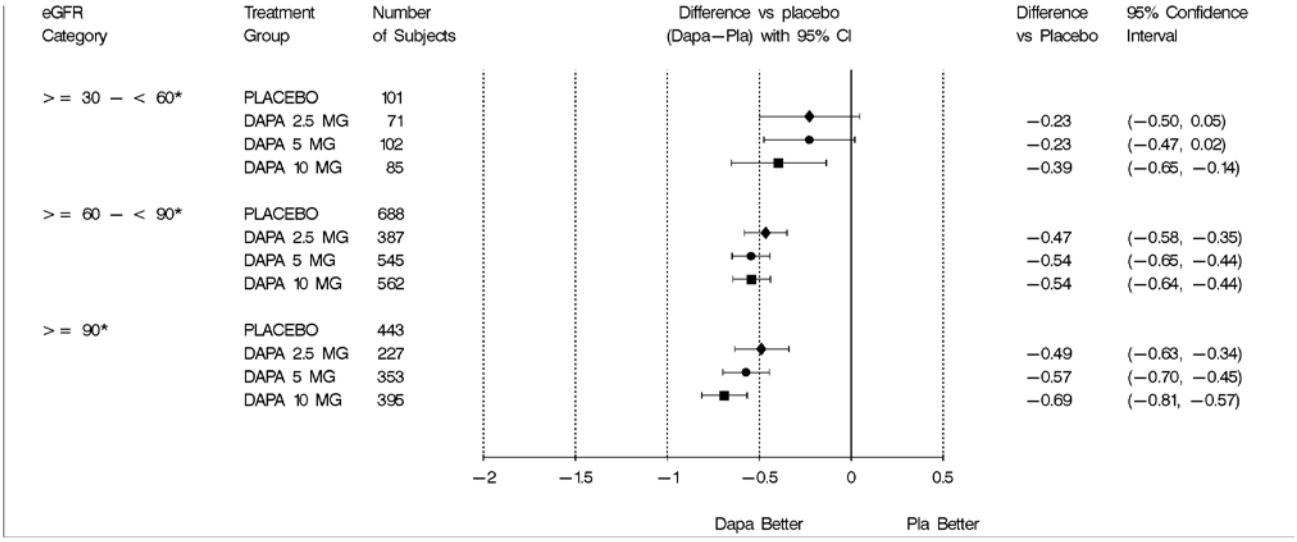


NA: Not applicable in Study D1690C00012 due to the baseline stratification factor for sex where females were included if 55-75 years of age while males were included if 30-75 years of age

Pooled Mono/Combo Group: (MB102013 [excluding Group 2 arms], MB102014, MB102021 [excluding 5 mg dapagliflozin arm], MB102030, MB102032 [excluding 1 mg dapagliflozin arm], MB102034 [excluding 10 mg dapagliflozin arm], D1690C00005, D1690C00006, D1690C00012

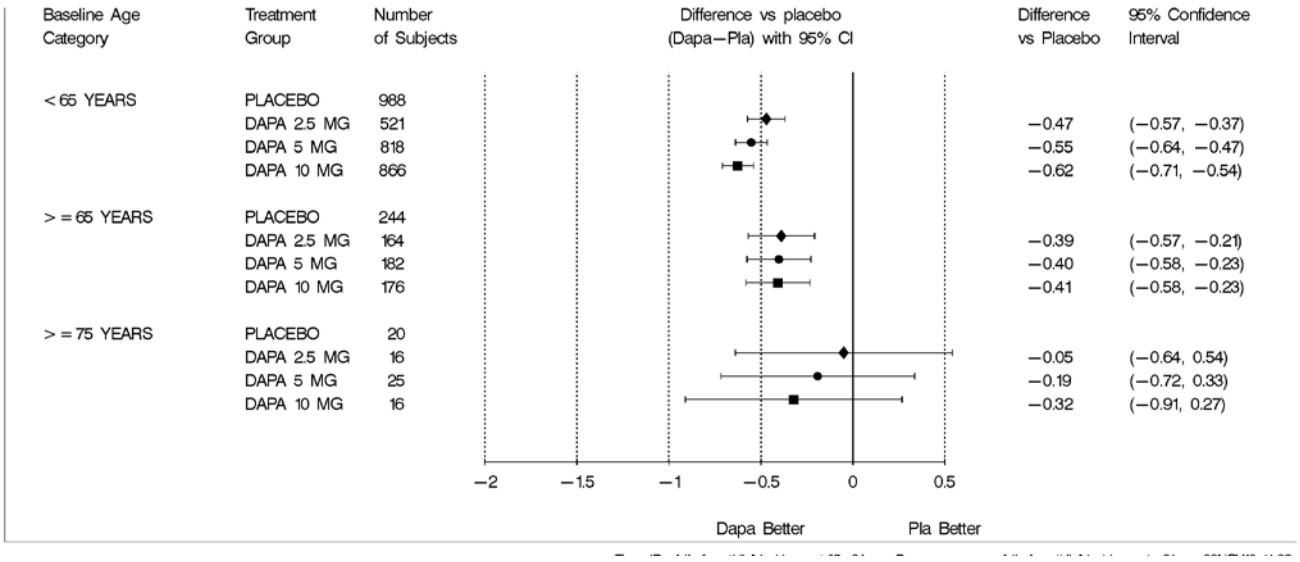
A decrease in effect was observed both with decreasing GFR and with increasing age. The data on elderly patients is very limited as reflected by the wide CI, however, further analyses provided by the Applicant during the evaluation showed that the decreased efficacy observed in the elderly is mainly related to a decrease in renal function with age.

Figure 16. Difference versus Placebo in Adjusted Mean Change from Baseline in HbA1c (%) at Week 24 (LOCF) Excluding Data after Rescue By eGFR Category (Pooled Monotherapy/Combination therapy Studies) Randomized Subjects/Full Analysis Set



Pooled Mono/Combo Group: (MB102013 [excluding Group 2 arms], MB102014, MB102021 [excluding 5 mg dapagliflozin arm], MB102030, MB102032 [excluding 1 mg dapagliflozin arm], MB102034 [excluding 10 mg dapagliflozin arm], D1690C00005, D1690C00006, D1690C00012

Figure 17. Difference versus placebo in adjusted mean change from baseline in HbA1c (percent) at Week 24 (LOCF) excluding data after rescue by baseline age category (Pooled Monotherapy/Combination therapy Studies) Randomized Subjects/Full Analysis Set



Pooled Mono/Combo Group: (MB102013 [excluding Group 2 arms], MB102014, MB102021 [excluding 5 mg dapagliflozin arm], MB102030, MB102032 [excluding 1 mg dapagliflozin arm], MB102034 [excluding 10 mg dapagliflozin arm], D1690C00005, D1690C00006, D1690C00012

Blood pressure

A decrease in blood pressure was consistently observed across the study program. This is a beneficial effect considering that the majority of patients with T2DM would also have a diagnosis of hypertension.

Table 28. Blood pressure (mmHg) adjusted mean change from baseline at Week 24 (or Week 52)(LOCF) versus comparator (95% CI) in overall study populations, excluding data after rescue, Efficacy Analysis Data Set

Study	Comparator [Background]	SBP (mmHg)			DBP (mmHg)		
		Dapa 2.5 mg	Dapa 5 mg	Dapa 10 mg	Dapa 2.5 mg	Dapa 5 mg	Dapa 10 mg
Monotherapy							
MB102013 QAM	Placebo	-1.4 (-5.4, 2.6)	-0.5 (-4.5, 3.5)	-1.3 (-5.2, 2.6)	-1.1 (-3.4, 1.2)	-0.6 (-2.9, 1.7)	0.2 (-2.1, 2.5)
QPM	Placebo	-1.0 (-4.9, 3.0)	-2.7 (-6.7, 1.2)	-1.3 (-5.2, 2.5)	-1.3 (-3.6, 1.0)	-0.4 (-2.7, 1.9)	-0.7 (-2.9, 1.5)
MB102032	Placebo	-5.4 (-9.1, -1.7)	-7.2 (-10.9, -3.4)	-	-2.4 (-4.9, 0.0)	-2.4 (-5.0, 0.1)	-
Add-on therapy							
MB102014	Placebo [Met]	-2.4 (-5.2, 0.4)	-4.5 (-7.3, -1.7)	-5.3 (-8.1, -2.5)	-2.5 (-4.2, -0.7)	-2.6 (-4.4, -0.8)	-2.4 (-4.2, -0.6)
D1690C00005	Placebo [SU]	-3.5 (-6.1, -0.9)	-2.8 (-5.5, -0.2)	-3.8 (-6.4, -1.2)	0.3 (-1.4, 1.9)	-0.3 (-1.9, 1.4)	-1.4 (-3.0, 0.3)
MB102030	Placebo [TZD]	-	-0.6 (-3.3, 2.0)	-4.5 (-7.2, -1.8)	-	-1.4 (-3.0, 0.3)	-3.5 (-5.2, -1.9)
D1690C00006	Placebo [Ins]	-0.7 (-3.2, 1.8)	-2.1 (-4.6, 0.4)	-3.0 (-5.5, -0.4)	-0.4 (-1.9, 1.0)	-0.9 (-2.3, 0.6)	-1.1 (-2.5, 0.4)
Body weight/composition							
D1690C00012	Placebo [Met]	-	-	-2.9 (-5.9, 0.1)	-	-	-0.9 (-2.9, 1.0)
Active comparator[a]							
D1690C00004	SU [Met]	-	-	-5.0 (-6.7, -3.4)	-	-	-1.2 (-2.3, -0.2)

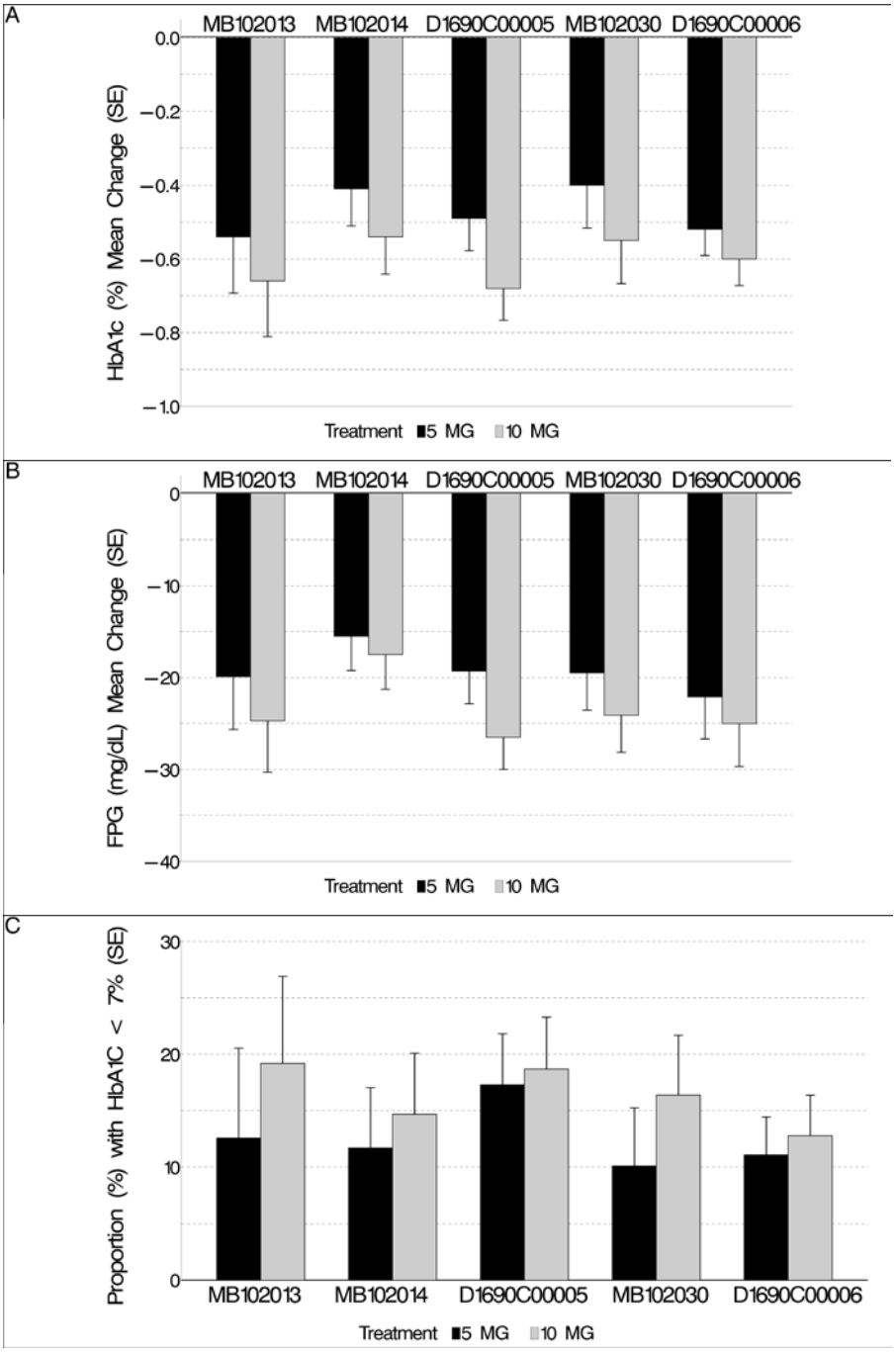
Initial combination therapy		Dapa 5 mg + Met	Dapa 10 mg + Met	Dapa 5 mg + Met	Dapa 10 mg + Met
MB102021	Metformin XR	-0.9 (-3.0, 1.1)[b]	-	-1.7 (-3.1, -0.4)[b]	-
	Dapa 5 mg	0.9 (-1.2, 2.9)[c]	-	0.3 (-1.0, 1.7)[c]	-
MB102034	Metformin XR	-	-2.7 (-4.8, -0.5)[b]	-	-1.5 (-2.8, -0.2)[b]
	Dapa 10 mg	-	0.6 (-1.5, 2.7)[c]	-	0.0 (-1.2, 1.3)[c]

Comparison of doses 5 mg and 10 mg across the study program

The results were very consistent among races and geographical regions. This is reassuring and would allow extrapolating the results from studies performed in non-European sites to the European population.

The 10 mg dose was more efficient than the 5 mg dose, supporting the dose recommendation proposed by the Applicant.

Figure 18. Comparison of Dapagliflozin 5 mg and 10 mg results at Week 24 (LOCF) from studies performed in general T2DM population where both doses are present, Placebo-corrected, adjusted mean change or proportion



Bars denote difference versus placebo in mean change from baseline (figures A and B for HbA1c and FPG, respectively) or proportion (figure C for subjects with HbA1c < 7%) at Week 24 (LOCF), adjusted for baseline HbA1c value and stratification factor if used. Error bars denote standard errors for the difference versus placebo in adjusted mean or proportion (approximated for proportions as the difference in the upper and lower 95% confidence limit divided by 2 x 1.96). Note: QAM doses only shown for Study MB102013.

Clinical studies in special populations

Study MB102029

Study MB102029 was a multicenter, double-blind, placebo-controlled, parallel group, randomized, Phase II/III trial to evaluate the glycaemic efficacy, renal safety, pharmacokinetics, and pharmacodynamics of dapagliflozin in subjects with T2DM and moderate renal impairment who have

inadequate glycaemic control. The primary objective was to compare the change from baseline in HbA1c achieved with each dapagliflozin treatment group versus placebo, after 24 weeks of oral administration of double-blind treatment.

In the 24-week short-term phase, 252 subjects were randomized and treated (84 placebo, 83 dapagliflozin 5 mg, and 85 dapagliflozin 10 mg). Eligible subjects completing the 24-week short-term, double-blind treatment period continued into the double-blind, 28-week long-term treatment period. Eligible subjects completing the 28-week long-term double-blind treatment period continued into the 52-week site and subject blinded long-term extension period (cumulative study data could range from 53 to 102 weeks long). In the total long-term phase, 202 subjects were treated (62 placebo, 71 dapagliflozin 5 mg, and 69 dapagliflozin 10 mg).

The placebo-corrected HbA1c mean changes from baseline in the dapagliflozin 5 mg and 10 mg treatment groups at Week 24 (LOCF) were not statistically significant. The adjusted mean change from baseline in HbA1c showed greater numerical reductions in all dapagliflozin treatment groups than in the placebo group. For the secondary endpoint FPG, the adjusted mean change from baseline in FPG at Week 24 (LOCF) showed reductions in the dapagliflozin treatment groups compared with an increase in the placebo group. These effects on glycaemia occurred in the setting of dapagliflozin-induced increments in glucosuria which were proportionately less than those seen in other studies of subjects with higher mean eGFR. At Week 24, the overall proportion of subjects discontinued or rescued for failing to achieve pre specified glycaemic targets, when adjusted for baseline HbA1c, was numerically lower in the dapagliflozin treatment groups at all timepoints compared with the placebo groups. For the remaining secondary endpoints, the adjusted mean change from baseline in body weight at Week 24 (LOCF) showed mean reductions in the dapagliflozin treatment groups compared with an increase in the placebo group.

Table 29. HbA1c (%) adjusted mean change from baseline at Week 24 (LOCF), excluding data after rescue - Moderate renal impairment study (MB102029), efficacy analysis data set

	Study MB102029		
Treatment	**Placebo**	**Dapa 5 mg**	**Dapa 10 mg**
HbA1c (%)	(N=84)	(N=83)	(N=85)
N#	82	83	82
Baseline mean (SD)	8.53 (1.285)	8.30 (1.040)	8.22 (0.973)
Mean at Week 24 (SD)	8.18 (1.204)	7.97 (1.150)	7.90 (0.930)
Adj. mean change (SE)	-0.32 (0.1701)	-0.41 (0.1701)	-0.44 (0.1708)
Difference vs PLA (95% CI)		-0.08 (-0.37, 0.20)	-0.11 (-0.40, 0.17)
p-value vs PLA		0.561	0.435

N is the number of subjects in the efficacy analysis data set (randomized subjects in BMS studies, full analysis set in AZ studies).
N# is the number of subjects in the efficacy data set with non-missing baseline and Week 24 (LOCF) values.
Sources: MB102029 CSR Table 7.1 in CTD Module 5.3.5.1

At Week 52, the placebo-corrected reductions in mean HbA1c were slightly larger than at Week 24 in the dapagliflozin 5 and 10 mg treatment groups. The small placebo-subtracted decreases from baseline in mean FPG that were evident at Week 24 persisted at Week 52. During the 52-week treatment period, clinically meaningful mean decreases from baseline in total body weight were observed in the dapagliflozin 5 and 10 mg treatment groups compared with the placebo group, however, statistical testing was not performed.

Post-hoc subgroup analyses

Given the differences in baseline renal function and the apparent discrepancy between the treatment results in MB102029 and the Pooled Monotherapy/Combination Therapy group, exploratory HbA1c subgroup analyses were performed for the subsets of subjects with baseline eGFR ≥45 and <60 mL/min/1.73m2 (performed separately in MB102029 and in the 9-study Pooled Monotherapy/Combination Therapy group) and eGFR ≥30 and <45 mL/min/1.73m2 (performed only in MB102029). These eGFR categories define lower- and higher- risk subgroups, respectively, of moderate renal impairment (stage 3A and 3B renal impairment).

In the MB102029 analysis, subjects with eGFR ≥45 and <60 mL/min/1.73m2 had placebo-corrected adjusted mean HbA1c reductions at Week 24 (LOCF) of –0.37% and –0.33% in the dapagliflozin 5 mg and 10 mg groups, respectively. Subject numbers were relatively small (n=32 to 40 per treatment group, 107 total), and 95% CI crossed zero in both dapagliflozin treatment groups. Consistent findings were observed in the 9-study Pooled Monotherapy/Combination Therapy group; placebo-corrected adjusted mean HbA1c reductions were -0.27%, -0.30%, and -0.33% in the dapagliflozin 2.5 mg, 5 mg, and 10 mg groups, respectively, and 95% CI excluded zero for the three treatment groups (n= 64 to 92 per treatment group, 316 total).

No HbA1c reductions were seen after correcting for placebo in the eGFR ≥30-<45 mL/min/1.73m2 subgroup analysis in MB102029. Placebo-corrected adjusted mean HbA1c changes in the ≥30 to <45 subgroup were 0.05% and 0.07% in the 5 mg and 10 mg groups, respectively (n=33 to 45 per treatment group, 119 total). No corresponding analysis was performed for the Pooled Monotherapy/Combination Therapy group because of insufficient subject numbers.

These results suggest that efficacy persists, although more modestly, at eGFR values ≥45 mL/min/1.73 m^2. There is no evidence for efficacy at eGFR values below 45 mL/min/1.73 m^2.

The efficacy of dapagliflozin decreased with decreasing GFR. Very modest effects were observed on HbA1c in the ITT analysis. In the subgroup analysis borderline decreases in HbA1c was observed in patients with GFR > 45. No placebo-corrected HbA1c decrease was observed in patients with GFR<45. The results of study MB102029 question the usefulness of dapagliflozin in patients with moderate renal impairment.

