31 January 2019
EMA/CHMP/213138/2019 Corr.1[1]
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Forxiga	dapagliflozin
Edistride	dapagliflozin

Procedure No. EMEA/H/C/xxxx/WS/1344

Note

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

[1] 11.02.2019

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List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
AUC	Area under the plasma concentration time curve
BMI	Body mass index
BRAT	Benefit Risk Action Team
CGM	Continuous glucose monitoring
CSII	Continuous subcutaneous insulin infusion
CSR	Clinical study report
CTD	Common Technical Document
DKA	Diabetic ketoacidosis
(e)GFR	(Estimated) glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
FDA	Food and drug administration
FPG	Fasting plasma glucose
HbA1c	Glycated haemoglobin
IVRS	Interactive Voice Response System
LT	Long-term
MAGE	Mean amplitude of glucose excursion
PBRER	Periodic benefit-risk evaluation report
PD	Pharmacodynamics
PhRMA	Pharmaceutical Research and Manufacturers of America
PK	Pharmacokinetics
PT	Preferred term
SAE	Serious adverse event
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology Studies
SCS	Summary of Clinical Safety
SGLT2	Sodium-glucose cotransporter type 2
ST	Short-term
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
UGE	Urinary glucose excretion
US	United States

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 12 February 2018 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following changes were proposed:

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

Extension of Indication to include new indication for the treatment of insufficiently controlled type 1 diabetes mellitus as an adjunct to insulin, when insulin does not provide adequate glycaemic control, for Forxiga and Edistride; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. The updated RMP version 16 has also been submitted.
In addition, the Worksharing applicant (WSA) took the opportunity to introduce minor editorial changes to SmPC and Package Leaflet.

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0302/2017 on the agreement of a paediatric investigation plan (PIP) and on the granting of a product-specific waiver concerning the paediatric population from birth to less than 2 years.

At the time of submission of the application, the PIP P/0302/2017 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The WSA received scientific advice from the CHMP on 20 February 2014 (EMEA/H/SA/1012/2/2013/II) and on 24 July 2014 (EMEA/H/SA/1012/2/FU/1/2014/II). The Scientific advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

Appointed (Co-)Rapporteurs for the WS procedure:

Kristina Dunder and Martina Weise

Timetable	Actual Dates
Submission date:	12 Feb 2018
Start of procedure:	03 Mar 2018
CHMP Rapporteur Assessment Report	27 Apr 2018
CHMP Co-Rapporteur Assessment Report	27 Apr 2018
PRAC Rapporteur Assessment Report	27 Apr 2018
PRAC members comments	07 May 2018
Updated PRAC Rapporteur Assessment Report	08 May 2018
PRAC endorsed relevant sections of the assessment report	17 May 2018
CHMP members comments	22 May 2018
Updated CHMP Rapporteur(s) (Joint) Assessment Report	24 May 2018
RSI:	31 May 2018
Submission:	16 Aug 2018
Start of procedure:	20 Aug 2018
CHMP Rapporteurs Assessment Report	18 Sep 2018
PRAC Rapporteur Assessment Report	18 Sep 2018
PRAC members comments	28 Sep 2018
Updated PRAC Rapporteur Assessment Report	28 Sep 2018
PRAC endorsed relevant sections of the assessment report	4 Oct 2018
CHMP members comments	8 Oct 2018
Updated CHMP Rapporteurs Joint Assessment Report	11 Oct 2018
2nd RSI	18 Oct 2018
Submission:	13 Nov 2018
Start of procedure:	14 Nov 2018
PRAC Rapporteur Assessment Report	19 Nov 2018
PRAC members comments	21 Nov 2018
AHEG Meeting	21 Nov 2018
Joint PRAC/CHMP Rapporteur Assessment Report	28 Nov 2018

PRAC endorsed relevant sections of the assessment report	29 Nov 2018
CHMP members comments	3 Dec 2018
Updated Joint PRAC/CHMP Rapporteur Assessment Report	6 Dec 2018
Oral explanation	12 Dec 2018
3rd RSI	13 Dec 2018
Submission:	21 Dec 2018
Start of procedure:	02 Jan 2019
PRAC/CHMP Rapporteur Assessment Report	16 Jan 2019
PRAC/CHMP members comments	21 Jan 2019
Updated PRAC/CHMP Rapporteur Assessment Report	24 Jan 2019
Opinion	31 Jan 2019

2. Scientific discussion

2.1. Introduction

Dapagliflozin is a selective, and orally active inhibitor of the human renal sodium-glucose cotransporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin (5 mg/10 mg) is currently approved in over 90 countries to improve glycaemic control in patients with type 2 diabetes mellitus (T2DM). Dapagliflozin has been approved in the European Union (EU) since November 2012 (FORXIGA procedure number: EMEA/H/C/002322, EDISTRIDE procedure number: EMEA/H/C/004161) and in the United States (US) since January 2014.

The MAH now seeks marketing approval for the use of dapagliflozin in adult patients with type 1 diabetes mellitus (T1DM) and the following indication was proposed (at time of submission of the application):

Forxiga / Edistride is indicated for the treatment of type 1 diabetes mellitus in adult patients as an adjunct to insulin, when insulin does not provide adequate glycaemic control.

The proposed dosing of dapagliflozin in patients with T1DM, as initially proposed, was 10 mg once daily.

