21 November 2013
EMA/620505/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xigduo

International non-proprietary name: DAPAGLIFLOZIN / METFORMIN

Procedure No. EMEA/H/C/002672/0000

Note

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

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Product information

Name of the medicinal product:	Xigduo
Applicant:	Bristol-Myers Squibb/AstraZeneca EEIG Bristol-Myers Squibb House Uxbridge Business Park Uxbridge UB8 1DH UNITED KINGDOM
Active substance:	METFORMIN / DAPAGLIFLOZIN
International Nonproprietary Name/Common Name:	DAPAGLIFLOZIN / METFORMIN
Pharmaco-therapeutic group (ATC Code):	Drugs used in diabetes, Combinations of oral blood glucose-lowering drugs (A10BD15)
Therapeutic indication:	Indicated in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control
Pharmaceutical form:	Film-coated tablet
Strengths:	5 mg / 850 mg and 5 mg / 1000 mg
Route of administration:	Oral use
Packaging:	blister (PVC/Aclar//Alu)
Package size:	14, 28, 56 and 60 tablets 60 x 1 tablet (unit dose) 196 (2 x 98) tablets (multipack)

Table of contents

List of abbreviations

Abbreviation / special term	Explanation
AACE	American Association of Clinical Endocrinologists
ADA	American Diabetes Association
ADR	Adverse Drug Reaction
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration curve
AUC(INF)	Area under the curve extrapolated to infinity
AUC(0-t)	Area under the curve from time of dosing to t
AUC(0-24)	Area under the curve from time of dosing to 24 hours
AUC(0-72)	Area under the curve from time of dosing to 72 hours
BID	Twice daily
BMS	Bristol-Myers Squibb
BMS-207150	Metformin
BMS-512148	Dapagliflozin
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
Cmax	Maximum plasma drug concentration
CNS	central nervous system
CrCl	Creatinine clearance
CSR	Clinical study report
CTD	Common technical document
CV	Cardiovascular
DAE	Discontinuations due to adverse event
Dapa/Met	Dapagliflozin/Metformin
DPP-4	Dipeptidyl peptidase-4
EASD	European Association for the Study of Diabetes

eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
FDC	Fixed dose combination
FPG	Fasting plasma glucose
GLP	Good Laboratory Practice
HbA1c	Haemoglobin A1c
ICH	International Conference on Harmonization
IDF	International Diabetes Federation
IR	Immediate release
kg	kilogram
LOCF	Last observation carried forward
LT	Long-term
MAA	Marketing Authorisation Application
mg	milligram
mL	milliliter
ng	nanogram
nm	nanometer
OAD	Oral antidiabetic drug
PPG	Postprandial glucose
PT	Preferred term
QD	Once a day; Once daily
RMP	Risk Management Plan
SAE	Serious adverse event
SGLT2	Sodium-dependent glucose co-transporter 2
SmPC	Summary of Product Characteristics
ST	Short-term
T2DM	Type 2 diabetes mellitus
ULN	Upper limit of normal
UTI	Urinary tract infection
XR	Extended release
µg	microgram

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Bristol-Myers Squibb/AstraZeneca EEIG submitted on 26 November 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Xigduo, 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 15 December 2011.

The applicant applied for the following indication

"Xigduo is indicated in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on metformin alone or in combination with other glucose-lowering medicinal products, including insulin (see sections 4.4, 4.5 and 5.1 for available data on different combinations); or those already being treated with the combination of dapagliflozin and metformin as separate tablets."

The legal basis for this application refers to:

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

The application submitted is a new fixed combination medicinal product, 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 tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/221/2011 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

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

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
Anagni, 03012
Italy

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP:

Rapporteur: Kristina Dunder Co-Rapporteur: Agnes Gyurasics

- The application was received by the EMA on 26 November 2012.
- The procedure started on 26 December 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 March 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 25 March 2013.
- During the meeting on 25 April 2013, 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 25 April 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 11 July 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 19 August 2013.
- During the CHMP meeting on 19 September 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 October 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 15 November 2013.
- During the meeting on 21 November 2013, 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 Xigduo.

2. Scientific discussion

2.1. Introduction

An important goal of diabetes care is to achieve adequate glycaemic control in order to reduce long-term microvascular and macrovascular complications caused by chronic hyperglycaemia. Achieving and maintaining glycaemic treatment goals is a challenge and, in practice, most patients will eventually require multiple medications during the course of their disease to maintain glycaemic control. Multiple professional organisations, including the ADA, AACE and IDF, advocate earlier use of combination therapy in patients with T2DM who have inadequate control with monotherapy, and at least two (EASD and Canadian Diabetes Association [CDA]) recommend earlier combination therapy when patients have more marked or persistent hyperglycaemia.

Adherence to therapy is especially important for the management of chronic diseases such as diabetes, but the need for multiple antidiabetic medications to achieve and then sustain adequate HbA1c control often leads to poor adherence. Recent reviews indicate that levels of non-adherence in patients with T2DM range from 10% to 30%. Poor adherence leads to inadequate glycaemic control and subsequently increased risk of associated complications. Thus, a new therapeutic combination of dapagliflozin and metformin available as one tablet would provide a treatment option for patients with T2DM, and should improve patient compliance.

Dapagliflozin propanediol monohydrate (dapagliflozin) is a first-in-class compound that inhibits the human renal sodium-dependent glucose co-transporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin's mechanism of action is different from and complementary to currently available treatment options, and results in the direct and insulin-independent elimination of glucose by the kidney. Thus dapagliflozin (INN) lowers plasma glucose by inhibiting the renal reabsorption of glucose, and by promoting its urinary excretion. Glucosuria, the result of the inhibition of glucose reabsorption, is the primary pharmacodynamic effect of the drug, and results in a lowering of fasting plasma glucose (FPG) concentrations within one week; improved glycaemic control as measured by a reduction in haemoglobin A1c (HbA1c), FPG and postprandial glucose (PPG); and the urinary loss of approximately 280 kcalories/day, which ultimately leads to a decrease in weight and body fat. This effect directly addresses one of the basic underlying problems in the pathogenesis of T2DM, namely caloric excess. In addition, the mild diuretic effect is also associated with modest blood pressure reductions. Furthermore, dapagliflozin is associated with a low risk of hypoglycaemia. Finally, as SGLT2 is primarily expressed in the kidney, the highly selective nature of dapagliflozin minimises the risk of off-target (non-kidney) effects.

Dapagliflozin marketing authorization (Forxiga - Dapagliflozin film-coated tablet 5 and 10 mg) was granted on 12 November 2012. The data submitted in this application is focused on the fixed dose combination. Further information on dapagliflozin free treatment can be found in the EPAR of Forxiga.

Metformin hydrochloride (metformin), a biguanide, is a well-characterised medicine that has been in widespread use for decades. It is the first-line agent of choice for T2DM, endorsed by professional organisations such as European Association for the Study of Diabetes (EASD);

American Diabetes Association (ADA); American Association of Clinical Endocrinologists (AACE); and International Diabetes Federation (IDF). Metformin lowers HbA1c, FPG and PPG concentrations in patients with T2DM, improving glycaemic control by reducing hepatic glucose production, decreasing intestinal absorption of glucose, and improving insulin sensitivity by increasing peripheral glucose uptake and utilisation.

A combination of drugs with complementary mechanisms of action, and with clinically important effects on HbA1c, FPG, PPG and weight loss, is expected to form a clinically relevant paradigm for achieving and maintaining glycaemic control in patients who have difficulty with maintaining glycaemic control on metformin alone, or in combination with other oral antidiabetic drugs (OADs) or insulin.

2.2. Quality aspects

The finished product is presented as film-coated tablets containing a fixed-dose combination of dapagliflozin propanediol monohydrate equivalent to 5 mg dapagliflozin and 850 mg and 1000 mg of metformin hydrochloride as the active substances.

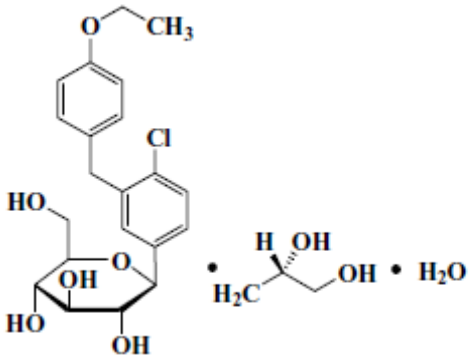
Other ingredients are hydroxypropylcellulose, microcrystalline cellulose, magnesium stearate, sodium starch glycollate type A and film coating composed of polyvinyl alcohol, macrogol 3350, talc, titanium dioxide, iron oxide yellow or iron oxide red.

The product is available in PVC/Aclar//Alu blister packs.

Active Substance

Dapagliflozin propanediol monohydrate

The chemical name of dapagliflozin propanediol monohydrate is (2*S*,3*R*,4*R*,5*S*,6*R*)-2-[4-Chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro- 2*H*-pyran-3,4,5-triol, (2*S*)-propane-1,2-diol (1:1) monohydrate and has the following structure:



Dapagliflozin (INN) is a white to off-white powder, soluble in many polar organic solvents and non-hygroscopic. Dapagliflozin is a chiral molecule with five stereogenic centres. Only one polymorphic form has been observed.

The same information on dapagliflozin was submitted in the marketing authorization application (MAA) of Forxiga (Dapagliflozin film-coated tablet 5 and 10 mg). It has been confirmed that this current application has taken into account all the amendments and responses applicable to the application Forxiga.

Manufacture

The manufacture of the final active substance was satisfactorily described including a flow-chartand consists in three main steps: synthesis of the two intermediates and synthesis of the final active substance .

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 GMP 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, 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.

The batch analysis data demonstrated the consistency in the quality of batches of dapagliflozin propanediol. No data was 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.

A post-approval change management (PACM) protocol for changes in the current supplier of starting material was provided as well as a commitment to update the PACM protocol as necessary.

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.

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 in accordance with the ICH guidelines.

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.

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, colour, 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

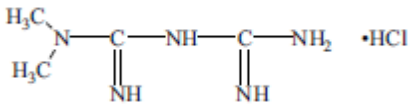
used for the control of the active substance apart from the X-ray method that was presented separately.

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.

Metformin hydrochloride

The chemical name of metformin hydrochloride (metformin HCl) is 1,1-Dimethylbiguanide hydrochloride and has the following structure:



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

As there is a monograph of metformin hydrochloride in the Phar. Eur., the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for metformin hydrochloride which has been provided within the current Marketing Authorisation Application.

Manufacture

This active substance is sourced by one manufacturer which provides a Certificate of Suitability (CEP) in support of its quality. Therefore, the relevant information has been assessed by the European Directorate for the Quality of Medicines (EDQM) before issuing the CEP.

Specification

The active substance specification includes the requirements of Ph Eur monograph Metformin Hydrochloride and some additional limits and tests.

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

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

Stability

Stability of this active substance is covered by the CEP which contains a re-test period without any storage condition when stored in the proposed container.

2.2.1. Finished Medicinal Product

Pharmaceutical Development

Dapagliflozin and metformin (Dapa/Met) film-coated tablets were developed as a fixed dose combination product to ensure their *in vivo* performance to be bioequivalent to the mono therapy products of dapagliflozin and metformin. Dapa/Met has been developed as four combinations of doses (2.5/850, 2.5/1000, 5/850 and 5/1000) but only doses 5mg/850 mg and 5/1000 mg are intended for commercial purposes.

A structured quality by design QbD approach including a science and risk-based model of pharmaceutical development of Dapa/Met was applied. Extensive, prior knowledge and experience within Bristol-Myers Squibb referring to both drug substances and also previous development of a dapagliflozin mono therapy drug product and combination drug products, were used in the development of Dapa/Met.

Quality risk assessments (on safety and efficacy) and design of experiments (DoE) were performed 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 quality target product profile (QTPP) for the finished product Dapa/Met was adequately designed.

The use of risk management was applied throughout the formulation and process development as well as for establishment of the control strategy. The risks were considered early in development phase.

These risks were reduced by selection of the process type. A fluid bed granulation process was chosen

The choice of the active substances has been discussed for this type II diabetes combination. Dapagliflozin has a high solubility over the clinical dose range and membrane permeability, it is a BCS III compound (high solubility/poor permeability based on <90% absolute oral bioavailability) but has BCS I-like characteristics (high solubility/high in vitro permeability and/or >90% absorbed from the gastrointestinal tract). Also, dapagliflozin is not regarded as an active substance with a narrow therapeutic range. The active substance showed satisfactory physical and chemical stability and was not sensitive to light. Metformin HCl is compendial a BCS Class III compound.

Compatibility between the two active substances was demonstrated in stability studies. The studies confirmed the compatibility of dapagliflozin and metformin HCl with the excipients used for the formulation.

Both dapagliflozin propanediol and metformin HCl are highly soluble throughout the physiological range, hence the dissolution is mainly controlled by the disintegration of the tablet resulting in

both drug substances dissolution being similar. The dissolution method was found to be satisfactory and discriminatory.

All excipients are well-known pharmaceutical ingredients and their quality is compliant with Ph. Eur. Standards and EC Directive 2009/35/EC. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The Dapa/Met 2.5+850 mg and Dapa/Met 5+1000 mg strengths were selected for the bioequivalence study to “bracket” the other two developed strengths of Dapa/Met 2.5+1000 mg and Dapa/Met 5+850 mg. Bioequivalence of each active ingredient in the fixed-dose combination product to that of the individual mono therapy products administered concomitantly for both strengths investigated was established.

Comparable in vitro dissolution profiles with regard to dapagliflozin and metformin have been provided for the respective Dapa/Met product strengths throughout the physiological pH range.

The proposed commercial manufacturing process is widely used in the pharmaceutical industry. All studies from laboratory scale to commercial scale included the same process steps and types of equipment, the only difference being adjustments of parameter ranges due to scale. The manufacturing process has been well investigated through Design of Experimental studies in different scales to gain knowledge and understanding of the manufacturing process.

In summary, the pharmaceutical development and the bioequivalence of the fixed-dose combination product were appropriately discussed and the robustness of the formulation was confirmed in manufacturing process studies. The manufacturing process studies performed have lead to a comprehensive understanding of the proposed manufacturing process, from laboratory to commercial scale.

The primary packaging is PVC/Aclar//Alu blister packs. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

It is confirmed that the magnesium stearate used in the formulation is of vegetable origin. No excipients derived from animal or human origin have been used.

Manufacture of the product

The manufacturing process consists of 8 main steps: metformin HCl/magnesium stearate blend, preparation of granulation liquid, fluid bed granulation, milling, final blending (two steps, blending and lubrication), compression, film coating and packaging. A narrative of the process as well as a flow chart has been provided including all the reagents, equipment, conditions, manufacturing steps and appropriate in-process controls.The process is considered to be a standard manufacturing process with a non-functional film-coating. A satisfactory validation protocol has been submitted and appropriate in-process controls and key process parameters have been put in place to ensure the quality of the drug product through all the manufacturing steps.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls and key process parameters are adequate for this standard film-coated tablet.

Product specification

The finished product release and end of shelf-life specifications include appropriate tests for this kind of dosage form: description (visual), identification dapagliflozin (HPLC and UV), identification metformin (HPLC and UV), assay dapagliflozin (HPLC), assay metformin (HPLC), related substances dapagliflozin (HPLC), related substances metformin (HPLC), disintegration (Ph.Eur.), dissolution (HPLC), uniformity of dosage units dapagliflozin (Ph.Eur. content uniformity, HPLC) and metformin (Ph.Eur. mass variation) and microbiological quality (Ph.Eur.).

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the European Pharmacopoeia and the ICH Q6A guideline. Non-compendial analytical methods have been described and validated satisfactorily in accordance with ICH guidelines.

Batch analysis data was presented for 3 pilot-scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability

Stability data on 3 pilot-scale batches of each strength (and 1 pilot-scale batch of each strength for intermediate, accelerated and stressed conditions) stored in commercial packaging PVC/Aclar//Alu blister under ICH long-term (24 months at 25°C/60%RH), accelerated (6 months at 40°C/75%RH) and stressed conditions (photostability testing , 13 months open dish storage at 25°C/60%RH and bulk container 24 months at 30°C/65%RH) were provided.

Samples were tested for description, assay dapagliflozin, assay metformin, organic impurities dapagliflozin, organic impurities metformin, dissolution dapagliflozin, dissolution metformin, microbial purity. The analytical procedures used are stability indicating.

In addition photostability investigations have been conducted according to ICH Q1B option 2 to confirm that Dapa/Met is not sensitive to light.

Based on available data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.2. Discussion on chemical, pharmaceutical and biological aspects

Quality Development

The applicant has applied QbD principles in the development of the active substance dapagliflozin and finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

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

2.2.3. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.4. Recommendation for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

This marketing authorisation application seeks to register Xigduo, containing the active substances dapagliflozin and metformin. It is intended as a fixed dose combination medicinal product for oral use in one pharmaceutical form (film-coated tablets) and two strengths (5mg/850 mg and 5 mg/1000 mg), and two presentations (perforated blisters and non-perforated blisters) in several pack sizes.

The proposed indication for Xigduo is for treatment in adults aged 18 years and older with type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on metformin alone or in combination with other glucose-lowering medicinal products, including insulin or those already being treated with the combination of dapagliflozin and metformin as separate tablets.

Dapagliflozin is an inhibitor of human renal sodium glucose co-transporter (SGLT2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin (Forxiga) was approved in the EU on 12 November 2012. Metformin is a biguanide that improves glycaemic control by improving insulin sensitivity. Metformin is a well-established product in the EU.

The excipients are commonly used in and do not raise any toxicological concerns.

The non-clinical overview provided an adequate summary and a critical review of relevant data. In the overview, the Applicant mainly refers to the data submitted for dapagliflozin and published data for metformin. A 3-month oral combination toxicity study and a 7-day oral toxicokinetic study in rat with dapagliflozin and metformin were submitted and evaluated.

All pivotal toxicity studies supporting the safety of the combination of dapagliflozin and metformin were appropriately designed and conducted in compliance with International Conference on Harmonization (ICH) guidelines and Good Laboratory Practice (GLP) regulations. Dose selection for the pivotal combination toxicity study was principally based upon a range-finding combination toxicity study or from preceding studies with each agent administered individually to ensure that adequate doses were evaluated.

2.3.2. Pharmacology

Dapagliflozin (BMS-512148) represents a novel mechanism for the treatment of type 2 diabetes mellitus. Dapagliflozin is a potent, selective, reversible, competitive inhibitor of human SGLT2, a sodium-glucose co-transporter responsible for the renal reabsorption of glucose. Administration of dapagliflozin in mice and normal and diabetic rats increases the urinary excretion of glucose resulting in decreased serum glucose.6. These effects have been also observed in patients administered dapagliflozin. In pharmacology studies, single doses of dapagliflozin as low as 0.1 mg/kg in normal rats and as low as 0.01 mg/kg in diabetic rats were demonstrated to be pharmacologically active.

Metformin is an antihyperglycemic agent that improves glucose tolerance in patients with type 2 diabetes by lowering both basal and postprandial plasma glucose. Metformin acts by decreasing hepatic glucose production and intestinal absorption of glucose and improving insulin sensitivity by increasing peripheral glucose uptake and utilization. These effects have been demonstrated in both experimental animals and in patients.

Based upon the different mechanisms of action for dapagliflozin and metformin and the available clinical data in patients treated with both drugs, no adverse pharmacologic interactions are anticipated. There were also no adverse safety findings noted in nonclinical combination toxicity studies conducted with dapagliflozin and metformin.

Therefore no additional nonclinical pharmacology studies assessing pharmacodynamics/efficacy were conducted.

Primary pharmacodynamic studies

No new studies have been conducted and submitted.

Secondary pharmacodynamic studies

No new studies have been conducted and submitted.

Safety pharmacology programme

In vitro and in vivo safety pharmacology studies evaluating the cardiovascular, central nervous, and respiratory systems were previously conducted for dapagliflozin. There were no adverse effects indicative of potential human safety concerns. Dedicated safety pharmacology studies were not conducted for metformin due to the lack of adverse outcomes derived from extensive cumulative clinical data. Therefore evaluation of the combination in a full battery of safety

pharmacology studies was considered unwarranted. Nevertheless, potential effects of the individual compounds and the combination on the central nervous system and respiratory function were evaluated as components of the pivotal 3-month dapagliflozin and metformin combination repeat-dose rat toxicity study. Dapagliflozin and metformin either alone or in combination had no effects on behaviour or respiration in this study at doses up to 5 mg/kg/day dapagliflozin (AUC 24.1 µg•h/mL, at Week 13) and 150 mg/kg/day metformin (AUC 28.7 µg•h/mL at Week 13).

Pharmacodynamic drug interactions

No specific nonclinical drug interaction studies were conducted with dapagliflozin in combination with metformin. However, toxicokinetics was assessed as a part of toxicity studies. Drug interactions in humans were previously assessed through the MAA of dapagliflozin. Briefly, the AUC for dapagliflozin was decreased only at high doses of metformin used in the 7-day range-finding study. In the 3-month combination study, dapagliflozin did not affect metformin AUC and Cmax nor did metformin affect dapagliflozin AUC and maximum concentration (Cmax).

2.3.3. Pharmacokinetics

Pharmacokinetic endpoints for dapagliflozin and metformin were previously assessed in nonclinical and clinical settings. Based on those assessments, no adverse pharmacokinetic interactions were expected. Therefore, no additional nonclinical studies were conducted with the compounds in combination. Toxicokinetics was assessed as a part of the toxicity studies and no significant increase or decrease in dapagliflozin exposure was observed in the presence of metformin in these studies.

2.3.4. Toxicology

The individual toxicities of dapagliflozin and metformin were previously established in a comprehensive investigational program. To support the safety of the dapagliflozin and metformin fixed-dose combination product, additional toxicity and toxicokinetics assessments including safety pharmacology endpoints (central nervous and respiratory systems) were conducted as part of a 3-month oral toxicity study in rats.

An 7 day oral toxicokinetic study was conducted in rats to assist in dose selection for the pivotal 3-month repeat-dose toxicity study.

The rat was selected for evaluation of potential toxicity based on the experience with dapagliflozin, which demonstrated increased sensitivity in this species including increased trabecular bone, exacerbated chronic progressive nephropathy, and tissue mineralization.

Single dose toxicity

Single-dose toxicity studies were previously conducted with dapagliflozin and metformin alone, but no single dose toxicity study was conducted with a combination of dapagliflozin and metformin.

Repeat dose toxicity

GLP-compliant repeat-dose toxicity studies have been previously conducted and reported for dapagliflozin alone for up to 6 months duration in rats and 12 months duration in dogs.

A seven-day non-GLP oral toxicokinetic study in rats (DN09023) was conducted to provide dose-selection data for the pivotal study. Oral doses of dapagliflozin and metformin up to 50 and 600 mg/kg/day respectively, were well tolerated either alone or when co-administered for seven days to rats. There were no significant drug-drug interactions noted in this study

A three-month GLP oral toxicity study in rats (DN10008) was conducted to determine the toxicologic or toxicokinetic interaction when dapagliflozin and metformin were administrated in combination to rats for 3 months. Dapagliflozin at 1 or 5 mg/kg/day was co-administered with 150 mg/kg/day metformin by oral gavage to groups of 10 rats per sex. Additional groups were treated with vehicle, 5 mg/kg/day dapagliflozin or 150 mg/kg/day metformin alone.

Dapagliflozin-related effects, which occurred with and without metformin, were consistent with effects observed in previous studies in rats and/or were generally considered to be a consequence of the pharmacological effects of dapagliflozin.

There was an apparent increase in urinary protein excretion in the dapagliflozin/metformin treated rats but this increase was not statistically significant when compared to rats treated with dapagliflozin alone. Increases in urinary protein in dapagliflozin/metformin treated rats were characterized as having significant variability and had no correlation with any treatment-related histopathology in the kidney or urinary tract. Dapagliflozin-induced increases in urinary protein were observed in previous rat repeat-dose toxicity studies in the absence of any drug-related histopathology and were hypothesized to be due to the osmotic diuretic effects of dapagliflozin. Therefore, there was no evidence of any new toxicities or biologically relevant exacerbation of existing dapagliflozin-related effects when administered together with metformin.

AUC exposure multiples for dapagliflozin and metformin at the NOAEL (5/150) relative to exposures at the maximal recommended human dose (MRHD) were 52× and 1.4×, respectively.

Genotoxicity

Neither dapagliflozin nor metformin were shown previously to be genotoxic, therefore additional genotoxicity studies were considered unwarranted.

Carcinogenicity

Individually, neither compound was previously shown to be carcinogenic; therefore a combination study was considered unwarranted. Two-year rodent carcinogenicity assays did not identify any tumorigenic activity for dapagliflozin. Dapagliflozin did not increase the incidence or shorten the latency period of tumours at exposure multiples > 100× the MRHD. There was also no indication of any dapagliflozin induced hyperplastic or proliferative signals in the rodent carcinogenicity studies. The combination of dapagliflozin with metformin would also not be expected to increase the carcinogenic potential of either drug.

Reproduction Toxicity

- **Fertility and early embryonic development**

No adverse effects on fertility or early embryonic development were previously observed with the individual active ingredients at clinically relevant exposures; therefore it was considered unwarranted to conduct studies with the combination.

- **Embryo-fœtal development**

There was no drug-related teratogenicity with either active ingredients; therefore it was considered unwarranted to conduct studies with the combination.

- **Prenatal and postnatal development, including maternal function**

In rat studies, exposure to dapagliflozin was associated with an increased incidence and/or severity of renal pelvic and tubular dilatations in offspring. These outcomes occurred with drug exposures during periods of animal development that correlate with the second and third trimesters of human pregnancy. Thus, dapagliflozin should not be used in the second and third trimesters of pregnancy or during first 2 years of life; therefore, no pre- and postnatal development studies were conducted with the combination.