Study D1690C00018

This was a multicenter, randomized, double-blind, age-stratified, placebo-controlled Phase III study with a 24-week short-term treatment period followed by a 28-week extension period to evaluate the effect of dapagliflozin 10 mg once daily (qd) in combination with pre-existing anti-hyperglycaemic treatment on HbA1c and on the proportion of subjects who achieved a clinical benefit in male subjects ≥45 years of age and female subjects ≥50 years of age with T2DM and CVD who have inadequate glycaemic control on monotherapy or dual combination therapy with oral anti-diabetic drugs (OADs), insulin therapy in combination with OADs, or insulin monotherapy.

In total 922 patients were randomized. Around 88% of the randomized subjects completed the 24-week short-term treatment period and around 86% continued into the 28-week extension period. Primary reason for not continuing into the 28-week extension period was occurrence of a discontinuation criterion (44 subjects). All treated subjects were included in the safety analysis set. The full analysis set included 914/922 subjects (526/530 subjects in age stratum <65 years and 388/392 subjects in age stratum ≥65 years).

In general, the treatment groups were balanced with respect to demographic and baseline characteristics. On average, subjects were around 63 years of age with around 42% aged ≥65 years. There were about 68% male and 32% female subjects in both treatment groups. Around 94% of the subjects were at least overweight (BMI ≥25 kg/m2), and almost two thirds were obese (BMI ≥30 kg/m2). Mean duration of T2DM was 12.4 years, and around 56% of the subjects had T2DM over 10 years. Mean HbA1c at baseline was about 8.1%.

Around 23% of the subjects had a normal renal function (eGFR ≥90 mL/min/1.73 m2) at baseline. A mild renal impairment (eGFR ≥60 and <90 mL/min/1.73 m2) was observed in 58% of the subjects. In almost 20% of the subjects eGFR was ≥30 and <60 mL/min/1.73 m2 which corresponds to a moderate renal impairment, and in 1 subject each in the dapagliflozin and placebo group eGFR ranged below 30 mL/min/1.73 m2 which corresponds to a severe renal impairment.

Most subjects reported coronary heart disease (75.2%) or stroke/transient ischemic attack (20.7%). All subjects had hypertension according to the inclusion criteria. The duration of hypertension was ≥3 years in almost 90% of the subjects and ≥10 years in 50% of the subjects. Hypertension was well controlled as indicated by a mean seated SBP and DBP of 133.2 mmHg and 76.9 mmHg, respectively. Almost 13% of the subjects had congestive heart failure.

Primary and key secondary efficacy endpoints are summarized for all subjects in the full analysis set in the table below.

Table 30. Summary of primary and key secondary efficacy endpoints – full analysis set

	PLA N = 459	DAPA 10 MG N = 455
Primary endpoints		
HbA1c (%) at week 24 (LOCF)		
Adjusted mean change from baseline (SE), N#	0.08 (0.0400), 451	-0.38 (0.0403), 448
p-value vs. PLA		<0.0001 *
Responders of a 3-item endpoint of clinical benefit at week 24 (LOCF)		
Percent, N#	0.9%, 451	11.7%, 444
p-value vs. PLA		<0.0001 *
Key secondary endpoints		
Seated SBP (mmHg) at week 8 (LOCF)		
Adjusted mean change from baseline (SE), N#	-0.99 (0.6651), 459	-2.96 (0.6755), 451
p-value vs. PLA		0.0126 *
Total body weight (kg) at week 24 (LOCF)		
Adjusted percent change from baseline (SE), N#	-0.30 (0.1645), 459	-2.56 (0.1630), 455
p-value vs. PLA		<0.0001 *
Seated SBP (mmHg) at week 24 (LOCF)		
Adjusted mean change from baseline (SE), N#	-1.03 (0.6908), 459	-2.99 (0.7016), 451
p-value vs. PLA		0.0174 *
Subjects with total body weight decrease of at least 5% at week 24 (LOCF) in subjects with baseline BMI ≥27 kg/m^2		
Percent adjusted (SE), N#	4.0% (0.986), 397	16.5% (1.884), 388
p-value vs. PLA		<0.0001 *

N: number of subjects in the full analysis set.
N#: number of subjects in the full analysis set with non-missing baseline and week t (LOCF) values.
BMI: body mass index; HbA1c: glycosylated hemoglobin; PLA: placebo; DAPA: dapagliflozin; LOCF: last observation carried forward; SBP: systolic blood pressure; SE: standard error.
* Significant p-value: the primary endpoints were tested at $\alpha = 0.025$ (two-sided); the secondary endpoints were tested following a sequential testing procedure at $\alpha = 0.05$ (two-sided).

Subjects in the dapagliflozin group showed a statistically significant mean reduction in HbA1c from baseline to week 24 (last observation carried forward [LOCF]) compared to placebo in all subjects of the full analysis set (-0.46%) and in both age strata (<65 years: -0.42%; ≥65 years: -0.53%).

In this study the most pronounced effect on HbA1c was observed in patients > 65 years of age. In these patients a mean reduction of 0.53 % was observed whereas the mean decrease in patients < 65 was 0.42 %. Reductions in both body weight and SBP were observed. The overall findings were consistent with those observed in previously assessed phase 3 studies.

Study D1690C00019

This was a multicenter, randomized, double-blind, age-stratified, placebo-controlled Phase III study with a 24-week short-term treatment period followed by a 28-week extension period to evaluate the effect of dapagliflozin 10 mg once daily (qd) in combination with pre-existing anti-hyperglycaemic treatment on HbA1c and on the proportion of subjects who achieved a clinical benefit in male subjects ≥45 years of age and female subjects ≥50 years of age with T2DM and CVD who have inadequate glycaemic control on monotherapy or dual combination therapy with oral anti-diabetic drugs (OADs), insulin therapy in combination with OADs, or insulin monotherapy.

In total 964 patients were randomized. Around 90% of the randomized subjects completed the 24-week short-term treatment period and continued into the 28-week extension period. Primary reason for not completing the 24-week short-term double-blind treatment period was occurrence of a discontinuation criterion (28 subjects). Two subjects in the dapagliflozin group and 1 subject in the placebo group died during the 24-week short-term treatment period. All treated subjects were included in the safety analysis set. The full analysis set included 962 subjects, 511 subjects in age stratum <65 years and 451 in age stratum ≥65 years.

In general, the treatment groups were balanced with respect to demographic and baseline characteristics. On average, subjects were around 64 years of age with around 47% aged ≥65 years. There were about 67% male and 33% female subjects in both treatment groups. Around 95% of the subjects were at least overweight (BMI ≥25 kg/m2), and more than two thirds were obese (BMI ≥30 kg/m2). Mean duration of T2DM was 13.2 years with around 58% of the subjects have had T2DM over 10 years. Mean HbA1c at baseline was about 8.1%.

Around 24% of the subjects had an eGFR ≥90 mL/min/1.73 m2 at baseline. An eGFR between 60 and 90 mL/min/1.73 m2 was observed in 61% of the subjects. In around 15% of the subjects eGFR was ≥30 and <60 mL/min/1.73 m2, and no subject's eGFR in the dapagliflozin and placebo groups ranged below 30 mL/min/1.73 m2.

As qualifying CV event, most subjects reported coronary heart disease (76.5%) or stroke/transitory ischemic attack (TIA) (19.6%). Almost 93% of subjects had hypertension. The duration of hypertension was ≥3 years in almost 87% of the subjects and ≥10 years in 55.1% of the subjects. Hypertension was well controlled as indicated by a mean seated SBP and DBP of 134.7 mmHg and 77.8 mmHg, respectively. Almost 16% of the subjects had cardiac heart failure (CHF).

Primary and key secondary efficacy endpoints are summarized in the table below.

Table 31. Summary of primary and key secondary efficacy endpoints – full analysis set

	PLA N=482	DAPA 10 MG N=480
Primary endpoints		
HbA1c (%) at week 24 last observation carried forward (LOCF)		
Adjusted mean change from baseline (SE), N#	0.07 (0.0435), 471	-0.33 (0.0434), 474
p-value vs. PLA		<0.0001 *
Responders of a 3-item endpoint of clinical benefit at week 24 (LOCF)		
Percent	1.9%, 469	10.0%, 468
p-value vs. PLA		<0.0001 *
Key secondary endpoints		
Total body weight (kg) at week 24 (LOCF)		
Adjusted percent change from baseline (SE), N#	-0.61 (0.1770), 481	-2.53 (0.1736), 480
p-value vs. PLA		<0.0001 *
Subjects with body weight decrease of at least 5% at week 24 (LOCF) in subjects with baseline BMI ≥27 kg/m^2		
Percent adjusted (SE), N#	4.8% (1.051), 415	18.4% (1.876), 428
p-value vs. PLA		<0.0001 *
Seated SBP (mmHg) at week 8 (LOCF)		
Adjusted mean change from baseline (SE), N#	0.86 (0.7105), 479	-1.85 (0.7135), 473
p-value vs. PLA		0.0007 *
Seated SBP (mmHg) at week 24 (LOCF)		
Adjusted mean change from baseline (SE), N#	0.32 (0.7109), 479	-2.70 (0.7140), 473
p-value vs. PLA		0.0002 *
Seated SBP (mmHg) at week 8 (LOCF) in subjects with baseline SBP≥130 mmHg		
Adjusted mean change from baseline (SE), N#	-1.89 (0.8612), 309	-5.33 (0.8612), 300
p-value vs. PLA		0.0004 *

* Significant p-value: the primary endpoints were tested at α=0.025 (two-sided); the secondary endpoints were tested following a sequential testing procedure at α=0.05 (two-sided).

Subjects in the dapagliflozin group showed a statistically significant mean reduction in HbA1c from baseline to week 24 (LOCF) compared to the placebo group in all subjects of the full analysis set (0.40%) and in both age strata (<65 years: -0.46%; ≥65 years: -0.34%).

A more pronounced effect on HbA1c was observed in patients < 65 years of age. In patients above the age of 65 a mean reduction of 0.34 % was observed. Reductions in both body weight and SBP were observed. The findings were consistent with those observed in previously assessed phase III studies.

Supportive studies

Phase III initial combination therapy with metformin XR studies in poorly-controlled treatment naïve subjects (studies MB102021 and MB102034)

Two multicenter, randomized, double-blind, active controlled, parallel group, Phase III trials (MB102021 and MB102034) were performed to evaluate the safety and efficacy of dapagliflozin 5 and 10 mg, respectively, in combination with metformin as initial therapy as compared with dapagliflozin monotherapy and metformin monotherapy. Patients included were treatment naive subjects with T2DM with inadequate glycaemic control. Studies MB102021 and MB102034 enrolled subjects with HbA1c ≥7.5 % and ≤12.0%. The primary objective was to compare the change from baseline in HbA1c, achieved with dapagliflozin plus metformin XR compared with dapagliflozin plus placebo, and compared with metformin XR plus placebo after 24 weeks of double-blind therapy. Study MB102034 also formally evaluated non-inferiority of dapagliflozin compared to metformin XR with regard to HbA1c and FPG.

In the 24-week double-blind phase of these studies, 598 and 638 subjects, respectively, were randomized and took the study medication.

In both studies, the adjusted mean change from baseline in HbA1c at Week 24 (LOCF) in the combination group was statistically significant and clinically relevantly larger compared to either monotherapy. The results on the primary endpoint favouring the combination treatment were supported by those on the secondary glycaemic endpoints. In addition, fewer patients needed rescue therapy in the combination group compared to either monotherapy. The data support an additive effect when dapagliflozin and metformin are co-administered.

In study MB102034, non-inferiority was formally assessed. In the monotherapy and combination therapy arm, 85.6% and 82.5 % of patients, respectively, received 2000 mg metformin daily, and only 2.9% and 4.2%, respectively, received doses < 1500 mg/d suggesting that the full glucose-lowering potential of metformin XR was achieved in most patients. The non-inferiority of the dapagliflozin treatment group compared to the metformin treatment group was demonstrated for HbA1c (treatment difference dapagliflozin vs. Met -0.01%, 95% CI [-0.22; 0.20]). Reduction in FPG was even superior (treatment difference dapagliflozin vs. Met -11.6 mg/dL, 95% CI [-18.6; -4.6]). However, since metformin XR is not widely licensed and used in the EU and it is not clear whether the efficacy of metformin XR is non-inferior to that of metformin IR, a definite conclusion on non-inferior efficacy of dapagliflozin compared to metformin IR is not possible from this study.

Table 32. HbA1c (%) adjusted mean change from baseline at Week 24 (LOCF), excluding data after rescue - Phase III initial combination therapy studies (MB102021 and MB102034), Efficacy Analysis Data Set

	MB102021			MB102034		
Treatment	Metformin XR up to 2000 mg	Dapa 5 mg	Combination of Metformin XR up to 2000 mg + Dapa 5 mg	Metformin XR up to 2000 mg	Dapa 10 mg	Combination of Metformin XR up to 2000 mg + Dapa 10 mg
Primary Efficacy Variable: HbA1c (%)						
N	(N=201)	(N=203)	(N=194)	(N=208)	(N=219)	(N=211)
N#	195	196	185	203	216	202
Baseline mean (SD)	9.14 (1.317)	9.14 (1.374)	9.21 (1.305)	9.03 (1.295)	9.03 (1.272)	9.10 (1.276)
Mean at Week 24 (SD)	7.79 (1.530)	7.96 (1.443)	7.13 (1.201)	7.60 (1.420)	7.59 (1.232)	7.10 (1.001)
Adj. mean change (SE)	-1.35 (0.0868)	-1.19 (0.0866)	-2.05 (0.0892)	-1.44 (0.757)	-1.45 (0.0734)	-1.98 (0.0759)
Difference vs Dapa (95% CI)			-0.86 (-1.11, -0.62)			-0.53 (-0.74; -0.32)
p-value vs Dapa			<0.0001 *			<0.0001*
Difference vs Met (95% CI)			-0.70 (-0.94, -0.45)			-0.54 (-0.75; -0.33)
p-value vs Met			<0.0001 *			<0.0001*
Difference Dapa vs Met (95% CI)					-0.01 (-0.22, 0.20)*	
p-value for Dapa vs Met					0.9144	

N is the number of subjects in the Efficacy Analysis Data Set (randomized subjects in BMS studies, Full Analysis Set in AZ studies).
N# is the number of subjects in the efficacy data set with non-missing baseline and Week 24 (LOCF) values.
(*) Significant p-value: Secondary endpoints are tested following a sequential procedure at alpha=0.05. When combination is compared to each control, significance is claimed only if is the combination is superior to both controls. In Study MB102034, a secondary objective was to compare Dapagliflozin 10 mg to Metformin, first by assessing non-inferiority using a margin of 0.35% for HbA1c (asterisk indicates non-inferiority successfully demonstrated, no p-value shown), and if successful, then by testing for superiority (p-value shown)

Body composition study (study D1690C00012)

A multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 study was performed to evaluate the effect of dapagliflozin 10 mg in combination with metformin on body weight in adult subjects with T2DM who have inadequate glycaemic control (HbA1c ≥6.5% and ≤8.5%) on metformin therapy alone. The primary objective was to evaluate the effect of dapagliflozin 10 mg daily in combination with metformin compared to placebo in combination with metformin on total body weight after 24 weeks of oral administration of double-blind treatment.

In the 24-week short-term treatment period, 182 subjects were randomized and received study medication (91 placebo + metformin and 91 dapagliflozin + metformin). The 78-week extension period is currently ongoing. One of the objectives of the extension period is to evaluate bone mineral density after 50 and 102 weeks, which is considered very important due to indications of increased fracture rate associated with dapagliflozin in patients with moderate renal insufficiency. No relevant changes in BMD were observed after 50 weeks.

Mean baseline weight was 90.91 and 92.06 kg and mean waist circumference was 104.52 and 105.55 cm in the placebo and dapagliflozin group, respectively. Treatment with dapagliflozin as add-on therapy to metformin over 24 weeks was effective in reducing body weight; the mean decrease in total body weight from baseline to Week 24 (LOCF) in the dapagliflozin 10 mg group was statistically significantly larger than in the placebo group (-2.08 kg difference versus placebo; p<0.0001).

All key secondary endpoints were statistically significant in favour of dapagliflozin treatment. Waist circumference and body fat mass showed mean decreases from baseline to Week 24 (LOCF) in both the dapagliflozin and placebo groups (waist circumference -1.52 cm difference versus placebo, p=0.0143; body fat mass -1.48 kg difference versus placebo, p=0.0001). Approximately 30% of the subjects in the dapagliflozin group and 4% of the subjects in the placebo group showed a decrease in body weight of at least 5% at Week 24 (LOCF) (p<0.0001). In the exploratory magnetic resonance (MR) sub study, treatment with dapagliflozin as add-on therapy to metformin over 24 weeks led to a mean reduction in visceral adipose tissue (VAT), but not in hepatic lipid content. Lean body mass was also reduced more in the dapagliflozin group (-1.1 kg) than in the placebo group (-0.6 kg). Since DXA is not able to distinguish between muscle mass/connective tissue and body water, it is not clear how much of the observed decrease in lean mass is due to loss in muscle mass or fluid loss.

The study indicates that dapagliflozin has a weight reducing potential although not of the magnitude that would allow any claims regarding weight reduction. Considering that the majority of patients with T2DM are overweight and that many of the current therapies induce a weight increase, this weight reducing effect could be beneficial. Furthermore, the data show a decrease in body fat, providing some reassurance that the weight reduction is mainly due to calorie loss and not to dehydration.

Table 33. Summary of primary and key secondary efficacy endpoints – FAS (Study D1690C00012)

	PLA + MET N = 91	DAPA 10MG + MET N = 89
Primary endpoint		
Total body weight (kg) at week 24 (LOCF)		
Adjusted mean change from baseline (SE) p-value vs. PLA + MET	-0.88 (0.2746)	-2.96 (0.2766) <0.0001 *
Key secondary endpoints		
Waist circumference (cm) at week 24 (LOCF)		
Adjusted mean change from baseline (SE) p-value vs. PLA + MET	-0.99 (0.4349)	-2.51 (0.4388) 0.0143 *
Body fat mass (kg) at week 24 (LOCF)		
Adjusted mean change from baseline (SE) p-value vs. PLA + MET	-0.74 (0.2670)	-2.22 (0.2626) 0.0001 *
Subjects with body weight decrease of at least 5% at week 24 (LOCF)		
Percent adjusted (SE) p-value vs. PLA + MET	4.3% (2.148)	30.5% (4.929) <0.0001 *

* Significant p-value: the primary endpoint was tested at $\alpha = 0.050$ (two-sided). If this p-value was significant, the results of the key secondary endpoints were interpreted using Hochberg's method.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The application is supported by a comprehensive study program consisting of 3 Phase II studies and 11 Phase III studies. The study program is in line with the adopted EMA Guideline "Note for Guidance on the Clinical Investigation of Medicinal Products for the treatment of diabetes mellitus (CPMP/EWP/1080/00)" and is generally in line with the given CHMP Scientific Advice. The duration of the studies is adequate with all but one pivotal study having a double-blind period of 24 weeks. The duration of the active comparator study was 52 weeks. Eight of the Phase III studies also include a long-term follow up of 24 to 78 weeks in order to obtain additional safety and efficacy data. The clinical trials generally were well-designed and conducted and during the review process no concerns regarding GCP compliance arose.

The efficacy of dapagliflozin has been studied in a total of 6026 patients in the Phase II/III clinical program. Efficacy data are available in 2000 subjects that have been exposed to the 10 mg dose and 461 subjects were exposed to the 10 mg dose for at least 77 weeks. Overall, about 30 % of patients included were European, about 17% from EU countries. Many of the studies did not include any European patients but the active controlled study (D1690C00004) and the placebo-controlled study D1690C00006 included more than 50 % of patients from the EU. However, efficacy was consistent across races and geographical regions, thus the results from studies performed at non-European sites could be extrapolated to the European population.

HbA1c was chosen as the primary endpoint in the dose-finding studies, which is in line with the adopted guideline "Note for Guidance on the Clinical Investigation of Medicinal Products for the treatment of diabetes mellitus (CPMP/EWP/1080/00)". The range of doses was chosen based on the data from the Phase I and II studies and is considered adequate.

The primary and secondary endpoints chosen for the Phase III program were adequate. Further to the evaluation of dapagliflozin on glucose metabolism, the effect of dapagliflozin on weight and blood pressure was investigated.

The patients included in the studies were representative for the target population. Patients with long-standing disease and diabetic complications such as (mild to moderate) renal impairment or CV disease were generally not excluded. However, experience with dapagliflozin in patients older than 75 years is still limited. No data are available for adolescents with T2DM but the Applicant currently does not seek a paediatric indication. Although drug naïve subjects were included in the monotherapy studies to support the restricted first line indication applied for, this is acceptable since the effect of dapagliflozin is not expected to be different in patients intolerant to metformin, which is the target population. Patients in the add-on studies were on adequate back-ground therapy and treatment failure was an inclusion criterion. In the add-on to TZD study, adequate measures were taken to assure that patients not previously treated with TZD were indeed treatment failures. The non-inferiority, active comparator study was adequately designed, with the vast majority of patients being treated with the target dose of both dapagliflozin and glipizide. Several important studies (e.g. in patients with CVD (and hypertension), in patients with inadequately controlled BP, dapagliflozin as add-on to sitagliptin) are currently ongoing. Those that will contribute to further elucidate potential safety concerns as stated in the RMP are listed within the Pharmacovigilance Plan of the RMP and will have to be conducted and their results submitted accordingly.