Background to T1DM

T1DM is a serious disorder of chronic hyperglycaemia that results from the autoimmune destruction of insulin-producing pancreatic β-cells. T1DM accounts for approximately 5% to 10% of all cases of diabetes worldwide (Daneman 2006). Approximately four fifths of patients with T1DM are diagnosed as children (Beck et al 2012). T1DM is therefore a disease that most patients live with for the greater part of their lives.

While the life expectancy of patients with T1DM has improved considerably over the past century, it remains significantly reduced compared with the nondiabetic population. The loss of life expectancy in patients with T1DM after attaining 20 years of age has recently been estimated to be more than 10 years compared with the general population, mainly due to the increased risk of ischaemic heart disease (Livingstone et al 2015). Glycaemic control is key to reducing morbidity and mortality (Distiller 2014).

However, HbA1c alone does not provide the complete picture; even in patients with good glycaemic control, T1DM is still associated with increased morbidity and mortality compared with the general population (Lind et al 2014). Mitigating other risk factors for micro- and macrovascular complications apart from glycaemic control (e.g., blood pressure, body weight, and lipids) is thus also of importance for the long-term outcomes in this patient population. New diabetes treatments for T1DM that also target some of these risk factors would be of advantage. Further, despite identical mean HbA1c, patients can have large differences in their glycaemic variability (ie, intraday glycaemic oscillations or excursions) (Kilpatrick et al 2007). There is evidence that glycaemic variability in itself can contribute to the pathogenesis of vascular complications in diabetes (Hirsch 2015). Added to this, the quality of daily life of T1DM patients is highly dependent on their glucose swings (Vanstone et al 2015).

Current treatment options

Patients with T1DM require lifelong insulin therapy due to their inability to produce enough endogenous insulin. However, a large proportion of the T1DM population is unable to achieve recommended glycaemic levels with insulin alone (ADA 2017, Soedamah-Muthu et al 2008). There are currently no

approved adjunct treatments to insulin for patients with T1DM in the EU and only 1 in the US (pramlintide), whose use is limited.

While insulin treatment is lifesaving in patients with T1DM, many patients suffer from hypoglycaemic events as a result of the treatment, which negatively impact their daily lives and can, conversely, be life-threatening.

The glycaemic variability associated with insulin treatment also negatively impacts patients' quality of life (Vanstone et al 2015). Reducing swings in glucose levels is therefore of importance to prevent insulin-induced hypoglycaemia/hyperglycaemia as well as to improve the quality of life in patients with T1DM.

Another risk associated with suboptimal insulin use is DKA. Clinical and registry studies have shown annual rates of DKA of approximately 5% to 7% in patients with T1DM (Weinstock et al 2013, Maahs et al 2015). In particular, T1DM patients treated with short-acting insulin via pump are at risk for DKA if their pumps fail as they do not have any reservoir of basal insulin (Phillip et al 2007). However, a meta-analysis has shown that in the context of proper education and good practice, the frequency of DKA is similar in patients injecting insulin and patients using insulin pumps (Weissberg-Benchell et al 2003).

Rationale for the proposed change

In patients with T2DM, dapagliflozin improves glycaemic control and promotes weight loss. In patients with T1DM, SGLT2 inhibition by dapagliflozin was expected to produce similar glucose-lowering effects, as well as modest reductions in body weight, blood pressure, and, potentially, glycaemic variability, as the amount of glucose excreted following dapagliflozin treatment is dependent on the plasma glucose concentration and independent of insulin (Defronzo et al 2013).

Success criteria for the development of dapagliflozin to treat T1DM

For a new add-on to insulin treatment for T1DM to add value for patients, it is the MAH's position that the treatment should produce a clinically relevant reduction in HbA1c without increasing the risk of hypoglycaemia and with a manageable safety profile with respect to DKA compared with insulin treatment alone. The benefit-risk evaluation for dapagliflozin is thus primarily focused on HbA1c reduction, incidence of severe hypoglycaemic events and DKA in patients with T1DM. It is the MAH's view that additional treatment effects, such as attenuating weight gain and reducing glycaemic variability, would further increase the value of a new add-on to insulin treatment.

Development program

The key studies demonstrating efficacy and safety in global populations are studies MB102229 and MB102230, which included subjects in Europe, the Americas, and Asia. The studies included 24-week short-term (ST) double-blind treatment periods, on which the efficacy analyses were primarily based. The studies also include 28-week long-term (LT) extension periods; the LT extension of MB102229 is completed, while the LT extension of MB102230 is ongoing.

Studies D1695C00001 and MB102072 provide PK/PD data for subjects with T1DM as well as additional safety data. Integrated analyses and comparisons with PK/PD data from studies in subjects with T2DM were also used for the characterisation of the PK/PD of dapagliflozin in subjects with T1DM.

Compliance with regulatory guidance

Treatment and regulatory authority guidance considered

The following guidelines were considered in the design and conduct of studies MB102229 and MB102230:

- Standards of medical care in diabetes 2014 (ADA 2014)
- Notes for guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus (CPMP 2002, CHMP 2012)
- Diabetes mellitus: developing drugs and therapeutic biologics for treatment and prevention – draft guidance for industry (FDA 2008)

The designs of studies MB102229 and MB102230 are in accordance with the recommendations of these guidelines regarding, eg, statistical methodology, choice of efficacy endpoints, safety assessments, and choice of comparator.