- **Studies in which the offspring (juvenile animals) are dosed and/or further evaluated**

An indication is not currently being sought for humans ≤ 18 years of age; therefore no juvenile studies were conducted with the combination.

Local Tolerance

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

Other toxicity studies

None

2.3.5. Ecotoxicity/environmental risk assessment

- **Dapagliflozin**

Table 1. 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) 0.14 (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 Transformation in Aquatic Sediment systems	OECD 308	Kd sediment = 12 L/kg Mineralisation: 35 and 68 % on day 99 45 and 76 % on day 148	Dapagliflozin is mineralised extensively.

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	37	mg/ L	freshwater green algae
Daphnia sp. Reproduction Test	OECD 211	NOEC	120	mg/ L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	1	mg/ L	feathead minnow
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	200	mg/ L	
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC	150	mg/ kg	Chironomus riparius

PEC/PNEC assessments			
	PEC (µg/L)	NPEC (µg/L)	PEC/PNEC
Microorganisms	0.14	20 000	7.0×10^{-6}
Surface water	0.14	100	1.4×10^{-3}
Groundwater	0.035	1000	3.5×10^{-5}
Sediment	1.68	1500	1.1×10^{-3}

- **Metformin**

Table 2. Summary of main study results

Substance (INN/Invented Name): Metformin					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	K_{ow} < 3 at 25^0			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)	10 (default) 28 (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	FDA 3.08	K_{oc} =32.1			
Ready Biodegradability Test	FDA 3.11	Not readily biodegradable.			
Aerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ whole\ system}$ = 6.59 and 55.0 for both high and low organic matter sediment systems			Biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	100	mg/L	green algea
Daphnia sp. Reproduction Test	OECD 211	NOEC	67	mg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	10	mg/L	Fathead minnow
Activated Sludge, Respiration Inhibition Test	FDA 4.02	NOEC	80	mg/L	*Anabaena flos-aquae*
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC	100	mg/kg	*Chironomus riparius*

PEC/PNEC assessments			
	PEC (µg/L)	NPEC (µg/L)	PEC/PNEC
Microorganisms	28	8000	3.5×10^{-3}
Surface water	28	1000	2.8×10^{-2}

Groundwater	7	6700	1.0×10^{-3}
Sediment	89.9	1000	8.99×10^{-2}

Based on the PEC/PNEC ratios (see above tables) dapagliflozin and metformin respectively are unlikely to present a risk to microorganisms, surface water, groundwater and sediment dwelling organisms as log Kow does not exceed 4.5.

In addition, dapagliflozin and metformin are already used as free combination therapy as approved marketed products and no significant increase in environmental exposure is anticipated.

2.3.6. Discussion on non-clinical aspects

Pharmacology

Dapagliflozin is a potent, selective, reversible, competitive inhibitor of human SGLT2, a sodium-glucose co-transporter responsible for the renal reabsorption of glucose. Administration of dapagliflozin in mice and normal and diabetic rats increases the urinary excretion of glucose resulting in decreased serum glucose. These effects have been also been observed in patients administered dapagliflozin. In pharmacology studies, single doses of dapagliflozin as low as 0.1 mg/kg in normal rats and as low as 0.01 mg/kg in diabetic rats were demonstrated to be pharmacologically active.

Metformin is an antihyperglycemic agent that improves glucose tolerance in patients with type 2 diabetes by lowering both basal and postprandial plasma glucose. Metformin acts by decreasing hepatic glucose production and intestinal absorption of glucose and improving insulin sensitivity by increasing peripheral glucose uptake and utilization. These effects have been demonstrated in both experimental animals and in patients.

Based upon the different mechanisms of action for dapagliflozin and metformin and the available clinical data in patients treated with both drugs, no adverse pharmacologic interactions are anticipated. There were also no adverse safety findings noted in nonclinical combination toxicity studies conducted with dapagliflozin and metformin. Therefore no additional nonclinical pharmacology studies assessing pharmacodynamics/efficacy were conducted. This approach is in line with The Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products (EMEA/CHMP/SWP/258498/2005).

In vitro and in vivo safety pharmacology studies evaluating the cardiovascular, central nervous, and respiratory systems were previously conducted for dapagliflozin. There were no adverse effects indicative of potential human safety concerns. Dedicated safety pharmacology studies were not conducted for metformin due to the lack of adverse outcomes derived from extensive cumulative clinical data. Therefore evaluation of the combination in a full battery of safety pharmacology studies was considered unwarranted. Nevertheless, potential effects of the individual compounds and the combination on the central nervous system and respiratory function were evaluated as components of the pivotal 3-month dapagliflozin and metformin combination repeat-dose rat toxicity study. Dapagliflozin and metformin either alone or in combination had no effects on behaviour or respiration in this study at doses up to 5 mg/kg/day

dapagliflozin (AUC 24.1 µg•h/mL, at Week 13) and 150 mg/kg/day metformin (AUC 28.7 µg•h/mL at Week 13).

Pharmacokinetics

Pharmacokinetic endpoints for dapagliflozin and metformin were previously assessed in nonclinical and clinical settings. Based on those assessments, no adverse pharmacokinetic interactions were expected. Therefore, no additional nonclinical studies were conducted with the compounds in combination. Toxicokinetics was assessed as a part of the toxicity studies.

Toxicology

The individual toxicities of dapagliflozin and metformin have been evaluated as a part of previous product review and approval processes. The toxicity of the combination of dapagliflozin and metformin in animals was formally evaluated in a GLP-compliant repeat-dose 3-month study in rats. Safety pharmacology endpoints (central nervous and respiratory systems) were incorporated into the repeat-dose rat toxicity study. No toxicokinetic interactions or any additive or synergistic toxicity were demonstrated in the rat following 3 months of dosing with the combination of dapagliflozin and metformin at doses up to 5 and 150 mg/kg/day, respectively. AUC exposure multiples for dapagliflozin and metformin at the NOAEL (5/150) relative to exposures at the maximal recommended human dose (MRHD) were 52× and 1.4×, respectively.

Individually, neither compound was shown to be genotoxic or carcinogenic; therefore additional studies on genotoxicity or carcinogenicity are considered unwarranted.

No adverse effects on fertility or early embryonic development were previously observed with the individual compounds at clinically relevant exposures; therefore it is considered unwarranted to conduct studies with the combination.

Environmental risk assessment

The Applicant has provided individual environmental risk assessments for dapagliflozin and metformin, including study reports. The introduction of this FDC is not expected to result in an increase in environmental exposure.

2.3.7. Conclusion on the non-clinical aspects

The CHMP considers that since both dapagliflozin and metformin are approved products and that the free combination of the two is included in the indication for dapagliflozin, no further data on pharmacology are needed. Also, for the assessment of this FDC there is no need to include a more detailed description of available data on the pharmacology of the two components.

It is agreed that no further data or discussion on pharmacokinetics are warranted.

No concerns were identified in the 3 month repeat-dose toxicity study in rats. The CHMP is of the view that no further studies with the combination on genotoxicity, carcinogenicity, reproductive and developmental toxicity are warranted.

Since dapagliflozin and metformin are already used in free combination therapy as existing marketed products the CHMP considers that no significant increase in environmental exposure is anticipated.

2.4. Clinical aspects

2.4.1. Introduction

The FDC clinical development programme included four studies specific to the FDC (D1691C00004, D1691C00002, D1691C00005 and D1691C00003), and an additional five studies (MB102014, D1690C00012, D1690C00004, D1690C00010 and D1690C00006) providing either existing information that is relevant to the FDC submission, or newer long term data and combination therapy data that was not available at the time of the initial dapagliflozin MAA submission.

The pharmacokinetic and pharmacodynamic properties of dapagliflozin are documented in the approved SmPC of Forxiga.

The Phase III programme for dapagliflozin was conducted using QD dosing. Hence it was necessary to bridge from QD to BID dosing; metformin IR is a BID formulation therefore the IR FDC needs to be a BID formulation. Furthermore, the efficacy study using BID dosing utilised individual monotherapy tablets. Hence it was necessary to bridge from the individual monotherapy tablets to the FDC. These aspects were taken into consideration when designing the four FDC specific studies.

The clinical development programme was designed in accordance with CHMP guidance (CPMP 2002); Guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus (CPMP/EWP/1080/00 Rev.1) (CHMP 2012); Guideline on Clinical Development of Fixed Combination Medicinal Products (CHMP/EWP/240/95 Rev.1) (CHMP 2009); and the 2010 Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1) (CHMP 2010).

No specific CHMP scientific advice relating to the FDC development programme has been received.

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.

Exemption

In accordance with the EMA guideline Investigation of Bioequivalence, 2010 (CPMP/QWP/EWP/1401/98 Rev. 1) (CHMP 2010) a waiver for demonstrating in vivo bioequivalence of the 5 mg/850 mg strength is requested by the applicant and is based on:

- Linear pharmacokinetics of dapagliflozin from 0.01 mg to 500 mg

• Demonstration of bioequivalence of both the Dapa/Met 2.5 mg/850 mg and Dapa/Met 5 mg/1000 mg strengths of the FDC to the individual monotherapy tablets administered concomitantly (D1691C00002)

• The products being manufactured by the same manufacturing process and the composition of the strengths being qualitatively and quantitatively similar or proportional and hence can be considered "formulation proportional"

• Comparable in vitro dissolution profiles with regard to dapagliflozin and metformin for the respective Dapa/Met IR FDC strengths throughout the physiological pH range.

- Tabular overview of clinical studies

Study number / Treatment duration	**Study description and treatment groups (Number of subjects)**
Phase 1 Clinical Pharmacology studies	
D1691C00004 (completed)	PK and PD effects of Dapa 10 mg QD vs Dapa 5 mg BID (n = 16)
D1691C00002 (completed)	Bioequivalence for FDC versus free drug combination Dapa 2.5 mg /Met 850 mg FDC vs free drug combination (n = 60) Dapa 5 mg/Met 1000 mg FDC vs free drug combination (n = 60)
D1691C00005 (completed)	Food effect study; Dapa 5 mg/Met 1000 mg FDC (n = 17)
Phase 3 Clinical studies	
D1691C00003 16 weeks (completed)	Add-on to metformin (metformin failure subjects) Dapa 2.5 mg BID (n = 100), Dapa 5 mg BID (n = 100), Dapa 10 mg QD (n = 99) or placebo (n = 101) + open-label Met ≥ 1500 mg
MB102014 24 plus 78 weeks (completed)	Add-on to metformin (metformin failure subjects) Dapa 2.5 mg QD (n = 137), 5 mg QD (n = 137), 10 mg QD (n = 135) or placebo (n = 137) + open-label Met ≥ 1500 mg
[a]D1690C00012 24 plus 26 plus 52 weeks (completed)	Add-on to metformin (metformin failure subjects) Dapa 10 mg QD (n = 91) or placebo (n = 91) + open-label Met ≥ 1500 mg
[b]D1690C00004 52 plus 52 weeks (completed) plus 104 weeks (ongoing)	Active comparator study: Noninferiority vs Glip (metformin failure subjects) Dapa titrated to 2.5 mg, 5 mg, 10 mg QD + open-label Met ≥ 1500 mg (n = 406) Glip titrated to 5 mg, 10 mg, 20 mg QD + open-label Met ≥ 1500 mg (n = 408)
D1690C00010 24 plus 24 weeks (completed)	Combination therapy with DPP-4 inhibitor (sitagliptin failure subjects) Overall population: Dapa 10 mg QD (n = 225) or placebo (n = 226) + open-label sitagliptin 100 mg ± open-label Met ≥ 1500 mg Stratum 2: Dapa 10 mg + Sita + Met (n = 114); Placebo + Sita + Met (n = 114)
D1690C00006 24 plus 24 plus 56 weeks (completed)	Combination therapy with insulin (insulin failure subjects) Overall population: Dapa 2.5 mg QD (n = 202), 5 mg/10 mg QD (n = 212), 10 mg QD (n = 196) or placebo (n = 197) + open-label insulin ± OADs Stratum: Subjects with OAD (Subgroup: Insulin plus Metformin alone): Dapa 2.5 mg + insulin + Met (n = 80); Dapa 5 mg + insulin + Met (n = 78); Dapa 10 mg + insulin + Met (n = 83); Placebo + insulin + Met (n = 78)

a The data from the short term and long-term 1 extension period (ST+LT1; 50 weeks) from study D1690C00012 is included in this application; although the second long term period (LT2; 102 weeks) has completed, data was not available at the cut-off date for this submission (24 November 2011)

b The second long term treatment period (LT2; 208 weeks) from study D1690C00004 was not yet complete at the time of submission; short term and long term period 1 (ST+LT1 data; 104 weeks) is included in the application

2.4.2. Pharmacokinetics

The pharmacokinetics of the active substances (dapagliflozin and metformin) has already been evaluated during the MAA for the respective mono-component.

For a fixed dose combination containing known active substances, bioequivalence should be demonstrated between the free combination of the reference formulations and the FDC in order to support the substitution indication and also to bridge from the monotherapy tablets used in the clinical studies. Furthermore, the pharmacokinetic interaction between the two active substances should be evaluated (*Guideline on clinical development of fixed dose combination medicinal products, CHMP/EWP/240/95 Rev. 1*).

The clinical pharmacology programme of dapagliflozin has been fully characterised across 26 studies, as described in the initial dapagliflozin MAA; a 2 way drug drug interaction study between dapagliflozin and metformin (MB102026) has shown no clinically meaningful effect of dapagliflozin on metformin pharmacokinetics parameters and vice versa.

Three clinical pharmacology studies have been conducted specific to the dapagliflozin/metformin FDC programme:

D1691C00004 demonstrates that dapagliflozin has similar pharmacokinetic and pharmacodynamic effects whether administered as 5 mg BID or 10 mg QD.

D1691C00002 demonstrates the bioequivalence of Dapa/Met IR FDC tablets versus individual dapagliflozin and metformin IR (European sourced Glucophage) tablets administered together, in the fed state. This study bridges the separate doses used in the clinical programme to the FDC formulation.

D1691C00005 documented the effect of food on the pharmacokinetics of the Dapa/Met IR FDC administered with or without food (high fat meal).

Absorption

- ***Bioavailability***

The individual biopharmaceutic profiles of dapagliflozin and metformin have already been evaluated during the initial MAA for Forxiga and Glucophage.

Dapagliflozin

Dapagliflozin is rapidly and well absorbed after oral administration. Maximum plasma concentrations are usually attained within 2 hours after administration in the fasted state. The absolute oral bioavailability is approximately 78%.

Metformin

After oral administration, metformin hydrochloride absorption is saturable and incomplete. Maximum plasma concentrations are reached in 2.5 hours. The absolute bioavailability is approximately 50-60 % in healthy subjects.

- ***Bioequivalence***

Study D1691C00002 - A two-part, open-label, randomised, single-centre, phase I bioequivalence study comparing (Part I) the fixed dose combination dapagliflozin/metformin IR tablet (2.5 mg/850 mg) versus the free combination of the dapagliflozin tablet (2.5 mg) and metformin IR tablet (850 mg); and (Part II) comparing the fixed dose combination dapagliflozin/metformin IR tablet (5 mg/1000 mg) versus the free combination of the dapagliflozin tablet (5 mg) and metformin IR tablet (1000 mg) in healthy volunteers, both parts in the fed state

Methods

Study design

The study was a single-centre, two-part, randomised, open-label, crossover bioequivalence study with 120 healthy volunteers (60 per study part). The first part was a two-way crossover comparing Xigduo 2.5 mg/850 mg to the individual mono components. The second part was a two-way crossover comparing Xigduo 5 mg/1000 mg to the individual mono components. Part I and Part II were independent of each other. Blood samples were collected pre-dose and at 1, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 30, 36, 42, 48, 54, 60 and 72 hours after drug administration. In both parts there was a wash-out period of at least seven days between the study periods. All treatments were administered in the fed state. Thirty minutes prior to drug administration the subjects received a standardised non-high fat meal (about 650 calories: 26 g protein, 43 g fat (32%) and 65 g carbohydrates).

Test and reference products

Drug:	dapagliflozin/metformin (LTSS batch 1201)
Formulation:	FDC tablet
Strength:	2.5 mg/850 mg; 5 mg/1000 mg
Batch number:	10-000074AZ (2.5 mg/850 mg); 10-000073AZ (5 mg/1000 mg)

Drug:	dapagliflozin (Clinical Phase 3 tablets)
Formulation:	tablet
Strength:	2.5 mg; 5 mg
Batch number:	8E39935 (2.5 mg); 7M21688 (5 mg)

Drug: Glucophage® (metformin hydrochloride) manufactured by Merck Santé, purchased from the Swedish market.

Formulation:	tablet
Strength:	850 mg; 1000 mg
Batch number:	09-006603AZ (850 mg); 09-006602AZ (1000 mg)

Populations studied

A total of 120 (60 in each part) adult healthy male and female volunteers, aged 19-45 years were enrolled. There were three drop-outs during the study. In part 1, one subject was discontinued due to non-compliance (tested positive for opiates). In part 2, one subject discontinued voluntarily and one subject was withdrawn due to safety reasons (elevated CK values). The PK-data of subject E0000167 of Period 2 in Part II of the study were excluded from the PK analysis due to vomiting shortly after administration of the FDC tablet.

Subject E0000279 had comparable plasma profiles of dapagliflozin and metformin with other individuals after administration of FDC dapagliflozin/metformin 5 mg/1000 mg (Treatment A in Part II). However, after administration of dapagliflozin 5 mg + metformin 1000 mg as two separated tablets (Treatment B in Part II) dapagliflozin plasma concentrations of this subject were below LLOQ at all time-points, but the metformin plasma profile was comparable to other individuals. The reason for this is unknown, but most likely, due to non-compliance. Therefore, for Subject E0000279, the plasma concentration of dapagliflozin at all time-points after administration of dapagliflozin 5 mg + metformin 1000 mg as two separated tablets (Treatment B in Part II) were treated as missing for calculation and analysis. As the lack of compliance could not be documented, a separate analysis was performed in which subject E0000279 was included in the statistical analysis for Treatment B with the dapagliflozin concentration values for this subject being set to LLOQ.

In total, 59 subjects (Part 1) and 58 subjects (Part 2) completed both study periods and were included in the pharmacokinetic analysis.

Analytical methods

Plasma concentrations of dapagliflozin and metformin were determined with an LC/MS/MS method using 13C6-dapagliflozin and metformin-d6 as internal standards. The calibration range was 0.200-50 ng/ml for dapagliflozin and 2.00-2000 ng/ml for metformin.

Pharmacokinetic variables

The primary objectives of the study are to determine AUC0-t, AUCinf and Cmax for dapagliflozin and metformin as single doses and within each FDC formulation and the and bioequivalence will be tested with respect to these two PK parameters for

> Part I: one 2.5 mg/850 mg FDC tablet and one single dose of 2.5 mg dapagliflozin together with one single dose of 850 mg metformin

and

> Part II: one 5 mg/1000 mg FDC tablet and one single dose of 5 mg dapagliflozin together with one single dose of 1000 mg metformin

all administered in the fed state.

The following PK parameters were determined:

- AUC(0-t) Area under plasma concentration-time curve from zero to time t

- [amount•time/volume]
- AUCinf Area under plasma concentration-time curve from zero to infinity
- [amount•time/volume]
- Cmax Maximum plasma (peak) drug concentration [amount/volume]
- tmax The time relative to administration to reach Cmax, [h]
- t1/2 The terminal phase half-life calculated as ln(2)/λz, [h-1]

The actual sampling times will be used in the PK parameter calculations. Plasma concentrations below limit of quantification (LOQ) will be excluded from the calculations except at time points prior to Cmax, where plasma concentrations below LOQ will be taken as zero at protocol time zero and as missing at all other time points in the calculation.

Statistical methods

The PK analysis will be performed using the PK analysis set including all subjects who received the investigational product and who have evaluable PK data appropriate for the comparison of interest (with no major protocol deviations or violations thought to significantly affect the pharmacokinetics of the drug).

The primary objectives of this study were to demonstrate bioequivalence for newly formulated FDC dapagliflozin/metformin 2.5 mg/850 mg and 5mg/1000 mg tablets versus individual dapagliflozin and metformin IR tablets (free combinations). For both objectives, bioequivalence was demonstrated if the 90% confidence interval (CI) for the formulation effect was contained within the interval of 0.800–1.250 for AUC(0-t), AUC(INF) and Cmax with respect to both dapagliflozin and metformin.

AUC(0-t), AUC(INF) and Cmax were log-transformed prior to analysis. All endpoints were analysed using an analysis of variance (ANOVA) model for each part separately, with sequence, period and formulation as fixed effects and subject within sequence as a random effect

Results

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for **dapagliflozin**, Part I (2.5 mg/850 mg)

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test (n=60)	**104 ± 23.5**	**22.9 ± 5.2**	**1.5 0.992-5.01**
Reference (n=59)	**103 ± 23.9**	**22.6 ± 7.03**	**1.5 0.491-5.05**
***Ratio (90% CI)**	**1.02 (0.998-1.04)**	**1.03 (0.969-1.10)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for **metformin**, Part I (2.5 mg/850 mg)

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test (n=60)	**8270 ± 1571**	**1136 ± 224**	**3.99 1.01-5.01**
Reference (n=59)	**8320 ± 1569**	**1184 ± 265**	**3.03 1.00-5.05**
***Ratio (90% CI)**	**1.00 (0.973-1.03)**	**0.966 (0.923-1.01)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

Table 5. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for **dapagliflozin**, Part II (5 mg/1000 mg)

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test (n=59)	**229 ± 57.9**	**49.5 ± 14.9**	**1.51 0.514-5.01**
Reference (n=57)	**232 ± 59.6**	**45.9 ± 14.0**	**1.01 0.494-5.02**
***Ratio (90% CI)**	**0.996 (0.975-1.02)**	**1.07 (0.989-1.15)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

Table 6. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for **metformin**, Part II (5 mg/1000 mg)

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test (n=59)	**9662 ± 1913**	**1330 ± 228**	**3.99 0.999-5.18**
Reference (n=58)	**9785 ± 2287**	**1334 ± 276**	**3.03 0.99-6.00**
***Ratio (90% CI)**	**0.997 (0.970-1.03)**	**1.00 (0.972-1.03)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

- ***Food Effect***

The effect of food on Xigduo was evaluated in a two-way cross-over study **(D1691C00005)** to assess the effect of food on the fixed dose combination dapagliflozin/metformin tablet (5 mg/100 mg) in 16 healthy male and female volunteers. Following an overnight fast a single oral dose of

the FDC was administered either in the fasting state or 30 min after a high-fat, high-calorie breakfast. The breakfast consisted of 800-1000 calories and derived approximately 150 calories from protein, 250 from carbohydrate and 500-600 from fat. There was a wash-out period of 7-14 days between the treatment periods.

Administration of the FDC under fed conditions had no effect on AUC for neither of the active substances. For dapagliflozin there was a 29% decrease in Cmax and tmax was delayed with 1h and for metformin there was a 17% decrease in Cmax and tmax was delayed with 2h after administration with food.

Table 7. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for **dapagliflozin** in the fasted or fed state, n=16

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Fasted	**272 ± 60.2**	**64.4 ± 18.4**	**1.00 0.50-1.50**
Fed	**272 ± 53.6**	**45.0 ± 10.0**	**2.00 1.00-5.00**
***Ratio fed/fasted (90% CI)**	**1.006 (0.9711-1.043)**	**0.7098 (0.6104-0.8254)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

Table 8. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for **metformin** in the fasted or fed state, n=16

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Fasted	**10900 ± 2630**	**1670 ± 473**	**2.03 1.00-4.00**
Fed	**11200 ± 2780**	**1360 ± 282**	**4.00 1.50-6.00**
***Ratio fed/fasted (90% CI)**	**1.038 (0.9500-1.134)**	**0.8289 (0.7281-0.9437)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

- ***Comparison of dapagliflozin PK 5 mg BID vs 10 mg QD***

Forxiga (dapagliflozin) should be administered once daily. Given that metformin is recommended to be administered twice daily, bid administration of Xigduo is proposed. A dedicated clinical study was performed in order to support the bid posology.

Study D1691C00004 was an open-label, randomized, two-period crossover study in 16 healthy volunteers to assess the effect of dapagliflozin dosed as 10 mg once a day versus 5 mg twice a

day. Each dose was administered for 5 days with a 7-10 days wash-out between. The study drugs were administered with a high carbohydrate meal (approximately 55% of the total calories) after an overnight fast.