The statistical methods used are well described and considered appropriate.

Overall discontinuation rate was small (13.5%), which is re-assuring. The dose selection for phase III (2.5 mg, 5 mg, 10 mg) based on efficacy and safety assessments is considered appropriate.

In several studies, patients violating HbA1c inclusion criteria were enrolled and treated. However, numbers were low and the efficacy analysis not affected by their inclusion. Background treatment was monitored in all important studies. Relevant deviations were usually observed in very small fractions of the study population and to a similar extent across treatment groups excluding a relevant impact on study results.

Efficacy data and additional analyses

Both dose-finding studies showed a significant effect on HbA1c for all doses tested when compared to placebo. However, a clear dose-response was only observed for FPG indicating that HbA1c might not yet have been fully stabilised at week 12. Only moderate increases in efficacy were observed for doses over 10 mg and for safety reasons (increased rates of hyperphosphataemia as well as genitourinary infections) the applicant decided to only investigate doses of 10 mg and lower in the Phase III program. This is endorsed by the CHMP.

In the phase 3 studies, efficacy of dapagliflozin appeared generally dose-dependent.

When dapagliflozin was given as monotherapy a moderate but clinically relevant placebo-corrected decrease in HbA1c of 0.54-0.66 % was observed in the 5 and 10 mg treated groups, respectively, in study MB102013, whereas clinically relevant changes (0.67-0.84 %) was seen for all doses tested in study MB102032. Baseline HbA1c was essentially similar between the two studies; however, a more pronounced decrease in HbA1c (0.23 % vs 0.03 %) was observed in the placebo treated group in study MB102013 indicating that this study population may have been less compliant to the diet and exercise regimen before inclusion. A dose-dependent decrease in HbA1c was observed in both studies. Efficacy appeared similar regardless of whether dapagliflozin was taken QAM or QPM. Secondary and exploratory endpoints supported the primary endpoint. A dose-dependent reduction in FPG of the same magnitude was observed in both monotherapy studies. As expected, a more pronounced effect on HbA1c was observed in patients with high baseline HbA1c. Clinically relevant reductions in body weight of about 2.5-3 kg were observed in both studies. However, in study MB102013 a weight reduction was also observed in the placebo group, thus the decrease did not reach statistical significance.

The results with regards to HbA1c were consistent across the four add-on studies. Clinically relevant effects on HbA1c were observed in all add-on studies with placebo-corrected HbA1c decreases in the order of 0.54-0.68 % for the 10 mg dose, slightly lower HbA1c changes observed for the 5 mg dose. The secondary endpoints supported the primary endpoint outcome. Of note, in the add-on to insulin study, patients in the dapagliflozin group could be kept on a stable insulin dose whereas the insulin dose increased somewhat over time in the placebo treated group, indicating an “insulin-saving” effect of dapagliflozin. A weight reducing effect was again observed in all add-on studies. In studies where dapagliflozin was added to metformin or SU a considerable proportion (24-28 % and 13-24 % in the metformin and SU studies, respectively) of patients had a weight reduction of more than 5 %.

Dapagliflozin 10 mg was shown to have non-inferior efficacy compared to glipizide (both as add-on to metformin) after 52 weeks of treatment in a thoroughly designed study using appropriate doses of glipizide. Although initially (up to week 18), glipizide produced a clearly more pronounced HbA1c reduction (approx. -0.8% from baseline), this effect waned rather quickly as is known for insulin secretagogues. Mean HbA1c reduction at week 52 was -0.52% in both treatment groups with an upper limit of the 95% CI of the treatment difference of 0.11, clearly below the non-inferiority margin of 0.35% and indicating non-inferiority. Notably, a higher proportion of patients in the glipizide treated group reached target HbA1c than in the dapagliflozin group (27.5 % versus 16.5 % reached HbA1c ≤6.5% at Week 52; 32 % versus 27.4 % reached HbA1c <7% at Week 52), however, drop-out due to lack of glycaemic control was more common in the glipizide treated group. Other benefits of dapagliflozin compared to glipizide were observed such as a lower hypoglycaemia incidence (3.5 vs. 40.8%) and weight loss (-3.22 kg vs. +1.44 kg), although, some of the weight loss may be due to fluid loss rather than reduction in fat mass. Although the vast majority of hypoglycaemic events were minor, hypoglycaemia is a frequent obstacle to achieving ideal glycaemic control with insulin or insulin secretagogues. The total planned study duration is 4 years. A report covering the first 52-week extension period of this study was provided during the evaluation. The data show a maintained effect up to two years, both with regards to glycaemic control and body weight.

Dapagliflozin 10 mg was also shown to have non-inferior efficacy compared to metformin XR in a 24-week, 3-arm initial combination trial performed in patients with high baseline HbA1c (mean about 9.1%) using appropriate doses of metformin XR. Mean HbA1c reduction was highly similar in both treatment groups (-1.45 and -1.44% in the dapagliflozin and metformin XR group, respectively) with an upper limit of the 95% CI of the treatment difference of 0.20 indicating non-inferiority. FPG reduction was even superior compared to metformin XR. However, since metformin XR is not widely licensed and used in the EU and it is not clear whether the efficacy of metformin XR is non-inferior to that of metformin IR, a definite conclusion on non-inferior efficacy of dapagliflozin compared to metformin IR is not possible from this study. Of note, dapagliflozin was also associated with a more pronounced weight loss (-3.33 kg) compared to metformin XR (-1.36 kg), although, some of the weight loss may be due to fluid loss rather than reduction in fat mass.

Long-term data (up to 102 weeks) from the monotherapy study showed a maintained effect of dapagliflozin in the groups receiving the 5 and 10 mg dose, whereas the data on the 2.5 mg dose are less convincing. Up to 36 weeks the risk of treatment failure was lower in the 5 and 10 mg treated groups compared to placebo and 2.5 mg, whereas some increase in risk was observed also at the higher doses after this time-point. The data from the monotherapy studies, including the long-term extension, together with data from the active control study are deemed sufficient to support the restricted first-line indication applied for.

In a pooled analysis performed across 9 phase 3 trials the effect of dapagliflozin was found to be independent of gender, race, ethnicity, geographical region, BMI and duration of T2DM, which is reassuring. Unsurprisingly, efficacy of dapagliflozin increased with increasing baseline HbA1c. This was expected from the mechanism of action of dapagliflozin (i.e. increasing glucose load leading to increasing urinary glucose excretion). A baseline HbA1c-dependent glucose-lowering effect is also known from other anti-hyperglycaemic agents. A decreasing effect was observed with age, which appears largely due to declining renal function. The effect in patients ≥ 65 years showed a HbA1c decrease of only about 0.4 % and in the patients ≥ 75 years the effect was even less. However, very few patients in this age group were included in the studies and the data need to be interpreted with caution. Considering the reduced efficacy in the elderly due to reduced renal function and the safety concerns in this population, initiation of dapagliflozin therapy in patients 75 years and older is not recommended.

Across the study program a decreasing effect of dapagliflozin has been observed with decreasing GFR, both in the subgroup analysis and in the study specifically designed to investigate the effect of dapagliflozin in patients with renal impairment. In the subgroup analysis the HbA1c decrease in patients with GFR 30-60 was only 0.39 % with the 10 mg dose, and in the renal impairment study the placebo-corrected treatment effect with the 10 mg dose was only 0.11 %. In this study a subgroup analysis was made using a cut-off of GFR 45-60 was made, showing an HbA1c decrease of 0.33 %. This effect could only be considered of marginal clinical relevance and, also considering safety concerns (see safety section) in patients with marked renal impairment, a cut-off of GFR 60 is therefore applied.

The weight reducing effect observed in the pivotal studies was further explored in a study dedicated to investigate body composition changes. Data from this study showed a significant decrease in body fat, thus showing that the weight loss is not only due to dehydration but also to loss of calories. A decrease in blood pressure was consistently observed in the Phase III studies.

2.5.4. Conclusions on the clinical efficacy

The clinical program supports the efficacy of dapagliflozin in lowering HbA1c. The effect size with the selected dose of 10 mg is considered clinically relevant and was consistent in all studies. The 10 mg dose was more efficacious than the 5 mg dose, supporting the dose recommendation proposed by the Applicant. In addition to the glucose lowering effect, a relevant weight reduction and a slight reduction of blood pressure was observed across the study program. These effects are considered beneficial.

Both the restricted monotherapy indication and the add-on indications are considered approvable from an efficacy point of view.

The efficacy of dapagliflozin in patients with moderate renal impairment is debatable due to the decrease in efficacy observed with declining GFR. Further to this, data indicate a decreased effect in elderly patients, which appears mainly due to the decrease in renal function with age. Due to the small effect size and safety concerns, dapagliflozin should not be used in patients with a GFR < 60 mL/min/1.73m^2.

In patients with severe hepatic impairment, the mean increase in dapagliflozin exposure was 67% and therefore, a lower starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg. This is the only recommended use for the 5 mg strength.

2.6. Clinical safety

Patient exposure

The primary assessment of safety in subjects with T2DM was based on 3 Phase IIb and 11 Phase III, double-blind, placebo/active-controlled, randomized clinical studies:

• Monotherapy in 4 studies.

• Add-on combination therapy with a wide variety of other antidiabetic medication in 6 studies.

• Initial combination therapy with metformin in 2 studies.

• A direct comparison with SU.

• Monotherapy in subjects with moderate renal impairment

Supportive safety information was provided from 26 clinical pharmacology studies.

The short-term (ST) treatment period was 12 weeks for the Phase IIb studies and 24 weeks for all of the Phase III studies, except one study with a 52-week short-term period (direct comparison to SU). Eight of the Phase 3 studies included long-term (LT) treatment periods ranging from 24 to 156 weeks.

Data were pooled into 4 main datasets for analyses (Placebo-controlled Pool, Monotherapy Pool, Dapagliflozin plus Metformin Pool and All Phase IIb and III Studies Pool). The Placebo-controlled pool represented the best controlled pool available for assessment of safety.

Clinical exposure to dapagliflozin 2.5 mg or higher, ST+LT treatment period for these 4 pools is shown in the table below.

Table 34. Clinical Exposure to Dapagliflozin 2.5 mg or Higher, Short-term Plus Long-term Treatment Period Including Data After Rescue, Treated Subjects

	Total Number of Subjects Exposed				
Population	Total	6 months	12 months	18 months	24 months
All Phase 2b and 3 Pool	4287	3333	2232	1317	441
Placebo-controlled Pool	3291	2481	1769	1017	429
Monotherapy	882	474	324	303	211
Dapagliflozin Plus Metformin	500	435	342	311	217

In addition to the 4 main pools, the safety of dapagliflozin in other populations with other antidiabetic compounds (add-on to either SU, insulin, or TZD, initial combination with metformin, direct comparison to SU, and diabetic subjects with moderate renal impairment) was evaluated.

Overall, there were 2.2 times more subjects exposed to dapagliflozin (n = 4287) compared with control (n = 1941). 2000 subjects were exposed to the 10 mg dose in the Phase IIb and III clinical program and 461 subjects were exposed to the 10 mg dose for at least 77 weeks.

Exposure by age: Mean exposure during short-term treatment was similar in subjects < 65 years and ≥ 65 years across the dapagliflozin groups. 67 subjects ≥ 75 years were exposed to dapagliflozin.

Exposure by renal function: Patients with severe renal impairment (eGFR < 30 mL/min/ 1.73 m^2) were excluded from the studies. A total of 684 subjects had moderate renal impairment at baseline (eGFR ≥30 to<60 mL/min/ 1.73 m^2) in the Phase IIb and III program.

Adverse events

The most common AEs in the dapagliflozin 10 mg group in descending order of frequency were nasopharyngitis, back pain, headache, diarrhoea, upper respiratory tract infection, urinary tract infection, dyslipidemia, nausea, hypertension, influenza, pollakiuria, and dysuria.

Adverse drug reactions (see table below) were identified based on the criteria; reported in ≥ 2% of subjects in the dapagliflozin 5 or 10 mg groups (regardless of investigator assessment of causality), and reported ≥ 1% more frequently in the dapagliflozin 5 or 10 mg groups compared with placebo, and reported in 3 subjects more in the dapagliflozin 5 or 10 mg groups compared with placebo.

	10 MG N=1193	Placebo N=1393
Hypoglycemia	10.2	7.0
Genital infection	4.8	0.9
Back pain	4.2	3.2
Polyuria	3.8	1.7
Dyslipidemia	2.5	1.5
Dysuria	2.1	0.7

Additional AEs considered by the investigator to be at least possibly drug-related and reported in ≥ 0.2% of subjects and ≥ 0.1% more and ≥ 3 more subjects treated with dapagliflozin 5 or 10 mg compared with placebo include (all occurring with uncommon frequency): thirst, constipation, blood creatinine increased, hyperhidrosis, vulvovaginal pruritus, blood urea increased, nocturia, weight decreased, dry mouth, glomerular filtration rate decreased, microalbuminuria.

Cardiovascular (CV) safety

The assessment of CV safety was based on a meta-analysis of independently confirmed, blindly adjudicated, CV events among Phase IIb and III studies (cut-off date: June 2010). Subjects with a wide range of duration of T2DM were included and 20% had a T2DM duration >10 years.

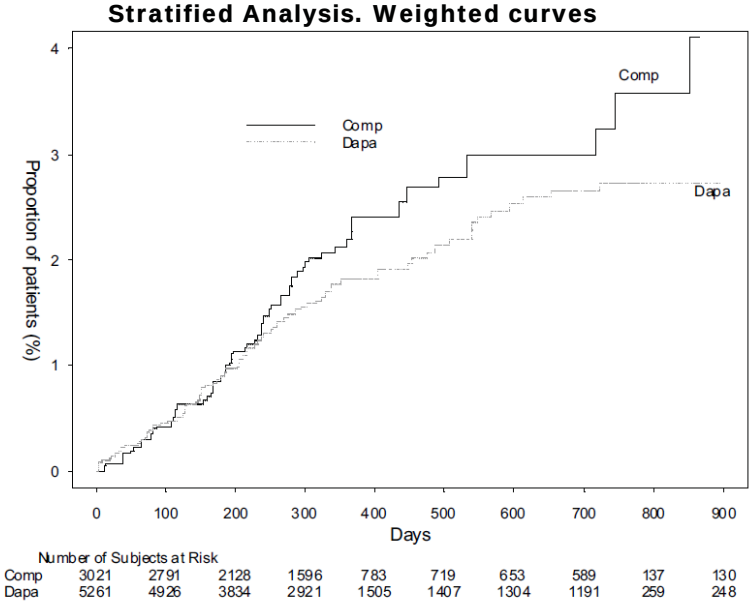
The meta-analysis did not show an increased CV risk for dapagliflozin treated patients. The estimated hazard ratio for the primary composite endpoint (time to first event of the following adjudicated events: CV death, MI, stroke, and hospitalization for unstable angina) using a Cox proportional hazards method was 0.674 (95% CI: 0.421, 1.078). The distribution of the type of events contributing to primary composite endpoint was similar in both treatment groups. MI was the most common event, and this is where the greatest reduction in event rate was observed in the dapagliflozin pool versus comparator pool (4.1 versus 9.7 subjects with events/1000 subject years). The estimated hazard ratio for the secondary composite endpoint (time to first event including events of the primary composite endpoint plus unplanned coronary revascularization and hospitalization for heart failure) was 0.632 (95% CI: 0.416, 0.959).

During the evaluation, the Applicant submitted an updated CV meta-analysis including safety data up to 15th July 2011. Of the 19 studies contributing to the updated analysis, 14 were completed: MB102008, MB102009, D1692C00005, MB102014, MB102021, MB102029, MB102030, MB102032, MB102034, MB102035, D1690C00005, D1690C00006, MB102013 and MB102045. Five studies completed their short-term periods, and were unblinded to the Sponsor (sites, investigators and subjects remained blinded), but their long-term periods were ongoing: D1690C00004 (104 week ST + LT completed), D1690C00010 and D1690C00012 (50 week ST + LT completed), D1690C00018 and D1690C00019. Studies MB102035, D1690C00010, D1690C00018 and D1690C00019 are new to the update of the CV events meta-analysis.

Studies D1690C00018 and D1690C00019 are randomized, double-blind, age-stratified, placebo-controlled Phase 3 studies with a 24-week short-term treatment period followed by a 80-week extension period to evaluate the effect of dapagliflozin 10 mg in combination with pre-existing anti-hyperglycemic treatment on HbA1c and on the proportion of subjects who achieved a clinical benefit in adult subjects with type 2 diabetes mellitus (T2DM), CV disease, and hypertension (only study D1690C00018) who have inadequate glycaemic control. These two studies were the largest contributors of added exposure to the updated meta-analysis.

For the primary composite endpoint, 145 events were included compared to 79 events in the previous analysis. The hazard ratio versus comparator was 0.819 (95% CI: 0.583, 1.152). Concerning the "harder" endpoint of major adverse cardiovascular events (MACE), consisting of CV death, MI and stroke, the hazard ratio was similar, 0.793 (95% CI: 0.537, 1.170).

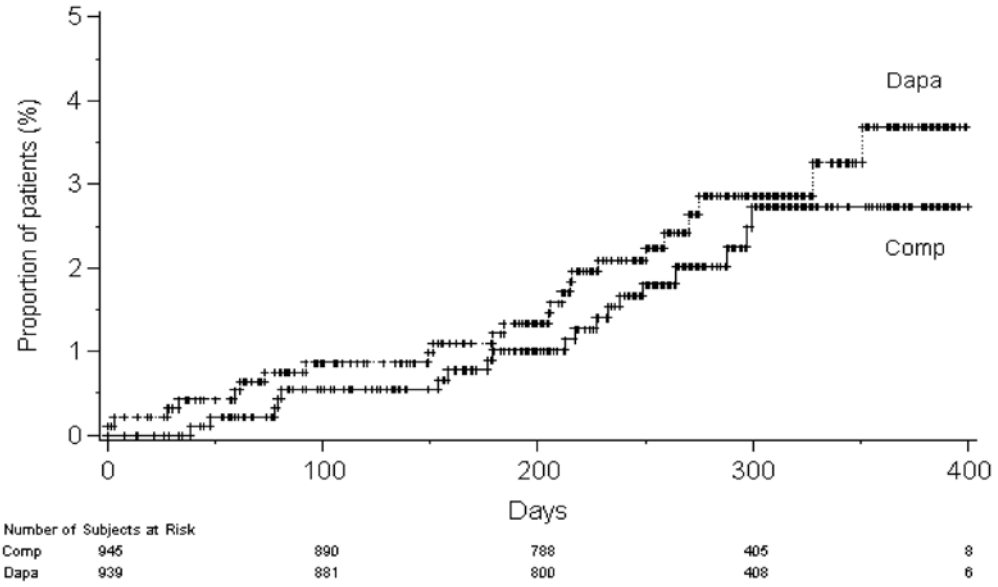
Figure 19. Cumulative Probability of Primary CV composite Endpoint over Time (Kaplan-Meier Estimate). During ST+LT Treatment Period. Overall Stratified Analysis. Weighted curves



Note: Studies MB102009, MB102032, MB102035 and MB102045 do not have at least one positively adjudicated event, hence exduded from analysis.

Even though the HR is somewhat higher compared to the previous analysis, the results still indicate that there is no signal of an increased risk of MACE associated with the use of dapagliflozin. This is an expected finding considering the lack of preclinical signals or reports of adverse events from the CV system in the phase II and III studies. However, in the pooled analysis of studies D1690C00018 and D1690C00019, the HR for MACE was 1.27 (95% CI 0.693-2.311), not favouring dapagliflozin, and the HR for the primary composite endpoint was 1.068 (95% CI 0.643-1.722).