Scientific advice

Key advice from the EMA on programme design was as follows:

- The conduct of 2 similar confirmatory studies, lead-in period and treatment period duration, choice of dapagliflozin doses, choice of comparator, and inclusion criterion of HbA1c ≥8.0% were endorsed.
- A drop in HbA1c of no more than 0.5% between enrolment and randomisation was initially recommended.
- The use of PK and PD data from T2DM patients can be used to support an indication in T1DM, and the different EC_{50} values observed between T1DM and T2DM patients should be discussed.
- Insulin treatment during the studies should be optimised to achieve best possible glycaemic control.
- Hypoglycaemia as the most important secondary endpoint was encouraged, and a combined response variable for glycaemic control and hypoglycaemia secondary variable was recommended (eg, a predefined decrease in Hb1Ac and without relevant hypoglycaemic event).

In accordance with the scientific advice, subjects whose HbA1c changed ≥0.5% between enrolment and randomisation were initially excluded from study MB102229. However, because this criterion accounted for approximately 80% of subjects being ineligible for randomisation after completing the lead-in period, the MAH sought renewed advice from the EMA and removed the criterion after agreement that doing so was appropriate.

Paediatric investigational plan

A waiver has been granted which applies to the paediatric population from birth to less than 2 years on the grounds that the medicinal product is likely to be unsafe in this population.

Thus the subset of the paediatric population concerned by the paediatric development in T1DM is children from 2 years to less than 18 years of age. The development plan includes the development of an age appropriate dosage form, two clinical studies in children from 10 to 18 years and children from 2 to 18 years as well as a modelling and simulation study for dose selection in children from 2 to 18 years.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.2.1. Ecotoxicity / environmental risk assessment

A re-evaluation of the Environmental Risk Assessment was conducted and submitted in the type II variation assessed in the current report. No new tests were performed. In the initial application, a refined market penetration factor (Fpen) was used to calculate the predicted environmental concentration (PEC). In the re-evaluated ERA the default value of Fpen was used (0.01) resulting in higher PEC values and PEC/PNEC ratios. The updated PEC/PNEC ratios for microorganisms, ground water, surface water, and sediment are, as in the initial application, below the trigger values.

Dapagliflozin- PEC / PNEC assessments

	PEC (µg/L)	PNEC (µg/L)	PEC/PNEC
Microorganisms	0.050	20000	2.5×10^{-6}
Surface water	0.050	100	5.0×10^{-4}
Groundwater	0.013	1000	1.3×10^{-5}
Sediment	0.78 (µg/kg dwt)	1500 (µg/kg/dwt)	5.2×10^{-4}

In the initial assessment of the environmental risk of dapagliflozin, it was concluded from the results of the aerobic and anaerobic transformation in aquatic sediment systems that dapagliflozin is persistent in sediments. In the submitted ERA however, dapagliflozin was considered not persistent. Since no new data was submitted, the initial assessment remains applicable, i.e. dapagliflozin is considered persistent.

2.2.2. Conclusion on the non-clinical aspects

Based on the updated data submitted in this application, the new indication leads to a significant increase in environmental exposure further to the use of dapagliflozin.

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- **Tabular overview of clinical studies**

Table 1 Studies pertinent to the use of dapagliflozin to treat T1DM

Study ID	Phase	Type of study	N	Subject characteristics	Treatments
MB102072	IIa	PK/PD	70	American subjects with T1DM and inadequate glycaemic control on insulin therapy	Dapagliflozin 1 mg, dapagliflozin 2.5 mg, dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo (all once daily and as add-on to insulin)
MB102229 (ST and LT)	III	Efficacy and safety	833[a]	Subjects with T1DM and inadequate glycaemic control on insulin therapy	Dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo (all once daily and as add-on to insulin)
MB102230 (ST and LT[b])	III	Efficacy and safety	813	Subjects with T1DM and inadequate glycaemic control on insulin therapy	Dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo (all once daily and as add-on to insulin)
D1695C00001 (Part A and Part B)	I (Part A), III (Part B)	PK/PD (Part A and B), safety and efficacy (Part B)	42 (Part A); 151 (Part B)	Japanese subjects with T1DM and inadequate glycaemic control on insulin therapy	Dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo (placebo during Part A only) (all once daily and as add-on to insulin)

[a] An Interactive Voice Response System randomisation system error affected the first 55 randomised subjects. These subjects were excluded from the full analysis set (the primary analysis set for efficacy analyses), which therefore includes 778 subjects. The safety analysis set includes all 833 randomised subjects.

[b] The LT extension of study MB102230 is ongoing and not included in this CTD.

CTD common technical document; LT Long-term; N Number of randomised subjects; PD Pharmacodynamics; PK Pharmacokinetics; ST Short-term; T1DM Type 1 diabetes mellitus

2.3.2. Pharmacokinetics

The complete pharmacokinetic profile of dapagliflozin was presented in the original dapagliflozin submission for T2DM (FORXIGA procedure number: EMEA/H/C/002322, EDISTRIDE procedure number: EMEA/H/C/004161), which summarised the absorption, distribution, metabolism, and excretion (ADME) characteristics of tofacitinib from relevant in vitro and in vivo studies.