Primary objective:

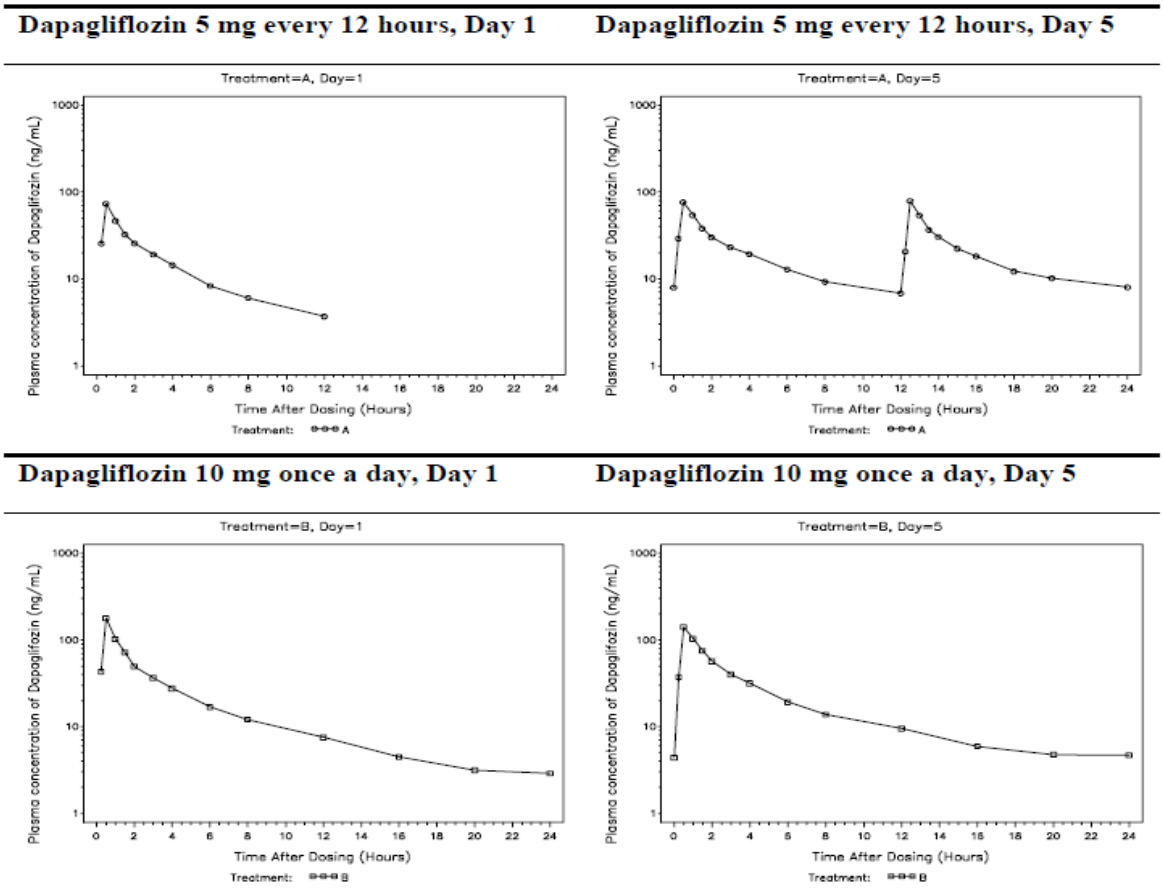
- To assess the effect of dapagliflozin on percent inhibition of renal glucose re-absorption (IRGRA (%)) when administered once a day versus twice daily.

Secondary objectives:

- To assess effect of dapagliflozin on urine glucose excretion when administered once a day versus twice daily.
- To examine the safety and tolerability of dapagliflozin dosed once a day versus twice daily
- To determine PK-parameters for dapagliflozin dosed once a day versus twice daily

Pharmacokinetic results:

Figure 1. Geometric mean **dapagliflozin** plasma concentrations (ng/mL) over time, linear-log scale – PK analysis set



Treatment A - 5 mg dapagliflozin administered every 12 hours for 5 days;
Treatment B - 10 mg dapagliflozin administered once a day for 5 days.

Table 9. Pharmacokinetic parameters for **dapagliflozin** administered as 5 mg twice daily or 10 mg once a day for five days, n=16

Treatment	$C_{ss,max}$ (ng/ml)	$C_{ss,min}$ (ng/ml)	$C_{ss,av}$ (ng/ml)	$AUC_{ss(0-24)}$ (ng*h/ml)
A: Dapagliflozin 5 mg every 12 h	**84.7 ± 31.1**	**7.15 ± 2.46**	**19.5 ± 4.96**	**474 ± 120**
B: Dapagliflozin 10 mg once a day	**181 ± 72.5**	**4.40 ± 1.57**	**20.3 ± 5.08**	**486 ± 122**
***Ratio (90% CI)**	**0.483 (0.425-0.548)**	**1.62 (1.47-1.79)**	**0.962 (0.931-0.994)**	**0.975 (0.949-1.00)**

AUC_{ss0-24} area under the plasma concentration-time curve from time zero to 24 hours
$C_{ss,max}$ maximum plasma concentration at steady state
$C_{ss,min}$ minimum plasma concentrations at steady state
$C_{ss,av}$ the average concentration at steady state

Distribution

Dapagliflozin

Dapagliflozin is approximately 91% protein bound. Protein binding was not altered in various disease states (e.g. renal or hepatic impairment). The mean steady-state volume of distribution of dapagliflozin was 118 L.

Metformin

Plasma protein binding is negligible. Metformin hydrochloride partitions into erythrocytes. The mean volume of distribution (Vd) ranged between 63-276 L.

Elimination

- **Excretion**

Dapagliflozin

Dapagliflozin and related metabolites are primarily eliminated via urinary excretion with less than 2% as unchanged dapagliflozin. After administration of a 50 mg [14C]-dapagliflozin dose, 96% was recovered, 75% in urine and 21% in faeces. In faeces, approximately 15% of the dose was excreted as parent drug. The mean plasma terminal half-life (t1/2) for dapagliflozin was 12.9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects.

Metformin

Metformin hydrochloride is excreted unchanged in the urine. No metabolites have been identified in humans.

Renal clearance of metformin hydrochloride is >400 ml/min, indicating that metformin hydrochloride is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

- **Metabolism**

Dapagliflozin

Dapagliflozin is extensively metabolised, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. The formation of dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme present in the liver and kidney, and CYP-mediated metabolism is a minor clearance pathway in humans.

Metformin

Metformin is not metabolised.

- **Inter-conversion**

Dapagliflozin

Dapagliflozin contains 5 defined stereocenters. No significant inter-conversion occurs *in vivo*.

Metformin

Metformin is not a chiral molecule.

- **Pharmacokinetics of metabolites**

No active metabolites of dapagliflozin or metformin have been identified.

Dose proportionality and time dependencies

Dapagliflozin

Dapagliflozin exposure increased proportional to the increment in dapagliflozin dose over the range of 0.1 to 500 mg. The pharmacokinetics of dapagliflozin did not change with time upon repeated daily dosing for up to 24 weeks.

Metformin

After oral administration, metformin hydrochloride absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin hydrochloride absorption is non-linear. No time dependency has been described.

Special populations

- **Impaired renal function**

Dapagliflozin

At steady-state, subjects with type 2 diabetes mellitus and mild, moderate or severe renal impairment had mean systemic exposures of dapagliflozin of 32%, 60% and 87% higher, respectively, than those of subjects with type 2 diabetes mellitus and normal renal function. The steady-state 24-hour urinary glucose excretion was highly dependent on renal function and 85, 52, 18 and 11 g of glucose/day was excreted by subjects with type 2 diabetes mellitus and

normal renal function or mild, moderate or severe renal impairment, respectively. The impact of hemodialysis on dapagliflozin exposure is not known. Since the efficacy of dapagliflozin is dependent on renal function, dapagliflozin is not recommended for use in patients with moderate to severe renal impairment.

Metformin

When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin hydrochloride in plasma. Metformin is contraindicated in patients with renal failure or renal dysfunction (creatinine clearance < 60 ml/min).

- **Impaired hepatic function**

Dapagliflozin

In subjects with mild or moderate hepatic impairment (Child-Pugh classes A and B), mean Cmax and AUC of dapagliflozin were up to 12% and 36% higher, respectively, compared to healthy matched control subjects. These differences were not considered to be clinically meaningful. In subjects with severe hepatic impairment (Child-Pugh class C) mean Cmax and AUC of dapagliflozin were 40% and 67% higher than matched healthy controls, respectively.

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.

Metformin

Metformin is contraindicated in patients with hepatic insufficiency due to the increased risk of lactic acidosis.

- **Elderly**

Dapagliflozin

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.

Metformin

In general, no dosage adjustment is recommended based on age. The risk of impaired renal function in the elderly should be taken into account.

- **Children**

Dapagliflozin

No data is available.

Metformin

After single doses of metformin hydrochloride 500 mg, paediatric patients have shown similar pharmacokinetic profile to that observed in healthy adults.

After repeated doses of 500 mg twice daily for 7 days in paediatric patients the peak plasma concentration (C_{max}) and systemic exposure (AUC_{0-t}) were reduced by approximately 33% and 40%, respectively compared to diabetic adults who received repeated doses of 500 mg twice daily for 14 days. As the dose is individually titrated based on glycaemic control, this is of limited clinical relevance.

Metformin can be used in children from the age of 10 years and in adolescents.

Pharmacokinetic interaction studies

Dapagliflozin/metformin

Study MB102026 (described in the initial dapagliflozin MAA) was an open-label, 3-period, 3-treatment, crossover study in 18 healthy fasted subjects randomized to receive single doses of 20 mg dapagliflozin, 1000 mg metformin and 20 mg dapagliflozin+1000 mg metformin. Dapagliflozin AUC and Cmax changed ≤7% and metformin AUC and Cmax ≤5% during co-administration.

Dapagliflozin

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. 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.

Metformin

The following interaction is included in the SmPC proposed by the applicant: Cationic substances that are eliminated by renal tubular secretion (e.g. cimetidine) may interact with metformin by competing for common renal tubular transport systems.

2.4.3. Pharmacodynamics

The pharmacodynamic properties as well as the mechanisms of action of active substances (dapagliflozin and metformin) have already been evaluated during the MAA for the respective mono-component.

Mechanism of action

Dapagliflozin inhibits the human renal sodium-dependent glucose co-transporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption. It is a highly potent (Ki = 0.55 nM), selective and reversible inhibitor of human SGLT2, which it inhibits selectively versus human

SGLT1, the major glucose transporter responsible for the absorption of glucose in the small intestine, and is also highly selective versus facilitative glucose transporters.

Dapagliflozin's mechanism of action is different from and complementary to currently available treatment options, and results in the direct and insulin-independent elimination of glucose by the kidney. Thus dapagliflozin lowers plasma glucose by inhibiting the renal reabsorption of glucose, and by promoting its urinary excretion. Glucosuria, the result of the inhibition of glucose reabsorption, is the primary pharmacodynamic effect of the drug, and results in a lowering of fasting plasma glucose (FPG) concentrations within one week; improved glycaemic control as measured by a reduction in haemoglobin A1c (HbA1c), FPG and postprandial glucose (PPG); and the urinary loss of approximately 280 kcalories/day, which ultimately leads to a decrease in weight and body fat.

In addition, the diuretic effect is also associated with modest blood pressure reductions. Furthermore, dapagliflozin is associated with a low risk of hypoglycaemia.

Metformin hydrochloride (metformin), a biguanide, is a well-characterised medicine that has been in widespread use for decades. Metformin lowers HbA1c, FPG and PPG concentrations in patients with T2DM, improving glycaemic control by reducing hepatic glucose production, decreasing intestinal absorption of glucose, and improving insulin sensitivity by increasing peripheral glucose uptake and utilisation.

Primary and Secondary pharmacology

Specifically for the fixed dose combination programme, an additional study (**D1691C00004**) was conducted to characterise the pharmacokinetics and pharmacodynamics to provide support for dosing with dapagliflozin 5 mg BID.

In this open-label, randomised, 2-period crossover, single-centre study the PD effects of dapagliflozin 10 mg QD versus 5 mg BID (every 12 hours) administered for 5 days were investigated. Both treatments were administered after a standard meal and each dosing period was separated by a 7- to10-day washout. The primary objective of the study was to compare the effects of the 2 dapagliflozin regimens on the percent inhibition of renal glucose re-absorption (IRGRA) at steady state (Day 5). This was calculated as the amount of glucose excreted in the urine (Uglu) divided by the amount of glucose filtered by the kidney during a collection interval.

At steady state, the IRGRA demonstrated no significant difference between the BID and QD dosing regimens (24-hour percent IRGRA = 34.4% vs 32.2%; ratio = 1.07 [90% CI: 0.95, 1.21]).

An exploratory objective was to determine whether dapagliflozin reduces the rate of absorption of a meal. The glucose and insulin responses after breakfast, lunch and dinner were determined by measurement of the area under the time-effect curves of the plasma levels of glucose and insulin over 180 minutes after the meal [AUE(0-180)]. The AUE(0-180) for meal-induced increases in glucose levels demonstrated no significant differences between the treatments. For insulin, there were no differences after breakfast or dinner but insulin levels were slightly lower with the BID regimen after lunch compared with the QD regimen of dapagliflozin [AUE(0-180) ratio = 0.84; 90% CI: 0.76, 0.93].

In study D1691C00004, the exposure-response relationship was explored by a non-linear maximum effect (Emax) regression model. Evaluated pharmacodynamic endpoints were percent inhibition of renal glucose re-absorption [IRGRA(%)] and the amount of glucose excreted over 24-hours. The analysis included the average dapagliflozin exposure in 4-hour intervals at steady state for both QD (6 points) and BID (3 points) administration. The analysis yielded an EC50 of 14.72 ng/mL and an Emax of 73.95% for IRGRA. For the average amount of glucose in urine per 24-hour interval the EC50 was 15.19 ng/mL and Emax of 100 mmol.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The results of the bioequivalence study (**D1691C00002**) show that for AUC0-t and Cmax the 90% confidence interval for the ratio of the test and reference products falls within the conventional acceptance range of 80.00-125.00% for both dapagliflozin and metformin. Based on the provided results the CHMP considers that the bioequivalence between Xigduo FDC and dapagliflozin and metformin administered as mono-components has been demonstrated, in an adequately designed bioequivalence study. This is crucial in order to support the substitution indication as well as bridging from the monotherapy tablets used in the clinical studies. The study was conducted under fed conditions, after administration of a low/medium-fat meal. In general bioequivalence studies under fed conditions should be performed with a high-fat meal to reflect a worst-case scenario. The effect of food on metformin and dapagliflozin is small. The effect of food on the FDC-tablet has also been evaluated in study D1691C00005. In this study the food-effect was roughly similar to what has previously been described for respective mono-component. Hence, it is unlikely that an additional bioequivalence study with a high-fat meal will provide any further contribution to the bioequivalence evaluation.

In the present dossier the applicant is seeking approval for 5 mg / 1000 mg and 5 mg / 850 mg strengths. Bioequivalence has been evaluated for the 5 mg/1000 mg and the 2.5 mg/850 mg (not applied for) strengths. Taking into consideration that the most extreme strengths (2.5 mg/850 mg and 5 mg/1000 mg) were evaluated in the bioequivalence study and all quality aspects of a biowaiver are fulfilled (see section 2.2.3 of this report for further details) so that the strengths can be considered “formulation proportional”, the CHMP considers that a biowaiver for the strength of 5 mg/850 mg can be granted based on a bracketing approach.

The effect of food on Xigduo FDC has been sufficiently evaluated (study **D1691C00005**). Administration of the FDC with a high-fat meal had no effect on AUC for neither of the active substances. For dapagliflozin there was a 29% decrease in Cmax and tmax was delayed with 1h and for metformin there was a 17% decrease in Cmax and tmax was delayed with 2h after administration with food. These finding were similar as previously reported for dapagliflozin. For metformin, a slightly larger food effect regarding both AUC and Cmax (25 and 40% decrease respectively) has previously been described. This discrepancy is considered to be of minor importance. Therefore the CHMP considers that the food-effect was roughly similar as previously reported for the mono-components. Taking into consideration that metformin is recommended to be administered with a meal to avoid gastro-intestinal adverse events the CHMP endorses the applicant’s proposal to have the same recommendations for Xigduo.

Study **D1691C00004** showed that there were no significant difference in AUCss0-24 or Css,av when dapagliflozin was administered as an oral 5 mg dose twice daily compared to a single daily dose of 10 mg. As expected, Css,max was lower and Css,min higher after administration of the lower dose twice daily. Similar exposure after administration of dapagliflozin 5 mg bid and 10 mg qd supports the proposed twice daily administration of Xigduo.

In all studies supporting the clinical pharmacology package, dapagliflozin and metformin concentrations were analysed using sufficiently validated LC/MS/MS methods.

The CHMP considers that the lack of PK-interaction between dapagliflozin and metformin has been sufficiently demonstrated and the pharmacokinetics of the new fixed dose combination (FDC) tablet has been studied to a sufficient extent.

Pharmacodynamics

With the current application only one study investigating the PD profile of the fixed dose combination has been provided. This is acceptable considering that both components in the combination are approved and well characterised. Data to support the mechanism of action of dapagliflozin was provided and assessed as part of the MAA for dapagliflozin. The mechanism of action for metformin is not entirely elucidated, but the compound is established in the treatment of diabetes. The complementary mechanisms of action for the two drugs form an adequate scientific basis for the fixed dose combination.

Study **D1691C00004** was performed in order to provide data in support of the 5 mg BID dosing of dapagliflozin since dapagliflozin as mono-component is dosed once daily. The PD parameters chosen are considered adequate for the purpose of the study and the study was well designed. The glucose excretion, adjusted for renal function (IRGRA), did not differ significantly between treatments. In addition, the effect of dapagliflozin on gastrointestinal glucose absorption was explored. No difference was observed between treatments. These findings support the proposed twice daily administration of Xigduo.

No data on secondary pharmacological effects of the combination with dapagliflozin of metformin has been provided with the current application. This is found acceptable by the CHMP since the PD effects of both compounds have been well described and the relevant findings documented in the SmPCs of the mono-components.

The relationship between the mean average exposure of dapagliflozin over 4-hours and the pharmacodynamic endpoints IRGRA and amount of glucose excreted over 24-hours was described by an Emax model. Based on this model, the 10 mg QD and 5 mg BID dose is expected to result in about 71% and 75 %, respectively of the maximum effect of dapagliflozin on 24 h urinary glucose excretion in healthy volunteers. For the endpoint IRGRA 54% and 56%, respectively, of the maximum effect is expected. These findings suggest that the two different administration schedules are expected to translate into a similar effect of dapagliflozin.

No new data concerning PD interactions has been provided for the fixed dose combination. The interaction with diuretics for dapagliflozin is adequately described in the SmPC of Forxiga. The interaction between metformin and diuretics is included in the European CSP for metformin “Diuretics especially loop diuretics, may increase the risk of lactic acidosis due to their potential

to decrease renal function." Therefore, at the CHMP request, the applicant updated Xigduo SmPC in accordance with metformin CSP.

2.4.5. Conclusions on clinical pharmacology

Bioequivalence between Xigduo FDC and dapagliflozin and metformin administered has mono-components has been demonstrated which is crucial in order to support the substitution indication and also to bridge from the monotherapy tablets used in the clinical studies.

The effect of food on Xigduo FDC has been sufficiently evaluated to support the proposed dosage recommendations. Similar exposure after administration of dapagliflozin 5 mg bid and 10 mg qd supports the proposed twice daily administration of Xigduo.

The CHMP considers that the lack of PK-interaction between dapagliflozin and metformin has been sufficiently demonstrated and the pharmacokinetics of the new fixed dose combination (FDC) tablet has been studied to a sufficient extent.

The PD data provided within the current application is deemed sufficient to support that there are no relevant differences in the PD profile with 5 mg BID dosing of dapagliflozin compared to 10 mg QD.

2.5. Clinical efficacy

An overview of the phase III clinical studies submitted in support of the FDC application is presented below.

- **Tabular overview of dapagliflozin phase III studies in subjects with type 2 diabetes included in FDC submission**

Study description/ Current status	Subject population	N per group/ N treated with dapagliflozin/ Total	Duration	Treatment groups/ Background therapy	Rescue treatment	Primary efficacy assessment
Placebo-controlled add-on to metformin studies						
D1691C00003 BID add-on to metformin vs placebo/ Completed	Subjects on metformin ≥ 1500 mg/day with HbA1c ≥ 6.5% - ≤ 10.0%	99 - 101/ 299/400	16 weeks	4 groups: dapagliflozin 2.5 mg BID, 5 mg BID, or 10 mg QD or placebo Background therapy: metformin ≥ 1500 mg/day	None	Superiority: change in HbA1c in the dapagliflozin 2.5 mg BID and 5 mg BID treatment groups at 16 weeks vs placebo
MB102014 Add-on to metformin vs placebo/ ST Completed/ LT Completed	Subjects on metformin ≥ 1500 mg/day with HbA1c ≥ 7.0% - ≤ 10.0%	135 - 137/ 409/546 (ST)	24 weeks + 78 weeks	4 groups: dapagliflozin 2.5 mg, 5 mg, or 10 mg or placebo Background therapy: metformin ≥ 1500 mg/day	Pioglitazone or acarbose	Superiority: change in HbA1c at 24 weeks vs placebo
D1690C00012 Add-on to metformin vs placebo/ ST Completed/ LT1 26 weeks Completed/ LT2 52 weeks Completed[a]	Subjects on metformin ≥ 1500 mg/day with HbA1c ≥ 6.5% - ≤ 8.5%	91/ 91/182 (ST)	24 weeks + 26 weeks + 52 weeks	2 groups: dapagliflozin 10 mg or placebo Background therapy: metformin ≥ 1500 mg/day	Sitagliptin	Superiority: change in total body weight at 24 weeks vs placebo

Active comparator study						
D1690C00004 Add-on to metformin vs active comparator (glipizide)/ ST Completed/ LT1 52 weeks Completed/ LT2 104 weeks Ongoing[b]	Subjects on metformin ≥ 1500 mg/day with HbA1c > 6.5% - ≤ 10.0%	406 - 408/ 406/814 (ST)	52 weeks + 52 weeks + 104 weeks	2 groups: dapagliflozin titrated dose of 2.5 mg, 5 mg, or 10 mg or glipizide titrated dose of 5 mg, 10 mg, or 20 mg Background therapy: metformin ≥ 1500 mg/day	DPP-4 inhibitor or insulin (LT2 104-week extension period only)	Noninferiority: change in HbA1c at 52 weeks vs glipizide
Placebo-controlled combination therapy studies						
D1690C00010 Add-on to sitagliptin vs placebo/ ST Completed/ LT Completed	Drug-naïve subjects, subjects on metformin ≥ 1500 mg/day or subjects on sitagliptin (100 mg/day) or vildagliptin (50 mg BID) alone or with metformin > 1500 mg/day with HbA1c ≥ 7.0% - ≤ 10.0%	225 - 226/ 225/451 (ST)	24 weeks + 24 weeks	2 groups: dapagliflozin 10 mg or placebo 2 strata: dapagliflozin + sitagliptin monotherapy and dapagliflozin + sitagliptin plus metformin Background therapy: sitagliptin 100 mg/day ± metformin ≥ 1500 mg/day	Glimepiride uptitration	Superiority: change in HbA1c at 24 weeks vs placebo
D1690C00006 Add-on to insulin vs placebo/ ST Completed/ LT1 24 weeks Completed/ LT2 56 weeks Completed	Subjects on insulin ≥ 30 IU/day ± maximum 2 OADs with HbA1c ≥ 7.5% - ≤ 10.5%	196 - 212/ 610/807 (ST)	24 weeks + 24 weeks + 56 weeks	4 groups: dapagliflozin 2.5 mg, 5 mg, or 10 mg or placebo Background therapy: insulin ≥ 30 IU/day ± maximum 2 OADs In LT, forced titration of dapagliflozin 5 mg to 10 mg	Insulin uptitration	Superiority: change in HbA1c at 24 weeks vs placebo

[a] *The data from the short-term and long-term 1 extension period (ST + LT1; 50 weeks) from study D1690C00012 is included in this application; although the second long-term period (LT2; 102 weeks) has completed, data was not available at the cut-off date for this submission (24 November 2011)*
[b] *The second long-term treatment period (LT2; 208 weeks) from study D1690C00004 was not yet complete at the time of submission; short-term and long-term period 1 (ST + LT1 data; 104 weeks) is included in the application*
BID Twice daily; DPP-4 Dipeptidyl peptidase-4; HbA1c Haemoglobin A1c; IU International unit; LT Long-term; LT1 Long-term 1 extension period; LT2 Long-term 2 extension period; OADs Oral anti-diabetic drugs; QD Once a day; ST Short-term; ST + LT1 Short-term plus long-term 1 extension period; vs Versus

2.5.1. Dose response studies

Efficacy has been demonstrated for dapagliflozin monotherapy, as assessed by improvements in HbA1c, weight loss and moderate lowering of blood pressure, in the clinical development programme that supported the initial dapagliflozin MAA (Forxiga). No dose finding studies were performed for the present FDC application since the doses applied for are covered by the already approved posology of Forxiga.

2.5.2. Main studies

The clinical programme supporting this submission consisted of six Phase III randomised, controlled, double-blind clinical studies, aimed to provide the following evidence to support efficacy:

- Dapagliflozin 5 mg BID as add-on therapy to metformin has glucose lowering efficacy (D1691C00003).
- Dapagliflozin 5 mg BID has consistent efficacy with dapagliflozin 10 mg QD, both coadministered with metformin BID (D1691C00003).
- Sustained effects during long-term administration of dapagliflozin and metformin (MB102014, D1690C00012).
- Noninferior efficacy of dapagliflozin 10 mg add-on to metformin versus a sulphonylurea plus metformin (D1690C00004).

- Evidence that dapagliflozin improves glycaemic efficacy in subjects not adequately controlled on a dipeptidyl peptidase-4 (DPP-4) inhibitor plus metformin (D1690C00010), or insulin plus metformin (with or without an additional OAD) (D1690C00006).

Study D1691C00003 is considered the key study supporting this application. Studies MB102014, D1690C00012, D1690C00006 and D1690C00004 were included in the original MAA for dapagliflozin. Additional long-term data from studies D1690C00012, D1690C00006 and D1690C00004 are included in the current submission. Study D1690C00010 investigates the use of dapagliflozin in combination with sitagliptin and includes a stratum with patients on metformin in combination with sitagliptin, relevant to this submission.

Based upon the similar pharmacodynamic and pharmacokinetic characteristics of dapagliflozin, when administered as 5 mg BID or 10 mg QD (study D1691C00004), the expectation was that dapagliflozin administered twice daily would have consistent efficacy to once daily administration.