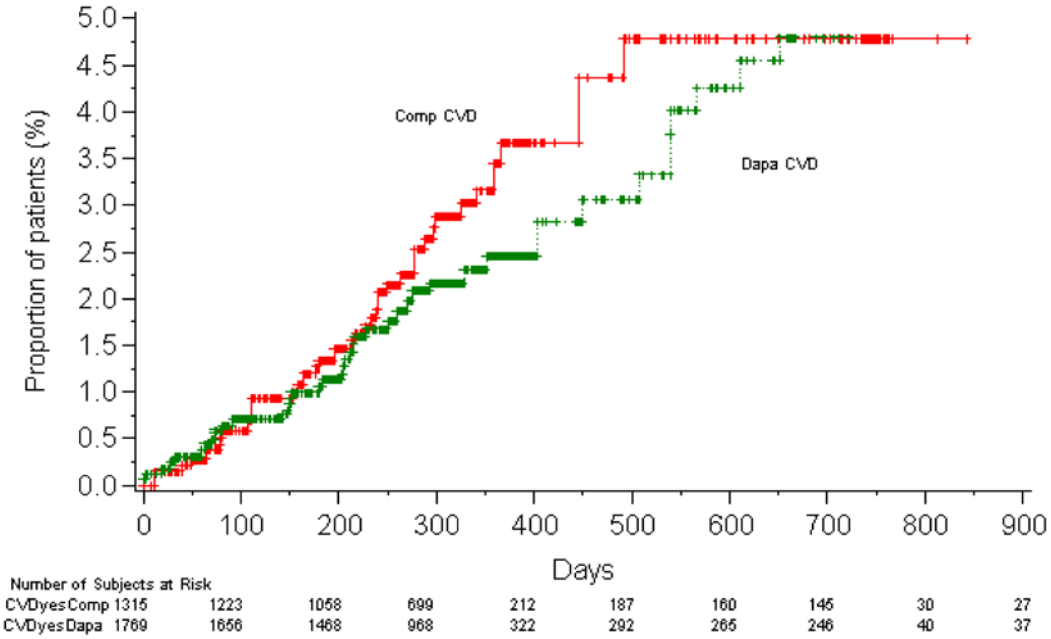
Figure 20. Cumulative probability for the composite endpoint of CV death, MI, and stroke (MACE) over time (Kaplan-Meier estimate). During ST+LT treatment period. Stratified analysis. D1690C00018 and D1690C00019 only. Weighted curves. 15 July 2011 data cut



With the responses to the 2nd Day 180 LOI, the Applicant provided detailed information on the early MACE events which mainly led to the imbalance of these events among treatment groups and has compiled the patient characteristics for all MACE cases in studies D1690C00018 and D1690C00019. Based on the information provided, it cannot be excluded that high CV risk patients concomitantly taking loop diuretics and/or antihypertensive drugs may be at increased risk for a CV events when starting dapagliflozin, possibly due to diuresis-induced decrease in blood pressure. However, the absolute number of CV events in these ongoing studies is still limited and the imbalance small and uncertain.

The Applicant also provided a Kaplan-Meier curve of MACE in all patients with CV disease from the Phase IIb/III study pool including the new trials 18 and 19. In this evaluation no increased MACE rate, neither at initiation of dapagliflozin therapy nor later on could be detected in the CVD population.

Figure 21. Cumulative probability for the composite endpoint of CV death, MI and stroke (MACE) over time (Kaplan-Meier estimate). ST+LT treatment period (including Studies 18 + 19). Stratified analysis. Subjects with history of CVD. 15 July 2011 data cut



Moreover, dapagliflozin administration did not cause any clinical relevant effects on the QTc interval.

Hypoglycaemia

Hypoglycaemia events were categorized using the following classes:

• Major episodes of hypoglycaemia: defined as symptomatic episodes requiring external (3rd party) assistance with a capillary or plasma glucose value < 3 mmol/L (< 54 mg/dL) and prompt recovery after glucose or glucagon administration.

• Minor episodes of hypoglycaemia: defined as either an symptomatic episode with a capillary or plasma glucose measurement < 3.5 mmol/L (< 63 mg/dL) regardless of the need for external assistance or an asymptomatic capillary or plasma glucose measurement < 3.5 mmol/L (< 63 mg/dL), that does not qualify as a major episode.

• Other episodes of hypoglycaemia: suggestive of hypoglycaemia but do not meet the above criteria.

Dapagliflozin had a low propensity for hypoglycaemia. There were no major episodes of hypoglycaemia when used as monotherapy. When dapagliflozin was used together with insulin and SU an increased risk of hypoglycaemic events was observed, mainly seen as an increase in minor hypoglycaemic events.

Study D1690C00006 (add-on to insulin) contributed, with >75% of the hypoglycaemia events, to the Placebo-controlled Pool. The proportion of subjects with major episodes of hypoglycaemia was 0.5% in the placebo+insulin group and 0.5-1% in dapagliflozin plus insulin groups. Most hypoglycaemia events were minor and were more common in subjects treated with dapagliflozin plus insulin (42.3% - 51.5%) compared with placebo plus insulin (35%).

In study D1690C00005 (add-on to glimeperide) hypoglycaemic events were reported in 6.9% to 7.3% of the subjects in the dapagliflozin groups and by 4.8% in the placebo group. One major episode of hypoglycaemia was reported in the dapagliflozin 2.5 mg group (associated with diarrhoea and decreased oral intake).

In contrast, in study D1690C00004 (Dapagliflozin plus Metformin vs Glipizide plus Metformin - direct comparison to SU), the proportion of subjects with at least 1 episode of hypoglycaemia was substantially lower in the dapagliflozin plus metformin (3%) group compared with the glipizide plus metformin group (40%) ($p < 0.0001$).

Genital infections

In the Placebo-controlled Pool, the overall proportion of subjects with events suggestive of genital infection events was higher in dapagliflozin-treated subjects than placebo-treated subjects (5.7%-4.8% in Dapa 5 and 10 mg vs 0.9% in placebo). Events suggestive of genital infection were more common in females than males. The most commonly reported events in females were vulvovaginal mycotic infection, vaginal infection, and vulvovaginal pruritus. The most commonly reported events in males were balanitis, genital pruritus, and fungal genital infection. More than 97% of all events suggestive of genital infection were mild or moderate in intensity. Of the 286 events reported in dapagliflozin-treated subjects, 3 (1.0%) were severe. No events suggestive of genital infection were very severe and none was serious.

Urinary tract infection (UTI)

In the Placebo-controlled Pool (ST) the overall proportion of subjects with events suggestive of UTI was higher in the dapagliflozin groups than in placebo (5.7%-4.3% in dapagliflozin 5 mg and 10 mg vs 3.7% in placebo). Events suggestive of UTI were more common overall in females than males.

Overall in the short-term period, kidney infections (all under the PT pyelonephritis) were reported rarely (0.1% in both the dapagliflozin groups and the placebo treated groups). Most events suggestive of UTI were mild or moderate in intensity. Four of 250 events in dapagliflozin-treated subjects and 1 of 72 events in placebo-treated subjects were severe. Amongst the 4 severe events that occurred in the dapagliflozin-treated subjects, all resolved. The recurrence rate was higher in the dapagliflozin group than in the placebo group (18% to 21% vs 11%).

UTI is identified as an important risk of dapagliflozin therapy and additional Pharmacovigilance activities are planned (clinical and epidemiological studies) in the RMP. Information is included in the SmPC (section 4.4 and 4.8).

Renal impairment

Adverse events related to renal impairment, especially increase in serum creatinine were seen in 1.2% of patients treated with dapagliflozin compared to 0.9 % in the placebo group with the difference being largest in patients with moderate renal impairment and older patients (see below, safety in special populations). Few AEs of renal impairment or failure were serious or led to discontinuation. The percentage of subjects discontinuing due to an adverse renal effect was fairly balanced between dapagliflozin and comparator. More patients with dapagliflozin than with comparator reached baseline serum creatinine after discontinuation (47.2% vs 27.9%, dapagliflozin vs. comp.) suggesting that at least part of the serum creatinine increase during dapagliflozin therapy was due to dehydration and not due to progressing renal insufficiency. Analyses of pooled and unpooled populations did not indicate that any medication regimen or combination (e.g. dapagliflozin monotherapy, dapagliflozin plus metformin, dapagliflozin add-on to insulin, etc.) was associated with evidence of renal impairment. Reversibility of serum creatinine increase will be followed post-marketing within the CV outcome study and a pharmacoepidemiological study will further assess the risk of renal impairment.

With the responses to the 2nd Day 180 LOI, the Applicant could convincingly show that virtually all renal effects of dapagliflozin reflect physiological adaptations that can be expected from and explained by the known mechanism of action (SGLT2 inhibition increasing diuresis). Data on the time course of eGFR (derived from serum creatinine level), show that mean serum creatinine increases and, in line with this, eGFR decreases after initiation of dapagliflozin treatment. However, after a few months, the baseline level is regularly reached again. This also indicates that serum creatinine increase may not be misinterpreted as renal damage. Thus, the effects of dapagliflozin on the kidney are well predictable and constant so that the suggested monitoring intervals of renal function are accepted (usually once a year, 2-4 times per year in patients approaching the limit of 60 ml/min/1.73 m^2). It should be noted that dapagliflozin was also studied in patients with moderate renal insufficiency, and no unacceptable hazard was identified in this population, at least for short-term use. Therefore, it is not considered problematic if a patient receives dapagliflozin for a limited period of time (i.e. until the next screening visit) while having an eGFR of below 60. In other words, setting the cut-off at 60 ml/min/1.73 m^2 includes a reasonable safety margin.

Volume depletion

Reactions related to volume depletion (including, but not limited to, reports of dehydration, hypovolaemia or hypotension) were reported in 0.8% and 0.4% of subjects who received dapagliflozin 10 mg and placebo, respectively. Hypotension was the most common event and there were no events of dehydration or hypovolaemia.

Hypotension was more common in the dapagliflozin groups compared with the placebo groups for elderly subjects, moderate renal impairment and in patients treated with loop diuretics. In subjects receiving loop diuretics (n=126) the incidences of volume depletion were 9.7% and 1.8%, respectively. The use of dapagliflozin is not recommended in patients with moderate renal impairment, who are volume depleted or taking loop diuretics.

Bone metabolism

In the dapagliflozin clinical program, the effect of treatment with dapagliflozin on bone metabolism was evaluated using a combination of monitoring of electrolytes and hormones involved in bone metabolism, as well as monitoring of biomarkers of bone metabolism.

No clinically important changes were observed for mean serum concentrations of calcium or urine calcium. However, renal excretion of calcium and phosphate was not studied extensively in patients although this was a prominent effect in animals and may have contributed to the increased fracture rate observed with dapagliflozin use in renally impaired patients (particularly with eGFR < 45 ml/min/1.73 m^2). A slightly greater mean increase in serum phosphorus from baseline was observed in the dapagliflozin groups in the short-term double-blind period, particularly in the 5 and 10 mg groups. There were small increases from baseline in mean serum phosphorous levels to Week 24 that remained relatively unchanged at Week 102 in all treatment groups. Urinary calcium excretion was highly variable and, overall, did not appear to increase with dapagliflozin use. Mean PTH levels increased slightly in the dapagliflozin groups (with no dose-dependent effect) compared with placebo with PTH increases being larger in patients with already elevated baseline PTH plasma concentrations.

Overall, mean change from baseline in bone resorption markers (serum C-terminal telopeptide of type I collagen and N-terminal telopeptides of type-I collagen, and urinary deoxypyridinoline) showed a numerically higher increase in dapagliflozin-treated groups compared with placebo. This trend did not appear to be dose-related. Mean changes in serum markers of bone formation (osteocalcin and P1NP) were inconsistent in dapagliflozin-treated subjects.

In the Placebo-controlled Pool (ST and ST+LT) and in the All Phase IIb and III Pool (ST+LT) there was no imbalance in fractures between dapagliflozin and comparator groups (≤1.6%). However in study

MB102029 (diabetic subjects with moderate renal impairment), AEs of fracture were reported in a higher proportion of dapagliflozin-treated subjects (4 [4.8%] and 8 [9.4%] in the 5 and 10 mg groups, respectively) compared with placebo-treated subjects (0%). Most of the events, eight, occurred in patients with eGFR<45 ml/min/1.73m^2. The 4 remaining events in patients with eGFR > 45 ml/min/1.73m2 were considered to be due to baseline characteristics imbalance, history of hypotension, syncope and increased risk of fracture.

The CHMP raised the concern that dapagliflozin might lead to bone loss based on the observation of increased fracture incidence in the dapagliflozin group of study MB102029, conducted in renally impaired patients.

An apparently dose-dependent increase in serum PTH was indeed observed after 52 weeks in the moderate renal impairment study MB102029. This is further addressed in the renal impairment section.

The Applicant also provided data on bone parameters demonstrating that dapagliflozin does not impair bone quality/bone mineral density in general. For study D1690C00012, no relevant changes in BMD (measured by DXA) of clinical relevance relative to baseline were observed after one year.

In conclusion there is no clear evidence that dapagliflozin induces bone demineralisation or increases fracture rate in a diabetic population with normal or mildly impaired renal function. However, dapagliflozin-related bone damage with long-term treatment cannot be fully excluded, which would be particularly relevant in patients with pre-existing or at risk of osteoporosis such as patients with relevant renal insufficiency. A potential mechanism could be the exaggerated serum PTH increase due to dapagliflozin-induced calcium loss. Thus, together with the fact that the efficacy of dapagliflozin sharply decreases under conditions of moderate renal impairment (eGFR<60), treatment with dapagliflozin is not be recommended in patients with moderate renal impairment. In addition, fracture rates will be assessed as part of the CV outcome study and two-year data on BMD assessments performed as part of ongoing study D1690C00012 will be provided.

Urinary lythiasis

An increase in urinary uric acid has been observed in phase I studies but a lower proportion of subjects treated with dapagliflozin compared with comparator (0.6% vs 1.2%) reported events of urinary lythiasis.

Hepatic disorders

In the Placebo-controlled Pool (ST) the proportion of subjects with elevated liver function tests was similar (overall and for different cut-offs) in the dapagliflozin and placebo groups (3.5-3.9% vs 4.0). Similar proportions of subjects in each treatment group (0.9% - 1.1% in the dapagliflozin groups; 0.9% in the placebo group) had AEs of hepatic disorder. There was, however, one case of possible drug-induced liver injury (study D1690C00004) with positive dechallenge. Although, liver biopsy in this patient revealed signs of autoimmune hepatitis, no auto-antibodies were detected that would support this diagnosis. Normalisation of liver function tests finally occurred under prednisolone therapy.

Drug-induced liver injury is addressed as a potential risk in the RMP

Haematology

Compared to placebo, small increases from baseline were observed in haematocrit, haemoglobin, red blood cells, and decreases were observed in platelets. At Week 24, the mean changes from baseline in haematocrit were 2.15% in the group treated with dapagliflozin 10 mg versus -0.40% in the placebo group. Haematocrit values > 55% were reported in 1.3% of the subjects treated with dapagliflozin 10 mg versus 0.3% of placebo subjects.

These hematologic changes either normalized or trended toward normalization after dapagliflozin discontinuation.

There was an initial imbalance in the incidence of venous thromboembolic events not favouring dapagliflozin but the absolute number of events was low. An updated analysis with a data cut-off 15 July 2011 that includes all patients exposed to dapagliflozin and comparator in Phase IIb and Phase III studies, provided with the responses to the 2nd Day 180 LOI, showed that a similar proportion of patients in the dapagliflozin treatment group (0.3 %) and the comparator group (0.3 %) had venous thromboembolic events (short term plus long term treatment period; in total, 5501 patients in the dapagliflozin group and 3184 patients in the comparator group were evaluated). Clinical consequences of increased haematocrit are addressed in the SmPC and as a potential concern in the RMP.

Serious adverse event / deaths / other significant events

The frequency of SAEs was similar in the pooled dapagliflozin vs. the placebo groups and also vs. the all-comparator groups. Mortality was similar in the pooled dapagliflozin versus the all-comparator groups but was initially somewhat increased versus the placebo-group. A later interim analysis of two studies submitted during the evaluation (studies D1690C00018 and D1690C00019), performed in patients with CV background disease, revealed a slight imbalance in MACE events not favouring dapagliflozin. The significance of these findings, possible explanations (and further analyses regarding CV events are presented and discussed in more details above (under “CV safety”).

Neoplasm related adverse events

Overall tumour incidence

In the Phase IIb/III study pool submitted in the initial marketing authorisation application, there was an imbalance in tumour AEs (all organ systems) between dapagliflozin and controls based on the SMQ of malignant or unspecified tumours (1.4% versus 1.0%). With the responses to the D120 LOQ, the Applicant provided updated safety data from the 12th of May 2011 cut-off date (11 months later than in the original submission). In this updated study pool there was no difference in the overall incidence rate of tumours between dapagliflozin and all controls (1.43% versus 1.30%, see table 36). This was confirmed in yet another update of the study data pool with a new 15th of July 2011 cut-off date (incidence rate: 1.47% for the dapagliflozin versus 1.35% for the placebo/comparator group).

Table 35. Effect of different data cut-off dates on exposure

	Dapagliflozin					Control				
		Patient-years of exposure		Days of exposure/patient			Patient-years of exposure		Days of exposure/patient	
	N	Total	Relative to MAA	Mean	Relative to MAA	N	Total	Relative to MAA	Mean	Relative to MAA
MAA (June 2010)	4287	4009	NA	342	NA	1941	1682	NA	317	NA
12 May 2011	4559	4977	+ 24%	398	+ 56	2239	2348	+ 40%	383	+ 66
15 July 2011	5501	5496	+ 46%	387	+ 45	3184	3004	+ 90%	397	+ 50

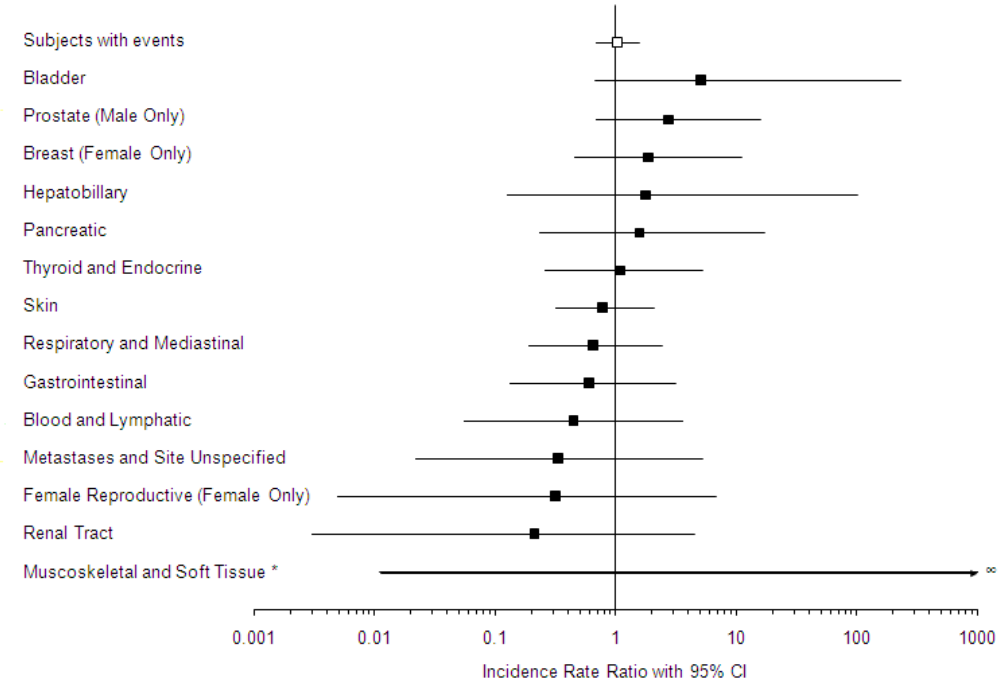
Table 36. Tumour incidence (malignant and unspecified) by organ system in the dapagliflozin Phase IIb and III pool. 12 May 2011 data cut-off

Organ system	Dapagliflozin (N=4559)				All control (N=2239			
	Subjects with event (%)	95% (CI)	Incidence rate[a]	95% (CI)	Subjects with event (%)	95% (CI)	Incidence rate[a]	95% (CI)
Subjects with events	65 (1.43%)	(1.10, 1.81)	1.29	(0.99, 1.67)	29 (1.30%)	(0.87, 1.85)	1.28	(0.88, 1.86)
Skin	12 (0.26)	(0.14, 0.46)	0.24	(0.12, 0.42)	8 (0.36)	(0.15, 0.70)	0.34	(0.15, 0.67)
Breast (Females only)	9 (0.40)	(0.19, 0.77)	0.37	(0.17, 0.71)	1 (0.09)	(0.00, 0.53)	0.09	(0.00, 0.51)
Prostate (Males only)	8 (0.34)	(0.15, 0.67)	0.31	(0.13, 0.61)	2 (0.17)	(0.02, 0.61)	0.16	(0.02, 0.57)
Bladder[b]	7 (0.15)	(0.06, 0.32)	0.14	(0.06, 0.29)	0 (0.00)	(0.00, 0.16)	0.00	(0.00, 0.16)
Thyroid and endocrine	7 (0.15)	(0.06, 0.32)	0.14	(0.06, 0.29)	3 (0.13)	(0.03, 0.39)	0.13	(0.03, 0.37)
Gastrointestinal	6 (0.13)	(0.05, 0.29)	0.12	(0.04, 0.26)	2 (0.09)	(0.01, 0.32)	0.08	(0.01, 0.31)
Respiratory and mediastinal	5 (0.11)	(0.04, 0.26)	0.10	(0.03, 0.23)	5 (0.22)	(0.07, 0.52)	0.21	(0.07, 0.49)
Pancreatic	4 (0.09)	(0.02, 0.22)	0.08	(0.02, 0.20)	1 (0.04)	(0.00, 0.25)	0.04	(0.00, 0.24)
Blood and lymphatic	2 (0.04)	(0.01, 0.16)	0.04	(0.00, 0.14)	2 (0.09)	(0.01, 0.32)	0.08	(0.01, 0.31)
Hepatobiliary	2 (0.04)	(0.01, 0.16)	0.04	(0.00, 0.14)	0 (0.00)	(0.00, 0.16)	0.00	(0.00, 0.16)
Female reproductive (Females only)	1 (0.04)	(0.00, 0.25)	0.04	(0.00, 0.23)	1 (0.09)	(0.00, 0.53)	0.09	(0.00, 0.51)
Metastases and site unspecified	1 (0.02)	(0.00, 0.12)	0.02	(0.00, 0.11)	2 (0.09)	(0.01 0.32)	0.08	(0.01, 0.31)
Musculoskeletal or Soft Tissue	1 (0.02)	(0.00, 0.12)	0.02	(0.00, 0.11)	0 (0.00)	(0.00, 0.16)	0.00	(0.00, 0.16)
Renal Tract	0 (0.00)	(0.00, 0.08)	0.00	(0.00, 0.07)	2 (0.09)	(0.01, 0.32)	0.08	(0.01, 0.31)

Incidence of tumours in specific organ systems

If one considers a longer treatment exposure (see table 35 above) no difference was observed between the overall proportion of subjects with malignant or unspecified tumours being 1.47% for the dapagliflozin and 1.35% for the placebo/comparator group. The incidence rate ratios with 95% CIs for malignant/unspecified tumours of all organ systems (with the 15th of July 2011 as new cut-off date) are provided graphically below. The outcome is in line with random fluctuation of the incidence rate of individual tumour types around unity, showing higher numbers of breast cancer, bladder cancer and prostate cancer, and lower of renal and female reproductive tract, blood and lymphatic cancer, with the remaing types of malignancies being essentially similar. Although the overall figures and the distribution of incidences per tumor type do not suggest an increased risk, it is worth to consider more in detail those types of cancer that present an increased frequency.