The following is a summary of the PK characteristics of dapagliflozin:

- After oral administration, systemic exposure of dapagliflozin increases in a dose proportional manner.
- The mean plasma terminal half-life for dapagliflozin is 12.9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects. The mean total systemic clearance of dapagliflozin administered intravenously is 207 ml/min.
- Dapagliflozin is rapidly absorbed and has an absolute bioavailability (BA) of 78% after oral administration.
- Approximately 91% of circulating dapagliflozin is bound to plasma proteins.
- Dapagliflozin is extensively metabolised, mainly mediated by UGT1A9, to inactive metabolites.

Special populations

Population Pharmacokinetics in Patients with T1DM

The PK of dapagliflozin in T1DM patients is based upon pooled population PK analysis of plasma concentrations from 1 phase IIa study (MB102072), and 2 phase III studies (MB102229 and MB102230). The objectives of this analysis were: (a) to describe pharmacokinetic properties of dapagliflozin in T1DM patients including individual covariate effects on the PK parameters, (b) to calculate individual dapagliflozin AUC estimates for exposure-response analyses, (c) and to descriptively compare dapagliflozin PK properties between T1DM and T2DM patients.

In study MB102072 patients were treated with placebo or dapagliflozin (1, 2.5, 5 or 10 mg) once daily for 14 days. PK samples were taken pre-dose and up to 24 h post-dose on day 7. In studies MB102229 and MB102230 patients with inadequate glycemic control (defined as HbA1c≥7.5%) were treated for 24 weeks with 5 mg or 10 mg dapagliflozin as add-on therapy to insulin. Dapagliflozin concentrations at Day 1 up to Week 24 were used for the analysis. In total, 5797 samples with quantifiable concentrations from 1151 subjects were used for the analysis. Data exclusions; 122 (1.9%) concentrations were below the lower limit of quantification, 10 (0.16%) samples had missing sampling time, 170 samples (2.7%) had wrong/missing dosing time, and 270 (4.3%) concentrations were judged as post- rather than pre-dose concentrations. The PK sampling characteristics for the three studies have been summarised in **Table 2**.

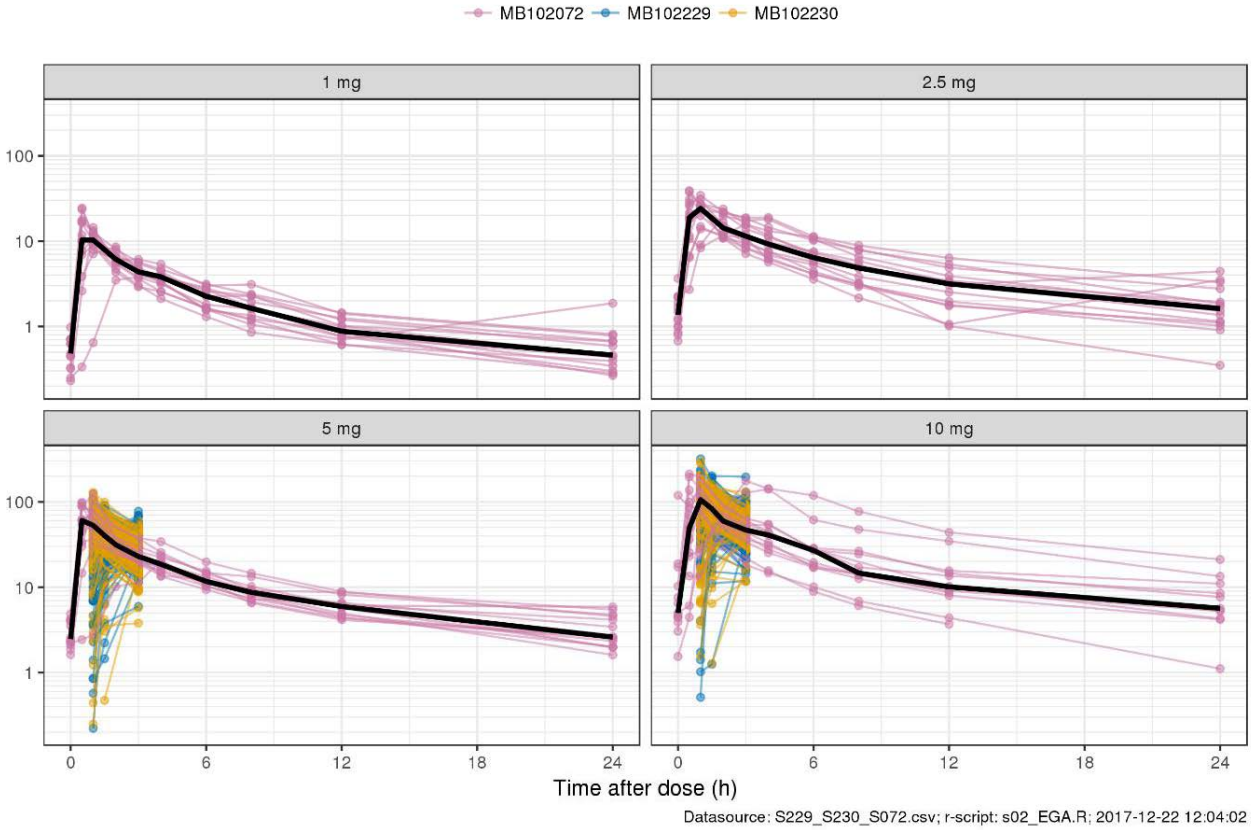
Table 2 Summary of studies and PK sampling characteristics of studies MB102072, MB102229 and MB102230.