Across the studies included in this submission, the range of metformin doses allowed was 1500 mg/day to 3000 mg/day. The mean dose of open label metformin ranged from 1800 mg/day to 2000 mg/day across all treatment groups, which conforms closely to the daily metformin doses of the different formulations of the FDC product.

As the study design was similar across the study program, the main methodological features are presented in the following.

Methods

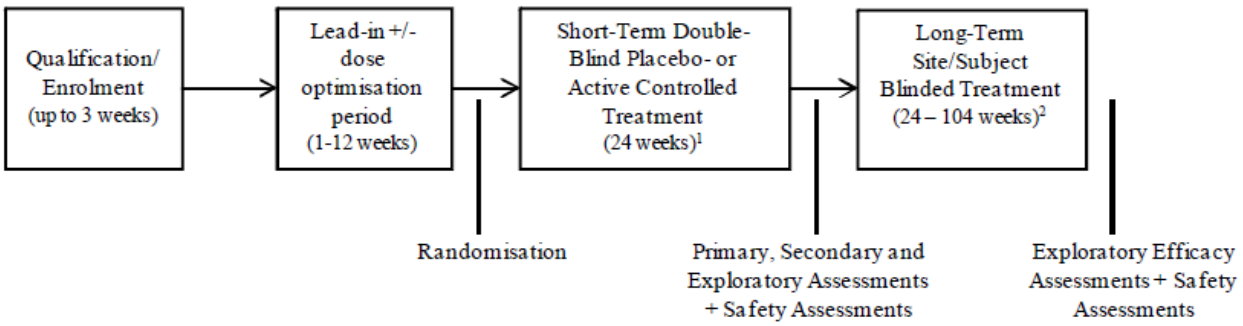
Study design

All studies included a qualification/enrolment phase of up to 3 weeks, followed in some studies by a dose optimisation period in which background medications were added or stabilised. A placebo lead-in period that usually lasted 2 weeks was included in all of the studies with the exception of the combination with insulin study (D1690C00006). During the placebo lead-in period, subjects were given diet and lifestyle instruction according to local practices, and adherence to placebo was assessed.

The studies included a short-term double-blind treatment period of 24 weeks, with the exception of studies D1691C00003 (BID add-on to metformin therapy) and D1690C00004 (active comparator study), which had ST periods of 16 weeks and 52 weeks, respectively. The primary endpoint was analysed at the end of the ST period.

In all the studies (with the exception of D1691C00003), the ST treatment period was followed by LT extension treatment periods of at least 24 weeks duration. Placebo-treated subjects entering the LT extension treatment periods continued treatment with placebo.

- **Study design overview of dapagliflozin studies**



[1] Study D1691C00003 had a 16-week short-term treatment period; study D1690C00004 had a 52-week short-term treatment period
[2] Study D1691C00003 did not include a long-term treatment period

Rescue therapy

In all studies, subjects who failed to meet pre-specified glycaemic targets (which became more stringent as the trials progressed) received rescue medication or were discontinued. In studies D1691C00003 (BID add-on to metformin study) and D1690C00004 (active comparator study), there was no rescue medication; in both studies, subjects with lack of glycaemic control based on FPG or HbA1c criteria were discontinued from the study. In study D1690C00006, the add-on to insulin study, insulin was uptitrated according to prespecified criteria in lieu of oral rescue therapy.

Study Participants

Males and females ≥ 18 years of age were eligible, and an upper age limit was imposed necessitated by the concomitant use of metformin. Similarly, subjects with mild to moderate renal impairment were included in the Phase 3 studies, but subjects with significant renal impairment were excluded in accordance with metformin labelling. Subjects with hepatic impairment or unstable cardiovascular (CV) disease, including Class III and IV heart failure, were also excluded from these studies. Phase 3 studies generally did not exclude subjects at advanced stages of T2DM, such as those with chronic complications of T2DM (retinopathy, neuropathy, mild nephropathy, or chronic CV disease).

Eligibility criteria for the Phase 3 studies were selected to include inadequately controlled T2DM patients with a wide range of baseline HbA1c values. The lower threshold of the HbA1c inclusion criterion was ≥ 7.0% in 2 studies (MB102014, D1690C00010). Studies D1691C00003, D1690C00004 and D1690C00012 had a lower HbA1c threshold of ≥ 6.5%. HbA1c entry criteria were lower (≥ 6.5% to ≤ 8.5%) in study D1690C00012 in order to minimise the need for potentially confounding rescue therapy during the 2-year treatment period so that the effects on weight loss (primary endpoint) could be analysed. In D1690C00006, the combination study with insulin, the lower boundary of HbA1c that defined inclusion was ≥ 7.5% due to the increased risk of hypoglycaemia in this population. In all the studies, the upper boundary of HbA1c that defined inclusion generally ranged between ≤ 10.0% and ≤ 10.5%.

Treatments

In study D1691C00003, 2.5 mg and 5 mg doses of dapagliflozin were administered BID and a 10 mg dose of dapagliflozin was administered QD.

The dapagliflozin doses of 2.5 mg, 5 mg, and 10 mg were administered as once daily doses in studies MB102014 and D1690C00006. At the start of the 56-week long-term 2 (LT2) extension period of study D1690C00006, a prespecified switch of dapagliflozin 5 mg to 10 mg (dapagliflozin 5/10 mg) was incorporated to evaluate the efficacy and safety of dapagliflozin 2.5 mg, 5/10 mg, and 10 mg.

Study D1690C00004, the active comparator study, used a dose titration procedure (dapagliflozin 2.5 mg → 5 mg → 10 mg) to match the gradual uptitration recommended for the active comparator, glipizide.

Studies D1690C00012 and D1690C00010 included only the 10 mg dapagliflozin dose.

Control groups

The selection of control study medication was based on the study objectives. For control groups in the studies designed to demonstrate efficacy and safety of dapagliflozin as add-on combination therapy, placebo plus on-going background oral antidiabetic therapy was administered in accordance with local country requirements and was an accepted standard of clinical care.

In study D1690C00004, dapagliflozin was compared to an active comparator, glipizide, on a background of metformin IR therapy.

Background therapy

Metformin IR was the background therapy used for the add-on studies D1691C00003, MB102014, D1690C00012, D1690C00004, and for Stratum 2 in study D1690C00010.

In study D1690C00006, the background therapy used was insulin with a maximum of 2 OADs. Subjects on metformin therapy (either metformin IR or metformin extended release [XR]) were on at least 1500 mg/day or at the maximum tolerable dose for at least 8 weeks prior to enrolment. Subjects on other OAD medication were on at least half the maximum daily recommended dose for at least 8 weeks prior to enrolment.

Objectives

- **Add-on to metformin versus placebo studies**

Study D1691C00003

This was a 16-week, multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel group, Phase III trial to evaluate the safety and efficacy of dapagliflozin 2.5 mg BID, 5 mg BID, and 10 mg QD versus placebo in combination with metformin in subjects with T2DM who were inadequately controlled on metformin-IR monotherapy.

The primary objective was to compare the change from baseline in HbA1c after 16 weeks of double-blind therapy, achieved with each of the 2 BID doses of dapagliflozin (2.5 mg BID and 5

mg BID) co-administered with metformin versus placebo plus metformin. In one of the treatment groups, 10 mg dapagliflozin QD was co-administered with metformin as a measure of assay sensitivity. Efficacy and safety in the 10 mg QD dapagliflozin with metformin treatment group were compared only to placebo plus with metformin. No comparison was made between 10 mg QD dapagliflozin versus the BID doses of dapagliflozin.

Study MB102014

This was a multicentre, randomised, double-blind, placebo-controlled, parallel group, Phase 3 trial to evaluate the safety and efficacy of 3 different doses of dapagliflozin (2.5 mg, 5 mg, and 10 mg) in combination with metformin in subjects with T2DM who have inadequate glycaemic control on metformin alone. The exploratory efficacy objectives were to assess the glycaemic parameters, for each dose of dapagliflozin, in the long-term treatment period. To characterize the distributions of change from baseline in haemoglobin A1c (HbA1c), fasting plasma glucose (FPG), and body weight for each treatment group.

The safety objective was to assess the safety and tolerability of each dose of dapagliflozin plus metformin after up to 102 weeks of oral administration of either double-blind or site- and subject-blinded treatment.

Study D1690C00012

This was an international, multicentre, randomised, double-blind, placebo-controlled, parallel-group Phase 3 study with a 24-week short-term treatment period followed by a 78-week extension period 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.

- **Active comparator study**

Study D1690C00004

This was an international, multicentre, randomised, parallel-group, double-blind, active-controlled, Phase 3 study with a 52-week short-term treatment period followed by a 52-week extension period 1 (LT1) and a 104-week extension period 2 (LT2) to evaluate the efficacy and safety of dapagliflozin as add-on therapy to metformin compared with glipizide (a sulphonylurea) plus metformin in adult subjects with T2DM who have inadequate glycaemic control (HbA1c > 6.5% and ≤ 10.0%) on metformin therapy alone with 1500 mg/day or more. The primary objective was to examine whether the absolute change from baseline in HbA1c with dapagliflozin plus metformin was non-inferior to glipizide plus metformin after 52 weeks of double-blind treatment. Key secondary objectives were weight loss and hypoglycaemic events.

- **Combination therapy studies**

Study D1690C00010

This was a 24-week, multicentre, randomised, double-blind, placebo-controlled, parallel-group, international Phase 3 study with a 24-week extension period to evaluate the safety and efficacy of dapagliflozin 10 mg daily in subjects with T2DM who had inadequate glycaemic control on a DPP-4 inhibitor (sitagliptin) alone or in combination with metformin.

Subjects were stratified according to their use of metformin. Primary objective for the 24-week ST treatment period was the change from baseline in HbA1c.

Study D1690C00006

This was a 24-week international, randomised, parallel-group, double-blind, placebo-controlled Phase 3 study with an 80-week extension period to evaluate the efficacy and safety of dapagliflozin therapy when added to the therapy of subjects with T2DM with inadequate glycaemic control (HbA1c ≥ 7.5% and ≤ 10.5%) on ≥ 30 IU insulin. The primary objective was to assess the efficacy of dapagliflozin 2.5 mg, 5 mg, and 10 mg compared to placebo as add-on therapy to insulin in improving glycaemic control in terms of the change in HbA1c from baseline to Week 24.

Outcomes/endpoints

HbA1c was the primary efficacy variable for five of the six Phase III studies included in this submission, and was analysed at 24 weeks in three studies; at 16 weeks in D1691C00003; and at 52 weeks in D1690C00004. Change from baseline body weight at 24 weeks was the primary efficacy variable in D1690C00012.

Secondary efficacy endpoints included change in FPG; proportion of subjects achieving a therapeutic response of HbA1c < 7.0%; reduction in blood pressure; and change from baseline body weight. Secondary endpoints in D1690C00012 evaluated additional variables relating to weight, while change in HbA1c was assessed as an exploratory endpoint.

Sample size

Study D1691C00003

The sample size for this study was selected to demonstrate a difference in the mean change in HbA1c from baseline to week 16 between one of the dapagliflozin treatment groups (2.5 mg BID and/or 5 mg BID) versus placebo co-administered with metformin. A review of variability estimates from BMS studies MB102013 and MB102014 suggested that the standard deviation (SD) associated with change in HbA1c from baseline to week 16 using LOCF was not more than 0.97%. Since the overall Type I error had to be controlled for the two treatment comparisons using a Hochberg procedure, sample size estimation was based on the conservative assumption that one dose comparison could not reach statistical significance. In this situation, in order to detect a 0.5% difference in mean change from baseline in HbA1c between one of the dapagliflozin treatment groups (2.5 mg BID and/or 5 mg BID) versus placebo using a 2-sample t-test at a 0.025, two-sided significance level with 90% power, 95 evaluable subjects were

required per treatment group in the Full Analysis Set. If one assumed 3% of the subjects did not have a baseline and post-baseline efficacy measurement, 98 subjects per group (392 total subjects) were needed to be randomized.

Further, if 40% of subjects failed to meet entry criteria for randomization (as seen in study MB102014), then approximately 654 subjects had to be enrolled.

Study D1690C00012

The sample size for this study was selected to demonstrate a difference in the mean change in body weight from baseline to week 24 between dapagliflozin in combination with metformin to metformin monotherapy (placebo as add-on therapy to metformin). An earlier study, MB102008, provided 12-week data for changes in body weight. The average, placebo corrected change in weight for the 10 mg dapagliflozin group was 1.3 kg at 12 weeks, and the SD across the dapagliflozin doses was 2.6 kg. It is anticipated that data over 24 weeks will demonstrate a greater weight reduction, 2 kg, as well as greater variability. Assuming an approximately 50% increase in variability, a SD of 4.0 kg is selected for this calculation. To detect a difference of 2 kg between the treatment groups, 86 evaluable subjects per treatment group are required for 90% power at a two-sided significance level of 0.050. Assuming that 5% of the randomized subjects will be excluded from the primary analysis because of missing data (eg, lost to follow-up), at least 182 subjects total need to be randomized.

Study D1690C00006

Each pairwise treatment group comparison will 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 are needed in each treatment group to provide 90% power. Assuming that 5% of the subjects will not be evaluable in the full analysis set, 161 subjects per treatment group (644 subjects total) are planned for randomization.

Study D1690C00004

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 per-protocol patients are needed in each treatment group to provide approximately 90% power (given a true difference of zero between the 2 treatment groups). Assuming a 25% exclusion rate from the per-protocol population, 373 patients per treatment group (746 patients total) are planned for randomisation.

Study D1690C00010

The sample size for this study was selected to demonstrate a difference in the mean change in HbA1c from baseline to week 24 between dapagliflozin and placebo within each of the two strata: patients on background therapy of sitagliptin monotherapy and patients on background therapy of sitagliptin plus metformin. To detect a difference of 0.5% between dapagliflozin versus placebo for change in HbA1c from baseline to week 24, assuming a standard deviation (SD) =1.1%, 103 evaluable patients (full analysis set) for each treatment group within each stratum would provide

>99% power for the analysis of the two strata combined at a significance level =0.050 or 90% power for the analysis of each stratum separately at a significance level =0.050. Assuming that 5% of the patients will not be evaluable in the full analysis set, 108 patients per treatment group within each stratum (432 patients total) are planned for randomisation.

In 6-month dapagliflozin studies, a SD of 1.1% was selected based upon the Phase II dapagliflozin study as well as historical data from other diabetes programs.

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.

Randomisation

All six studies were randomized studies. Following the assessment of the inclusion/ exclusion criteria the subjects meeting the eligibility criteria were randomized to study treatment via an Interactive Web Response System (IWRS). In study D1691C00003 the subjects were stratified by HbA1c at randomisation (Stratum 1, Stratum 2) and in study D1690C00012 by gender. The randomization for each stratum was done within balanced blocks to ensure approximately equal numbers of subjects across the treatment groups within each stratum (when applicable). The IWRS allocated a randomisation code according to a pre-defined randomisation scheme.

Blinding (masking)

All investigational products (dapagliflozin 2.5 mg, 5 mg and matching dapagliflozin 2,5 / 5 mg placebo as well as dapagliflozin 10 mg and matching dapagliflozin 10 mg placebo) were identical in appearance, smell and taste. The dapagliflozin 2.5 mg and 5 mg tablets and the matching placebo were identical in size, whereas dapagliflozin 10 mg tablets and matching placebo were slightly larger. They were also packaged into identical bottles.

Until the completion of the ST of the randomised period, the sponsor, the subjects, the investigators, the study monitors and any CRO handling data did not have access to the randomisation scheme, with the exception of the IWRS company, the CRO designated to pack the investigational products and the drug safety department at Bristol-Myers Squibb and AstraZeneca.

During the LT extension period, investigators, subjects, and study monitors continued to be blinded until completion of the extension phase without any knowledge of the treatment codes, except for cases of medical emergencies.

Statistical methods

Analysis of Covariance (ANCOVA) was used to analyse 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 (D1691C00003 being the exception). In D1691C00003, the Hochberg procedure was used to control the overall Type I error in the groups (2.5 mg BID and 5 mg BID) comparisons versus placebo for the primary efficacy variable.

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.

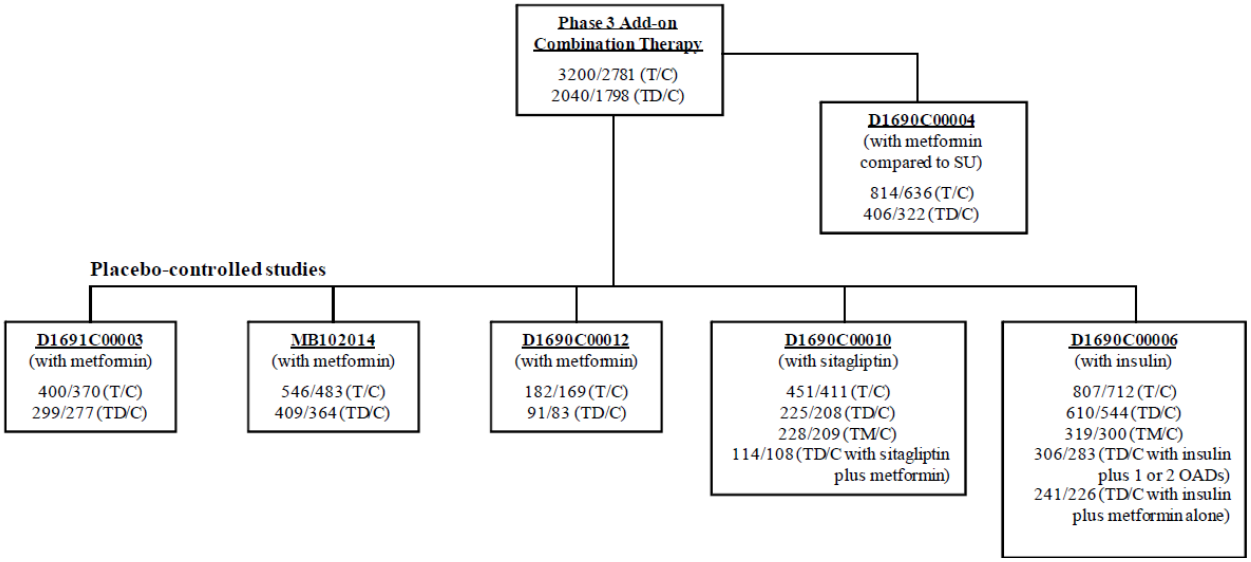
Missing HbA1c data from the ST period were handled in main analyses using LOCF (last observation carried forward) methodology, excluding data obtained after rescue therapy (except D1690C00004 and D1691C00003 where no rescue therapy was used and D1690C00012 where the primary efficacy variable was weight change). Robustness of study conclusions was evaluated with respect to the primary endpoint through sensitivity analyses by (i) including versus excluding data after rescue therapy, (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 ST period of studies were based on LOCF values while exploratory analyses from the ST plus LT periods were based on observed values.

For D1690C00006, a post-hoc analysis of the primary and key secondary endpoints for ST and ST plus LT periods was performed on subjects from stratum 2 who took dapagliflozin or placebo in combination with insulin plus the OAD of metformin alone. The methodology was similar to that described in the study D1690C00006 ST and LT Statistical Analysis Plans (SAPs), with the exception that strata as a fixed effect was removed from the ANCOVA and logistic regression models.

Long-term efficacy and safety of dapagliflozin was evaluated over the entire duration of the ST combined with the LT treatment period (and extension period if applicable). No p-values were calculated for LT 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.

Results

- **Summary of subject disposition in dapagliflozin combination studies including metformin**



T: treated; C: completed; TD: treated with dapagliflozin; TM: treated with metformin; CSR: Clinical study report; CTD: Common technical document; OADs: Oral antidiabetic drugs; SU: Sulphonylurea

Baseline data

The six Phase III studies enrolled a wide range of subjects, and the demographic and baseline characteristics were representative of T2DM patients with inadequate glycaemic control in real world practice. Across these studies, the mean age ranged from 52.7 years to 60.8 years, and 22.8% subjects were ≥ 65 years of age. The proportion of males (51.7%) was similar to the proportion of females (48.3%).

The regions of Europe (59.0%; D1691C00003, D1690C00012, D1690C00004, D1690C00010 and D1690C00006); Latin America (23.4%; MB102014, D1690C00004 and D1690C00010); and North America (15.2%; MB102014, D1690C00010 and D1690C00006); and South Africa (2.4%; D1691C00003) were well represented across the six Phase 3 studies. The majority of subjects across the studies were White (86%), with 4% each of Black/African American and Asian subjects. Hispanic/Latino ethnicity was reported for 16% of the subjects. Although some regions and races were less well represented, the effects of dapagliflozin are expected to be applicable to all regional populations as available data suggest that SGLT2 polymorphisms while apparent, are infrequent across racial and ethnic groups, and are not known to alter the pharmacodynamic action of dapagliflozin.

While subjects ≥ 65 years were well represented in these studies, there were relatively few subjects ≥ 75 years old (2%; 67 subjects). The Forxiga SmPC does not recommend initiation of therapy in patients aged ≥ 75 years.

The duration of T2DM was generally similar across the studies (range of means: 4.80 years to 6.55 years), except for D1690C00006 where duration of T2DM for the overall study population was longer (range of means: 13.13 years to 14.15 years).

Across the studies, the range of mean baseline HbA1c was 7.16% to 8.16%, and the range of mean baseline FPG was 148.0 mg/dL to 169.3 mg/dL [8.21 mmol/L to 9.40 mmol/L]. D1690C00006 had higher baseline HbA1c (~8.5%) and FPG levels (range of means: 170.6 mg/dL to 185.4 mg/dL [9.47 mmol/L to 10.29 mmol/L]) for the overall study population because of the higher HbA1c inclusion threshold (≥ 7.5%). The range of mean BMI (body mass index) was 31.22 kg/m2 to 33.41 kg/m2, representative of the T2DM population.

The Phase III studies included subjects with mild or moderate renal impairment (baseline estimated glomerular filtration rate (eGFR) of ≥ 60 to < 90 mL/min/1.73 m2 and ≥ 30 to < 60 mL/min/1.73 m2, respectively). There was a variation in exclusion criteria for renal impairment across the dapagliflozin studies, and eligibility was usually determined before the baseline visit. The small percentage of subjects with baseline values indicating moderate renal impairment did not constitute violations to the study inclusion criteria.

Numbers analysed

In general, discontinuation rates were low (5-10 %) in the short-term parts of the studies where rescue therapy was allowed with no gross differences observed between actively treated groups and placebo. Discontinuation rates were higher in the active comparator study (23 % for SU and 21 % for dapagliflozin) as no rescue medication was allowed. In studies where rescue therapy was applied, rescue rates were higher in the placebo treated groups.

Outcomes and estimation

- **Add-on to metformin versus placebo studies**

Table below summarises the outcome of the primary endpoint (HbA1c) and one of the secondary endpoints (body weight) across the add-on to metformin versus placebo studies.