Figure 22. Incidence rate ratio and 95% CI for dapagliflozin versus control, by organ system. Tumour incidence (malignant or unspecified neoplasms) from SMQ. Short-term plus long-term treatment period including data after rescue. Phase IIb and III pool. 15 July 2011 integrated safety database



* There were 1 and 0 subjects in the dapagliflozin and control groups, respectively, leading to a incidence rate ratio point estimate of infinity.

Breast cancer

In the initial and the updated (12th of May 2011) safety data pool the incidence of breast cancer was 0.37 versus 0.09% for dapagliflozin and comparators, respectively. At the 15th of July 2011 cut-off date, the difference was less pronounced with 0.40 versus. 0.22 cases of breast cancer per 100 patient years reported for dapagliflozin and comparators, respectively.,

Considering the expected incidence based on epidemiological literature data, the incidence of breast cancer is around 0.25 per 100 patient years in the relevant age group but the incidence in diabetic patients may be somewhat higher. The remarkably low incidence initially observed in the comparator group (0.09 versus 0.37 in the dapagliflozin group) is most likely a chance finding

All breast tumours reported in the clinical studies were diagnosed within 48 weeks after inclusion of the patients in the trials. Thus, patients were exposed to dapagliflozin for less than one year to diagnosis;

this time frame is short in terms of tumour development and it is therefore likely that the tumours were pre-existing.

Histology of the tumours in the study population did not reveal special features but were of the same types as found in the general population, which is in line with the assumption of pre-existence of these neoplasms. Further, direct or indirect hormonal action of dapagliflozin as a mechanistic basis for breast cancer induction is unlikely. If so, alterations in other hormone-dependent organs (uterus, ovaries) would have been obvious in human and/or animal studies, which was not the case. Taken together, a causal relationship between dapagliflozin and breast cancer is unlikely.

Bladder cancer

At the 15th of July 2011 cut-off date, the incidences of bladder cancer were 0.16 versus 0.03 cases per 100 patient years in the dapagliflozin and the comparator group, respectively. After adjusting the analysis to take into account only those events that had been exposed for one year or longer (a more plausible latency for development of malignancies), there was an imbanlance with 4 cases (0.07%) in the dapagliflozin and no case in the placebo/comparator group.

The incidence observed in the pooled dapagliflozin group is above expectation (the incidence of bladder cancer is below 0.1 per 100 patients years), but not statistically significant compared to comparators.

The increase in cumulative bladder cancer incidence over time is virtually the same as for malignant/unspecified tumours in total (i.e. steady increase over two years and only few new cases later). As most of the bladder tumour patients had a history of (micro)-haematuria, the bladder tumours diagnosed during the trials may have been already present when the patients were recruited for the trials but were too small to be detected.

Potential and established risk factors (age, male gender, smoking status) were well balanced between the dapagliflozin and the comparator group.

There was also a concern that a mechanistic basis could exist for bladder cancer, in particular repeated urinary tract infections (UTIs) and increased glucose concentrations in urine due to dapagliflozin treatment. Data from published literature give no support that UTIs are a relevant risk factor for bladder cancer except in patients with long-term indwelling urinary catheters. The potential role of the dapagliflozin induced glucosuria in growth promotion of bladder cancer remains unclear, but lacks scientific support. Thus, the observed difference in the incidence of bladder cancer may well be explained by random variation or detection bias due to an increased frequency of urogenital adverse reactions with dapagliflozin.

Prostate cancer

At the 15th of July 2011 cut-off date, the incidences for prostate cancer in the dapagliflozin and in the comparator group were 0.34 versus 0.16 cases per 100 patient years. After adjusting the analysis to take into account only those events that had been exposed for one year or longer (a more plausible latency for development of malignancies), there was 1 case (0.034%) with dapagliflozin and 1 case (0.055%) with placebo/comparator.

Thus, almost all patients were exposed to dapagliflozin for less than one year to diagnosis; this time frame is short in terms of tumour development and it is therefore likely that the tumours were pre-existing. A specific underlying mechanism, in particular direct or indirect androgenic effects of dapagliflozin are unlikely because - as discussed for breast cancer - these hormonal actions most likely would have manifested themselves also otherwise.

Thyroid cancer

In the data presented with the first cut-off date, there was an imbalance in thyroid neoplasms reported as nodules (7 cases for dapagliflozin versus 1 for comparators). At the 15th of July 2011 cut-off date, the incidence was well balanced. Thus, the original signal was most likely due to random fluctuation.

Hormone analyses

Analyses of aldosterone, C-peptide and erythropoietin levels have been further analysed by the Applicant since these hormones have been suggested to have a tumour promoting effect. The data provided show that patients on dapagliflozin had minor increases in aldosterone and erythropoietin levels whereas the C-peptide levels decreased. Thus a tumour promoting effect of dapagliflozin by activation of these hormones appears unlikely.

Relevant non-clinical data

The carcinogenic potential of dapagliflozin was also investigated in non-clinical standard carcinogenicity studies. Furthermore, non-clinical data may reveal indications whether primary or secondary pharmacodynamic effects of dapagliflozin may impact tumour development. The Safety Working Party (SWP) of the CHMP was consulted to give advice to these aspects. SWP identified no shortcomings in the non-clinical carcinogenicity studies and concluded that these studies revealed no evidences of a carcinogenic action of dapagliflozin. Regarding potential pharmacodynamic effects, it was concluded that dapagliflozin is able to activate the renin-angiotensin-aldosterone system but that this activation does not lead to a concern since established diuretics, e.g. hydrochlorothiazide have the same effect (probably even more pronounced) and do not lead to increased tumour rate. SWP stated that it cannot be decided whether or not glucosuria may affect the proliferation of pre-existing bladder tumours. However, the scientific support for this mechanism is weak.

Deaths

There was no imbalance in mortality between dapagliflozin and combined comparators in the All Phase IIb/III study pool, i.e. mortality was 0.5% in both the dapagliflozin and in the comparator group of this pool. However, mortality was increased by around factor 3 in the dapagliflozin group when compared to placebo, see table below. However, the absolute numbers were small.

placebo-controlled Phase IIb/III studies (study MB102029 conducted in renally impaired patients does not belong to this pool)		
	dapagliflozin 3291 patients treated 2687.4 patient years	**placebo** 1393 patients treated 777.6 patient years
number of deaths % of treated patients deaths per 1000 patient years	18 0.55 6.7	2 0.14 2.6

Laboratory findings

Changes from baseline in parameters related to renal function, serum phosphorus, serum calcium, hepatic function and haematology are described above.

Concerning serum electrolytes, in the overall study population increased serum sodium (>150 mEq/L) was reported in 1.4 % of patients on dapagliflozin compared to 0.7 % in controls. In the age group > 65 the corresponding reporting was 2.0 % in the dapagliflozin compared to 0.6 % for placebo.

There was no evidence for increased risk of acidosis with dapagliflozin (due to induced catabolism), which could be of concern with concomitant metformin therapy.

There was a small increase in LDL-C and total cholesterol after 24 weeks with a further increase after 102 weeks which was higher in the dapagliflozin group than in the placebo group. There was also an increase in HDL-C and no difference between the groups was seen in the LDL-C/HDL-C ratio up to 102 weeks.

Safety in special populations

Elderly subjects

Treatment with dapagliflozin in subjects ≥ 65 years of age was associated with a higher proportion of events of renal impairment/failure (2.5% vs 1.1%, with no apparent dose-dependency). The difference was driven by AEs of blood creatinine increase. An overall slight increase in events considered related to hypovolaemia (primarily events of hypotension) was also observed in this age group. There is only limited data for patients ≥75 year (67 dapagliflozin treated subjects in the ST placebo-controlled pool) and the safety of this group was not evaluated separately.

Therefore the CHMP requested further analysis in elderly patients > 65 years particularly prone to adverse reactions with dapagliflozin treatment such as volume depletion, hematocrit increase and potential serious sequelae due to frequent concomitant diseases (e.g. cerebro- and cardio-vascular disease) and medication (i.e. diuretics) and a physiologically decreased sense of thirst.

The Applicant provided during the evaluation a thorough analysis of the elderly subjects enrolled in the studies. More than 1300 elderly patients were included in the studies and in the consecutive safety analysis so that the data base is considered large enough for reliable conclusions. Placebo controlled pooled data include 776 dapagliflozin treated patients >65 years and 245 placebo treated patients. Only 97 patients (20 placebo and 77 dapagliflozin treated) above the age of 75 were included in this group. In addition, data from 314 patients included in comparator trials was analysed. As expected, the older age group included a higher proportion of patients with mild to moderate renal impairment, this being most prominent in the age group > 75 years of age.

The overall reporting of AEs and SAEs was not markedly different in the older patients as compared to the overall population. Data were also stratified according to co-treatment but thereby the number of patients per group grew rather small so that conclusions are limited. In most categories there was no meaningful difference between dapagliflozin and placebo treatment. No change in the reporting pattern was observed in the long-term follow-up when older patients were compared to the overall population. No alarming imbalances with regards to SAEs including deaths, were observed although somewhat higher rates of SAEs and deaths were observed compared to the overall population.

Overall the reporting rate of hypovolemia associated AEs was rather low (about 2-3 %). Rates were generally higher in the dapagliflozin treated group compared to placebo. There is no apparent dose related reporting. The concomitant use of loop diuretics was associated with a higher reporting rate. In the long term-follow up in the study recruiting patients with moderate renal impairment, a rather marked difference was observed between dapagliflozin and placebo treated patients (8 vs 2 %). This did not differ from the overall population in this study but supports that this is a vulnerable population. In the study comparing dapagliflozin and glipizide, no marked difference was observed between treatment groups. When analysing hypovolemia associated events by concomitant medication, again loop diuretics were associated with a higher risk.

A moderate mean increase in hematocrit was observed during treatment: This was also seen in the total study population (i.e. not only in elderly). However, it is conceivable that elderly patients, often with co-morbidities, tolerate hematocrit increase less well than younger diabetics. Thus, increased hematocrit (or dehydration in general) may pose a particular risk for elderly patients. In patients with any degree of renal impairment, a markedly increased hematocrit > 55% or Na^+ > 150 mEq/L was observed in 2 or 11 patients (out of 502), respectively, whereas no such case occurred in the placebo group (N=221) or in elderly patients with normal renal function, albeit the number of patients in the latter group was rather small (placebo, n=51; dapagliflozin, n=116). Use of dapagliflozin is not recommended for patients at risk of volume depletion/electrolyte imbalances.

Hypoglycaemia events were rare in the pooled analysis and were less common in the dapagliflozin treated group compared to glipizide. No differences were observed when compared to the overall population. Notably, hypoglycaemia was lower in the dapagliflozin treated patients with moderate renal impairment compared to placebo.

No imbalances compared to placebo rate or when compared to younger patients were observed with regards to fractures, UTI and CV risk.

Renal function appears to be more important for determining dapagliflozin's safety and efficacy than the chronological age per se. It does not appear necessary to exclude patients aged 65 or above from dapagliflozin treatment as long as they have an appropriate renal function. However, it is considered advisable to not to recommend the use in very elderly (aged 75 or above) because for these patients the data base is very small (only a few percent of the total study population) and renal function more likely to be impaired. Furthermore, elderly patients at increased risk of water/electrolyte imbalances due to concomitant medications or co-morbidities are expected to be at an increased risk of hypotension and falls and possibly also thrombosis due to increased hematocrit. Therefore treatment with dapagliflozin in elderly patients 75 years and above is not recommended due to the lack of data and since these patients are at high risk of volume depletion/electrolyte imbalances.

Gender

Events suggestive of genital infection and UTI were reported for a greater proportion of females than males in all treatment groups.

Renal impairment

In patients with mild renal impairment (eGFR ≥ 60 to <90 ml/min/1.73m^2) the safety profile was consistent with the overall population.

There were 684 subjects (11%) with moderate renal impairment (eGFR ≥30 to <60 ml/min/ 1.73m^2) included in the program, 252 of these subjects were included in the dedicated study MB102029. In this study patients had generally lower eGFR values than in the remaining studies and more fractures were reported for subjects receiving dapagliflozin compared to placebo, particularly in patients with the lowest eGFR values (see section "fractures" above). There were mean increases in the concentrations of serum phosphorus and magnesium in subjects receiving dapagliflozin, with mean values remaining within the normal ranges for these analytes. The mean concentration of serum PTH, which exceeded the upper limit of normal at baseline in all treatment groups, increased more in subjects treated with dapagliflozin than with placebo. AE reports in the hypotension/ dehydration/hypovolemia category, consisting mainly of reports of hypotension, were more frequent in the dapagliflozin groups than in the placebo group.

In a subgroup analysis of patients with eGFR ≥45 to <60 ml/min/1.73m^2, initially proposed by the applicant to be appropriate for treatment with dapagliflozin, increase in blood creatinine (5.2 % vs 0 %), phosphorus (5.2 % vs 2.9 %), PTH (mean increase 5.5 pg/mL vs 2.6 pg/mL) and volume depletion (3.0%, 2.3%, and 4.7% of subjects in the dapagliflozin 2.5, 5, and 10 mg groups, respectively, and 1.4% in the placebo group) was more evident than in the placebo-controlled pool. Due to limited efficacy and potentially increased safety issues, the use of dapagliflozin is not recommended in this patient group.

Patients with severe renal impairment (eGFR <30 ml/min/1.73m^2) were excluded throughout the study program due to expected lack of efficacy.

Severe hepatic impairment

A phase I study (MB102027) was designed to evaluate the effects of hepatic impairment on the single dose PK of dapagliflozin 10 mg in non diabetic subjects with Child-Pugh Class A, B, and C hepatic impairment. Exposure (AUC) to dapagliflozin increased about 70% in subjects with severe hepatic impairment. A reduced starting dose of 5 mg dapagliflozin is recommended in patients with severe hepatic impairment.

Heart failure

Patients with heart failure NYHA class III and IV were excluded from the phase III studies. Use in these patients is addressed as missing/limited information in the RMP. There are two Phase IIIb studies ongoing (D1690C00018 and D1690C00019), which include patients with NYHA class III.

Safety based on thiazide diuretic or ACE-I and/or ARB use

In dapagliflozin-treated subjects with thiazide diuretic use and ACE-I and/or ARB use, marketed laboratory abnormality for high serum potassium (≥ 6 mEQ/L) was seen more frequently.

Pregnancy and lactation

Dapagliflozin has not been studied in pregnant or lactating women. Due to preclinical renal findings dapagliflozin should not be used during the second and third trimesters of pregnancy.

Safety related to drug-drug interactions and other interactions

Interaction studies in healthy volunteers suggest that the PK of dapagliflozin was not altered for the most commonly used concomitant medications in T2DM patients.

Discontinuation due to adverse events

In the Placebo-controlled pool (ST) similar proportions of subjects across the treatment groups (2.5% in the placebo group vs 2.2 to 3.2% in the 2 doses dapagliflozin groups).

Across all dapagliflozin treatment groups, the most commonly reported AEs leading to discontinuation (i.e., reported in at least 3 subjects) were blood creatinine increased (protocol driven discontinuation) and urinary tract infection.

2.6.1. Discussion on clinical safety

The safety database is considered sufficiently large. The most common AEs (≥ 2%) in the dapagliflozin 10 mg group during the short-term period were (in descending order of frequency): nasopharyngitis, back pain, headache, diarrhoea, upper respiratory tract infection, urinary tract infection, dyslipidemia, nausea, hypertension, influenza, pollakiuria, and dysuria.

There was no imbalance in mortality between dapagliflozin and combined comparators in the all Phase IIb/III study pool, i.e. mortality was 0.5% in both the dapagliflozin and in the overall comparator group of this pool.

Overall, the frequency of SAEs was similar in the dapagliflozin and the placebo groups.

In the Phase IIb/III study pool submitted in the initial marketing authorisation application, there was an imbalance in tumour AEs (all organ systems) between dapagliflozin and controls (1.4% versus 1.0%). With the responses to the D120 LOQ, the Applicant provided updated safety data from the 12th of May 2011 cut-off date (11 months later than in the original submission). In this updated study pool (with an overall increased exposure in patient-years of 40% in the control group and 26% in the dapagliflozin group) there was no difference in the overall incidence rate of tumours between dapagliflozin and all controls (1.43 versus 1.30%). This was confirmed in yet another update of the study data pool with a new 15th of July 2011 cut-off date (incidence rate: 1.47% for the dapagliflozin and 1.35% for the placebo/comparator group).

When considering the cases of tumours occuring in the different organ systems, the relative risk associated with dapagliflozin was above 1 for some tumours (bladder, prostate, breast) and below 1 for others (e.g. blood and lymphatic, ovary, renal tract), not resulting in an overall increased tumour risk associated with dapagliflozin. The increased/decreased risk was not statistically significant in any of the organ systems.

However, due to the numerical imbalances (15th of July 2011 cut-off date) in cases of breast cancer (10 cases versus 3), bladder neoplasms (PTs; bladder cancer, bladder neoplasm, bladder transitional cell carcinoma and bladder transitional cell carcinoma stage II) (9 cases versus 1) and prostate cancer (PTs; prostate cancer, prostate cancer recurrent) (10 cases versus 3), possible explanations to these imbalances were carefully examined during the assessment procedure.

Concerning both breast and prostate cancer, it appears likely that the vast majority of them were pre-existing since, except for two cases of prostate cancer, all of them occurred within the first 48 weeks of treatment. Further, direct or indirect hormonal action of dapagliflozin as a mechanistic basis for breast/prostate cancer induction is unlikely. If so, alterations in other hormone-dependent organs (uterus, ovaries) would have been obvious in human and/or animal studies, which was not the case.

Bladder cancer was reported in 0.16 % of dapagliflozin treated subjects (9 cases) compared to 0.03 % in the all control group (1 case; note that the control group was smaller than the verum group). On the other hand, renal tract tumours were numerically lower with dapagliflozin. Known risk factors for bladder cancer (age, male gender and smoking) were equally distributed among treatment groups. Two 24-month carcinogenicity studies performed in rats and mice with a maximum exposure of 72 to 186 times (depending on species and sex) above the therapeutic exposure in humans, did not reveal a carcinogenic potential of dapagliflozin, which is reassuring. The CHMP is not aware of a case where a drug found to induce tumours in humans has not created a signal in long-term carcinogenicity studies. The potential role of the dapagliflozin induced glucosuria in growth promotion of bladder cancer remains unclear, but lacks scientific support. Thus, the observed difference in the incidence of bladder cancer may well be explained by random variation or detection bias due to an increased frequency of urogenital adverse reactions with dapagliflozin.

In conclusion, with more exposure data available at the latest cut-off date, the imbalance of tumour events observed in the dataset provided for the initial application was no longer discernible and there was no difference in overall tumour incidence. Considering the lack of tumour findings in non-clinical studies as well as the short latency between first drug exposure and tumor diagnosis, a causal relationship is considered as unlikely. However, since a numerical imbalance of bladder and breast cancer and to some extent prostate cancer remained, and must be addressed with the utmost vigilance, neoplasms (i.e. bladder, breast and prostate cancer) have been included among the potential risks in the RMP and Pharmacovigilance activities described. It is proposed that bladder, breast and prostate cancer are specifically investigated as part of the planned CV outcome study. Considering the possible association of pioglitazone and bladder cancer, the combination of dapagliflozin and pioglitazone is not recommended.