Study Number	Study Description	Study Population	Number of subjects	Sample design	Samples/subject median (range)
MB102072	R, DB, 5-arm, PG, PC exploratory Ph2a.	Adult T1DM patients on insulin	57	PK samples as day 7 (pre-dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24 h pose-dose)	10 (9-10)
MB102229	MC, R, DB, PC, PG, Ph3	Adult T1DM patients on insulin	573	PK samples at day 1(60, 90 and 180 min post-dose) and weeks: 12, 18 and 24	6 (1-6)
MB102230	MC, R, DB, PC, PG, Ph3	Adult T1DM patients on insulin	541	PK samples at day 1(60, 90 and 180 min post-dose) and weeks: 12, 18 and 24	6 (1-7)

DB: double-blind, MC: multicentre, min: minutes, PC: placebo controlled, PG: parallel group, Ph2A: Phase 2A, Ph3: Phase 3, PK: pharmacokinetic, R: randomized, T1DM: Type 1 diabetes.

Dapagliflozin plasma concentration-time profiles up to 24 h shown in **Figure 1** indicated no major differences between the studies or sampling times.

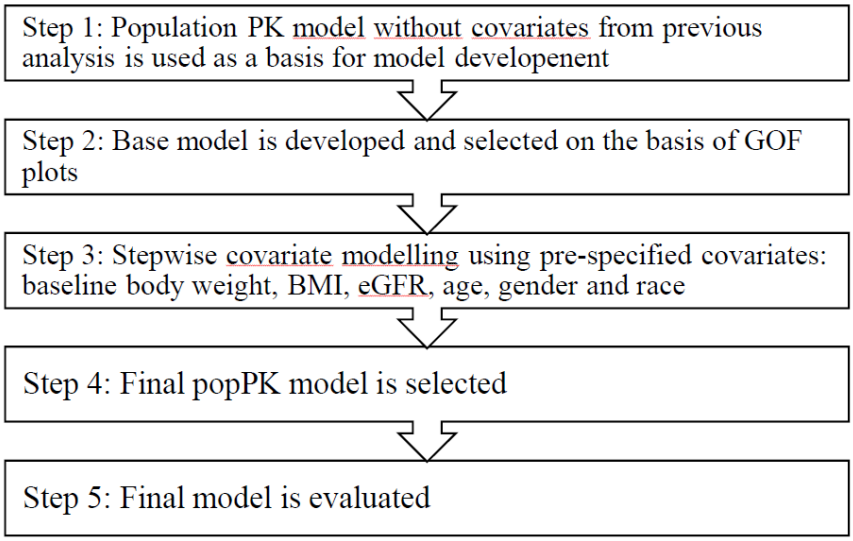
Figure 1 Plasma dapagliflozin concentration-time profiles up to 24 h in T1DM patients, stratified by dose. Black lines: median plasma dapagliflozin concentration. Lines and circles: observations



Population PK analysis was conducted using nonlinear mixed-effects modelling method using the software package NONMEM, version 7.3.0 (Icon Development Solutions, ICON Development Solutions, Hanover, Maryland, USA). Model fitting was performed in a Linux environment (CentOS 5, equivalent to Redhat Enterprise Linux 5) with GFortran FORTRAN Compiler, version 4.7.3 (Gnu Compiler Collection, GCC). Xpose4, version 4.5.3 (xpose.sourceforge.net), PsN, version 4.4.8 (psn.sourceforge.net) and R, version 3.2.4 (R-project, www.r-project.org) were used for the exploratory analysis, executing NONMEM runs and post-processing of NONMEM output, for example to assess goodness-of-fit. The estimation routine was FOCE with interaction.

The modelling steps are summarised in **Figure 2**.

Figure 2 Overview of Population PK analysis of dapagliflozin in T1DM patients.



GOF: Goodness of fit plots, BMI: body mass index, eGFR: estimated glomerular filtration rate

Base model

The previously developed dapagliflozin structural model was a linear 2-compartment model with first order absorption and lag time. This model was used as the basis for model development. The model was initially estimated using only data from the phase 2 study (MB102072), before the phase 3 data was added (MB102229 and MB102230). The sampling schedule did not allow for estimation of the absorption rate constant which was fixed to the previous parameter estimate. No further disposition models were evaluated. The random effect model was based on the T1DM patient data.

Stepwise covariate model development

Graphical covariate screening was performed to evaluate the potential influence of pre-specified covariates on selected PK parameters (**Table 3**). For continuous covariates, scatter plots of random effects against covariates overlaid with a non-parametric smoother and/or regression line were used to help identify potentially important relationships. For categorical covariates, box and whisker plots of individual (post-hoc) pharmacokinetic parameters for each of the groups were used to identify differences between groups.

Pre-specified covariates listed in **Table 3** were selected based on physiological plausibility and prior knowledge. Estimated glomerular filtration rate (eGFR) was derived using the Modification of Diet in Renal Disease (MDRD, Levey et al. 2007) formula. The proposed list of covariates was intended to be included in covariate testing if the available data support the planned evaluation.