Table 10. Summary of HbA1c (%) and body weight (kg) results in placebo-controlled dapagliflozin add-on to metformin studies up to 24 weeks (LOCF)

	Add-on to metformin versus placebo studies						
		D1691C00003[a] BID Metformin		MB102014 Metformin		D1690C00012 Metformin	
Variable	**DAPA 5 MG BID + MET** N = 99	**DAPA 10 MG QD + MET** N = 99	**PLA + MET** N = 101	**DAPA 10 MG + MET** N = 135	**PLA + MET** N = 137	**DAPA 10 MG + MET** N = 89	**PLA + MET** N = 91
HbA1c (%)							
Baseline (mean)	7.79	7.71	7.94	7.92	8.11	7.19	7.16
Change from baseline[b]	-0.65	-0.59	-0.30	-0.84	-0.30	-0.39	-0.10
Difference from Placebo[b]	-0.35[c]	-0.29[d]		-0.54[c]		-0.28[e]	
(95% CI)	(-0.52, -0.18)	(-0.45, -0.12)		(-0.74, -0.34)		(-0.42, -0.15)	
Body weight (kg)							
Baseline (mean)	93.62	90.58	88.82	86.28	87.74	92.06	90.91
Change from baseline[b]	-2.74	-2.34	-0.86	-2.86	-0.89	-2.96	-0.88
Difference from Placebo[b]	-1.88[f]	-1.48[d]		-1.97[c]		-2.08[c]	
(95% CI)	(-2.52, -1.24)	(-2.12, -0.84)		(-2.63, -1.31)		(-2.84, -1.31)	

N is the number of subjects in the Randomised Subjects (BMS study) or Full Analysis Set (AZ studies)
a Placebo-controlled 16-week study
b Least squares mean adjusted for baseline value
c p-value < 0.0001
d In study D1691C00003, comparisons of dapagliflozin 10 mg QD to placebo were performed with nominal p-values but were not part of the primary or key secondary
objectives of the study. No direct comparison was made between the dapagliflozin 5 mg BID and dapagliflozin 10 mg QD treatment groups
e HbA1c was an exploratory endpoint in study D1690C00012: nominal p-value < 0.0001
f Change in total body weight was an exploratory endpoint in study D1691C00003: nominal p-value < 0.0001

Efficacy of dapagliflozin 5 mg BID and 10 mg QD as add-on therapy to metformin BID (D1691C00003)

Table 11. Summary of primary and key secondary efficacy endpoints – full analysis set

	PLA + MET N=101	DAPA 2.5MG BID + MET N=100	DAPA 5MG BID + MET N=99	DAPA 10MG QD + MET N=99
Primary endpoint				
HbA1c (%) at week 16 (LOCF)				
Adjusted mean change from baseline (SE)	-0.30 (0.0593)	-0.52 (0.0594)	-0.65 (0.0600)	-0.59 (0.0598)
p-value vs. PLA + MET		0.0106 *	<.0001 *	0.0007
Difference in adjusted mean change from baseline vs. PLA + MET (SE)		-0.22 (0.0840)	-0.35 (0.0843)	-0.29 (0.0844)
Key secondary endpoints				
Percent change in body weight (%) at week 16 (LOCF)				
Adjusted mean percent change from baseline (SE)	-1.04 (0.3105)	-2.84 (0.3099)	-3.20 (0.3125)	-2.76 (0.3086)
p-value vs. PLA + MET		<.0001 *	<.0001 *	<.0001
Difference in adjusted mean change from baseline vs. PLA + MET (SE)		-1.82 (0.3630)	-2.18 (0.3636)	-1.73 (0.3635)
Fasting plasma glucose (mg/dL) at week 1				
Adjusted mean change from baseline (SE)	2.0 (2.584)	-13.7 (2.657)	-14.7 (2.672)	-15.5 (2.634)
p-value vs. PLA + MET		<.0001 *	<.0001 *	<.0001
Difference in adjusted mean change from baseline vs. PLA + MET (SE)		-15.7 (3.040)	-16.7 (3.039)	-17.5 (3.044)
Fasting plasma glucose (mg/dL) at week 16 (LOCF)				
Adjusted mean change from baseline (SE)	-10.4 (2.669)	-20.8 (2.738)	-25.6 (2.759)	-20.4 (2.720)
p-value vs. PLA + MET		0.0010 *	<.0001 *	0.0015
Difference in adjusted mean change from baseline vs. PLA + MET (SE)		-10.4 (3.132)	-15.3 (3.139)	-10.0 (3.145)
Proportion of subjects with HbA1c <7.0% after 16 weeks of double-blind treatment, in subjects with an HbA1c ≥7.0% at baseline				
Percent adjusted (SE)	21.4% (4.170)	33.6% (4.567)	38.2% (4.651)	28.1% (4.619)
p-value vs. PLA + MET		0.0455 *	0.0062 *	0.2755
Difference vs. PLA + MET, percent		12.2% (6.097)	16.8% (6.153)	6.7% (6.145)

HbA1c change from baseline

Statistically significant adjusted mean changes from baseline HbA1c were achieved at Week 16 (LOCF) for the dapagliflozin 5 mg BID treatment group (-0.65% [CI: -0.77, -0.53]), and for the dapagliflozin 2.5 mg BID treatment group (-0.52%). Consistent with the results achieved with dapagliflozin 5 mg BID, treatment with dapagliflozin 10 mg QD resulted in an adjusted mean change from baseline HbA1c of -0.59% [CI: -0.70, -0.47]. The placebo group showed an adjusted mean change from baseline in HbA1c of -0.30%. The range of mean baseline HbA1c level across treatment groups was 7.71% to 7.94%.

Statistically significant placebo-corrected mean reductions in HbA1c at Week 16 were achieved for dapagliflozin 5 mg BID (-0.35%) and dapagliflozin 2.5 mg BID (-0.22%). The placebo-corrected mean reduction in HbA1c for dapagliflozin 10 mg QD (-0.29%; nominal p-value < 0.05 [CI: -0.45, -0.12]), was consistent with the placebo-corrected mean reductions in HbA1c achieved in the dapagliflozin 5 mg BID treatment group (-0.35% [CI: -0.52, -0.18]).

Other glycaemic variables

Statistically significant placebo-corrected mean reductions in FPG were observed (-15.7 mg/dL [-0.87 mmol/L] and -16.7 mg/dL [-0.93 mmol/L] at Week 1, and -10.4 mg/dL [-0.58 mmol/L] and -15.3 mg/dL [-0.85 mmol/L] at Week 16, for dapagliflozin 2.5 mg BID and 5 mg BID, respectively). FPG reductions for dapagliflozin 5 mg BID were consistent for dapagliflozin 10 mg QD (placebo-corrected mean reductions of -17.5 mg/dL [-0.97 mmol/L] at Week 1, and -10.0 mg/dL [-0.56 mmol/L] at Week 16).

Average FPG levels achieved after 16 weeks treatment with dapagliflozin 2.5 mg BID and 5 mg BID were 135.2 mg/dL [7.50 mmol/L] and 131.3 mg/dL [7.29 mmol/L], respectively; this was not achieved in the placebo group (FPG of 147.7 mg/dL [8.20 mmol/L]). Overall the above results were consistent with FPG reductions at Week 24 reported previously in MB102014 and D1690C00012.

Treatment with dapagliflozin 2.5 mg BID and 5 mg BID led to a statistically significantly higher placebo-corrected proportion of subjects achieving a therapeutic glycaemic response, defined as HbA1c < 7.0%, (12.2% and 16.8%, respectively). This is consistent with MB102014, where a higher proportion of subjects treated with dapagliflozin achieved a therapeutic response compared with placebo.

Weight variables

Treatment with dapagliflozin 2.5 mg BID and 5 mg BID coadministered with metformin achieved statistically significant placebo-corrected mean reductions from baseline body weight (-1.62 kg [-1.82%] and –1.88 kg [-2.18%], respectively; corresponding mean reductions for treatment with dapagliflozin 10 mg QD were -1.48 kg (-1.73%).

Additional data on efficacy of dapagliflozin add-on to metformin therapy (MB102014 and D1690C00012)

Both pivotal placebo-controlled add-on to metformin studies were included in the initial dapagliflozin MAA submission package.

During the 24-week placebo-controlled study MB102014, treatment with 2.5 mg, 5 mg and 10 mg dapagliflozin add-on to metformin resulted in statistically significant placebo-corrected mean reductions from baseline HbA1c (-0.38%, -0.41% and -0.54%, respectively).

In study D1690C00012, treatment with dapagliflozin 10 mg add-on to metformin resulted in a placebo-corrected mean reduction in HbA1c of -0.28%; this comparatively modest reduction at Week 24 was expected as ~38% of subjects had a mean baseline HbA1c value of < 7.0%.

Statistically significant and clinically relevant FPG reductions at Week 24 were also reported in MB102014 (placebo-corrected mean reductions of –11.8 mg/dL [-0.65 mmol/L], -15.5 mg/dL [-0.86 mmol/L] and -17.5 mg/dL [-0.97 mmol/L] for dapagliflozin 2.5 mg, 5 mg and 10 mg,

respectively). Average FPG levels were 136.2 mg/dL [7.56 mmol/L] at 24 weeks in the dapagliflozin 10 mg group in MB102014. Clinically relevant FPG reductions at Week 24 were also reported in D1690C00012 (placebo-corrected mean reductions of -17.1 mg/dL [-0.95 mmol/L] for dapagliflozin 10 mg).

Additionally in MB102014, a statistically significant placebo-corrected higher proportion of subjects achieved a therapeutic response of HbA1c < 7.0% (11.7% and 14.7% for dapagliflozin 5 mg and 10 mg, respectively).

In MB102014 and D1690C00012, treatment with dapagliflozin add-on to metformin resulted in statistically significant placebo-corrected mean reductions in body weight of approximately 2 kg. The majority of the weight loss in D1690C00012 was attributable to a statistically significant placebo-corrected mean reduction in total body fat mass of -1.48 kg, as measured by dual energy x-ray absorptiometry (DXA); a statistically significant placebo-corrected mean reduction of -1.5 cm in waist circumference was also achieved.

Long-term efficacy of dapagliflozin add-on to metformin therapy (MB102014 and D1690C00012)

In MB102014, placebo-corrected mean reductions in HbA1c achieved at Week 24 were maintained until Week 102 in the dapagliflozin treatment groups in a dose dependent manner (-0.50%, -0.60% and -0.80% for dapagliflozin 2.5 mg, 5 mg and 10 mg, respectively; excluding data after rescue therapy). Similarly for D1690C00012, subjects in the dapagliflozin treatment group showed a placebo-corrected mean reduction of HbA1c from baseline to Week 24 that was maintained at Week 50 (-0.40%; excluding data after rescue therapy).

In MB102014, the placebo-corrected proportions of subjects who were rescued or discontinued for lack of efficacy was -7.0%, -16.1%, and -16.0% in the dapagliflozin 2.5 mg, 5 mg and 10 mg treatment groups, respectively, at Week 102.

In MB102014, differences in total body weight achieved at Week 24 in the dapagliflozin treatment groups were maintained until Week 102 (placebo-corrected mean reductions of -2.46 kg, -3.06 kg and -3.10 kg in the dapagliflozin 2.5 mg, 5 mg and 10 mg treatment groups, respectively; including data after rescue therapy).

In D1690C00012, further mean reductions in total body weight were observed from Week 24 to Week 50; placebo-corrected changes from baseline (including data after rescue therapy) at Week 50 were –2.37 kg in the dapagliflozin treatment group.

- **Active comparator study and combination therapy studies**

Table 12 summarises the outcome of the primary endpoint (HbA1c) and one of the secondary endpoints (body weight) across the active comparator study and combination therapy studies.

Table 12. Summary of HbA1c (%) and body weight (kg) results in active comparator study (at Week 52 LOCF) and placebo-controlled combination therapy studies up to 24 weeks (LOCF)

			Combination therapy studies			
	D1690C00004		D1690C00010		D1690C00006	
	Active comparator (Glipizide)		Stratum 2: Sitagliptin plus Metformin		Stratum: Subjects with OAD (Subgroup: Insulin plus Metformin alone)	
Variable	**DAPA + MET** N = 400	**GLIP + MET** N = 401	**DAPA 10 MG + SIT + MET** N = 113	**PLA + SIT + MET** N = 113	**DAPA 10 MG + INS + MET** N = 83	**PLA + INS + MET** N = 78
HbA1c (%)						
Baseline (mean)	7.69	7.74	7.80	7.87	8.52	8.43
Change from baseline[a]	-0.52	-0.52	-0.43	-0.02	-0.93	-0.31
Difference from Placebo[a]			-0.40[c]		-0.61[d]	
Difference from glipizide + metformin[a]	0.00[b]					
(95% CI)	(-0.11, 0.11)		(-0.58, -0.23)		(-0.83, -0.40)	
Body weight (kg)						
Baseline (mean)	88.44	87.60	93.95	94.17	95.68	98.69
Change from baseline[a]	-3.22	1.44	-2.35	-0.47	-1.77	-0.06
Difference from Placebo[a]			-1.87[c]		-1.71[d]	
Difference from glipizide + metformin[a]	-4.65[c]					
(95% CI)	(-5.14, -4.17)		(-2.61, -1.13)		(-2.47, -0.95)	

N is the number of subjects in the Full Analysis Set. In D1690C00006, N is the number of subjects in the Full Analysis set in subjects with OAD who took metformin alone
a Least squares mean adjusted for baseline value
b Noninferior to glipizide + metformin
c p-value < 0.0001
d nominal p-value < 0.0001
CI Confidence interval; CSR Clinical study report; CTD Common technical document; DAPA Dapagliflozin; GLIP Glipizide; HbA1c Haemoglobin A1c; INS Insulin;
LOCF Last observation carried forward; MET Metformin; OAD Oral antidiabetic drug; PLA Placebo; SIT Sitagliptin

Non-inferior efficacy of dapagliflozin add-on to metformin versus a sulphonylurea (glipizide) plus metformin (D1690C00004)

In the active comparator study D1690C00004, dapagliflozin add-on to metformin was compared to glipizide plus metformin. This study included a dose titration scheme in accordance with the dosing recommendations for glipizide. At the end of the titration period, 87% of subjects had been titrated to the maximum dapagliflozin dose (10 mg), and 73% to the maximum glipizide dose (20 mg). This study was part of the initial dapagliflozin MAA submission package.

The mean reduction from baseline in HbA1c at Week 52 (LOCF) was -0.52% for both treatment groups: dapagliflozin (titrated to 10 mg) add-on to metformin, and glipizide (titrated to 20 mg) plus metformin. This decrease was statistically significantly non-inferior for dapagliflozin compared to glipizide (non-inferiority margin = 0.35%, with 95% confidence interval completely below the pre-defined margin).

Subjects in both treatment groups also showed a mean reduction in FPG from baseline to Week 52 of approximately -20 mg/dL [-1.11 mmol/L]. Although a higher percentage of subjects treated with glipizide achieved a therapeutic glycaemic response (HbA1c ≤ 6.5%),

discontinuations due to lack of glycaemic control were numerically more frequent in the glipizide group (3.6%, versus 0.2% for the dapagliflozin group).

A secondary efficacy assessment in this study was a comparison between dapagliflozin and glipizide of the proportion of subjects reporting at least one episode of hypoglycaemia over 52 weeks. There were ten times as many subjects in the glipizide group (40.8%) who experienced at least one event of hypoglycaemia compared with the dapagliflozin group (3.5%); the difference was statistically significant ($p < 0.0001$).

Treatment with dapagliflozin resulted in statistically significant mean weight loss from baseline of -3.22 kg versus mean weight gain of +1.44 kg with glipizide (Week 52; LOCF), together with a statistically significant mean decrease in waist circumference of -2.33 cm with dapagliflozin compared with a mean increase of +1.09 cm with glipizide. The divergence in these effects between dapagliflozin and glipizide on weight was maintained during the LT extension treatment period up to Week 104.

Long-term efficacy of dapagliflozin add-on to metformin versus a sulphonylurea (glipizide) plus metformin (D1690C00004)

Persistent glycaemic benefits were observed with dapagliflozin during the LT extension treatment period up to Week 104, whereas the magnitude of effect achieved with glipizide was reduced from the HbA1c reductions observed at Week 52.

Mean HbA1c reductions for dapagliflozin and glipizide observed at Week 104 were -0.32% and -0.14%, respectively. Mean FPG reductions achieved at Week 52 were also maintained at Week 104 with dapagliflozin (-20.2 mg/dL [-1.12 mmol/L]), but not with glipizide (-12.2 mg/dL [-0.68 mmol/L]).

The proportion of subjects discontinuing due to lack of glycaemic control was lower with dapagliflozin (14.5%) compared with glipizide (21.6%). Thus treatment with dapagliflozin add-on to metformin demonstrated glycaemic efficacy maintained up to 104 weeks compared with glipizide plus metformin.

The mean reduction in body weight achieved from baseline to Week 52 was stable to Week 104 (-3.70 kg) for the dapagliflozin group. In contrast, subjects in the glipizide group showed an increase in mean body weight from baseline to Week 52 and also at Week 104 (+1.36 kg).

Efficacy of dapagliflozin in combination with a DPP-4 inhibitor (sitagliptin) plus metformin (D1690C00010)

Stratum 2 of study D1690C00010 assessed the efficacy of dapagliflozin 10 mg in combination with the DPP-4 inhibitor sitagliptin plus metformin in subjects who were inadequately controlled on sitagliptin 100 mg plus ≥ 1500 mg/day metformin.

Subjects treated with dapagliflozin 10 mg in combination with sitagliptin plus metformin (Stratum 2) showed a statistically significant placebo-corrected mean reduction in HbA1c (-0.40%) from baseline to Week 24 (LOCF), which was consistent with the HbA1c mean reduction achieved in the overall study D1690C00010 population (-0.48%).

Statistically significant placebo-corrected mean reductions in FPG from baseline to Week 24 (LOCF) were also achieved (-29.18 mg/dL [-1.62 mmol/L] for Stratum 2), which were again consistent with the overall study population results (-27.92 mg/dL [-1.55 mmol/L]).

Additionally, the placebo-corrected proportion of subjects achieving a therapeutic glycaemic response, defined as HbA1c < 7.0% at Week 24, was 8.9% (nominal p-value was < 0.05).

Statistically significant placebo-corrected mean decreases in total body weight from baseline to Week 24 (LOCF) were also achieved (-1.87 kg for Stratum 2), consistent with the overall population results (-1.89 kg). These effects were maintained during the LT extension treatment period up to 48 weeks.

Long-term efficacy of dapagliflozin in combination with a DPP-4 inhibitor (sitagliptin) plus metformin (D1690C00010)

Reductions in HbA1c achieved at Week 24 were maintained or improved at Week 48 for subjects receiving dapagliflozin in combination with sitagliptin plus metformin (Stratum 2), with placebo-corrected mean reductions of –0.59% (excluding data after rescue therapy), and –0.58% (including data after rescue therapy).

The placebo-corrected mean change in total body weight observed at Week 24 was also maintained or improved at 48 weeks (-2.07 kg, excluding data after rescue therapy; and -2.58 kg, including data after rescue therapy; Stratum 2).

Efficacy of dapagliflozin in combination with insulin with or without other OADs, including metformin (D1690C00006)

Study D1690C00006 assessed the efficacy of dapagliflozin 2.5 mg, 5 mg and 10 mg in combination with insulin, with or without OADs; a post-hoc subgroup analysis was performed on the subset of subjects who received dapagliflozin or placebo in combination with insulin plus metformin. This study was part of the initial dapagliflozin MAA submission.

For the post-hoc subgroup analysis of subjects who received dapagliflozin in combination with insulin plus metformin, judged at a nominal two-sided alpha-level of 0.05, placebo-corrected mean reductions in HbA1c of -0.44%, -0.59% and -0.61% were achieved for dapagliflozin 2.5 mg, 5 mg and 10 mg treatment groups, respectively, which were consistent with the results of the overall population.

Long-term efficacy of dapagliflozin in combination with insulin with or without other OADs, including metformin (D1690C00006)

For the subgroup of subjects who received dapagliflozin in combination with insulin plus metformin, glycaemic efficacy was maintained until 104 weeks in all dapagliflozin treatment groups, with placebo-corrected HbA1c mean reductions of –0.88% for the dapagliflozin 5 mg/10 mg and dapagliflozin 10 mg treatment groups.

Ancillary analyses

- **Dapagliflozin effect on blood pressure**

Blood pressure reductions were expected due to the mode of action of SGLT2 inhibition, which is associated with a mild osmotic diuretic effect. Treatment with dapagliflozin add-on to metformin therapy resulted in moderate reductions in systolic and diastolic blood pressures (MB102014, D1690C00012 and D1691C00003). Similar reductions were achieved in combination with sitagliptin plus metformin (Stratum 2 of D1690C00010); or in combination with insulin plus metformin, with or without other OADs (D1690C00006).

Summary of main studies

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

Table 13. 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: Duration of Run-in phase: Duration of Extension phase:		24 weeks 14 day lead-in period 78 weeks
Hypothesis	Superiority after 24 weeks and 102 weeks		
Treatments groups	Dapa 2.5 mg		Dapagliflozin 2.5 mg on a background therapy of metformin ≥ 1500 mg/day, 102 weeks, 137 randomized
	Dapa 5 mg		Dapagliflozin 5 mg on a background therapy of metformin ≥ 1500 mg/day, 102 weeks, 137 randomized
	Dapa 10 mg		Dapagliflozin 10 mg on a background therapy of metformin ≥ 1500 mg/day, 102 weeks, 135 randomized
	Placebo		Placebo on a background therapy of metformin ≥ 1500 mg/day, 102 weeks, 137 randomized
Endpoints and definitions	Primary endpoint	HbA1c	Change from baseline in HbA1c at 24 weeks and 102 weeks
	Secondary endpoint	FPG	Change from baseline in FPG at 24 weeks and 102 weeks
	Secondary endpoint	TBW	Change from baseline in total body weight at 24 weeks and 102 weeks
Database lock	29 January 2009 (ST), 15 June 2010 (ST+LT)		
Results and Analysis of the main ST 24-week phase			

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, 3.7810, 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	
Notes	The LOCF principle was used for the main analyses in the 24-week CSR.				
Results and Analysis for the main 24-week ST plus 78-week extension phase (ST + LT, 102 weeks)					
Analysis description	Exploratory 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)	0.02	-0.48	-0.58	-0.78
	Standard error	0.1098	0.0995	0.0995	0.0918
	FPG (mg/dL) (adjusted mean change)	-10.41	-19.26	-26.45	-24.50
	Standard error	3.5649	3.1626	2.8047	2.6966
	TBW (kg) (adjusted mean change)	1.36	-1.10	-1.70	-1.74
	Standard error	0.4244	0.4115	0.3997	0.3948
Effect estimate per comparison	Primary endpoint: HbA1c (%)	Comparison groups		Dapagliflozin 2.5, 5 and 10 mg vs placebo	
		Difference from placebo		-0.50, -0.60, -0.80	
		Standard error		0.1464, 0.1448, 0.1421	
		P-value (ANCOVA)		Not Calculated (NC)	
	Secondary endpoint: FPG (mg/dL)	Comparison groups		Dapagliflozin 2.5, 5 and 10 mg vs placebo	
		Difference from placebo		-8.85, -16.04, -14.08	
		Standard error		4.5213, 4.3905, 4.2826	
		P-value (ANCOVA)		NC	
	Secondary endpoint: TBW (kg)	Comparison groups		Dapagliflozin 2.5, 5 and 10 mg vs placebo	
		Difference from placebo		-2.46, -3.06, -3.10	
		Standard error		0.5906, 0.5825, 0.5794	
		P-value (ANCOVA)		NC	
Notes	A Longitudinal repeated measures analysis over time model was used for the analysis of the 102-week data.				

Table 14. 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: a 52-week extension period 1 (LT1) and a 104-week extension period 2 (LT 2)
Hypothesis	Non-inferiority to a sulphonylurea after 52 weeks and 104 weeks		
Treatments groups	Dapagliflozin		Dapagliflozin titrated to 2.5, 5 or 10 mg on a background of open label metformin ≥1500 mg/day, 104 weeks, 406 randomized
	Glipizide		Glipizide titrated to 5, 10 or 20 mg on a background of open label metformin ≥1500 mg/day, 104 weeks, 408 randomized
Endpoints and definitions	Primary endpoint	HbA1c	Change from baseline in HbA1c at 52 weeks and 104 weeks
	Key secondary endpoint	TBW	Change from baseline in total body weight at 52 weeks and 104 weeks
	Key secondary endpoint	FPG	Change from baseline in fasting plasma glucose (FPG) at 52 weeks and 104 weeks
Database lock	23 February 2010 (ST [52 weeks]), 3 March 2011 (ST + LT1)		
Results and Analysis for the main ST 52-week phase			
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
		Non-inferiority 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	The LOCF principle was used for the main analyses in the 52-week CSR.		
Results and Analysis for the main ST 52-week plus 52-week extension phase 1 (ST + LT1, 104 weeks)			
Analysis description	Exploratory 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)	-0.32	-0.14
	Standard error	0.0536	0.0551
	TBW (kg) (adjusted mean change)	-3.70	1.36
	Standard error	0.2352	0.2427
	FPG (mg/dL) (adjusted mean change)	-20.2	-12.2
	Standard error	1.856	1.930
Effect estimate per comparison	Primary endpoint: HbA1c (%)	Comparison groups	Dapagliflozin vs glipizide
		Difference from active comparator	-0.18
		Standard error	0.0764
		P-value (ANCOVA)	Not Calculated (NC)
	Secondary endpoint: TBW (kg)	Comparison groups	Dapagliflozin vs glipizide
		Difference from active comparator	-5.06
		Standard error	0.3379
		P-value (ANCOVA)	NC
	Secondary endpoint: FPG (mg/dL)	Comparison groups	Dapagliflozin vs glipizide
		Difference from active comparator	-8.0
		Standard error	2.667
		P-value (ANCOVA)	NC

Notes	A Longitudinal repeated measures analysis over time model was used for the analysis of the 104-week data.