For dapagliflozin treated patients bone resorption markers, serum phosphorus and serum PTH were higher than in the comparator group with PTH increases being higher in patients with already elevated baseline PTH plasma concentrations. Follow-up (52 week) data of study MB102029 (in patient with moderate renal impairment) indicate a small and dose-dependent increase in serum PTH in the dapagliflozin groups. Moreover, an increase in fracture rate for the dapagliflozin group was observed in the same study, particularly in those with the most profound renal impairment (GFR<45 ml/min). On the other hand, the 1-year DXA results from an ongoing study did not reveal any relevant changes in bone mineral density associated with dapagliflozin in either patients with normal or mildly impaired renal function. However, dapagliflozin-related bone loss with long-term treatment cannot be fully excluded even with a slight increase in PTH, which would be particularly relevant in patients with pre-existing or at risk of osteoporosis. Bone fracture is included as a potential risk in the RMP. Bone fractures will be further studied as part of the CV outcome study.

Regarding dapagliflozin use in elderly, in patients ≥ 65 years the difference from placebo was more evident for events of renal impairment and volume depletion, especially hypotension. There is only limited data for patients ≥75 years of age. Elderly patients are likely more prone to water/electrolyte imbalance due to frequent concomitant medication and baseline impaired renal function, which, together with a decreased sense of thirst, may increase the vulnerability for volume depletion with dapagliflozin use leading to haematocrit increase and potentially other sequelae including hypotension. After thorough review of the available data this concern remains and the initiation of dapagliflozin therapy is not recommended in patients > 75 years of age. Dapagliflozin should be used with caution in elderly patients, especially in those on concomitant diuretics. Due to diminishing effect of dapagliflozin with decreasing GFR and safety concerns, the B/R ratio of dapagliflozin is considered negative in all patients with moderate to severe renal impairment (GFR < 60 ml/min/1.73 m^2).

There were no major episodes of hypoglycaemia when dapagliflozin was used as monotherapy. When dapagliflozin was used together with insulin and SU an increased risk of hypoglycaemic events was observed, mainly seen as an increase in minor hypoglycaemic events. This information is reflected in the SmPC.

An increased risk of UTI and genital infection was identified, which was considered a consequence of urinary excretion of glucose. A majority of these events were of mild or moderate intensity and responded well to a single course of antibiotics. Events of kidney infections were reported rarely and with similar frequency in dapagliflozin treated subjects and placebo. There is a possible risk of severe UTI and the applicant's plan to follow this risk via a planned epidemiological study (see the RMP) is endorsed. The recurrence rate of UTI was higher in dapagliflozin group than in placebo. This information is reflected in the SmPC.

Dapagliflozin has a diuretic effect and AEs of volume depletion (e.g hypotension) was more frequent in some of the safety pools. In the subgroups of subjects ≥ 65 years of age, subjects with baseline eGFR ≥ 45 and < 60 mL/min/1.73 m2 and subjects receiving loop diuretics events were more common in the dapagliflozin groups compared with the placebo groups.

Overall, there was no imbalance between dapagliflozin and comparator in events of renal impairment. However, in elderly and in patients with renal impairment (eGFR 45-60mL/min/m2) events of renal impairment or failure and creatinine increase (≥ 1.5 pre-treatment creatinine) were more frequent in the dapagliflozin group. Upon discontinuation of therapy, increased serum creatinine values returned more frequently to baseline values in patients treated with dapagliflozin than with comparator (47.2% vs 27.9%). This may indicate that at least part of the serum creatinine increase during dapagliflozin therapy was due to dehydration and not due to progressing renal insufficiency. In fact, the time course of eGFR (derived from serum creatinine level) which was provided by the Applicant during the evaluation, shows that mean serum creatinine increases and, in line with this, eGFR decreases after initiation of dapagliflozin treatment, probably because of dehydration. However, after a few months, the baseline level is regularly reached again, most likely because counter-regulatory mechanisms such as enhanced activity of the renin-angiotensin system come into play. This again indicated that serum creatinine increase may not be misinterpreted as renal damage. Thus, the effects of dapagliflozin on the kidney are well predictable and constant so that the suggested monitoring intervals of renal function are accepted (usually once a year, 2-4 times per year in patients approaching the limit of 60 ml/min/1.73 m^2). It should be noted that dapagliflozin was also studied in patients with moderate renal insufficiency, and no unacceptable hazard was identified in this population, at least for short-term use. Therefore, it is not considered problematic if a patient receives dapagliflozin for a limited period of time (i.e. until the next screening visit) while having an eGFR of below 60. In other words, setting the cut-off at 60 ml/min/1.73 m^2 includes a reasonable safety margin.

Across the studies, similar proportions of subjects with elevations of ALT or AST (overall and for different cut-offs) were observed for dapagliflozin and placebo/comparator. There was, however, one case of possible drug-induced liver injury. Renal failure and liver injury are included in the RMP as potential risks and an epidemiological study is planned to study the prevalence of serious cases post-marketing.

Clinical trials revealed that dapagliflozin consistently increases the haematocrit, albeit generally to a small degree, which could favour thrombotic and embolic events. Nevertheless, the latest analysis in around 8700 patients, provided in the responses to the 2nde LOI, showed that a similar proportion of patients in the dapagliflozin treatment group and the comparator group had venous thromboembolic events (0.3 % in both groups).

An increase in urinary uric acid has been observed in phase I studies but no increased risk of urinary stones was found. The clinical relevance of the observed increase in uric acid excretion and subsequent lowering of serum uric acid levels with longer term treatment will be further investigated in the planned cardiovascular outcome study.

No increased cardiovascular risk was found for dapagliflozin treated subjects in the CV meta-analysis.

The results of the pooled analysis of study D1690C00018 and D1690C00019 in patients with high CV risk have been further discussed by the Applicant. The data provided suggests that high CV risk patients concomitantly taking loop diuretics and/or antihypertensive drugs may be at increased risk for a CV event when starting dapagliflozin, possibly due to a diuresis-induced decrease in blood pressure. However, the absolute number of CV events in these ongoing studies is still limited and the imbalance small and uncertain.

Additional analysis in all patients with CV disease from the Phase IIb/III study pool including the new studies D1690C00018 and D1690C00019 showed no increased MACE rate, neither at initiation of dapagliflozin therapy nor later in the CVD population. This is reassuring since it demonstrates that the risk for CVD patients in general is not appreciably increased. Nevertheless, patients with more severe CVD as included in studies D1690C00018 and D1690C00019 may be more susceptible to the haemodynamic changes induced by dapagliflozin, especially with concomitant intake of antihypertensive medication. Since the indication of dapagliflozin is for treatment of diabetes, physicians and patients may not be aware of the blood pressure-lowering effect and potential safety issues in vulnerable patients. A warning for patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on anti-hypertensive therapy with a history of hypotension has been included in the SmPC.

A small increase in LDL-C and total cholesterol was observed after 24 weeks with a further increase after 102 weeks which was higher in the dapagliflozin group than in the placebo group. No difference between the groups was seen in the LDL-C/HDL-C ratio after 24 weeks (due to an increase in HDL-C). The LDL-C/HDL-C ratio remained unchanged up to 102 weeks. No potential mechanism for the change in lipids has been identified but the clinical relevance with long term treatment will be investigated within the planned cardiovascular outcome study.

Events of marked serum electrolyte abnormalities were generally balanced between dapagliflozin (all doses) and controls, except for hypernatraemia that was reported more often in the dapagliflozin group. Hyperkalemia (>6 mEQ/L) was observed more frequently in dapagliflozin treated patients with thiazides as well as with ACE-I and/or ARB use compared with placebo. The Applicant outlined that changes in electrolytes and in the renin-angiotensin system are in general larger with standard diuretics therapy than with dapagliflozin. Thus, these changes are deemed clinically manageable and are therefore not considered to be of particular concern.

In the sub-group analysis of patients with eGFR ≥ 45 and < 60 mL/min/1.73m2 the increase in blood creatinine, phosphorus, PTH and hypotension was more evident for dapagliflozin treated subjects than seen in the placebo-controlled pool. Information on the more frequently observed AEs (events of renal impairment, phosphorus and PTH increase, hypotension) in this patient group has been added to the SmPC.

Additional expert consultations

As per CHMP request, a Scientific Advisory Group (SAG) expert meeting for diabetes/endocrinology was convened on 9 January 2012 to obtain input on the efficacy and safety of dapagliflozin and to provide advice on the list of questions adopted by the CHMP at its October 2011 meeting. The SAG provided the following answers to the questions raised by the Committee:

1. **The clinical importance of the effects seen in the studies with dapagliflozin taking into account the magnitude of the HbA1c reduction, the effect on body weight and blood pressure as well as the influence of renal function on the effect.**

The observed reduction in HbA1c, the principal outcome parameter, was of the order of 0.5-0.7%. Although relatively modest, this met the criteria for non-inferiority in comparison with metformin or sulfonylureas, and was (in the view of some experts) comparable to the effect achieved with the gliptins. It was however noted that the effect of dapagliflozin diminished with declining renal function, as commonly encountered in older people with diabetes, and was overall about 0.4% in those over the age of 65 as a group, although it is important to note that efficacy was retained in older people with normal renal function. These observations emphasised the need for careful patient selection, since the risk/benefit ratio could otherwise be considered borderline or unfavourable in unselected older patients, and recent large studies have confirmed that longer term benefit from this degree of improved glucose control could not reasonably be expected. The patient representative emphasized that from his point of view even such a moderate effect was still very welcome for those striving for improved control in type 2 diabetes.

Dapagliflozin also produces small reductions in weight and blood pressure. Fluid depletion is likely to represent a proportion of the loss in weight, and to be responsible for the reduction in blood pressure. Although limited in scale, these responses nonetheless contribute to a favourable overall effect of treatment. The pharmacological principle represented by dapagliflozin is novel, offering the additional benefit that this agent can usefully be combined with other therapies with differing pharmacological actions. The net effect of SGLT2 inhibition is achieved by loss of glucose from the body, together with the fluid loss occasioned by an osmotic diuresis. The glucose loss might be considered a form of involuntary carbohydrate restriction, but the experts were not convinced that the catabolic effects associated with this were identical to those that might be anticipated from, e.g., the equivalent reduction in dietary intake. The pattern of reduction of lean versus fat body mass (derived from DEXA data) did not raise concern, but the experts considered that more data should be obtained regarding protein turnover, and suggested that this should be investigated further, e.g. by the use of tracer studies. In general, there were concerns that more needs to be known about the longer term metabolic consequences of use of a novel agent to which people might potentially be exposed for many years.

2. The safety profile of dapagliflozin, in particular the influence of renal function as well as the diuretic effect which, in some susceptible patients may result in hypotension, electrolyte derangements and increased haematocrit.

The SAG focused upon the more common safety effects related to the mechanism of action of dapagliflozin, and did not spend much time in discussion of rarer potential off-target effects. In general, the unwanted consequences of glycosuria coupled with osmotic diuresis were predictable, with a marked increased in genital infections, a smaller increase in urinary tract infections, and an increased risk of fluid depletion in those already predisposed to this for other reasons. The SAG noted that such unwanted effects, although classed as minor, could impact adversely upon an individual's quality of life. Such effects would include genital infection and (potentially) aggravation of urinary urgency or incontinence. With respect to the latter point, however, it was noted that there was no apparent effect upon the frequency of nocturia. Overall, the safety profile for the period of observation appears to be acceptable in those with normal renal function, and also in those with mildly reduced renal function; the diminishing benefit in the latter might however be expected to influence the risk/benefit balance adversely. As mentioned in response to the previous question, longer term consequences of a forced osmotic diuresis (for example, the increase in plasma phosphate and PTH) also need to be considered, and the experts would have liked to see stronger evidence of a commitment to longer term research monitoring. The risk posed by volume depletion was also of some concern, since older people have restricted renal function and reduced appreciation of thirst. They are therefore more likely to present late with features of fluid depletion, and in conditions of everyday clinical practice these might not be easily recognized and acted upon. It might be justified to consider specific circumstances leading to volume depletion in more detail, e.g. reduced fluid intake, gastrointestinal illness, severe infection leading to diarrhoea and/or vomiting, although the current advice to stop treatment during such episodes was considered appropriate. The role of renal function is considered further in the response to question 3, and appropriate restrictions upon its use in the answer to question 4.

3. The appropriate target population (with respect to e.g. age, renal function, co-morbidities, concomitant medications) for treatment with dapagliflozin considering the responses to question 1 and 2.

The applicant has proposed the following restrictions: therapy not to be initiated in patients with GFR < 60 ml/min/1.73 m^2, therapy not to be initiated in patients over the age of 75 and therapy not recommended in patients receiving loop diuretics. The applicant has investigated the effect of treatment in those with more advanced renal insufficiency (GFR >45, <60 ml/min/1.73 m^2), and adverse effects were not markedly increased in this group. The higher cut-off of <60 ml/min/1.73 m^2 was therefore considered to offer an appropriate prudential margin of safety.

The use of eGFR to define the treatment cut off came in for much discussion, since there is considerable imprecision in widely-used estimates such as the Cockcroft-Gault formula or the MDRD (Modification of Diet in Renal Disease) formula, which themselves tend to give different results. The "safety margin" referred to in the previous paragraph would however suggest that this degree of imprecision is nonetheless acceptable in clinical use. Extreme old age apart, age would not be an appropriate cut-off, but was noted to be correlated with deteriorating kidney function, lesser life-expectancy, more comorbidities, and (in many circumstances) to require less aggressive glucose-lowering therapy.

The SAG noted that, although the mode of action of this agent is unique, there are no unique clinical indications for its use, and therefore no specific target population in mechanistic terms. Older patients in general were considered less suitable because of diminishing efficacy (except in those with normal renal function), less likelihood of benefit in terms of glucose-responsive outcome measures, and overall susceptibility to adverse consequences such as infections, urinary problems and fluid depletion. There is a clear risk that this product might be over-used or inappropriately used in older individuals, but it would not seem appropriate to with-hold its potential benefits from those who have been appropriately screened and monitored. After extensive discussion, therefore, SAG (with some reluctance) felt that the agreed restrictions were appropriate. It further noted that clinical experience with this therapy is still very limited, and that greater clinical experience will be needed before its position and value within the clinical armamentarium can be established upon a sounder basis.

4. The adequate monitoring of a possibly restricted target population taking into account that patients treated with dapagliflozin may develop impaired renal function and other co-morbidities as well as start new concomitant medications which may change the effect and safety of dapagliflozin. Would this constitute a problem in clinical practice?

The SAG accepted that annual monitoring of serum creatinine is already accepted clinical practice, and would therefore be performed effectively. It was less convinced that more intensive monitoring, as suggested by the applicant, would prove practicable in clinical practice, and there are other clinical situations in which this has proved to be the case. The patient representative emphasized that both patients and doctors should accept the responsibility for monitoring therapy. The SAG proposes a simpler cut off, for which a precedent already exists with metformin therapy, and recommends that therapy should be discontinued when the threshold has been breached on a single occasion (whilst excluding laboratory errors and allowing resumption of therapy in individual cases with clear temporary cause for deterioration), instead of requiring treatment to be stopped only after further confirmation of the biochemical abnormality. The applicant pointed out that a transient reduction in eGFR is to be expected in those starting therapy, but repeat estimations are not performed routinely at this stage of treatment, and the effect is likely to be seen only in those with borderline eGFR who are anyway less likely to derive benefit. Other measures were briefly considered. Haematocrit could potentially be an indicator of increased risk of thromboembolic events, but a rise in haematocrit would most often reflect dehydration, which could be measured in other ways.

5. The value of dapaglifozin as an additional tool in the treatment of patients with T2DM taking into account the mechanism of action, the magnitude of the effects as well as the potential limitations discussed in previous questions.

The SAG agreed that there is a need for new and innovative therapies for type 2 diabetes, and the introduction of a novel therapeutic principle is therefore of considerable potential interest. More than one of the participants commented on the frustrations of attempting to achieve good control, the usefulness of relatively minor glycaemic benefits, and the potential advantage of another therapeutic option when seeking to individualize therapy. This having been said, none expressed strong enthusiasm for this particular approach to therapy. Several were lukewarm in support, and one advised against its introduction (on the grounds that it did not address the mechanisms of disease, represented a distortion of normal physiology, and that its place in therapy was not yet established). Another was concerned about the limitations inherent in monitoring renal function, the stopping rules, the so far not widely tested mechanism of action, and the bladder cancer issue.

It was agreed that dapagliflozin currently has limited potential for use as monotherapy, even in those intolerant to metformin, and that no single patient group is likely to derive unique benefit. It will

therefore need to compete on an equal basis with a number of established second line treatment options. It was also agreed that longer-term metabolic consequences required further investigation, and that the potential role of this new agent in therapy is not as yet soundly established. Notwithstanding, the overall view of the SAG was that dapagliflozin has potential value as an adjunct to the existing therapeutic options, and that the risk/benefit ratio supported its cautious introduction into wider clinical use, with the exclusions described above. The SAG would like to see careful post-marketing monitoring of its use and real-world efficacy, together with more data on the risk/benefit ratio in older people. Finally, the SAG commended the Rapporteur and Co-Rapporteur for their work concerning restrictions on the use of this agent, and endorsed their recommendations in all but minor respects.

2.6.2. Conclusions on the clinical safety

Several of the risks of dapagliflozin are associated with its mechanism of action (glucosuria and diuretic effect), such as genital and urinary tract infections, hypoglycaemia, volume depletion and elevated haematocrit. The majority of these events were mild or moderate and manageable.

The finding of more neoplasms in the dapagliflozin groups (i.e. bladder, breast and prostate cancer) was unexpected based on the results of the non-clinical development program. All breast and prostate cancer cases occurred early on, and no potential tumour promoting mechanism has been identified for either breast or prostate cancer. The potential role of the dapagliflozin induced glucosuria in growth promotion of bladder cancer remains unclear, but lacks scientific support. Further evaluation of this safety concerns is warranted post-approval (pharmacoepidemiological study and CV outcome study, as reflected in the RMP).

The one case of possible drug-induced liver injury is of concern despite otherwise reassuring data on hepatic toxicity. Liver injury has been included as an important potential risk in the RMP and will be further evaluated in a pharmacoepidemiological study.

The incidence of bone fractures was increased in patients with relevantly impaired renal function when treated with dapagliflozin, although the absolute numbers were low. Due to decreased efficacy in conjunction with the noted safety concerns, treatment of patients with moderate to severe renal insufficiency is not recommended. Despite an absence of an imbalance in fracture incidence and reassuring 1-year data on BMD in patients with normal or mildly impaired renal function, a potential negative effect of dapagliflozin on bone metabolism with long-term treatment cannot be ruled out in this population. Bone facture is included in the RMP as an important potential risk. Two-year data on BMD (study D1690C00012) are expected and bone fractures will be followed post-marketing as part of the planned CV outcome study.

Dapagliflozin treatment results in weight reduction due to nutrient loss by glucosuria. Concerns arose whether the long-term catabolic effects elicited by dapagliflozin may differ from those caused by reduction in dietary intake, e.g. with regard to protein turnover. However, published data have been provided indicating that the observed effects are not qualitatively or quantitatively different to those observed with a reduction in dietary intake. There was no evidence for increased risk of acidosis with dapagliflozin, which would be of particular concern with concomitant metformin therapy.

Concerns also arose with regard to the potential long term consequences of the dapagliflozin-induced osmotic diuresis, e.g. with respect to effect on serum electrolytes. By inducing osmotic diuresis and weak natriuresis, dapagliflozin exerts qualitatively similar effects as thiazide diuretics. Since the latter are a well-established and widely prescribed substance class the potential risk and necessary precautions are understood by the prescribers. It has been demonstrated that dapagliflozin causes similar adaptive changes as hydrochlorothiazide albeit, in general to a smaller extent. Thus, the risks associated with dapagliflozin-induced diuresis appear manageable.

Due to the safety profile of dapagliflozin and its decreasing efficacy with decreasing renal function, dapagliflozin is not recommended in very elderly (> 75 years) or in patients with moderate renal impairment (GFR <60) or in patients at risk of water/electrolyte imbalance. Although the safety profile would not pose an unacceptable risk, no indication have been granted by the CHMP as the submitted date are not considered sufficient to support a positive B/R in this target.

Off-label use is included in the RMP as an important potential risk and will be studied post-marketing (drug utilisation study), which is considered appropriate.

Patients at high CV risk may be more susceptible to the haemodynamic changes induced by dapagliflozin, especially with concomitant intake of antihypertensive medication. Since the indication of dapagliflozin is for treatment of diabetes, physicians and patients may not be aware of the blood pressure-lowering effect and potential safety issues in vulnerable patients. Therefore clear warnings regarding the diuretic and blood pressure-lowering effect of dapagliflozin have been included in the SmPC.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for Pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Union or in a third country.

Risk Management Plan

The applicant submitted a risk management plan.