Table 3 List of covariates investigated for their potential impact on the pharmacokinetic parameters

Parameter	Covariates
Apparent Clearance, CL/F (L/h)	Age, body weight, eGFR, race, sex
Central Volume, Vc/F (L)	Age, body weight, race, gender

eGFR: estimated glomerular filtration rate

Covariates were identified using a stepwise covariate modelling (SCM) procedure. Stepwise testing of linear and power relationships was performed in a forward inclusion (ΔOFV of 6.63, p <0.01 for 1

degrees of freedom) and backward exclusion (ΔOFV of 10.8, p <0.001 for 1 degrees of freedom) procedure. In case of categorical covariates, ΔOFV at the respective p - values may be different depending on the degrees of freedom. Retaining the covariate relationships identified by SCM was based on the reliability of the parameter estimate describing the covariate relationship (%RSE < 40).

The impact of all pre-specified covariates not identified in the SCM procedure was investigated using the full covariate approach. Only covariates with a correlation coefficient ≤|0.4| were added to the model. The effect on CL/F (i.e. AUC) was of interest for the current analysis. The precision in the covariate effects or relationship was based on the variance-covariance matrix generated by NONMEM. The influence, or lack of influence, of the covariates on primary PK parameters was illustrated graphically in forest plots.

Final model

The PK of dapagliflozin in T1DM patients was described by a 2-compartment model with first order absorption and linear clearance. The model was parameterised in terms of first-order absorption rate constant, apparent clearance (CL/F), apparent volume of distribution (Vc/F), apparent peripheral volume of distribution, and apparent inter-compartmental clearance (Q/F). Exponential inter-individual variability (IIV) was estimated for CL/F, Vc/F, and Q/F. The residuals were described by a proportional error model. The final parameter estimates and the associated relative standard errors are presented in **Table 4**.

Table 4 Final pharmacokinetic parameters for dapagliflozin in T1DM patients

Parameters	Units	Population mean	RSE (%)	Shrinkage (%)
KA	h-1	2.97[a]	NA	-
CL/F	L/h	20.6	1.93	-
Vc/F	L	86.2	2.52	-
Vp/F	L	141	7.45	-
Q/F	L/h	12.3	5.89	-
BWT~CL/F		0.41	14.8	-
eGFR~CL/F		0.33	15.9	-
SEX~CL/F		-0.14	14.7	-
AGE~Vc/F		-0.00338	27.9	-
SEX~Vc/F		-0.175	12.9	-
BWT~Vc/F		0.00811	8.5	-
Between subject variability				
CL/F	% CV	34.1	3.86	8.23
Vc/F	% CV	16.6	13.3	60.1
Q/F	% CV	35.4	11.3	59.5
Residual variability				
Proportional error for MB10229 and MB102230	% CV	37.3	1.91	9.54
Proportional error for MB102072	% CV	32.3	8.52	7.06

Source: PopPK Report Table 8 in CTD Module 5.3.3.5.

[a] Fixed value from estimate in subjects with T2DM.

Note: The ~CL/F parameters describe the covariate effect of BWT/eGFR/sex on CL/F. The ~Vc/F parameters describe the covariate effect of BWT/sex/age on Vc/F.

BWT body weight; CL/F apparent clearance; % CV percent coefficient of variation; eGFR estimated glomerular filtration rate; KA first-order absorption rate constant; Q/F apparent intercompartmental clearance; RSE relative standard error; Vc/F apparent central volume of distribution; Vp/F apparent peripheral volume of distribution.

Model evaluation in terms of goodness-of-fit diagnostics and prediction corrected visual predictive checks are displayed in **Figure 3** and **Figure 4**, respectively.

Figure 3 Goodness of fit plots for the final dapagliflozin T1DM population PK model including data from all studies