Table 15. Summary of efficacy for trial D1690C00006

Title: A 24-week international, randomized, parallel-group, double-blind, placebo-controlled phase III study with a 24-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 (A second 56-week extension period was introduced with Amendment 2 to the CSP)					
Study identifier	Study code: D1690C00006 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: Long-term 1 (LT1) 24 weeks plus long-term 2 (LT2) 56 week treatment periods			
Hypothesis	Superiority after 24 weeks, 104 weeks				
Treatments groups	Dapagliflozin 2.5 mg	Dapagliflozin 2.5 mg on a background of insulin ≥30 IU/day ± maximum 2 oral anti-diabetic drugs, 104 weeks, 202 randomized			
	Dapagliflozin 5 mg	Dapagliflozin 5 mg on a background of insulin ≥30 IU/day ± maximum 2 oral anti-diabetic drugs, 104 weeks, 212 randomized			
	Dapagliflozin 10 mg	Dapagliflozin 10 mg on a background of insulin ≥30 IU/day ± maximum 2 oral anti-diabetic drugs, 104 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 and 104 weeks		
	Key secondary endpoint	TBW	Change from baseline in total body weight at 24 weeks and 104 weeks		
	Key secondary endpoint	FPG	Change from baseline in FPG at 24 weeks and 104 weeks		
Database lock	11 August 2009 (ST), 14 March 2011 (ST + LT1 + LT2)				
Results and Analysis of main ST 24-week phase					
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, 0.2523, 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	The LOCF principle was used for the main analyses in the 24-week CSR. All results shown here from the ST 24-week CSR are Excluding data after insulin up-titration				

Results and Analysis of main ST 24-week plus extension phase 1 (LT1) 24-week plus extension phase 2 (LT2) 56 week treatment periods (ST + LT1 + LT2, 104 weeks)

Analysis description	Exploratory 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)	-0.06	-0.49	-0.71	-0.71
	Standard error	0.0986	0.0766	0.0763	0.0753

	TBW (kg) (adjusted mean change)	0.91	-1.47	-1.52	-1.97
	Standard error	0.4884	0.3737	0.3713	0.3645
	FPG (mg/dL) (adjusted mean change)	-11.2	-13.9	-31.1	-18.2
	Standard error	5.376	4.073	4.021	3.901
Effect estimate per comparison	Primary endpoint: HbA1c (%)	Comparison groups		Dapagliflozin 2.5, 5 and 10 mg vs placebo	
		Difference from placebo		-0.43, -0.65, -0.65	
		Standard error		0.1247, 0.1246, 0.1242	
		P-value (ANCOVA)		Not Calculated (NC)	
	Secondary endpoint: TBW (kg)	Comparison groups		Dapagliflozin 2.5, 5 and 10 mg vs placebo	
		Difference from placebo		-2.38, -2.43, -2.88	
		Standard error		0.6133, 0.6130, 0.6094	
		P-value (ANCOVA)		NC	
	Secondary endpoint: FPG (mg/dL)	Comparison groups		Dapagliflozin 2.5, 5 and 10 mg vs placebo	
		Difference from placebo		-2.7, -20.0, -7.0	
		Standard error		6.747, 6.742, 6.628	
		P-value (ANCOVA)		NC	
Notes	A Longitudinal repeated measures analysis over time model was used for the analysis of the 104-week data All results shown here from the ST + LT1 + LT2 104-week CSR are Excluding data after insulin up-titration				

Table 16. Summary of efficacy for trial D1691C00003

Title: A 16-week, Multicentre, Randomised, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Safety and Efficacy of Dapagliflozin 2.5 mg BID, 5 mg BID and 10 mg QD Versus Placebo in Patients with Type 2 Diabetes Who Are Inadequately Controlled on Metformin-IR Monotherapy		
Study identifier	D1691C00003 EudraCT No.: 2010-019511-37 ClinicalTrials.gov identifier: NCT01217892	
Design	Multicentre, randomised, double-blind, placebo-controlled	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	16 weeks 5 weeks Not applicable
Hypothesis	Superiority after 16 weeks	
Treatments groups	Dapagliflozin 2.5 mg BID	Dapagliflozin 2.5 mg BID on a background treatment of metformin ≥1500 mg/day, 16 weeks, 100 randomized
	Dapagliflozin 5 mg BID	Dapagliflozin 5 mg BID on a background treatment of metformin ≥1500 mg/day, 16 weeks, 100 randomized

	Dapagliflozin 10 mg QD		Dapagliflozin 10 mg QD on a background treatment of metformin ≥1500 mg/day, 16 weeks, 99 randomized
	Placebo		Placebo on a background treatment of metformin ≥1500 mg/day, 16 weeks, 101 randomized
Endpoints and definitions	Primary endpoint	HbA1c	Change in HbA1c from baseline to week 16
	Key Secondary endpoint	TBW	Percent change in body weight from baseline to week 16
	Key Secondary endpoint	FPG	Change in FPG from baseline to week 1
	Key Secondary endpoint	FPG	Change in FPG from baseline to week 16
	Key Secondary endpoint	HbA1c	Proportion of subjects with HbA1c <7.0% at week 16, in subjects who had HbA1c ≥7.0% at baseline
Database lock	18 November 2011		

Results and Analysis for the 16-week treatment period

Analysis description	Primary Analysis				
Analysis population and time point description	Full Analysis Set (FAS), included all randomized subjects (as randomized) who received at least one dose of double-blind study medication and who had a non-missing baseline value and at least one post-baseline value for at least one efficacy variable.				
Descriptive statistics and estimate variability	Treatment group	Placebo	Dapa 2.5 mg BID	Dapa 5 mg BID	Dapa 10 mg QD
	Number of subjects	101	100	100	99
	HbA1c (%) (adjusted mean change, week 16)	-0.30	-0.52	-0.65	-0.59
	Standard error	0.0593	0.0594	0.0600	0.0598
	Body weight, (adjusted mean change in percent, week 16)	-1.04	-2.84	-3.20	-2.76
	Standard error	0.3105	0.3099	0.3125	0.3086
	FPG (adjusted mean change from baseline to week 1)	2.0	-13.7	-14.7	-15.5

	Standard error	2.584	2.657	2.672	2.634
	FPG (adjusted mean change from baseline to week 16)	-10.4	-20.8	-25.6	-20.4
	Standard error	2.669	2.738	2.759	2.720
	HbA1c (adjusted % subjects with HbA1c <7% at week 16)	21.4%	33.6%	38.2%	28.1%
	Standard error	4.170	4.567	4.651	4.619

Effect estimate per comparison	Primary endpoint, HbA1c (%), change at week 16	Comparison groups	Dapagliflozin 2.5 mg BID, 5 mg BID and 10 mg QD vs placebo
		Difference from placebo	-0.22, -0.35, -0.29
		Standard error	0.0840, 0.0843, 0.0844
		P-value	0.0106, <.0001, 0.0007
	Key secondary endpoint, TBW percent change (kg) at week 16	Comparison groups	Dapagliflozin 2.5 mg BID, 5 mg BID and 10 mg QD vs placebo
		Difference from placebo	-1.82, -2.18, -1.73
		Standard error	0.3630, 0.3636, 0.3635
		P-value	<.0001, <.0001, <.0001
	Key secondary endpoint, FPG (mg/dL) at week 1	Comparison groups	Dapagliflozin 2.5 mg BID, 5 mg BID and 10 mg QD vs placebo
		Difference from placebo	-15.7, -16.7, -17.5
		Standard error	3.040, 3.039, 3.044
		P-value	<.0001, <.0001, <.0001
	Key secondary endpoint, FPG (mg/dL) at week 16	Comparison groups	Dapagliflozin 2.5 mg BID, 5 mg BID and 10 mg QD vs placebo
		Difference from placebo	-10.4, -15.3, -10.0
		Standard error	3.132, 3.139, 3.145
		P-value	0.0010, <.0001, 0.0015
	Key secondary endpoint, HbA1c, percent subjects with HbA1c <7% at week 16	Comparison groups	Dapagliflozin 2.5 mg BID, 5 mg BID and 10 mg QD vs placebo
		Difference from placebo	12.2%, 16.8%, 6.7%
		Standard error	6.097, 6.153, 6.145
		P-value	0.0455, 0.0062, 0.2755
Notes	The dapagliflozin 10 mg QD treatment group was provided as a measure of assay sensitivity. Comparisons of dapagliflozin 10 mg QD to placebo were performed with nominal p-values but were not part of the primary or key secondary objectives of the study. The LOCF principle was used for the main analyses in the 16-week CSR.		

Table 17. Summary of efficacy for trial D1690C00010

Title: A 24-week, Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group, International Phase III Study with a 24-week Extension Period to Evaluate the Safety and Efficacy of Dapagliflozin 10 mg Daily in Patients with Type 2 Diabetes who have Inadequate Glycaemic Control on a DPP-4 inhibitor (Sitagliptin) Alone or in Combination with Metformin			
Study identifier	D1690C00010 (add-on to DPP-4 inhibitor) EudraCT No: 2009-012806-37 ClinicalTrials.gov identifier: NCT00984867		
Design	Multicentre, randomised, double-blind, placebo-controlled, parallel-group		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks 2 week placebo lead-in period 24 weeks
Hypothesis	Superiority at 24 weeks		
Treatments groups	Dapagliflozin 10 mg QD		Dapagliflozin 10 mg QD on a background treatment of open-label sitagliptin 100 mg QD ± metformin ≥ 1500 mg/day, 48 weeks, 225 randomized
	Placebo		Placebo on a background treatment of open-label sitagliptin 100 mg QD ± metformin ≥ 1500 mg/day, 48 weeks, 226 randomized
Endpoints and definitions	Primary endpoint	HbA1c	Change in HbA1c from baseline to Week 24
	Key secondary endpoint	TBW	Change in total body weight from baseline to Week 24
	Key secondary endpoint	HbA1c	Change in HbA1c in subjects with baseline HbA1c ≥ 8% at Week 24
	Key secondary endpoint	FPG	Change in FPG from baseline to Week 24
	Key secondary endpoint	SBP	Change in seated SBP in subjects with baseline seated SBP ≥ 130 mmHg at Week 8
	Key secondary endpoint	2h post liquid meal glucose	Change in 2 hour post liquid meal glucose from baseline to Week 24
	Key secondary endpoint	HbA1c responders	Proportion of subjects achieving a therapeutic glycemic response, defined as a reduction in HbA1c of ≥ 0.7% from baseline to Week 24
Database lock	5 May 2011 (ST), 24 November 2011 (ST + LT)		
Results and Analysis of the main ST 24-week phase			
Analysis description	Primary Analysis		
Analysis population and time point description	Full Analysis set, included all randomized subjects (as randomized) who received at least one dose of double blind study medication and who had a non-missing baseline value and at least one post-baseline value for at least 1 efficacy variable.		

Descriptive statistics and estimate variability	Treatment group	Placebo	Dapagliflozin 10 mg QD
	Number of subjects	224	223
	HbA1c (%), adjusted mean change from baseline at Week 24	0.04	-0.45
	Standard error	0.0509	0.0509
	Body weight (kg), adjusted mean change from baseline at Week 24	-0.26	-2.14
	Standard error	0.1741	0.1745
	HbA1c in subjects with HbA1c ≥ 8.0% at baseline, adjusted mean change from baseline at Week 24	0.03	-0.80
	Standard error	0.0775	0.0797
	FPG (mg/dL) adjusted mean change from baseline at Week 24	3.81	-24.11
	Standard error	2.3474	2.3474
	Seated SBP (mmHg) in subjects with baseline seated SBP ≥ 130 mmHg, adjusted mean change from baseline at Week 8	-5.12	-5.98
	Standard error	1.0211	1.0638
	2 h post liquid meal glucose (mg/dL), adjusted mean change from baseline at Week 24	-6.84	-21.65
	Standard error	2.5098	2.4604
	Adjusted % of subjects with HbA1c decrease ≥ 0.7% at Week 24	16.6	35.3
	Standard error	2.491	3.040
Effect estimate per comparison	Primary endpoint, Change in HbA1c (%) from baseline to Week 24	Comparison groups	Dapagliflozin 10 mg QD vs placebo
		Difference from placebo	-0.48
		Standard error	0.0720
		P-value	<0.0001
	Secondary endpoint, Change in total body weight (kg) from baseline to Week 24	Comparison groups	Dapagliflozin 10 mg QD vs placebo
		Difference from placebo	-1.89
		Standard error	0.2466
		P-value	<0.0001
	Secondary endpoint, Change in HbA1c (%) in subjects with baseline HbA1c ≥ 8% at Week 24	Comparison groups	Dapagliflozin 10 mg QD vs placebo
		Difference from placebo	-0.83
		Standard error	0.1106
		P-value	<0.0001
	Secondary endpoint, Change in FPG (mg/dL) from baseline to Week 24	Comparison groups	Dapagliflozin 10 mg QD vs placebo
		Difference from placebo	-27.92
		Standard error	3.3200
		P-value	<0.0001
	Secondary endpoint, Change in seated SBP (mmHg) in subjects with baseline seated SBP ≥ 130 mmHg at Week 8	Comparison groups	Dapagliflozin 10 mg QD vs placebo
		Difference from placebo	-0.86

		Standard error	1.4659
		P-value	0.5583
	Secondary endpoint, Change in 2 hour post liquid meal glucose (mg/dL) from baseline to Week 24	Comparison groups	Dapagliflozin 10 mg QD vs placebo
		Difference from placebo	-14.82
		Standard error	3.5160
		P-value	<0.0001
	Secondary endpoint, Proportion of subjects (%) achieving a therapeutic glycemic response, defined as a reduction in HbA1c of ≥ 0.7% from baseline to Week 24	Comparison groups	Dapagliflozin 10 mg QD vs placebo
		Difference from placebo	18.7
		Standard error	3.916
		P-value	<0.0001
Notes	The LOCF principle was used for the main analyses in the 24-week CSR.		
Results and analysis of the main 24-week ST plus 24-week extension phase (ST + LT, 48 weeks)			
Analysis description	Exploratory Analysis		
Analysis population and time point description	Full Analysis set, included all randomized subjects (as randomized) who received at least one dose of double blind study medication and who had a non-missing baseline value and at least one post-baseline value for at least 1 efficacy variable.		
Descriptive statistics and estimate variability	Treatment group	Placebo	Dapagliflozin 10 mg QD
	Number of subjects	224	223
	HbA1c (%), adjusted mean change from baseline at Week 48	0.38	-0.30
	Standard error	0.0810	0.0644
	Body weight (kg), adjusted mean change from baseline at Week 48	0.18	-2.03
	Standard error	0.3061	0.2462
	HbA1c in subjects with HbA1c ≥ 8.0% at baseline, adjusted mean change from baseline at Week 48	0.26	-0.72
	Standard error	0.2287	0.1261
	FPG (mg/dL) adjusted mean change from baseline at Week 48	13.5	-19.7
	Standard error	3.405	2.608
	Seated SBP (mmHg) in subjects with baseline seated SBP ≥ 130 mmHg, adjusted mean change from baseline at Week 48	-5.19	-5.40
	Standard error	1.8216	1.4041
	2 h post liquid meal glucose (mg/dL), adjusted mean change from baseline at Week 48	-12.1	-43.0
	Standard error	4.709	3.536
	Adjusted % of subjects with HbA1c decrease ≥ 0.7% at Week 48	5.0	25.9
	Standard error	1.444	2.899
Effect estimate per comparison	Primary endpoint, Change in HbA1c (%) from baseline to Week 48	Comparison groups	Dapagliflozin 10 mg QD vs placebo

		Difference from placebo	-0.68
		Standard error	0.1016
		P-value	NC
	Secondary endpoint, Change in total body weight (kg) from baseline to Week 48	Comparison groups	Dapagliflozin 10 mg QD vs placebo
		Difference from placebo	-2.22
		Standard error	0.3931
		P-value	NC
	Secondary endpoint, Change in HbA1c (%) in subjects with baseline HbA1c ≥ 8% at Week 48	Comparison groups	Dapagliflozin 10 mg QD vs placebo
		Difference from placebo	-0.98
		Standard error	0.2569
		P-value	NC
	Secondary endpoint, Change in FPG (mg/dL) from baseline to Week 48	Comparison groups	Dapagliflozin 10 mg QD vs placebo
		Difference from placebo	-33.2
		Standard error	4.269
		P-value	NC
	Secondary endpoint, Change in seated SBP (mmHg) in subjects with baseline seated SBP ≥ 130 mmHg at Week 48	Comparison groups	Dapagliflozin 10 mg QD vs placebo
		Difference from placebo	-0.21
		Standard error	2.3092
		P-value	NC
	Secondary endpoint, Change in 2 hour post liquid meal glucose (mg/dL) from baseline to Week 48	Comparison groups	Dapagliflozin 10 mg QD vs placebo
		Difference from placebo	-30.9
		Standard error	5.899
		P-value	NC
	Secondary endpoint, Proportion of subjects (%) achieving a therapeutic glycemic response, defined as a reduction in HbA1c of ≥ 0.7% from baseline to Week 48	Comparison groups	Dapagliflozin 10 mg QD vs placebo
		Difference from placebo	21.0
		Standard error	3.246
		P-value	NC
Notes	A Longitudinal repeated measures analysis over time model was used for the analysis of the 48-week data		

Table 18. Summary of efficacy for trial D1690C00012

Title: A 24-week, Multi-centre, International, Double-blind, Randomized, Parallel-group, Placebo-controlled, Phase III Study with a 78-week Extension Period to Evaluate the Effect of Dapagliflozin in Combination with Metformin on Body Weight in Subjects with Type 2 Diabetes Mellitus Who Have Inadequate Glycaemic Control on Metformin Alone	
Study identifier	D1690C00012 EudraCT No.: 2008-004913-93 ClinicalTrials.gov identifier: NCT00855166

Design	Multi-centre, bouble-blind, randomized, parallel-group, placebo-controlled		
	Duration of main phase: Duration of Run-in phase: Duration Extension phase 1: Duration Extension phase 2:		24 weeks 2 weeks 26 weeks 52 weeks
Hypothesis	Superiority after 24 weeks		
Treatments groups	Dapagliflozin 10 mg		Dapagliflozin 10 mg on a background treatment of open-label metformin ≥1500 mg/day, 50 weeks, 91 randomized
	Placebo		Placebo on a background treatment of open-label metformin ≥1500 mg/day, 50 weeks, 91 randomized
Endpoints and definitions	Primary endpoint	TBW	The absolute change in total body weight from baseline to week 24 (LOCF)
	Key secondary endpoint	Waist circum-ference	Change in waist circumference from baseline to week 24 (LOCF)
	Key secondary endpoint	DXA	Change in body fat mass (absolute value, kg) as measured by Dual Energy X-ray Absorptiometry (DXA) from baseline to week 24 (LOCF)
	Key secondary endpoint	TBW	Proportion of subjects with body weight decrease ≥5% from baseline to week 24 (LOCF)
Database lock	7 July 2010 (ST), 3 February 2011 (ST + LT1), 3 February 2013 (ST + LT1 + LT2)		

Results and Analysis of the main ST 24-week phase

Analysis description	Primary Analysis		
Analysis population and time point description	Full Analysis Set including all randomized subjects (as randomized) who received at least one dose of double-blind study medication during the 24-week short-term, double-blind treatment period, who have a non-missing baseline value and at least one post-baseline efficacy value for at least one efficacy variable to be analyzed at week 24.		
Descriptive statistics and estimate variability	Treatment group	Placebo	Dapagliflozin 10 mg
	Number of subjects (Full analysis set)	91	89
	TBW (kg) at week 24 (adjusted mean change from baseline)	-0.88	-2.96
	Standard error	0.2746	0.2766
	Waist circumference (cm) at week 24 (adjusted mean change from baseline)	-0.99	-2.51
	Standard error	0.4349	0.4388
	DXA (body fat mass, kg) (adjusted mean change from baseline)	-0.74	-2.22
	Standard error	0.2670	0.2626
	TBW, subjects with decrease ≥5% at week 24 (percent adjusted)	4.3%	30.6%

	Standard error	2.148	4.859
Effect estimate per comparison	Primary endpoint TBW (kg)	Comparison groups	Dapagliflozin 10 mg vs placebo
		Difference vs placebo	-2.08
		Standard error	0.3885
		P-value	<.0001
	Key secondary endpoint Waist circumference (cm)	Comparison groups	Dapagliflozin 10 mg vs placebo
		Difference vs placebo	-1.52
		Standard error	0.6162
		P-value	0.0143
	Key secondary endpoint DXA (body fat mass, kg)	Comparison groups	Dapagliflozin 10 mg vs placebo
		Difference vs placebo	-1.48
		Standard error	0.3731
		P-value	0.0001
	Key secondary endpoint TBW, subjects with decrease ≥5%	Comparison groups	Dapagliflozin 10 mg vs placebo
		Difference vs placebo	26.3%
		Standard error	5.309
		P-value	<.0001
Notes	The LOCF principle was used for the main analyses in the 24-week CSR.		

Results for the main short-term 24-week plus 26-week extension 1 phase (ST + LT1, 50 weeks)

Analysis description	Exploratory Analysis		
Analysis population and time point description	Full Analysis Set including all randomized subjects (as randomized) who received at least one dose of double-blind study medication, who had a non-missing baseline value and at least one post-baseline efficacy value for at least one efficacy variable to be analyzed.		
Descriptive statistics and estimate variability	Treatment group	Placebo	Dapagliflozin 10 mg
	Number of subjects (Full analysis set)	84	81
	TBW (kg) at week 50 (adjusted mean change from baseline)	-2.03	-4.39
	Standard error	0.4461	0.4663
	Waist circumference (cm) at week 50 (adjusted mean change from baseline)	-3.0	-5.0
	Standard error	0.773	0.815
	TBW, subjects with decrease ≥5% at week 50 (percent adjusted)	14.0%	38.7%
	Standard error	3.633	5.116
Effect estimate per comparison	Primary endpoint TBW (kg)	Comparison groups	Dapagliflozin 10 mg vs placebo
		Difference vs placebo	-2.37
		Standard error	0.5288
		P-value	Not Calculated (NC)
	Key secondary endpoint Waist circumference (cm)	Comparison groups	Dapagliflozin 10 mg vs placebo

		Difference vs placebo	-2.0
		Standard error	0.856
		P-value	NC
	Key secondary endpoint TBW, subjects with decrease ≥5%	Comparison groups	Dapagliflozin 10 mg vs placebo
		Difference vs placebo	24.6%
		Standard error	6.239
		P-value	NC
Notes	Body fat mass (DXA) was not determined at week 50 A Longitudinal repeated measures analysis over time model was used for the analysis of the 50-week data		
Results for the main 24-week ST plus 26-week extension 1 plus 52-week extension 2 phase (ST + LT1 + LT2, 102 weeks)			
Analysis description	Exploratory analysis		
Analysis population and time point description	Full Analysis Set including all randomized subjects (as randomized) who received at least one dose of double-blind study medication, who had a non-missing baseline value and at least one post-baseline efficacy value for at least one efficacy variable to be analyzed.		
Descriptive statistics and estimate variability	Treatment group	Placebo	Dapagliflozin 10 mg
	Number of subjects (Full analysis set)	71	69
	TBW (kg) at week 24 (adjusted mean change from baseline)	-2.12	-4.54
	Standard error	0.4315	0.4499
	Waist circumference (cm) at week 24 (adjusted mean change from baseline)	-2.9	-5.0
	Standard error	0.640	0.669
	DXA (body fat mass, kg) (adjusted mean change from baseline)	-1.46	-2.80
	Standard error	0.3985	0.4403
	TBW, subjects with decrease ≥5% at week 24 (percent adjusted)	16.5%	27.1%
	Standard error	3.888	4.699
Effect estimate per comparison	Primary endpoint TBW (kg)	Comparison groups	Dapagliflozin 10 mg vs placebo
		Difference vs placebo	-2.42
		Standard error	0.6167
		P-value	NC
	Key secondary endpoint Waist circumference (cm)	Comparison groups	Dapagliflozin 10 mg vs placebo
		Difference vs placebo	-2.1
		Standard error	0.914
		P-value	NC
	Key secondary endpoint	Comparison groups	Dapagliflozin 10 mg vs placebo

	DXA (body fat mass, kg)	Difference vs placebo	-1.34
		Standard error	0.5600
		P-value	NC
	Key secondary endpoint TBW, subjects with decrease ≥5%	Comparison groups	Dapagliflozin 10 mg vs placebo
		Difference vs placebo	10.6%
		Standard error	6.102
		P-value	NC
Notes	A Longitudinal repeated measures analysis over time model was used for the analysis of the 102-week data		

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

- **Comparison of results in subpopulations**

The pooled data presented in the initial dapagliflozin MAA remain the most comprehensive data to describe efficacy results in the subpopulations and is more relevant than data from individual studies within this submission, as data from the individual studies presented here would be based on smaller numbers of subjects and therefore, may show variability in the subgroup categories. It is important to note that data from studies included in this submission (except D1691C00003 and D1690C00010) are also included in the pooled data presented in the initial dapagliflozin MAA.

Subgroup analyses in studies D1691C00003 and D1690C00010 were generally consistent with results in the overall pool in the initial dapagliflozin MAA.

The subgroup analyses show that no dose adjustment is required based on age, gender, race or body weight.

Clinical studies in special populations

No new data have been submitted with the current application.

- **Use in patients with renal or hepatic impairment**:

The efficacy of dapagliflozin is, due to its mechanism of action, dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment. Therefore the dapagliflozin/metformin FDC should not be used in patients with moderate to severe renal impairment (CrCl < 60mL/min, or eGFR < 60mL/min/1.73 m2). Further to this, metformin is contraindicated in patients with moderate to severe renal impairment due to an increased risk of lactic acidosis. No dosage adjustment is recommended for patients with mild renal impairment.

Similarly, as the risk of lactic acidosis associated with metformin is increased in patients with impaired hepatic function, the dapagliflozin/metformin FDC should not be used in patients with hepatic impairment; this recommendation is consistent with the contraindications for metformin monotherapy.

- **Use in patients at risk for volume depletion, hypotension and/or electrolyte imbalances**:

Due to its mechanism of action, dapagliflozin increases diuresis, leading to a modest decrease in blood pressure, which may be more pronounced in patients with high blood glucose concentrations. Thus, the dapagliflozin/metformin FDC 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). Caution should also be exercised in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients with known CV disease, patients on anti-hypertensive therapy with a history of hypotension, or elderly patients. Careful monitoring of volume status (physical examination, blood pressure measurements and laboratory tests including haematocrit) and electrolytes is recommended for patients receiving the dapagliflozin/metformin FDC, especially during intercurrent conditions that may lead to volume depletion. Temporary interruption of treatment with the dapagliflozin/metformin FDC is recommended for patients who develop volume depletion until the depletion is corrected.

- **Use in elderly patients (≥ 65 years):**

Because metformin is eliminated in part by the kidney, and because elderly patients are more likely to have decreased renal function, the dapagliflozin/metformin FDC should be used with caution as age increases. Monitoring of renal function is necessary to prevent metformin-associated lactic acidosis, particularly in the elderly. Risk of volume depletion with dapagliflozin should also be taken into account. Due to the limited therapeutic experience with dapagliflozin in patients ≥ 75 years, initiation of the dapagliflozin/metformin FDC in this population is not recommended.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

No dose finding studies were performed which is acceptable considering that the doses applied for in this application is already approved. Sufficient data has been provided with the PK/PD study D1691C00004 to conclude that the 5 mg BID dapagliflozin dose is bioequivalent to the 10 mg QD dose and that comparable pharmacodynamic effects are achieved with both doses.

In the clinical study program for dapagliflozin, the metformin doses were not fixed but ranged between 1500 to 3000 mg per day across the study program. The mean dose ranged from 1800 to 2000 mg which support that the majority of patients were treated with doses of metformin corresponding to the doses proposed for the fixed dose formulation.