Table 37. Summary of the risk management plan

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
Important Identified Risks		
Genital Infections	Routine Pharmacovigilance Activities	Routine Risk Minimisation activities (Product Labeling) Undesirable Effects: "Vulvovaginitis, balanitis and related genital infections were reported in 4.8% and 0.9% of subjects who received dapagliflozin 10 mg and placebo, respectively. Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females (9.7 % and 3.4 % for dapagliflozin and placebo, respectively), and subjects with a prior history were more likely to have a recurrent infection." Vulvovaginitis, balanitis and related genital infections are listed as a common ADR.
Urinary Tract Infections	Routine Pharmacovigilance Activities A pharmaco-epidemiology study is planned to estimate and compare the incidence of emergency room visit or hospitalization due to severe complications of UTI (MB102103: Comparison of the Risk of Severe Complications of UTI Between Patients with T2DM Exposed to Dapagliflozin and those Exposed to Other Anti-diabetic Treatments). Study D1690C000019 Screening for asymptomatic bacteriuria in the ongoing study (around 40% of all randomized subjects)	Routine Risk Minimisation activities (Product Labeling) Special Warnings and Precautions for use: Urinary tract infections were more frequently reported for dapagliflozin 10 mg compared to placebo in a pooled analysis up to 24 weeks. Pyelonephritis was uncommon and occurred at a similar frequency to control. Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of dapagliflozin should be considered when treating pyelonephritis or urosepsis. Undesirable Effects: "Urinary tract infections were more frequently reported for dapagliflozin 10 mg compared to placebo (4.3% versus 3.7%,

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
		respectively). Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females, and subjects with a prior history were more likely to have a recurrent infection." Urinary tract infection is listed as a common ADR.
Important Potential Risks		
Hypoglycemia	Routine Pharmacovigilance Activities	Routine Risk Minimisation activities (Product Labeling) Posology and method of administration: The recommended dose is 10 mg dapagliflozin once daily for monotherapy and add-on combination therapy with other glucose lowering drugs including insulin. When dapagliflozin is used in combination with insulin or an insulin secretagogue, such as a sulphonylurea, a lower dose of insulin or insulin secretagogue may be considered to reduce the risk of hypoglycaemia. Included in Undesirable Effects: The most frequently reported adverse reaction was hypoglycaemia, which depended on the type of background therapy used in each study. The frequency of minor episodes of hypoglycaemia was similar between treatment groups, including placebo, with the exceptions of studies with add on sulphonylurea (SU) and add on insulin therapies. Combination therapies with sulphonylurea and add on insulin had higher rates of hypoglycaemia. Hypoglycaemia The frequency of hypoglycaemia depended on the type of background therapy used in each study.

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
		The frequency of minor episodes of hypoglycaemia was similar (< 4%) between treatment groups, including placebo. Across all studies, major events of hypoglycaemia were uncommon and comparable between the groups treated with dapagliflozin or placebo. Studies with add-on sulphonylurea and add on insulin therapies had higher rates of hypoglycaemia. In an add on to glimepiride study, minor episodes of hypoglycaemia excluding rescue were reported more frequently in the group treated with dapagliflozin 10 mg plus glimepiride (6.0%) than in the placebo plus glimepiride group (2.1%). In an add on to insulin study, minor episodes were reported more frequently in the group treated with dapagliflozin 10 mg plus insulin (40.3%) than in the placebo plus insulin group (34.0%). “Hypoglycaemia (when used with SU or insulin)” is listed as a very common ADR.
Volume Depletion	Routine Pharmacovigilance Activities	Routine Risk Minimisation activities (Product Labeling) Special Warnings and Precautions for use: Use in patients at risk for volume depletion, hypotension and/or electrolyte imbalances Due to its mechanism of action, dapagliflozin increases diuresis associated with a modest decrease in blood pressure (which may be more pronounced in patients with very high blood glucose concentrations. Dapagliflozin is not recommended for use in patients receiving loop diuretics or who are volume depleted, e.g. due to acute illness (such as gastrointestinal illness).

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
		Caution should be exercised in patients for whom a dapagliflozin induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on anti hypertensive therapy with a history of hypotension or elderly patients. For patients receiving dapagliflozin, in case of intercurrent conditions that may lead to volume depletion, careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit) and electrolytes is recommended. Temporary interruption of treatment with dapagliflozin is recommended for patients who develop volume depletion until the depletion is corrected. Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics. In subjects ≥ 65 years of age, a higher proportion of subjects treated with dapagliflozin had adverse reactions related to volume depletion. Posology and method of administration: Elderly (≥ 65 years) In general, no dosage adjustment is recommended based on age. Renal function and risk of volume depletion should be taken into account. Due to the limited therapeutic experience in patients 75 years and older, initiation of dapagliflozin therapy is not recommended. Undesirable Effects: Volume depletion Reactions related to volume depletion (including, reports of dehydration, hypovolaemia or hypotension) were reported in

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
		0.8% and 0.4% of subjects who received dapagliflozin 10 mg and placebo, respectively; serious reactions occurred in < 0.2% of subjects balanced between dapagliflozin 10 mg and placebo. Elderly patients (≥ 65 years) In subjects ≥ 65 years of age, adverse reactions of volume depletion, most commonly reported as hypotension, were reported in 1.5% and 0.4% of dapagliflozin treated subjects and placebo treated subjects, respectively. Listed as an uncommon ADR.
Clinical Consequences of Increased Hematocrit	Routine Pharmacovigilance Activities CV blinded adjudication in ongoing Phase 2b and 3 clinical studies. CV events investigated in CV outcomes study (D1693C00001).	Routine Risk Minimisation activities (Product Labeling) Special Warnings and Precautions for use: Increased haematocrit was observed with dapagliflozin treatment; therefore, caution in patients with already elevated haematocrit is warranted. Haematocrit increased is listed as a common ADR, with footnote: “Mean changes from baseline in haematocrit were 2.15% for dapagliflozin 10 mg versus 0.40% for placebo.”
Renal Impairment/ Failure	Routine Pharmacovigilance Activities A pharmaco-epidemiology study is planned to evaluate the risk of hospitalizations for acute renal failure (MB102110: Comparison of Risk of Acute Renal Failure between Patients with T2DM Exposed to Dapagliflozin and Those Exposed to other Anti-diabetic Treatments).	Routine Risk Minimisation activities (Product Labeling) Special Warnings and Precautions for use: Use in patients with renal impairment The efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment. In subjects with moderate renal impairment (patients with CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m2), a higher proportion of subjects treated with dapagliflozin had adverse reactions of increase in creatinine, phosphorus, parathyroid hormone (PTH) and hypotension, compared with

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
		placebo. Forxiga is not recommended for use in patients with moderate to severe renal impairment (patients with CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m2). Forxiga has not been studied in severe renal impairment (CrCl < 30 ml/min or eGFR < 30 ml/min/1.73 m2) or end stage renal disease (ESRD). Monitoring of renal function is recommended as follows: • Prior to initiation of dapagliflozin and at least yearly, thereafter. • Prior to initiation of concomitant medicinal products that may reduce renal function and periodically thereafter • For renal function approaching moderate renal impairment, at least 2 to 4 times per year. If renal function falls below CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m2, dapagliflozin treatment should be discontinued. Elderly patients Elderly patients are more likely to have impaired renal function, and/or to be treated with anti hypertensive medicinal products that may cause changes in renal function such as angiotensin converting enzyme inhibitors (ACE I) and angiotensin II type 1 receptor blockers (ARB). The same recommendations for renal function apply to elderly patients as to all patients. In subjects ≥ 65 years of age, a higher proportion of subjects treated with dapagliflozin had adverse reactions related to renal impairment or failure compared with placebo. The most commonly reported adverse reaction related to renal function was serum creatinine increases, the majority of which were

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
		transient and reversible. Undesirable effects: Elderly patients (≥ 65 years) In subjects ≥ 65 years of age, adverse reactions related to renal impairment or failure were reported in 2.5% of subjects treated with dapagliflozin and 1.1% of subjects treated with placebo (see section 4.4). The most commonly reported adverse reaction related to renal function was increased serum creatinine. The majority of these reactions were transient and reversible. Blood creatinine increased and Blood urea increased are listed as an uncommon ADR.
Bone Fracture	Routine Pharmacovigilance Activities D1690C00012: Phase 3 study to evaluate bone density by DXA as a safety objective with assessments at Years 1 and 2 and to study biochemical markers of bone formation and bone resorption. Bone fractures will be assessed in the CV outcomes study (D1693C00001).	No risk minimization activities have been proposed.
Liver Injury	Routine Pharmacovigilance Activities Liver injury events will be adjudicated and analyzed in the CV outcomes study (D1693C00001) including both investigator reported events as well as cases identified through liver function test reports. A pharmaco-epidemiology study is planned to evaluate the risk of hospitalizations for acute liver failure (MB102104: Comparison of Risk of Acute Hepatic Failure between Patients with T2DM Exposed to Dapagliflozin and Those Exposed to other Anti-diabetic Treatments). Blinded adjudication of liver cases in Phase 3 clinical studies.	Routine Risk Minimisation activities (Product Labeling) Undesirable Effects: One subject receiving dapagliflozin experienced a liver adverse event with diagnoses of drug induced hepatitis and/or autoimmune hepatitis.
Bladder Cancer	Routine Pharmacovigilance Activities Bladder cancer events will be adjudicated and analyzed in the CV outcomes study (D1693C00001). See Table 2.6. Pharmaco-epidemiology program for characterization of cancer (MB102118:	Routine Risk Minimisation activities (Product Labeling) Special Warnings and Precautions for use with regard to use of Dapagliflozin in combination with pioglitazone: Use in patients treated with

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
	Comparison of the risk of cancer among patients with T2DM exposed to dapagliflozin and those exposed to other anti-diabetic therapies)	pioglitazone While a causal relationship between dapagliflozin and bladder cancer is unlikely, as a precautionary measure, dapagliflozin is not recommended for use in patients concomitantly treated with pioglitazone. Available epidemiological data for pioglitazone suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone. Bladder cancer is included in Undesirable Effects: Malignancies During clinical trials, the overall proportion of subjects with malignant or unspecified tumours was similar between those treated with dapagliflozin (1.47%) and placebo/comparator (1.35%), and there was no carcinogenicity or mutagenicity signal in animal data (see section 5.3). When considering the cases of tumours occurring in the different organ systems, the relative risk associated with dapagliflozin was above 1 for some tumours (bladder, prostate, breast) and below 1 for others (e.g. blood and lymphatic, ovary, renal tract), not resulting in an overall increased tumour risk associated with dapagliflozin. The increased/decreased risk was not statistically significant in any of the organ systems. Taking into account the lack of tumour findings in non-clinical studies as well as the short latency between first drug exposure and tumour diagnosis, a causal relationship is considered unlikely. Since the numerical imbalance of breast, bladder and prostate tumours must be considered with caution, it will be further investigated in post-authorisation studies.
Breast Cancer	Routine Pharmacovigilance Activities	Routine Risk Minimisation

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
	Female breast cancer events will be adjudicated and analyzed in the CV outcomes study (D1693C00001). Pharmaco-epidemiology program for characterization of cancer (MB102118: Comparison of the risk of cancer among patients with T2DM exposed to dapagliflozin and those exposed to other anti-diabetic therapies)	activities (Product Labeling) Breast cancer is included in Undesirable Effects: Malignancies During clinical trials, the overall proportion of subjects with malignant or unspecified tumours was similar between those treated with dapagliflozin (1.47%) and placebo/comparator (1.35%), and there was no carcinogenicity or mutagenicity signal in animal data (see section 5.3). When considering the cases of tumours occurring in the different organ systems, the relative risk associated with dapagliflozin was above 1 for some tumours (bladder, prostate, breast) and below 1 for others (e.g. blood and lymphatic, ovary, renal tract), not resulting in an overall increased tumour risk associated with dapagliflozin. The increased/decreased risk was not statistically significant in any of the organ systems. Taking into account the lack of tumour findings in non-clinical studies as well as the short latency between first drug exposure and tumour diagnosis, a causal relationship is considered unlikely. Since the numerical imbalance of breast, bladder and prostate tumours must be considered with caution, it will be further investigated in post-authorisation studies.
Prostate Cancer	Routine PV Prostate cancer events will be adjudicated and analyzed in the CV outcomes study (D1693C00001). Pharmaco-epidemiology program for characterization of cancer (MB102118: Comparison of the risk of cancer among patients with T2DM exposed to dapagliflozin and those exposed to other anti-diabetic therapies)	Product labeling: Prostate cancer is included in Undesirable Effects: Malignancies During clinical trials, the overall proportion of subjects with malignant or unspecified tumours was similar between those treated with dapagliflozin (1.47%) and placebo/comparator (1.35%), and there was no carcinogenicity or mutagenicity signal in animal data (see

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
		section 5.3). When considering the cases of tumours occurring in the different organ systems, the relative risk associated with dapagliflozin was above 1 for some tumours (bladder, prostate, breast) and below 1 for others (e.g. blood and lymphatic, ovary, renal tract), not resulting in an overall increased tumour risk associated with dapagliflozin. The increased/decreased risk was not statistically significant in any of the organ systems. Taking into account the lack of tumour findings in non-clinical studies as well as the short latency between first drug exposure and tumour diagnosis, a causal relationship is considered unlikely. Since the numerical imbalance of breast, bladder and prostate tumours must be considered with caution, it will be further investigated in post-authorisation studies.
Off-label use of dapagliflozin in specific populations	Routine Pharmacovigilance Activities To assess compliance with the labeling, the Sponsors will conduct a Drug utilization study to specifically describe initiation of dapagliflozin in elderly patients (75 years old and older), combination use with loop diuretics or pioglitazone, and use in patients with moderate or severe renal impairment or kidney failure.	Routine Risk Minimisation activities (Product Labeling) Therapeutic experience in patients 75 years and older is limited. Initiation of dapagliflozin therapy in this population is not recommended. Use in patients at risk for volume depletion, hypotension and/or electrolyte imbalances Dapagliflozin is not recommended for use in patients receiving loop diuretics or who are volume depleted, e.g. due to acute illness (such as gastrointestinal illness). Use in patients with renal impairment The efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment. In subjects

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
		with moderate renal impairment (patients with CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m2), a higher proportion of subjects treated with dapagliflozin had adverse reactions of increase in creatinine, phosphorus, parathyroid hormone (PTH) and hypotension, compared with placebo. Forxiga is not recommended for use in patients with moderate to severe renal impairment (patients with CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m2). Forxiga has not been studied in severe renal impairment (CrCl < 30 ml/min or eGFR < 30 ml/min/1.73 m2) or end stage renal disease (ESRD). Monitoring of renal function is recommended as follows: • Prior to initiation of dapagliflozin and at least yearly, thereafter (see sections 4.2, 4.8, 5.1 and 5.2) • Prior to initiation of concomitant medicinal products that may reduce renal function and periodically thereafter • For renal function approaching moderate renal impairment, at least 2 to 4 times per year. If renal function falls below CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m^2, dapagliflozin treatment should be discontinued. Special Warnings and Precautions for use with regard to use of Dapagliflozin in combination with pioglitazone: Use in patients treated with pioglitazone While a causal relationship between dapagliflozin and bladder cancer is unlikely, as a precautionary measure, dapagliflozin is not recommended for use in patients concomitantly treated with pioglitazone. Available epidemiological data for

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
		pioglitazone suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone.
Important Missing/Limited Information		
Pediatric population	Routine Pharmacovigilance Activities	Routine Risk Minimisation activities (Product Labeling) Posology and method of administration: *Paediatric population* The safety and efficacy of dapagliflozin in children aged 0 to < 18 years have not yet been established. No data are available.
Elderly population	Routine Pharmacovigilance Activities Studies D1690C0018 and D1690C0019 are stratified to deliver 40% subjects > 65 years of age.	Routine Risk Minimisation activities (Product Labeling) Special Warnings and Precautions for use: Elderly patients Elderly patients are more likely to have impaired renal function, and/or to be treated with anti hypertensive medicinal products that may cause changes in renal function such as angiotensin converting enzyme inhibitors (ACE I) and angiotensin II type 1 receptor blockers (ARB). The same recommendations for renal function apply to elderly patients as to all patients. In subjects ≥ 65 years of age, a higher proportion of subjects treated with dapagliflozin had adverse reactions related to renal impairment or failure compared with placebo. The most commonly reported adverse reaction related to renal function was serum creatinine increases, the majority of which were transient and reversible. Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics. In subjects ≥ 65 years of age, a higher proportion of subjects treated with dapagliflozin had adverse reactions related to volume depletion. Therapeutic experience in

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
		patients 75 years and older is limited. Initiation of dapagliflozin therapy in this population is not recommended. Posology and method of administration: Elderly (≥ 65 years) In general, no dosage adjustment is recommended based on age. Renal function and risk of volume depletion should be taken into account. Due to the limited therapeutic experience in patients 75 years and older, initiation of dapagliflozin therapy is not recommended. Undesirable effects: Elderly patients (≥ 65 years) In subjects ≥ 65 years of age, adverse reactions related to renal impairment or failure were reported in 2.5% of subjects treated with dapagliflozin and 1.1% of subjects treated with placebo. The most commonly reported adverse reaction related to renal function was increased serum creatinine. The majority of these reactions were transient and reversible. In subjects ≥ 65 years of age, adverse reactions of volume depletion, most commonly reported as hypotension, were reported in 1.5% and 0.4% of dapagliflozin treated subjects and placebo treated subjects, respectively.
Pregnancy/Nursing Mothers	Routine Pharmacovigilance Activities	Routine Risk Minimisation activities (Product Labeling) Fertility, pregnancy and lactation: <u>Pregnancy</u> There are no data from the use of dapagliflozin in pregnant women. Studies in rats have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy. Therefore, the use of dapagliflozin is not recommended during the

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
		second and third trimesters of pregnancy. When pregnancy is detected, treatment with dapagliflozin should be discontinued. <u>Breast-feeding</u> It is unknown whether dapagliflozin and/or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of dapagliflozin/metabolites in milk, as well as pharmacologically-mediated effects in nursing offspring. A risk to the newborns/infants cannot be excluded. Dapagliflozin should not be used while breast-feeding. <u>Fertility</u> The effect of dapagliflozin on fertility in humans has not been studied. In male and female rats, dapagliflozin showed no effects on fertility at any dose tested.
Patient with severe renal impairment including end-stage renal disease (ESRD) requiring haemodialysis, or undergoing peritoneal dialysis	Routine Pharmacovigilance Activities	Routine Risk Minimisation activities (Product Labeling) Special Warnings and Precautions for use: Use in patients with renal impairment The efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment. [...] Forxiga is not recommended for use in patients with moderate to severe renal impairment (patients with CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m2). Forxiga has not been studied in severe renal impairment (CrCl < 30 ml/min or eGFR < 30 ml/min/1.73 m2) or end stage renal disease (ESRD). Posology and method of administration:

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimization Activities (Routine and Additional)
		Renal impairment The efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment. Forxiga is not recommended for use in patients with moderate to severe renal impairment (patients with creatinine clearance [CrCl] < 60 ml/min or estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m2).
Moderate/Severe hepatic impairment	Routine Pharmacovigilance Activities	Routine Risk Minimisation activities (Product Labeling) Special Warnings and Precautions for use: Use in patients with hepatic impairment There is limited experience in clinical trials in patients with hepatic impairment. Dapagliflozin exposure is increased in patients with severe hepatic impairment. Posology and method of administration: Hepatic impairment No dosage adjustment is necessary for patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, a starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg.
Congestive heart failure (CHF) defined as NYHA class III and IV	Routine Pharmacovigilance Activities CV blinded adjudication in Phase 2b and 3 clinical studies. Phase 3b studies include high risk CV patients, and as of May 2009, no exclusion criteria for NYHA class III in some studies including planned CV outcomes study.	Routine Risk Minimisation activities (Product Labeling) Included in Special Warnings and Precautions for use: Cardiac failure Experience in NYHA class I-II is limited, and there is no experience in clinical studies with dapagliflozin in NYHA class III-IV.

No additional risk minimisation activities were required beyond those included in the product information.

The CHMP, having considered the data submitted, was of the opinion that the below Pharmacovigilance activities in addition to the use of routine Pharmacovigilance is needed to investigate further some of the safety concerns:

Description	Due date
Study MB102103: Pharmacoepidemiology study assessing the risk of severe complications of UTI	Final Protocol Submission estimated to be 30 November 2012. The data will be analyzed initially 18 months after dapagliflozin has been on the market. Interim analyses will be performed every 18-months as noted in final protocol. The final analysis will be conducted after dapagliflozin has been available for approximately 36 months. Final Report Submission estimated to be 01 April 2016.
Study MB102110: Pharmacoepidemiology study assessing the risk of acute renal failure	Final Protocol Submission estimated to be 30 November 2012. The data will be analyzed initially 18 months after dapagliflozin has been on the market. Interim analysis will be performed every 18-months as noted in the final protocol. The final analysis will be conducted after dapagliflozin has been available for approximately 60 months. Final Report Submission estimated to be 01 April 2018.
Study MB102104: Pharmacoepidemiology study assessing the risk of acute hepatic failure	Final Protocol Submission estimated to be 30 November 2012. The data will be analyzed initially 12 months after dapagliflozin has been on the market, and annually thereafter. The final analysis will be conducted after dapagliflozin has been available for approximately 60 months. Final Report Submission estimated to be 01 April 2018.
Study MB102118: Pharmacoepidemiology study assessing the risk of cancer	Final Protocol Submission estimated to be 30 November 2012. The data will be reported initially 24 months after dapagliflozin has been on the market, and every 2 years thereafter. Interim analyses will be performed every 2 years. The final analysis will be conducted after dapagliflozin has been available for approximately 120 months.