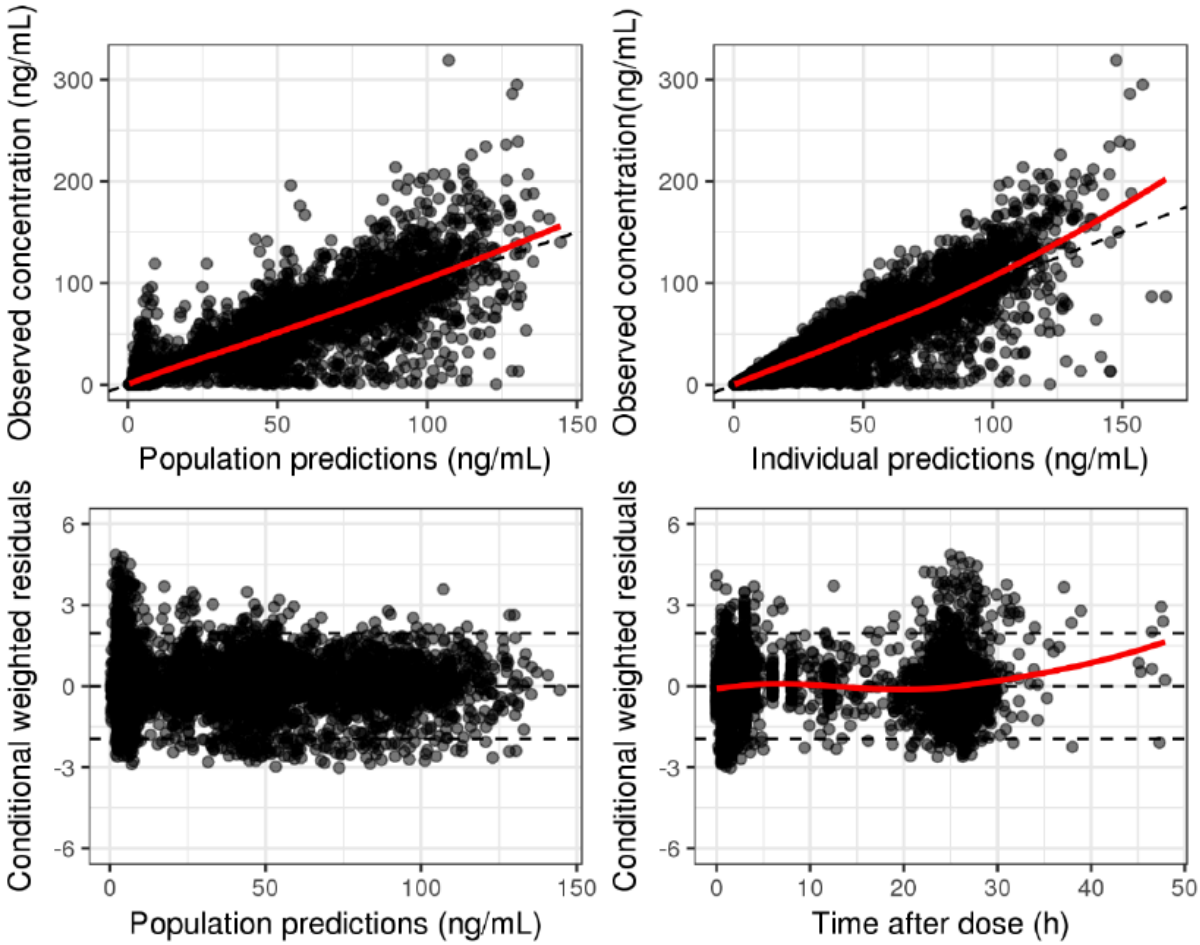
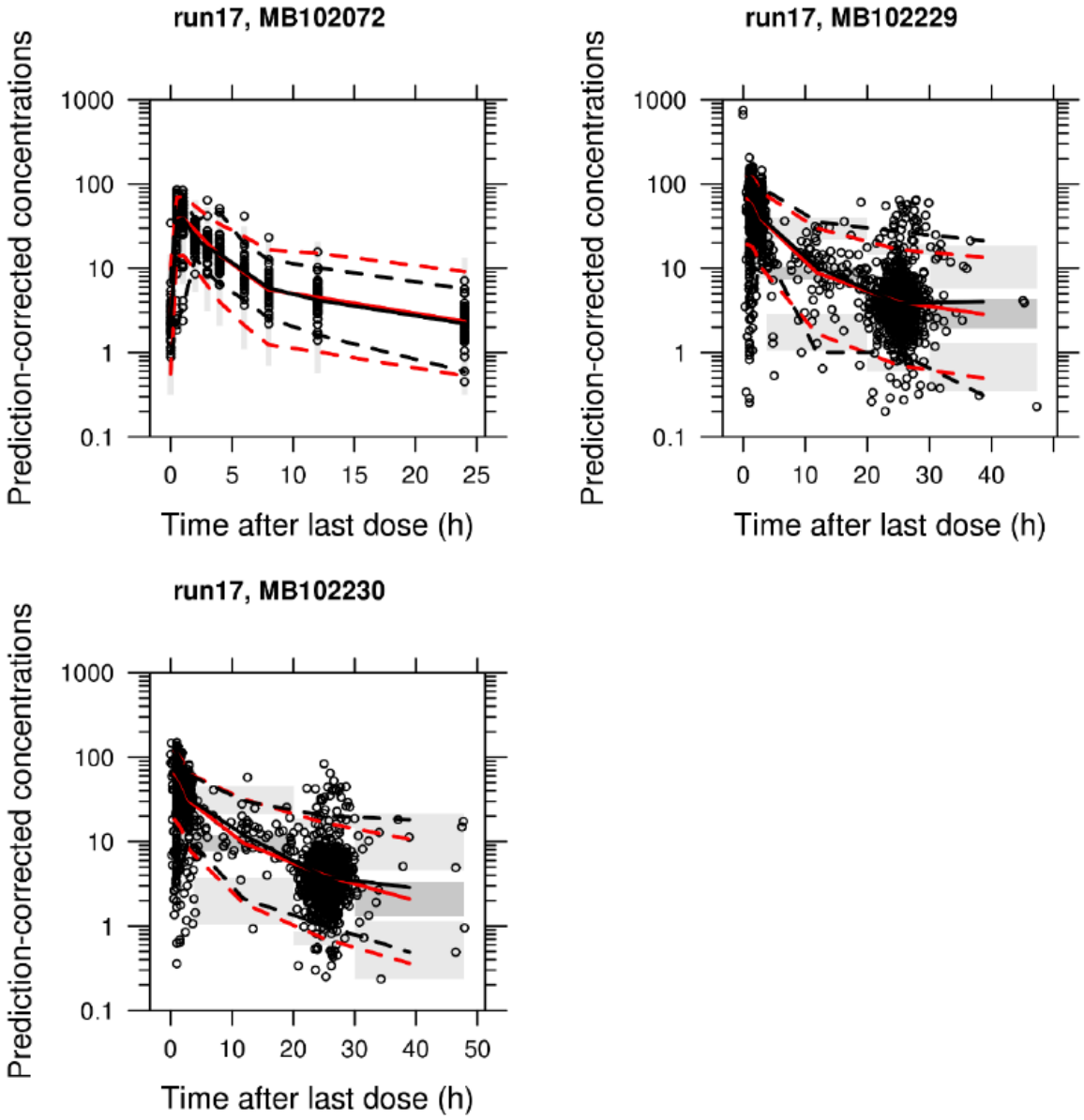