A similar study design was applied across the study program and the overall study design was adequate and in line with the scientific guidelines. The use of rescue therapy was pre-defined and adequate. The inclusion and exclusion criteria were adequate and would enrol a population representative for the target population, i.e. patients with inadequate metabolic control on metformin where dapagliflozin treatment is adequate. It should be noted that the lower HbA1c limit for inclusion differ between studies and that the limit was relatively low (≥ 6.5%) in three of the studies.

The choice of primary and secondary endpoints in the studies were adequate and in line with the scientific guidelines. Statistical methods applied were adequate.

All studies investigated the dapagliflozin 10 mg QD dose. In addition, study D1691C00003 included one group treated with dapagliflozin 5 mg BID. In all studies, the inclusion criteria stated that patients should be on their maximally tolerated dose of metformin or a minimum dose of 1500 mg.

The study program is considered adequately designed and conducted in order to support the proposed fixed dose combination.

Efficacy data and additional analyses

In the original MAA for dapagliflozin clinical data supporting the combination of dapagliflozin 10 mg QD with metformin was presented and information on this combination is included in the SmPC of Forxiga. The current application is for a fixed dose combination with metformin. As metformin is dosed twice daily, the main objective from an efficacy point of view is to provide clinical data to support that dapagliflozin 5 mg BID treatment effect is comparable to the 10 mg QD dosing regimen. Such data were provided with study DC1690C00003.

The clinical studies provided with this submission included more than 1,500 patients treated with metformin in combination with dapagliflozin and more than 1,000 patients treated with metformin in combination with placebo or active comparator.

Overall, the subjects enrolled are representative of the target population for the fixed dose combination. European patients were well represented in the submitted studies. The study groups were well balanced with regards to baseline characteristics within the studies. Due to the differences in HbA1c inclusion criteria the mean HbA1c differed between studies, which have to be taken into account when assessing the primary outcome of the studies. In general, there were very few patients with impaired renal function included in the studies, thus exclusion criteria were complied with.

In general, discontinuation rates were low in the short-term parts of the studies with no gross differences observed between actively treated groups and placebo/active comparator. In studies where rescue therapy was applied, rescue rates were higher in the placebo treated groups.

In study D1690C00003, a comparable placebo-corrected effect on lowering of HbA1c was observed with the 5 mg BID (-0.35 %) and 10 mg OD dosing (-0.29 %). The placebo-corrected HbA1c reduction was lower than previously observed in study MB MB102014. The Applicant has provided adequate arguments for this finding, one important issue being the higher proportion of subjects with a baseline HbA1c < 7.0%. The outcome was comparable to that observed in study D1690C00012 where the baseline HbA1c was even lower than in study D1690C00003. The small difference observed between the 2.5 mg BID treated group (-0.22 %) and the 5 mg BID group may be explained by the overall lower HbA1c reduction figures.

The primary outcome was supported by the secondary glycaemic endpoints. The effect on HbA1c lowering was observed within 12 weeks and no further reduction was seen at 16 weeks. Notably the placebo group showed a rather large response. Comparable weight reduction of about 1.5 kg was observed in all dapagliflozin treated groups.

In study MB102014, a weak dose-response was observed with the most prominent effect in patients treated with 10 mg dapagliflozin daily. A less marked effect was observed in study

D1690C00012, which could be explained by the low HbA1c at baseline. Secondary endpoints results supported the primary endpoint. These data were assessed as part of the original MAA for dapagliflozin and formed the basis for the inclusion of information on the free combination of depagliflozin and metformin in the Forxiga SmPC. Long-term data up to 102 weeks of treatment in study MB102014 show that the glucose-lowering effect of dapagliflozin is maintained over time. Fewer patients in the actively treated groups discontinued due to lack of efficacy compared to placebo.

The data from the active comparator study D1690C00004 were assessed within the original MAA for dapagliflozin. After 52 weeks of treatment, non-inferiority for dapagliflozin vs glipizide could be shown, both treatments given in combination with metformin. Hypoglycaemia was less common in the dapagliflozin treated group. At 104 weeks, the HbA1c reduction was more pronounced in the dapagliflozin treated group compared to glipizide. Furthermore, the weight reduction observed at 52 weeks was maintained at 104 weeks in the dapagliflozin treated group.

In study D1690C00010, which included a stratum with patients on dual therapy with sitagliptin and metformin, the addition of dapagliflozin resulted in a clinically relevant and statistically significant reduction in HbA1c. These data have also been assessed within the on-going Forxiga variation EMEA/H/C/2322/II/03. It was concluded that balanced information regarding the study could be included in the SmPC section 5.1. Long-term data indicate a maintained and clinically relevant effect of dapagliflozin over the 48 week period.

In study D1690C00006, clinically relevant HbA1c reductions were observed with the three dapagliflozin doses investigated, with statistically more responders achieving a HbA1c < 7.0% observed in groups treated with 5mg and 10 mg dapagliflozin. Results comparable with those of the overall population were observed in the subgroup treated with the triple combination insulin/dapagliflozin/metformin. The long-term data show that efficacy was maintained over the 104 week period. These data were assessed within the original MAA and supported the combination of dapagliflozin with insulin.

The blood pressure lowering effect of dapagliflozin was well documented in the original MAA.

With regards to special populations, no new data have been provided. The restrictions and recommendations regarding the use of the dapagliflozin/metformin FDC in patients with renal or hepatic impairment, elderly patients and patients at risk of volume depletion, hypotension and/or electrolyte imbalances are based on data for the two components and these data are adequately reflected in the SmPC section 4.3 and 4.4.

No new subgroup analyses in pooled data have been provided with the current submission. The subgroup analysis assessed with the MAA for dapagliflozin show that no dose adjustment is required based on age, gender, race or body weight.

Based on the submitted data the CHMP considers that the effect of dapagliflozin as add-on to metformin has been adequately shown. The fixed dose combination should only be used when dapagliflozin is to be given as add-on in patients already on metformin treatment, fact that is clearly described in sections 4.1 and 4.2 of the SmPC.

2.5.4. Conclusions on the clinical efficacy

The clinical program carried out in order to support of the dapagliflozin and metformin FDC application is considered adequate. The use of dapagliflozin and metformin as free combination is already approved.

In the placebo controlled studies treatment with 2.5 mg, 5 mg and 10 mg dapagliflozin add on to metformin resulted in statistically significant placebo corrected mean reductions from baseline HbA1c at week 24. These results were supported by the clinically relevant FPG reductions and statistically significant placebo corrected mean reductions in body weight of approximately 2 kg. Long-term data up to 102 weeks of treatment show that the glucose-lowering effect of dapagliflozin is maintained over time.

A comparable placebo-corrected clinical effect on lowering of HbA1c was observed with the 5 mg BID (-0.35 %) and 10 mg QD dosing (-0.29 %) which along with the similar exposure shown after administration of dapagliflozin 5 mg BID and 10 mg QD supports the proposed twice daily administration of Xigduo.

The indication clearly states that Xigduo is to be used – either when dapagliflozin is to be given as add-on to metformin (although combination with additional OADs is possible) or as substitution therapy.

2.6. Clinical safety

Safety data from the ST treatment periods for studies MB102014, D1690C00004, D1690C00006 and D1690C00012 were already extensively reviewed in the initial dapagliflozin MAA. In order to provide a comprehensive overview of all relevant data supporting the safety of LT administration of dapagliflozin add on to metformin, the analyses of safety included in Xigduo application focus on the latest available data for each study (i.e., all data from the ST + LT treatment periods, and not only the LT extension periods, of previously reported studies). For D1690C00010, ST + LT data (48 weeks) are presented for the overall study population and for Stratum 2 (sitagliptin plus metformin). For D1691C00003, only ST data are available (16 weeks). All analyses include data after the initiation of rescue therapy, except for studies D1691C00003 and D1690C00004, as rescue therapy was not available in these studies. For D1690C00006, a post hoc analysis of the safety data was performed on a subgroup of the stratum of subjects with OADs who took dapagliflozin in combination with insulin, or placebo plus insulin, with the OAD of metformin alone.

Patient exposure

In the six Phase III studies included in this submission, 3200 subjects were randomised and treated with at least one dose of study medication. Of the 3200 randomised subjects, 1562 received dapagliflozin plus metformin (some in combination with sitagliptin or insulin), 478 received dapagliflozin (plus sitagliptin alone, or in combination with insulin with or without other OADs [other than metformin alone]), and 1160 received control/comparator. The database for studying the safety of the dapagliflozin/metformin immediate release (IR) fixed dose combination (FDC) in subjects with T2DM is considered sufficient. Data concerning subjects ≥ 65 years is

limited. There was some variation across the studies in exclusion criteria for renal impairment. In most of the studies, eligibility was based on CrCl > 60 mL/min. Patients with severe renal impairment (eGFR < 30 mL/min/ 1.73 m2) and cardiac failure, NYHA class III and IV, have been excluded from studies.

Overall, the subjects enrolled were representative of the proposed target population, and were considered to be suitable to assess the safety of dapagliflozin add-on to metformin therapy.

The number of patients exposed to dapagliflozin at the recommended dosages (10 mg QD) in combination with metformin ≥1500 mg is considered sufficient since 1,252 patients have been exposed, among these are 100 patients exposed to dapagliflozin 5 mg BID in combination with metformin ≥1500 mg. Overall, 1,053 patients have been exposed to dapagliflozin (10 mg QD) in combination with metformin ≥1500 mg for at least 48 weeks, among these are 737 patients exposed for at least 102 weeks. The extent of exposure to open-label metformin was generally similar to the extent of exposure to double-blind study medication.

Cumulative exposure and mean duration of exposure were comparable across treatment groups in 4 of the 6 studies, and slightly shorter in the placebo group than in the dapagliflozin groups in 2 of the studies (MB102014 and D1690C00006).

Adverse events

In study D1691C00003, most common AEs at PT level in the BID 5 mg dapagliflozin/metformin IR FDC group were creatinine renal clearance decreased 3.0% (vs 4.0% in placebo), back pain 3.0% (vs 2.0% in placebo), vulvovaginal candidiasis 3.0% (vs. 0 in placebo), blood creatinine phosphokinase increased 3.0% (vs. 1.0% in placebo), upper respiratory tract infection 2.0 % (vs 1.0% in placebo), UTI 2.0% (vs 1.0% in placebo), pharyngitis 2.0% (vs 0 in placebo), and vulvovaginal mycotic infection 2.0% (vs 0 in placebo).

The adverse events occurring with a frequency ≥2% for the 5 mg BID dapagliflozin/metformin IR FDC group and >1.5 times the incidence in the placebo were upper respiratory tract infection (2.0% vs 1.0% in placebo), vulvovaginal candidiasis (3.0% vs 0 in placebo), UTI (2.0% vs 1.0% in placebo), pharyngitis (2.0% vs 0 in placebo) and vulvovaginal mycotic infection (2.0% vs 0 in placebo).

The most common AEs reported in dapagliflozin-treated subjects in the studies included in the Phase 3 safety program were generally consistent with the most common AEs reported for the pooled safety datasets in the initial dapagliflozin MAA.

Adverse drug reactions previously identified for dapagliflozin and likely related to expected pharmacodynamic effects of dapagliflozin such as glucosuria or other urine composition alterations and genitourinary symptoms were reported at generally similar rates in subjects receiving dapagliflozin BID and those receiving dapagliflozin QD or placebo. Thus, vulvovaginitis, balanitis, and related genital infections were reported in 0%, 5%, 3% and 1% of subjects in the dapagliflozin 2.5 mg BID, 5 mg BID, 10 mg QD and placebo groups, respectively; UTI was reported in 2%, 4%, 2% and 1% of subjects, respectively; thirst was reported in 0%, 0%, 1% and 0% of subjects, respectively; hyperhidrosis was reported in 1%, 1%, 1% and 0% of subjects, respectively; dysuria was reported in 0%, 1%, 1% and 2% of subjects, respectively; and polyuria/pollakiuria was reported in 1%, 0%, 0% and 1% of subjects, respectively. The

following adverse drug reactions were not reported in study D1691C00003: vulvovaginal pruritis, volume depletion, nocturia, haematocrit increased, blood creatinine increased, and blood urea increased.

In study D1691C00003, dapagliflozin co-administered with metformin did not increase the frequency of gastrointestinal AEs commonly observed with metformin use (abdominal pain, nausea, vomiting, and diarrhoea. Gastrointestinal AEs occurred at similar frequency in the dapagliflozin groups and in the placebo group (abdominal pain 0% to 1.0% and 0%, respectively; nausea 0% to 1.0% and 1.0%, respectively; vomiting 0% and 1.0%, respectively; diarrhoea 0% to 4.0% and 3.0%, respectively. During the 16-week treatment period, the proportion of subjects with at least one AE was slightly higher in the dapagliflozin 2.5 mg BID and 10 mg QD groups (40.0% and 46.5%, respectively) compared with the dapagliflozin 5 mg BID and placebo groups (33.0% and 36.6%, respectively). Hypoglycaemic events were rare, reported by 3 subjects (0.8%) across all treatment groups (1 subject in the dapagliflozin 2.5 mg BID group [1%] and 2 subjects in the dapagliflozin 10 mg QD group [2%]). No major episode of hypoglycaemia was reported and no subject discontinued study treatment due to a hypoglycaemic event. In the long term extensions (LT) of the Phase 3 studies of dapagliflozin administered QD as add-on to metformin in combination with sitagliptin (D1690C00010)a higher incidence of adverse events was observed and hypoglycaemic events was higher in the dapagliflozin group (5.3%) than in the placebo group (2.6%)

The proportion of subjects experiencing at least one AE increased with increasing duration of study treatment, with a low proportion of around 40% of the subjects in all treatment groups in D1691C00003 (16 weeks duration); 56% to 58% in D1690C00012 (50 weeks); and around 80% across all treatment groups in MB102014 (102 weeks).

Overall, no new safety signals were observed in the more recently reported Phase III studies of dapagliflozin administered BID as add-on to metformin alone (D1691C00003) or administered QD as add-on to metformin in combination with a DPP-4 inhibitor (D1690C00010).

Serious adverse event / deaths / other significant events

Deaths

A total of 47 deaths have occurred (dapagliflozin integrated safety database, includes data from 19 Phase 2b/3 studies in the dapagliflozin clinical development program; data cut-off date 15 July 2011). Deaths were balanced across the placebo population (0.6%); the population receiving dapagliflozin and metformin (0.4%); and the population receiving dapagliflozin without metformin (0.6%). Twenty-three deaths were due to cardiac/vascular disorders, and 4 deaths were due to neoplasms. No deaths were reported in study D1691C00003. One death was reported in study D1690C00010. No events with outcome of death were considered related to study treatment.

Serious adverse events

In the initial dapagliflozin MAA, for the placebo-controlled pool (ST period), the most commonly reported SAEs across all dapagliflozin treatment groups (n = 3291) were pneumonia (0.3%), angina pectoris (0.2%), acute myocardial infarction (0.1%), cholelithiasis 0.1%), pulmonary

tuberculosis (0.1%), rotator cuff syndrome (0.1%), coronary artery disease (0.1%) and cerebrovascular accident (0.1%).

D1691C00003 (add-on to metformin, dapagliflozin BID and QD)

The following SAEs were reported.

Table 19. D1691C00003: All serious adverse events, by System Organ Class and Preferred Term (16-week double-blind treatment period, safety analysis set)

System Organ Class (%) Preferred Term (%)	PLA + MET N = 101	DAPA 2.5MG BID + MET N = 100	DAPA 5MG BID + MET N = 100	DAPA 10MG QD + MET N = 99
TOTAL SUBJECTS WITH AN EVENT	0	4 (4.0)	1 (1.0)	2 (2.0)
CARDIAC DISORDERS	0	0	1 (1.0)	1 (1.0)
SICK SINUS SYNDROME	0	0	0	1 (1.0)
CARDIAC FAILURE	0	0	1 (1.0)	0
VASCULAR DISORDERS	0	1 (1.0)	0	1 (1.0)
HYPERTENSIVE CRISIS	0	0	0	1 (1.0)
FEMORAL ARTERY OCCLUSION	0	1 (1.0)	0	0
INFECTIONS AND INFESTATIONS	0	1 (1.0)	0	0
ENDOMETRITIS	0	1 (1.0)	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	2 (2.0)	0	0
EPISTAXIS	0	1 (1.0)	0	0
HAEMOPTYSIS	0	1 (1.0)	0	0

MedDRA Version: 14.0
N is the number of subjects in the safety analysis set.
Includes serious adverse events with onset on or after the first date of double-blind treatment and on or prior to the last day of double-blind treatment plus 30 days or up to follow-up visit if earlier.
Includes serious adverse events of hypoglycaemia.
System organ class/ Preferred term sorted based on the frequency in DAPA 10MG QD + MET.

D1690C00004 (add-on to metformin, direct comparison to SU): During the 104-week ST + LT1 period, the proportion of subjects with an SAE was higher in the glipizide group (15.2%) than in the dapagliflozin group (12.6%). SAEs of myocardial infarction, diverticulitis, hypoglycaemia and anaemia were each reported in three subjects in the glipizide group and SAEs of prostate cancer were reported in three subjects in the dapagliflozin group. All other SAEs were reported by ≤ 2 subjects in either treatment group.

Malignant or unspecified tumours (ST+LT1) in study D1690C00004 are shown in the table below.

Table 20. D1690C00004: Serious adverse events, by System Organ Class and Preferred Term (104-week ST + LT1 period, safety analysis set)

System Organ Class (%) Preferred Term (%)	DAPA + MET N = 406	GLIP + MET N = 408
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	7 (1.7)	3 (0.7)
PROSTATE CANCER	3 (0.7)	1 (0.2)
BREAST CANCER	1 (0.2)	0
GASTRIC CANCER	1 (0.2)	0
PANCREATIC CARCINOMA	1 (0.2)	0
PANCREATIC CARCINOMA METASTATIC	1 (0.2)	0
BASAL CELL CARCINOMA	0	1 (0.2)
BRONCHIAL CARCINOMA	0	1 (0.2)

MedDRA Version: 13.1
N is the number of subjects in the safety analysis set.
Includes serious adverse events with onset on or after the first date of double-blind treatment and on or prior to the last day of short-term or long-term 1 double-blind treatment plus 30 days or up to follow-up visit if earlier, or up to and including the start date of the long-term 2 period if earlier.
Includes serious adverse events of hypoglycaemia.
System organ class/ preferred term sorted based on the frequency in DAPA + MET.

No new cases of breast and bladder cancer were observed in the six Phase III studies included in this analysis of the 15 July 2011 integrated safety database, and one new post-study event of prostate cancer was reported in the comparator treatment group of study D1690C00004.

The overall SAE profile observed in the six Phase III studies seems to be consistent with that previously reported for pooled datasets in the initial dapagliflozin MAA.

Laboratory findings

Increases in Serum Creatinine and Decreases in Creatinine Clearance and eGFR

- In the short term D1691C00003 (add-on to metformin, dapagliflozin BID and QD, 16 w data):

Mean serum creatinine concentration: subjects in the dapagliflozin groups showed a slight increase at Week 1 followed by a gradual decrease to baseline values at Week 16 (reversed at follow up). Subjects in the placebo group showed no clinically relevant changes.

Mean calculated creatinine clearance: subjects in the dapagliflozin groups showed a decrease from baseline to Week 1 that remained almost stable until Week 16 (partially reversed at follow up). Subjects in the placebo group showed no clinically relevant changes.

Mean eGFR: subjects in the dapagliflozin groups showed a slight decrease from baseline to Week 8. The decrease remained stable until Week 16 in the dapagliflozin 2.5 and 5 mg BID groups, while subjects in the dapagliflozin 10 mg QD group showed a slight recovery at Weeks 12 and 16. Subjects in the placebo group showed no clinically relevant changes.

- In the long term MB102014 (add-on to metformin, dapagliflozin QD, 102w data):

Mean serum creatinine concentration and mean calculated creatinine clearance showed no clinically relevant changes from baseline were seen for any treatment group.

Mean eGFR: increases from baseline in eGFR were consistently observed in all treatment groups beginning at Week 24. At Week 102, the mean increases were larger in the dapagliflozin 5 mg and 10 mg groups than in the placebo and dapagliflozin 2.5 mg group.

- In the long term D1690C00006 (add-on to insulin, 104w data):

Mean serum creatinine concentration and mean calculated creatinine clearance showed no clinically relevant changes from baseline were seen for any treatment group.

Mean eGFR: subjects in the dapagliflozin groups showed a slight decrease from baseline to Week 48 followed by a gradual increase to baseline level in the dapagliflozin 5/10 mg group but not in the other dapagliflozin groups. At follow-up, most of the changes observed at Week 104 in the dapagliflozin 2.5 and 10 mg groups were reversible in the safety analysis set as well as in all subjects completing the study.

Serum electrolytes

No clinically relevant changes or trends from baseline in serum electrolytes were observed in the treatment groups.

Vital signs

Consistent with the initial dapagliflozin MAA, slight mean reductions in systolic blood pressure (SBP) and diastolic blood pressure (DBP) were observed during ST and LT treatment periods in dapagliflozin-treated subjects in the Phase 3 studies.

In the add-on to sitagliptin study (D1690C00010) the dapagliflozin treatment group, placebo-corrected mean reduction in SBP in subjects with baseline seated SBP ≥ 130 mmHg was -0.86 mmHg at Week 8 (ST). Seated SBP was evaluated regarding change from baseline to week 24 (LOCF). Analyses including and excluding data after rescue showed a mean decrease of -1.8 and -2.1 mmHg in seated SBP respectively, in the dapagliflozin group and no meaningful mean change in seated SBP in the placebo group ($p<0.05$ including data after rescue, $p>0.05$ excluding data after rescue for the difference between groups). Proportions of subjects with orthostatic hypotension (fall in SBP of > 20 mmHg or DBP of > 10 mmHg [supine to standing]) during the ST + LT treatment periods were consistent across all treatment groups, including placebo.

Safety in special populations

All recommendations and contraindications outlined in this section are based on the proposed wording of the SmPC for the dapagliflozin/metformin IR FDC, which reflects the current understanding of the safety profile of dapagliflozin when used in combination with metformin.

Elderly

There is only limited data for patients ≥75 year (n=67 in the ST placebo-controlled pool in the initial MAA for Forxiga) and the safety of this group has not been evaluated separately. Due to the limited therapeutic experience with dapagliflozin in patients ≥75 year, initiation of dapagliflozin/metformin IR FDC therapy is not recommended.

Monitoring of renal function is necessary to prevent metformin associated lactic acidosis, particularly in the elderly (≥65 years). In subjects ≥65 years of age, a higher proportion of subjects treated with dapagliflozin had adverse reactions related to volume depletion.

Gender

All of the Phase III safety and tolerability data were generated in relatively balanced proportions of male and female patients with T2DM.

In the Phase III programme events suggestive of genital infection and events suggestive of UTI were reported for a greater proportion of females than males in all treatment groups.

Renal impairment and lactic acidosis

Metformin is excreted by the kidney and moderate to severe renal insufficiency increases the risk of lactic acidosis. Therefore, the dapagliflozin/metformin IR FDC should not be used in patients with moderate to severe renal impairment (patients with CrCl < 60 mL/min or eGFR < 60 mL/min/1.73 m2). This recommendation is consistent with the contraindications for metformin monotherapy (Glucophage SmPC). No dose adjustment will be recommended for patients with mild renal impairment receiving the dapagliflozin/metformin IR FDC

Hepatic impairment and lactic acidosis

Because of the risk of lactic acidosis associated with metformin in patients with impaired hepatic function described in the Glucophage SmPC, the dapagliflozin/metformin IR FDC will be contraindicated in patients with hepatic impairment.

Tissue hypoxia

Because of metformin, Xigduo is contraindicated in patients with acute or chronic disease which may cause tissue hypoxia such as: cardiac or respiratory failure, recent myocardial infarction and shock.

Heart failure

Experience in NYHA class I-II is limited, and there is no experience in clinical studies with dapagliflozin in NYHA class III-IV.

Safety based on pioglitazone use

Available epidemiological data for pioglitazone suggest a small increased risk of bladder cancer in diabetic patients treated with pioglitazone. While a causal relationship between dapagliflozin and bladder cancer is unlikely, as a precautionary measure, the dapagliflozin/metformin IR FDC will not be recommended for use in patients concomitantly treated with pioglitazone. This recommendation is consistent with the recommendations for the use of dapagliflozin monotherapy.

Pregnancy and lactation

The dapagliflozin/metformin IR FDC will not be recommended during the second and third trimesters of pregnancy. Treatment with the dapagliflozin/metformin IR FDC should be discontinued when pregnancy is detected. The dapagliflozin/metformin IR FDC must not be used while breast feeding.

Safety related to drug-drug interactions and other interactions

No dedicated interaction studies have been performed for the dapagliflozin/metformin IR FDC. The following statements reflect the current knowledge on the individual active substances.

Dapagliflozin has a low potential for drug-drug interactions and no clinically relevant interactions have been shown for the most commonly used concomitant medications in adult T2DM patients.

The SmPC includes the wording of the European Core Safety Profile for metformin with regards to interaction with diuretics.

Metformin is excreted by the kidney and moderate to severe renal insufficiency increases the risk of lactic acidosis (Glucophage SmPC). The dapagliflozin/metformin IR FDC will not be recommended for use in patients receiving loop diuretics or who are volume depleted, e.g. due to acute illness (such as gastrointestinal illness). 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. Careful monitoring of volume status (physical examination, blood pressure measurements, and laboratory tests including haematocrit) and electrolytes will be recommended for patients receiving the dapagliflozin/metformin IR FDC, especially during intercurrent conditions that may lead to volume depletion. Temporary interruption of treatment with the dapagliflozin/metformin IR FDC will be recommended for patients who develop volume depletion until the depletion is corrected. These recommendations are consistent with the recommendations for the use of dapagliflozin monotherapy (Forxiga SmPC).