Description	Due date
	Final Report Submission estimated to 01 April 2023.
Study D1693C0001: CV outcome study: Dapagliflozin Effect on Cardiovascular Event Incidence in Patients with Diabetes Mellitus: A Multicentre, Randomized, Double-Blind, Placebo-Controlled Phase IV Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients with Type 2 Diabetes	Final Protocol Submission two weeks after Commission Decision. Final Report Submission 28 February 2020.
Study D1690C0018: Safety for patients with high CV risk, including patients with CHF NYHA class III stratified to 50% subjects ≥65years of age	52 week report, two weeks after Commission Decision
Study D1690C0019: Safety for patients with high CV risk, including patients with CHF NYHA class III stratified to 50% subjects ≥65years of age	52 week report, two weeks after Commission Decision
Drug utilisation study	The study protocol will be developed within 6 months of marketing authorization (study protocol estimated in October 2012). The study protocol will be submitted to the CHMP for review and agreement before commencing the study. The first drug utilization study analysis report will be submitted in Q2 2014, and annually thereafter, with the corresponding PSUR.

2.8. User consultation

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

3. Benefit-Risk Balance

Benefits

Beneficial effects

Dapagliflozin is the first compound to inhibit SGLT2. By blocking this transporter protein, renal glucose reabsorption is decreased which leads to increased urinary glucose excretion and an osmotic diuresis. Dapagliflozin represents an entirely new concept for the treatment of T2DM.

A dose-dependent increase in glucose excretion has been demonstrated associated with calorie loss.

The clinical program to support the proposed indications includes 4287 patients receiving dapagliflozin whereof around 2000 patients have been treated with the proposed dose of 10 mg per day. Compared to placebo, dapagliflozin 10 mg provided statistically significant and clinically relevant improvements in glycaemic control (placebo-corrected HbA1c decrease of 0.52-0.68 % at 24 weeks) when given as monotherapy or as add-on to metformin, SU (glimepiride), TZD (pioglitazone) or insulin.

Dapagliflozin 10 mg was also shown to have non-inferior efficacy compared to glipizide (when added to metformin) after 52 weeks of treatment and non-inferior efficacy compared to metformin XR (both as monotherapy) with both comparators titrated to a sufficiently high dose to achieve full glucose-lowering potential. Although initially glipizide produced a more pronounced HbA1c reduction (maximum -0.81% from baseline at week 18), this extra effect waned rather quickly as is known for insulin secretagogues and was virtually identical to dapagliflozin at week 52.

The 10 mg dose was more efficacious than the 5 mg dose, supporting the dose recommendation proposed by the Applicant. In patients with severe hepatic impairment, the mean increase in dapagliflozin exposure was 67% and therefore, a lower starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg. This is the only recommended use for the 5 mg strength.

Long-term data of 48 to 102 weeks in duration indicate maintenance of the glucose-lowering effect of dapagliflozin. About 60 % of dapagliflozin patients completed the 102 week study periods.

Reductions of body weight of about 2-3 kg have been observed in all studies. Approximately 20-25 % of subjects treated with doses of 5 to 10 mg had a weight reduction of more than 5 %. Data indicate that the effect is maintained for at least 102 weeks. The majority of the weight loss was shown to be due to decrease in body fat (-1.5 kg over 24 weeks) including visceral fat, and not to dehydration, and can be explained by the renal nutrient (glucose) loss. Furthermore, a slight and consistent decrease in blood pressure was observed across the study program.

As the effect of dapagliflozin is dependent on the GFR, less prominent decreases in HbA1c were observed in patients with moderate renal impairment (0.37 % in patients with eGFR 45-60 ml/min/1.73mg^2) and essentially no improvement in glycaemic control in patients with GFR below 45 ml/min/1.73mg^2. Further to this, a decrease in effect was seen with increasing age (0.32 % in patients ≥ 75 years), which was related to the decrease in renal function with age rather than age per se. Sufficient data has been provided to conclude that the monitoring of renal function as currently proposed in the SmPC is able to identify patients with declining renal function in an acceptable way, also taking into consideration that the proposed restrictions in the target population are set with a reasonable safety margin.

Dapagliflozin has a low hypoglycaemic potential. This was especially evident in comparison to glipizide (hypoglycaemia incidence 3.5 versus 40.8%), although most hypoglycaemic events were classified as minor.

Dapagliflozin can be taken orally once a day and its efficacy appears independent of whether it is taken in the morning or in the evening, with or without food. Dapagliflozin has a favourable pharmacokinetic profile with low potential for pharmacokinetic interactions and moderate influence of intrinsic factors on dapagliflozin's PK. Influence of age (up to 70 years), gender, fatness, mild renal impairment and mild and moderate hepatic impairment on dapagliflozin exposure was estimated to be on average less than 40% and were not considered clinically relevant.

Except for a PD interaction with diuretics, dapagliflozin appears to have low potential of interaction with other antihyperglycaemic agents or other medication frequently co-administered in patients with T2DM.

Uncertainty in the knowledge about the beneficial effects

Data in patients above age 75 are limited although a pooled data analysis suggested that age is not an independent predictor of effect (when adjusted for renal function). However, renal function is frequently reduced in elderly subjects and the risk of renal impairment is even higher in patients with diabetes.

By decreasing serum glucose levels through renal glucose elimination, dapagliflozin may lower endogenous insulin requirements thereby decreasing the burden on beta cells.

Dapagliflozin appears to decrease blood pressure which, in the frequently obese and hypertensive patients with T2DM, could be beneficial. This effect is currently investigated in clinical studies in hypertensive patients.

Risks

Unfavourable effects

In the Placebo-controlled Pool (Short term treatment period), there was an observed imbalance for the following events: genital infections (5.7%-4.8% in dapagliflozin 5 and 10 mg versus 0.9% in placebo), UTI (5.7%-4.3% in dapagliflozin 5 and 10 mg versus 3.7% in placebo) and hypotension (0.6%-0.7% in dapagliflozin 5 mg and 10 mg versus 0.4% in placebo). Serious complications of UTI were not seen in the studies, but will be assessed in a planned pharmacoepidemiological study.

The proportions of subjects with elevated liver function tests and AEs of hepatic disorder were similar in the dapagliflozin and placebo groups. There was, however, one case of possible drug-induced liver injury with positive dechallenge. Thus, liver injury has been included as an important potential risk that in the RMP and will be further evaluated in a pharmacoepidemiological study.

Patients with severe hepatic impairment have on average about 70% increased exposure. It cannot be excluded that some patients may have more than 2-fold increase in exposure. There is no clinical experience in this sub-group. Hence, in patients with severe hepatic impairment a starting dose of 5 mg is recommended.

There were no major episodes of hypoglycaemia when used as monotherapy. When dapagliflozin was used together with insulin and SU an increased risk of hypoglycaemic events was observed, mainly seen as an increase in minor hypoglycaemic events (6.6 versus 2.1%).

Reactions related to volume depletion (including, but not limited to, reports of dehydration, hypovolaemia or hypotension) were reported in 0.8% and 0.4% of subjects who received dapagliflozin 10 mg and placebo, respectively. In subjects who received loop diuretics (n=126) the incidences of volume depletion were 9.7% and 1.8%, respectively. The use of dapagliflozin is not recommended in combination with loop diuretics.

An increase in LDL-C and total cholesterol (2.7 % and 1.4 % from baseline) was observed after 24 weeks with a further increase after 102 weeks, which was higher in the dapagliflozin group than in the placebo group. There was also an increase in HDL-C and no difference between the groups was seen in the LDL-C/HDL-C ratio up to 102 weeks. The clinical relevance of the small increase in LDL cholesterol is questionable. This issue will be addressed in the CV outcome study.

Adverse events related to renal impairment, especially increase in serum creatinine, were seen in 1.2% of patients treated with dapagliflozin compared to 0.9 % in the placebo group. The percentage of subjects discontinuing due to an adverse renal effect was fairly balanced between dapagliflozin and comparator. More patients with dapagliflozin than with comparator reached baseline serum creatinine after discontinuation (47.2% versus 27.9%, dapagliflozin versus. comparator) suggesting that at least part of the serum creatinine increase during dapagliflozin therapy was due to dehydration and not due to progressing renal insufficiency. It has been shown that dapagliflozin treatment results in an initial decline in GFR which usually is restored to baseline levels after a few months indicating a transient functional effect rather than renal toxicity. Yearly monitoring of renal function is considered acceptable with closer monitoring (2-4 times per year) in patients approaching the limit of 60 ml/min/ 1.73m^2 to capture the time point when dapagliflozin should be discontinued (due to decreasing efficacy and potentially increasing safety issues). The GFR cut-off of 60 ml/min/ 1.73m^2 provides a reasonable safety margin.

Reversibility of serum creatinine increase will be followed post-marketing within the CV outcome study and a pharmacoepidemiological study will further assess the risk of renal impairment.

At Week 24, the mean changes from baseline in haematocrit were 2.15% in the group treated with dapagliflozin 10 mg versus -0.40% in the placebo group. Haematocrit values > 55% were reported in 1.3% of the subjects treated with dapagliflozin 10 mg versus 0.3% of placebo subjects.

The increase in haematocrit with dapagliflozin compared to placebo did not translate into an increased incidence of venous thromboembolic events. No further action besides excluding patients at high risk for dehydration from treatment is considered necessary at the present time. The planned CV outcome study is expected to provide a broader database allowing firmer conclusions.

Concerning serum electrolytes, in the overall study population increased serum sodium (>150 mEq/L) was reported in 1.4 % of patients on dapagliflozin compared to 0.7 % in controls. In the age group > 65 years the corresponding reporting was 2.0 % in the dapagliflozin compared to 0.6 % for placebo. No other differences with regards to electrolytes were observed compared to placebo.

Uncertainty in the knowledge about the unfavourable effects

The assessment of uncertainties around unfavourable effects focused on risks that are at this time considered as potential and not identified, on the basis of the available information. These potential risks are discussed in more details in the paragraphs below.

All types of cancer: the analyses of data with a cut off of June 2010 (dataset submitted with the initial MAA) revealed an imbalance in the incidence of all types of cancer between dapagliflozin and controls (1.4% versus 1.0%). Additional analyses provided by the applicant during the evaluation (with a longer cut-off date of 15th of July 2011, allowing the evaluation of a longer observation period and larger patient population) showed no observed difference between dapagliflozin and controls (1.47% versus 1.35%, incidence rate ratio: 1.047 (95% CI: 0.702-1.579)).

When the incidence of different types of cancer was examined in detail (see Figure 22 in section 2.6 Clinical safety) it was observed that, while some malignancies appear top have a lower incidence than in the control (in particular renal cancer), other were increased (namaley bladder, prostate and breast cancer) in patients receiving dapagliflozin. It seems therefore a good precautionary measure to consider this observation as a concern, and encourage gathering further data in order to either confirm or dismiss this risk. It should be noted that non-clinical carcinogenesis studies did not reveal tumourigenic effects of dapagliflozin. A causal relationship of dapagliflozin administration and breast cancer appears unlikely due to the lack of plausible underlying mechanism (e.g. increased estrogens levels). Furthermore, all observed breast cancers and almost all prostate cancers were detected early in study course which may indicate pre-existing tumours. For prostate cancer a causal relationship appears unlikely for similar reasons. On the other hand, there may, theoretically, be a plausible mechanism by which dapagliflozin could increase growth of pre-existing neoplasms in the bladder (i.e. by increasing glucose concentration in the urine) even though the scientific support of this hypothesis is very limited, and it may contradict the observed lower incidence of renal tract tumours with dapagliflozin compared to comparator. Thus, the observed difference in the incidence of bladder cancer may well be explained by random variation or detection bias due to an increased frequency of urogenital adverse reactions with dapagliflozin.

In summary, post-marketing surveillance of breast, prostate and bladder cancer as the most appropriate means to further evaluate this potential risk is foreseen within planned studies (as detailed in the RMP), including the planned CV outcome study and an epidemiological study. Considering the possible association of pioglitazone and bladder cancer, the combination of dapagliflozin and pioglitazone is not recommended, and, as a precautionary measure, this information has been included in the SmPC.

For dapagliflozin treated patients, bone resorption markers, serum phosphorus and PTH were somewhat higher than in the comparator group with PTH increases being higher in patients with already elevated baseline PTH plasma concentrations. Moreover, in a study of diabetic subjects with moderate renal impairment (eGFR ≥30 to <60 ml/min/ 1.73m^2), AEs of fracture were reported in a higher proportion of dapagliflozin-treated subjects (3 [3.6%] and 7 [8.2%] in the 5 and 10 mg groups, respectively) compared with placebo-treated subjects (0%), particularly in those patients with the lowest eGFR values at baseline. One-year data in patients with no or only mild renal impairment and treated with dapagliflozin did not reveal any relevant changes in BMD. However, dapagliflozin-related bone loss with long-term treatment cannot be fully excluded even with a slight increase in PTH, which would be particularly relevant in patients with pre-existing or at risk of osteoporosis. Two-year BMD data are awaited post-marketing (as detailed in the RMP).

The assessment of CV safety was based on a meta-analysis of independently confirmed, blindly adjudicated, CV events among Phase IIb and III studies. No increased CV risk was observed, neither in the original, nor in the updated analysis for the primary composite endpoint (HR 0.819, 95% CI: 0.583, 1.152 in the updated analysis) or for MACE events (HR 0.793, 95% CI: 0.537, 1.170). However, in the pooled analysis of studies D1690C00018 and D1690C00019 including only patients at high CV risk, the HR for MACE was 1.27 (95 % CI 0.693-2.311). The absolute number of cases in these ongoing trials is still small and the small imbalance among treatment groups should be interpreted with caution. Further, an analysis of data in all patients with CV disease from the Phase IIb/III study pool including the new studies D1690C00018 and D1690C0019 showed no increased MACE rate, neither at initiation of dapagliflozin therapy nor later on. However, it cannot be excluded that patients at high CV risk concomitantly taking loop diuretics and/or antihypertensive drugs may be at increased risk for a CV events when starting dapagliflozin, possibly due to diuresis-induced decreased blood pressure. The SmPC has been amended to highlight the blood pressure-lowering effect and potential safety issues in vulnerable patients.

In a subgroup analysis of patients with eGFR ≥45 to <60 ml/min/1.73m^2, initially proposed to be appropriate for treatment with dapagliflozin, increase in blood creatinine (5.2 % versus 0 %), phosphorus (5.2 % versus 2.9 %), PTH (mean increase 5.5 pg/mL versus 2.6 pg/mL) and hypotension (volume depletion 3.0%, 2.3%, and 4.7% of subjects in the dapagliflozin 2.5, 5, and 10 mg groups, respectively, and 1.4% in the placebo group) was more evident than in the placebo-controlled pool. Due to limited efficacy and potentially increased safety issues, the use of dapagliflozin is not recommended in this patient group.

The overall safety profile in elderly with minor renal impairment or normal renal function does not indicate major differences compared to younger patients. However in patients ≥ 65 years (1335 patients) the difference from placebo was more evident for events of renal impairment (2.5 % versus 1.1 % ST; 4.5 % versus 1.9 % LT), hypotension and volume depletion (3.1%, 0.5%, and 1.5% in the dapagliflozin 2.5, 5, and 10 mg groups, respectively; versus 0.4 % for placebo). Data in the elderly patient group > 75 years (157 patients) is limited and initiation of treatment is not recommended in these patients.

Concerns arose whether the long-term catabolic effects elicited by dapagliflozin-induced nutrient loss may differ from those caused by reduction in dietary intake, e.g. with regard to protein turnover. However, published data have been provided indicating that the observed effects are not qualitatively or quantitatively different to those observed with a reduction in dietary intake. There was no evidence for increased risk of acidosis with dapagliflozin, which would be of particular concern with concomitant metformin therapy. Concerns also arose with regard to the potential long term consequences of the induced osmotic diuresis, e.g. with respect to effect on serum electrolytes. By inducing osmotic diuresis and weak natriuresis, dapagliflozin exerts qualitatively similar effects as thiazide diuretics. Since the latter are a well-established and widely prescribed substance class the potential risk and necessary precautions are understood by the prescribers. It has been demonstrated that dapagliflozin causes similar adaptive changes as hydrochlorothiazide albeit, in general to a smaller extent. Thus, the risks associated with dapagliflozin-induced diuresis appear manageable.

Benefit-risk balance

Importance of favourable and unfavourable effects

Dapagliflozin, at the proposed dose of 10 mg/d, has been shown to effectively lower HbA1c when given alone or in combination with various antidiabetics with different mechanism of action with the effect being similar to that of glipizide (at week 52) and metformin XR. The effect of dapagliflozin appears to be maintained in the long-term (up to 102 weeks).

Dapagliflozin has a unique mechanism of action, not involving the stimulation of beta cells. This may be of great importance for patients with unsatisfactory glycaemic control due to beta-cell failure.

The additional beneficial effects on body weight and blood pressure are of special interest in the T2DM population where overweight associated with increased insulin resistance as well as hypertension constitute significant treatment challenges. Further to this, increase in body weight is commonly seen when hyperglycaemia is successfully treated.

The low propensity of dapagliflozin to cause hypoglycaemia is considered a beneficial effect which may be particularly relevant in patients at increased risk of hypoglycaemia.

Other potentially clinically relevant beneficial effects such as reduction in blood pressure in hypertensive patients or long-term improvement in beta cell function are not clear and would need to be further investigated.

It should however be noted that the efficacy of dapagliflozin is dependent on renal function and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment.

For dapagliflozin, several of the safety issues are associated with the mechanism of action (glucosuria and diuretic effect). Genital and urinary tract infections can be troublesome for the patients but are considered as manageable in clinical practice. The increase in urinary tract infections associated with dapagliflozin was relatively small and events were generally mild or moderate in intensity not indicating a major safety issue.

The incidences of adverse events possibly secondary to osmotic diuresis (hypotension, volume depletion, changes in electrolytes and elevated haematocrit) were low in the studied population. These issues are reflected in the product information and will be further studied in planned studies. There are however patient groups who may be more sensitive to consequences of osmotic diuresis, e.g. elderly and volume depleted patients (e.g treated with diuretics) as well as patients with renal impairment. The numbers of such patients in the clinical trials were limited, but data indicate a higher incidence of adverse events. Appropriate warnings and restrictions have been included in the SmPC to minimise the risk in vulnerable patients. The current cut-off for renal function of 60 mg/min/1.73 m^2 for treatment with dapagliflozin includes a reasonable safety margin. Off-label use is intended to be studied post-marketing, which is considered appropriate.

It seems to be appropriate to conduct long term post-marketing studies in order to assess the potential risk of bladder, breast and prostate cancers in dapagliflozin-treated patients; Although the incidence of all types cancer was not increased in dapagliflozin-treated patients, long treatment periods and a possible wide spread use warrant a careful and cautious evaluation of accrued clinical data. It is reassuring that data from carcinogenicity studies in animals are not indicating a genotoxic or carcinogenic effect of dapagliflozin. This approach of gathering further data and carefully assessing it is considered sufficient by the CHMP.

Several CV meta-analyses including the general study population or only patients with CV disease do not indicate an increased CV risk associated with the use of dapagliflozin. Nevertheless, it cannot be excluded that high risk patients, especially those concomitantly taking loop diuretics and/or antihypertensive drugs may be at increased risk for a CV events when starting dapagliflozin, possibly due to a diuresis-induced decrease in blood pressure. Therefore, the product information has been amended to create awareness of the diuresis-inducing and blood pressure-lowering effect of dapagliflozin among physicians and patients.

Benefit-risk balance

The balance between favourable and unfavourable effects of dapagliflozin is considered positive. Dapagliflozin, at the proposed dose of 10 mg/d, has been shown to effectively lower HbA1c when given alone or in combination with various glucose-lowering agents with different mechanisms of action. In addition, beneficial effects on body weight and blood pressure have been observed. Common adverse events are associated with the mechanism of action (glucosuria and diuretic effect) and are considered as manageable in clinical practice. Due to increased exposure to dapagliflozin in patients with severe hepatic impairment, a lower starting dose of 5 mg is recommended in this population. If well tolerated, the dose may be increased to 10 mg.

Discussion on the benefit-risk balance

The overall benefit/risk of dapagliflozin is considered positive for the indication: *"In adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as:*

Monotherapy

When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.

Add-on combination therapy

In combination with other glucose lowering drugs including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 for available data on different combinations)."

Due to the dependence of efficacy on renal function and the observation of an increased likelihood to experience adverse drug reactions with relevant renal impairment, the use of dapagliflozin should be restricted to patients with normal or mildly impaired renal function (i.e. GFR > 60 ml/min/1.73 m^2) and to patients under the age of 75 year. Precautions regarding use of dapagliflozin in patients at risk of volume depletion and in patients in whom the blood pressure-lowering effect of dapagliflozin could pose a potential risk has been included in the SmPC. The potential risk of bladder, breast and prostate cancers in dapagliflozin-treated patients as well as CV safety in high CV risk patients will be further investigated in planned post-marketing studies which is considered sufficient.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Forxiga in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as:

Monotherapy

When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance.

Add-on combination therapy

In combination with other glucose lowering drugs including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (see sections 4.4, 4.5 and 5.1 for available data on different combinations).

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that dapagliflozin is to be qualified as a new active substance.