There is increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic impairment) due to the metformin active substance of the dapagliflozin/metformin IR FDC. Consumption of alcohol and medicinal products containing alcohol should be avoided.

The intravascular administration of iodinated contrast agents in radiological studies may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis. Therefore, the dapagliflozin/metformin IR FDC must be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Lactic acidosis is identified as important identified risk in the dapagliflozin/metformin IR FDC RMP. No events of lactic acidosis were observed in the dapagliflozin development program.

Discontinuation due to adverse events

Overall, in the Phase III program, no consistent pattern in DAEs was observed that would suggest new safety concerns for dapagliflozin/metformin IR FDC. The PTs leading to the discontinuation of more than 1 dapagliflozin treated (dapagliflozin + met) subject reported consistently across most of the individual studies were creatinine renal clearance decreased (0.4% to 4.0% of total subjects) and blood creatinine increased (0.2% to 1.5% of total subjects). In metformin + placebo treated subjects creatinine renal clearance decreased in 0.4% to 3.0% of total subjects and blood creatinine increased in 0 to 0.7% of total subjects. During the 102-week ST + LT period, AEs leading to discontinuation of study therapy were reported by similar proportions of subjects across treatment groups (3.7% to 5.1% in the dapagliflozin groups and 6.6% in the placebo group.

Post marketing experience

At the time of the submission dapagliflozin was not marketed anywhere in the world. There is extensive clinical experience with metformin as a widely available and well-established treatment for T2DM.

2.6.1. Discussion on clinical safety

The database for studying the safety of the dapagliflozin/metformin immediate release (IR) fixed dose combination (FDC) in subjects with T2DM is considered sufficient. Data on subjects ≥ 65 years is limited. There was some variation across the studies in exclusion criteria for renal impairment. In most of the studies, eligibility was based on CrCl > 60 mL/min. Patients with severe renal impairment (eGFR < 30 mL/min/ 1.73 m2) and cardiac failure, NYHA class III and IV, have been excluded from studies. The extent of exposure to open-label metformin was generally similar to the extent of exposure to double-blind study medication. The daily mean dose of open-label metformin ranged from 1800 to 2000 mg daily across all treatment groups, which conforms closely to the daily metformin doses of the different formulations of the FDC product; metformin 1700 mg (850 mg BID) and 2000 mg (1000 mg BID). The safety profile of metformin is well-known. The safety profile of the dapagliflozin/metformin IR FDC is expected to be similar to the safety profile of dapagliflozin and metformin as individual components taken as combination therapy.

The deaths observed in the completed studies (as of 15 July 2011) were unrelated to dapagliflozin treatment. No deaths were reported in the short term key study BID 5 mg dapagliflozin/metformin IR FDC study D1691C00003 (as of 18 Nov 2011). No new cases of breast and bladder cancer were observed in the six Phase III studies included in this analysis of the 15 July 2011 integrated safety database, and one new post-study event of prostate cancer was reported in the comparator treatment group of study D1690C00004. The overall SAE profile observed in the six Phase III studies seemed consistent with that previously reported for pooled datasets in the initial dapagliflozin MAA.

In the six Phase III studies proportions of subjects with AEs of cardiac disorders were 2 to 13.4% in the dapagliflozin and 2 to 13.2% in the placebo group in the LT extensions of add-on

metformin. SAEs were balanced between groups. Even though these six Phase III studies (add-on Metformin) were not designed to evaluate CV safety on an individual study basis, no new safety signal regarding CV-related AEs was observed either with BID dosing of dapagliflozin add-on to metformin, or in the LT extensions of the Phase III studies. 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. According to the well-known safety profile of metformin the dapagliflozin/metformin IR FDC is contraindicated in acute or chronic disease which may cause tissue hypoxia and information is included in the SmPC. At the CHMP request, the applicant has submitted a summary of mean percent change from baseline for dapagliflozin and metformin groups versus placebo, respectively, of: total cholesterol (TC), high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides. When looking at the individual studies, the data is not consistent across the studies and there is variability over time. This may in part be explained by the limited data set. However, the pooled data show that TC continues to increase over time. The increase in HDL over time appears greater than the increase in LDL, whereas TG tend to decrease over time. The clinical relevance of the observed changes will have to be further investigated in the planned CV outcomes study. Adequate information is included in the SmPC.

Incidence of hypoglycaemic events is relatively low and similar (3.6-5.2%) across treatment groups when used as add-on to metformin, or as add-on to sitagliptin with no major episode of hypoglycaemia reported, and no subject discontinued study treatment due to a hypoglycaemic event. As expected, the incidence is high (42.6-69.3%) in both the dapagliflozin + metformin and placebo groups with add-on insulin therapy. The majority of hypoglycaemic events were classified as minor. Data from the Phase III studies indicate that BID dosing of dapagliflozin add-on to metformin, as well as LT treatment with dapagliflozin were generally consistent with those reported in the initial dapagliflozin MAA.

Proportions of subjects with AEs of genital infections were larger in the dapagliflozin (3 to 14.6%) than in the placebo group (1.0 to 5.1%) in the LT extensions of add-on metformin. This confirms the importance the information included in the SmPC. Most infections were mild to moderate, and subjects responded to an initial course of standard treatment, and infections rarely resulted in discontinuation of treatment. These infections were more frequent in females. No new safety signal regarding genital infections was observed in the LT extensions of the Phase III studies.

Proportions of subjects with AEs of UTI were larger in the dapagliflozin (2 to 11.8%) than in the placebo group (1.0 to 5.1%) in the LT extensions of add-on metformin. This confirms the importance the warnings included in the SmPC. Most infections were mild to moderate, and subjects responded to an initial course of standard treatment, and infections rarely resulted in discontinuation of treatment. Pyelonephritis was uncommon and occurred at a similar frequency to control.

Proportions of subjects with AEs of renal impairment or failure were larger in the dapagliflozin (1.5 to 4.4%) than in the placebo group (1.5 to 2.0%) in the LT extensions of add-on metformin. Metformin is excreted by the kidney and moderate to severe renal insufficiency increases the risk of lactic acidosis (Glucophage SmPC). Therefore, the dapagliflozin/metformin IR FDC should not

be used in patients with moderate to severe renal impairment (patients with CrCl < 60 mL/min or eGFR < 60 mL/min/1.73 m2).

Proportions of subjects with AEs of volume depletion were slightly higher in the dapagliflozin (0 to 2.5%) than in the placebo group (0 to 1.5%) in the LT extensions of add-on metformin. Few events of syncope (3) and the events were balanced between groups. Small but consistent increases in haematocrit were observed among dapagliflozin-treated subjects across the entire Phase III dapagliflozin clinical programme, which are likely related to mild plasma volume depletion associated with the diuretic effect of dapagliflozin. Proportions of subjects with AEs of haematocrit values >55% were larger (0.5 to 2.3%) in the dapagliflozin than in the placebo group (0 to 0.7%) in the LT extensions of add-on metformin and in the dapagliflozin group (1.3%) vs comparator (SU) (0) and in 4.5% of subjects in the dapagliflozin group vs 0.4% of subjects in the placebo group in add-on combination therapy with sitagliptin. This confirms the importance the warnings in the SmPC.No subjects reported associated thromboembolic AEs, except for one subject in the dapagliflozin 5/10 mg group.

Liver injury is included as a potential risk in the RMP due to one subject in study D1690C00004 diagnosed with drug-induced hepatitis and/or autoimmune hepatitis. The event is described in the current SmPC. A detailed post marketing plan for liver safety monitoring has been proposed, including a pharmacoepidemiology programme and follow-up in the planned CV outcomes study. An analysis based on the 15 July 2011 integrated safety database to investigate the risk of liver toxicity found that there was no clear association between dapagliflozin treatment and liver toxicity, and no evidence of severe drug-induced liver injury. No new hepatic safety signals were observed either with BID dosing of dapagliflozin add-on to metformin or in the LT extensions of the Phase III studies. Proportions of subjects with AEs of hepatic disorders were slightly higher (0 to 3.3%) in the dapagliflozin than in the placebo group (1 to 2.2%) in the LT extensions of add-on metformin and modestly higher in the dapagliflozin group (2.7%) vs comparator (SU) (1.7%) and lower in 1.3% of subjects in the dapagliflozin group vs 3.5% of subjects in the placebo group in add-on combination therapy with sitagliptin. Xigduo will be contraindicated for use in patients with hepatic impairment, in line with metformin SmPC, because of the risk of lactic acidosis associated with metformin in patients with impaired hepatic function.

Bone fracture is identified as a potential risk in the RMP based on mean increases in markers of bone resorption in dapagliflozin-treated subjects compared with placebo-treated subjects observed in the early dapagliflozin clinical programme. In the Phase III studies proportions of subjects with AEs of bone fracture were 0 to 3.6% in the dapagliflozin and 0 to 3.0% in the placebo group in the placebo group in the LT extensions of add-on metformin. Bone fractures were balanced between groups. At the CHMP request, the applicant has submitted a summary of mean percent change from baseline for dapagliflozin and metformin groups versus placebo for the Phase 3 studies of: 25(OH)D, PTH and calcium and phosphorus. A summary of results of bone mineral density measurements (dapagliflozin+ metformin compared to placebo from baseline to 102 weeks) in study D1690C00012, was also submitted. In most of the studies, an increase in PTH was observed ranging from 2 % to 25 % vs placebo. The clinical relevance of this observation remains unclear. The data provided does not indicate an adverse effect of dapagliflozin either on calcium, phosphorus, 25(OH)D or BMD. Bone fractures are included as an important potential risk in the RMP and adequate information on PTH changes is included in the SmPC which is considered sufficient.

Across the dapagliflozin Phase III clinical programme, the overall proportion of subjects with malignant or unspecified tumours was balanced between dapagliflozin and placebo/comparator treatment groups. However, a numerical imbalance between dapagliflozin and comparator is still evident for bladder, breast, and prostate cancer. No new cases of breast and bladder cancer were observed in the six Phase III studies included in this submission since the analysis of the 15 July 2011 integrated safety database, and one new post-study event of prostate cancer was reported in the comparator treatment group of study D1690C00004. The reported events occurred across the clinical programme and in different treatment combinations, indicating no increased risk when dapagliflozin is combined with metformin specifically. The overall reported neoplasms indicate no change or increased risk associated with dapagliflozin long term therapy (up to 2 years). Dapagliflozin will not be recommended for patients who use pioglitazone because of a small increase in the risk of bladder cancer ascribed to pioglitazone in recent independent pharmacoepidemiology studies.

At the CHMP request the applicant submitted pooled safety data from five of the six Phase III studies. The data from the active comparator study was not included due to differences in study design which is acceptable. The pooled data for the short-term parts of the studies (presented by number of patients to be consistent with the presentation of safety data for dapagliflozin) showed that the safety profile for the FDC is comparable to that of dapagliflozin. Thus the data support the inclusion of Genital Infection, Urinary tract infection and Hypoglycaemia in the adverse reaction table in section 4.8 of the SmPC with the same frequencies as for dapagliflozin. No additional adverse reactions were deemed to be included.

2.6.2. Conclusions on the clinical safety

The findings resulting from the submitted data reflecting treatment with dapagliflozin/metformin IR for up to 104 weeks show that the safety profile of the FDC is comparable to that observed for dapagliflozin. There were tendencies to higher incidences of AEs of elevated haematocrit and renal impairment, which emphasizes the importance of the warnings and precautions to be included in the SmPC, especially in the elderly population.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The applicant has submitted a signed summary of pharmacovigilance system. The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 3, the PRAC considers by consensus that the risk management system for dapagliflozin propanediol / metformin hydrochloride (Xigduo) in the treatment of diabetes is acceptable.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

The applicant identified the following safety concerns in the RMP:

Summary of Safety Concerns

Important identified risks	• Genital Infections • Urinary Tract Infection • Lactic Acidosis
Important potential risks	• Hypoglycemia • Volume Depletion • Clinical Consequences of Increased Haematocrit • Renal Impairment/Failure • Bone Fracture • Liver Injury • Bladder Cancer • Breast Cancer • Prostate Cancer • Off-label Use of Dapagliflozin in Specific Populations
Missing information	• Pediatric Population • Pregnancy and Lactation • Elderly (≥ 65 years) • Severe renal impairment • Moderate and severe hepatic impairment • Congestive heart failure defined as New York Heart Association (NYHA) class III and IV

- **Pharmacovigilance plans**

There are no specific studies proposed specifically for dapagliflozin and metformin FDC. Patients treated with dapagliflozin and metformin FDC will be included in the pharmacoepidemiology program described in the dapagliflozin RMP.

On-Going and Planned Additional PhV Studies/ Activities in the Pharmacovigilance Plan

Study/ Activity Type Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
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. Non-Interventional" and "2" Based on Classification[a]	Primary Objective: To compare, by insulin use at the index date, the sex-specific incidence of hospitalization or emergency department (ED) visit for severe complications of UTI, defined as pyelonephritis and urosepsis, among patients with T2DM who are new users of dapagliflozin with those who are new users of antidiabetic drugs (ADs) in classes other than SGLT2 inhibitors, insulin, metformin monotherapy, or sulfonylurea monotherapy.	Severe complications of UTI	Ongoing	The data will be reported initially 18 months after dapagliflozin has been on the market Final Report Submission estimated to be 01-Apr-2016
MB102104: Comparison of The Risk of Acute Liver Failure Between Patients With T2DM Exposed to Dapagliflozin and Those Exposed to Other Antidiabetic Treatments[a]	Primary Objective: To compare, by insulin use at the index date, the incidence of hospitalization for acute liver injury(ALI) among patients with T2DM who are new users of dapagliflozin with those who are new users of ADs in classes other than SGLT) inhibitors, insulin, metformin monotherapy, or sulfonylurea monotherapy.	Risk of Acute Hepatic Failure	Ongoing	The data will be reported initially 12 months after dapagliflozin has been on the market, and annually 60 months post launch Final Report Submission estimated to 01-Apr-2018
MB102110: Comparison of The Risk of Acute Kidney Failure Between Patients With Type 2 Diabetes Exposed to Dapagliflozin and Those Exposed to Other Antidiabetic Treatments[a]	Primary Objective: To compare, by insulin use at the index date, the incidence of hospitalization for acute kidney injury (AKI) among patients with T2DM who are new users of dapagliflozin with those who are new users of ADs in classes other than sodium-glucose cotransporter 2 (SGLT2) inhibitors, insulin,	Risk of Acute Renal Failure	Ongoing	The data will be reported initially 18 months after dapagliflozin has been on the market, and periodically thereafter every 18 months, 60 months post launch Final Report Submission estimated to 01-Apr-2018
MB102118: Comparison of The Risk of Cancer Among	The primary objectives of this study are (1) to compare the incidence of breast cancer, by insulin use at	Risk of cancer	Ongoing	The data will be reported initially 24 months after

On-Going and Planned Additional PhV Studies/ Activities in the Pharmacovigilance Plan

Study/ Activity Type Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
Patients with T2DM Exposed to Dapagliflozin and Those Exposed to Other Anti-Diabetic Therapies[a]	cohort entry, among females with T2DM who are new initiators of dapagliflozin and females who are new initiators of ADs in classes other than SGLT2 inhibitors, insulin, metformin monotherapy, or sulfonylurea monotherapy and (2) to compare the incidence of bladder cancer, by insulin use at cohort entry and pioglitazone use, among male and female patients with T2DM who are new initiators of dapagliflozin			dapagliflozin has been on the market, and every 2 years thereafter 120 months post launch Final Report Submission estimated to 01-Apr-2023
CV outcome study (D1693C00001): 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	The primary safety objective of this trial is to establish whether the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of the composite endpoint of cardiovascular death, myocardial infarction or ischemic stroke, in patients with T2DM with either established cardiovascular disease or at least two cardiovascular risk factors in addition to T2DM, observed with dapagliflozin to that observed in the placebo group is less than 1.3. Evaluation of the incidence of adjudicated bladder cancer and liver injury	Cardiovascular risk, bladder cancer, liver injury	Ongoing	Final Report Submission estimated to be 2020
Study D1690C00018: Safety for Patients with High CV Risk, Including Patients with CHF NYHA Class III Stratified to 50% Subjects ≥ 65 Years of Age	Primary objectives: To compare the glycaemic efficacy of dapagliflozin 10 mg versus placebo when added to usual care in T2D patients with cardiovascular disease and hypertension, measured as the mean change in haemoglobin A1c (HbA1c) from baseline to week 24, in the overall population and in the two predefined age subgroups (<65 years, ≥65 years). To compare the clinical benefit of	Use in elderly	Ongoing	104 week report, 25-May-2013

On-Going and Planned Additional PhV Studies/ Activities in the Pharmacovigilance Plan

Study/ Activity Type Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
	dapagliflozin 10 mg versus placebo when added to usual care in T2D patients with cardiovascular disease and hypertension at week 24, measured as the proportion of responders for a 3-item endpoint of clinical benefit, defined as: • an absolute drop of 0.5% or more from baseline HbA1c, and • a relative drop of 3% or more from baseline for total body weight, and • an absolute drop of 3 mmHg or more from baseline in seated systolic blood pressure, in the overall population and in the two predefined age subgroups (<65 years, ≥65 years).			
Study D1690C00019: Safety for Patients with High CV Risk, Including Patients with CHF NYHA Class III Stratified to 50% Subjects ≥ 65 Years of Age	Primary objectives: To compare the glycaemic efficacy of dapagliflozin 10 mg versus placebo when added to usual care in T2D patients with cardiovascular disease, measured as the mean change in haemoglobin A1c (HbA1c) from baseline to week 24, in the overall population and in the two predefined age subgroups (<65 years, ≥65 years). To compare the clinical benefit of dapagliflozin 10 mg versus placebo when added to usual care in T2D patients with cardiovascular disease at week 24, measured as the proportion of responders for a 3-item endpoint of clinical benefit, defined as: • an absolute drop of 0.5% or more from baseline HbA1c, and • a relative drop of 3% or more from baseline for total body weight, and • an absolute drop of 3 mmHg or	Use in elderly	Ongoing	104 week report, 5-Jun-2013

On-Going and Planned Additional PhV Studies/ Activities in the Pharmacovigilance Plan

Study/ Activity Type Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim or Final Reports
	more from baseline in seated systolic blood pressure, in the overall population and in the two predefined age subgroups (<65 years, ≥65 years).			
Observational Single-Cohort Database Study of Dapagliflozin Utilization in Europe[a]	Primary objective: To describe the characteristics of European patients prescribed dapagliflozin by age, sex, dapagliflozin dose, country, selected co-morbidities, and selected concomitant medications.	Off-label use	Planned Final protocol September 2013.	The first drug utilization study analysis report will be submitted in Q1 2015, and annually thereafter, with the corresponding PSUR.

[a] The study will include patients on dapagliflozin as well as combination therapies with dapagliflozin, e.g. dapagliflozin metformin FDC

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

- **Risk minimisation measures**

Summary table of Risk Minimisation Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures - none or assessment ongoing
Important Identified Risks		
Genital Infections	Yes	None
Urinary Tract Infections	Yes	None
Lactic acidosis	Yes	None
Important Potential Risks		
Hypoglycemia	Yes	None
Volume Depletion	Yes	None
Clinical Consequences of Increased Haematocrit	Yes	
Renal Impairment/ Failure	Yes	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures - none or assessment ongoing
Bone Fracture	Yes	None
Liver Injury	Yes	
Bladder Cancer	Yes	None
Breast Cancer	Yes	None
Prostate Cancer	Yes	None
Off-label use of Dapagliflozin in Specific Populations	Yes	None
Missing Information		
Pediatric population	Yes	None
Pregnancy/Nursing mothers	Yes	None
Elderly population	Yes	None
Patient with severe renal impairment including end-stage renal disease (ESRD) requiring haemodialysis, or undergoing peritoneal dialysis	Yes	None
Patient with moderate and severe hepatic impairment	Yes	None
Patients with compromised cardiac function (CF) NYHA class III and IV	Yes	None

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice without changes.

2.9. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Ebyont (now named Forxiga, containing dapagliflozin) and Gluality (now named Komboglyze, containing the combination of saxagliptin

and metformin). The bridging report submitted by the applicant has been found acceptable by the CHMP.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The main goal in the treatment of type 2 diabetes mellitus is to achieve adequate glycaemic control in order to reduce long-term microvascular and macrovascular complications caused by chronic hyperglycaemia. In practice, most patients will eventually require multiple medications during the course of their disease to maintain glycaemic control. The need for multiple antidiabetic medications, however, often leads to poor adherence to therapy. Thus, the combination of dapagliflozin and metformin available as one tablet could provide an additional treatment option for patients with T2DM, and may improve patient compliance.

The clinical data provided with this application show that the addition of dapagliflozin in patients with inadequate control on metformin alone or metformin in combination with other OADs such as sulphonylureas, DPP4-inhibitors or insulin results in clinically relevant and statistically significant reductions in HbA1c. The combination of dapagliflozin and metformin has already been approved for dapagliflozin, based in most parts on the same data as presented in the current application.

Dapagliflozin when used as single component is dosed once daily. Therefore pharmacokinetic, pharmacodynamic and clinical data has been provided to support the 5mg BID dosing needed when dapagliflozin is combined with metformin. The proposed metformin dose is well established and is covered by the range of doses used in the clinical programme.

Pharmacokinetic data showing similar exposure after administration of dapagliflozin 5 mg BID and 10 mg OD supports the proposed twice daily administration of Xigduo. This is further supported by a similar pharmacodynamic response in terms of inhibition of renal glucose re-absorption for the 5 mg BID and 10 mg OD.

Bioequivalence between Xigduo FDC and dapagliflozin and metformin administered has mono-components has been demonstrated which is crucial in order to support the substitution indication and also to bridge from the monotherapy tablets used in the clinical studies.

In the clinical study DC1691C00003, comparable placebo-corrected reductions in HbA1c were observed for the dapagliflozin 5 mg BID (-0.35 %) and 10 mg OD (-0.29 %) dosing. The outcome was somewhat less than observed for the dapagliflozin 10 mg OD group in study MB102014 where a placebo-corrected HbA1c reduction of -0.54 % was observed, but in line with the outcome in study D1690C00012 (-0.28 %). The outcome of the primary endpoint was supported by the outcome of the secondary variables. A clinically relevant weight reduction ranging between 1.5 and 2.0 kg was observed across studies.

Uncertainty in the knowledge about the beneficial effects

The efficacy of the combination has been adequately shown and no uncertainties remain. Long-term data up to 104 weeks has been provided showing a maintained effect on glycaemic control and maintained weight reduction.

Risks

Unfavourable effects

As for dapagliflozin, the most common adverse events in the Phase 3 studies were genital (6.6 % vs 1.1 %) and urinary tract infections (4.8 % vs 3.2 %), which are related to the mechanism of action for dapagliflozin. Hypoglycemia was also commonly reported (7.9 % vs 6.7 %), although the difference between treatment groups were less prominent. There were tendencies to higher but reversible incidences of AEs of elevated haematocrit and renal impairment, which emphasizes the importance of the warnings and precautions included in the SmPC, especially in the elderly population with increased risk for volume depletion. Data is limited in the elderly population.

The FDC with metformin could increase the risk of lactic acidosis in type 2 diabetes patients with significant renal impairment and therefore precaution is needed in this subpopulation. Lactic acidosis is a very rare but serious (more than 50% mortality in the absence of prompt treatment), metabolic complication that can occur due to accumulation of metformin, a component of Xigduo. It is of importance to monitor the renal function before start and during treatment with dapagliflozin and inform patients of a healthy intake of water and nutrition to balance volume depletion and metabolic changes that could interact with lipid metabolism. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any conditions associated with hypoxia.

The pooled long-term safety data from five of the six Phase 3 studies does not indicate any change in the safety profile of Xigduo over time.

Uncertainty in the knowledge about the unfavourable effects

Lipid changes with increased in total cholesterol, HDL and LDL have been observed with both dapagliflozin and dapagliflozin/metformin treatment. The clinical relevance of these changes remains unclear and will be further investigated in the planned CV outcomes study which is deemed sufficient.

In most of the studies, an increase in PTH was observed ranging from 2 % to 25 % vs placebo. The clinical relevance of this observation remains unclear. The data provided does not indicate an adverse effect of dapagliflozin either on calcium, phosphorus, 25(OH)D or BMD. Bone fractures are included as an important potential risk in the RMP and adequate information on PTH changes is included in the SmPC which is considered sufficient. Bone fractures will also be monitored in the planned CV outcomes study.

Benefit-risk balance

Importance of favourable and unfavourable effects

When dapagliflozin is added to metformin in patients with inadequate metabolic control, a clinically relevant reduction of HbA1c is observed. The improved metabolic control is achieved with a concomitant decrease in body weight, which is considered a benefit in type 2 diabetes mellitus patients with overweight often being a problem. Providing the treatment in a fixed dose combination has the potential of improving compliance.

The safety profile for dapagliflozin/metformin IR FDC has been adequately described and identified safety issues are taken care of within the SmPC and the risk management plan.

Discussion on the benefit-risk balance

The benefit-risk balance for concomitant treatment with dapagliflozin and metformin has already been accepted as positive for the free combination.

The CHMP considered that the benefit-risk balance of dapagliflozin/metformin fixed dose combination is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Xigduo in treatment of

“adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control

• in patients inadequately controlled on their maximally tolerated dose of metformin alone

• in combination with other glucose lowering medicinal products, including insulin, in patients inadequately controlled with metformin and these medicinal products (see sections 4.4, 4.5 and 5.1 for available data on different combinations)

• in patients already being treated with the combination of dapagliflozin and metformin as separate tablets”

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

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

Not applicable.