Figure 4 Prediction-corrected VPC of the final dapagliflozin T1DM population PK model versus time after last dose, stratified by study.

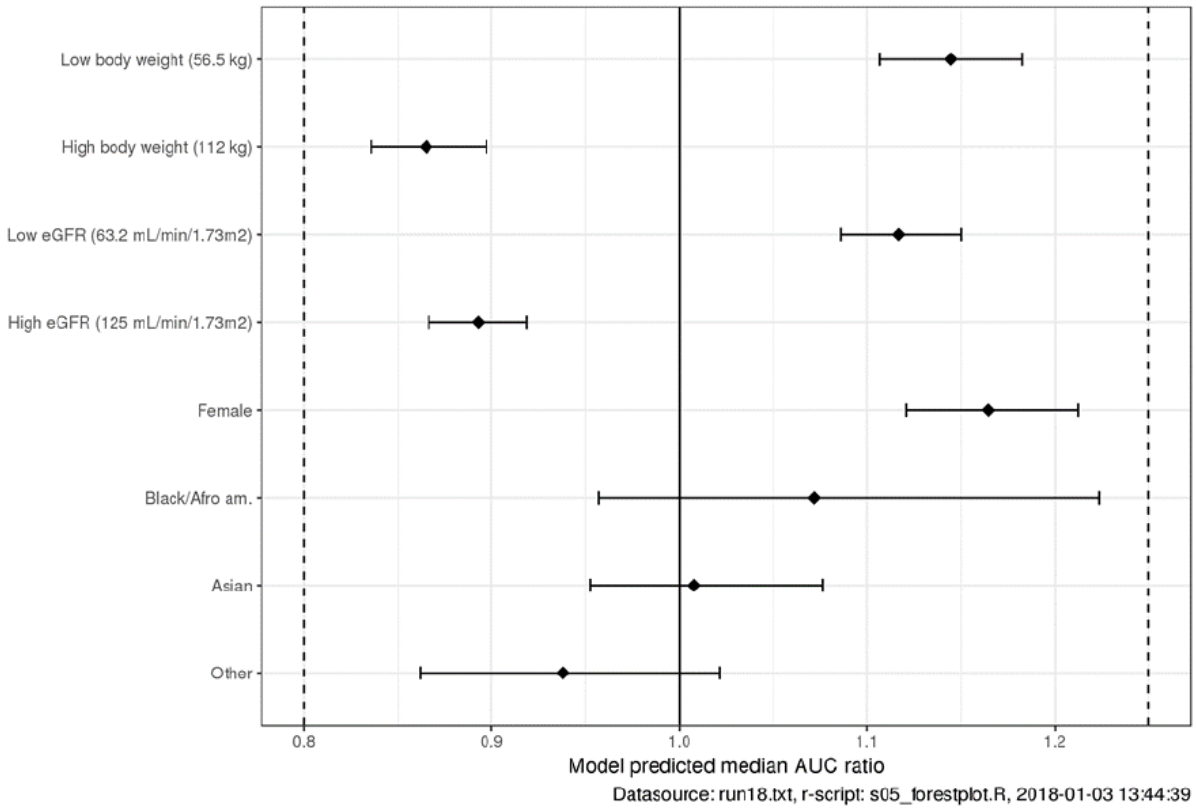


Datasource: pc-vpc tald_run17.tiff; path:./Models/vpc_17_predcorr_week/; r-script: s04a_VPC.R, 2018-01-05 15:05:09

The solid and dashed lines represent the median, 2.5th, and 97.5th percentiles of observed (in black) and simulated (in red) data; the grey areas represent the 95% confidence interval of the median, 2.5th, and 97.5th percentiles of the simulated data. VPC: visual predictive check

The identified covariate relationships in T1DM patients were similar to the covariate relationships previously reported (adult T2DM patients and healthy subjects); estimated glomerular filtration rate (eGFR)/creatinine clearance on CL/F (increased CL/F with higher renal function), and sex on CL/F (higher CL/F in males), and body weight on Vc/F (higher Vc/F with higher body weight). In addition, body weight was identified as a covariate on CL/F (higher CL/F with higher body weight), and sex (higher Vc/F for males) and age (lower Vc/F with higher age) on Vc/F. Within the studied range of covariates, no covariates affected systemic dapagliflozin exposure more than 25% compared to the reference individual (Caucasian male with body weight of 78.7 kg and eGFR of 88.6 mL/min/1.72 m^2) as visualised in

Figure 5 Covariate effect of the full covariate model for model-predicted AUC

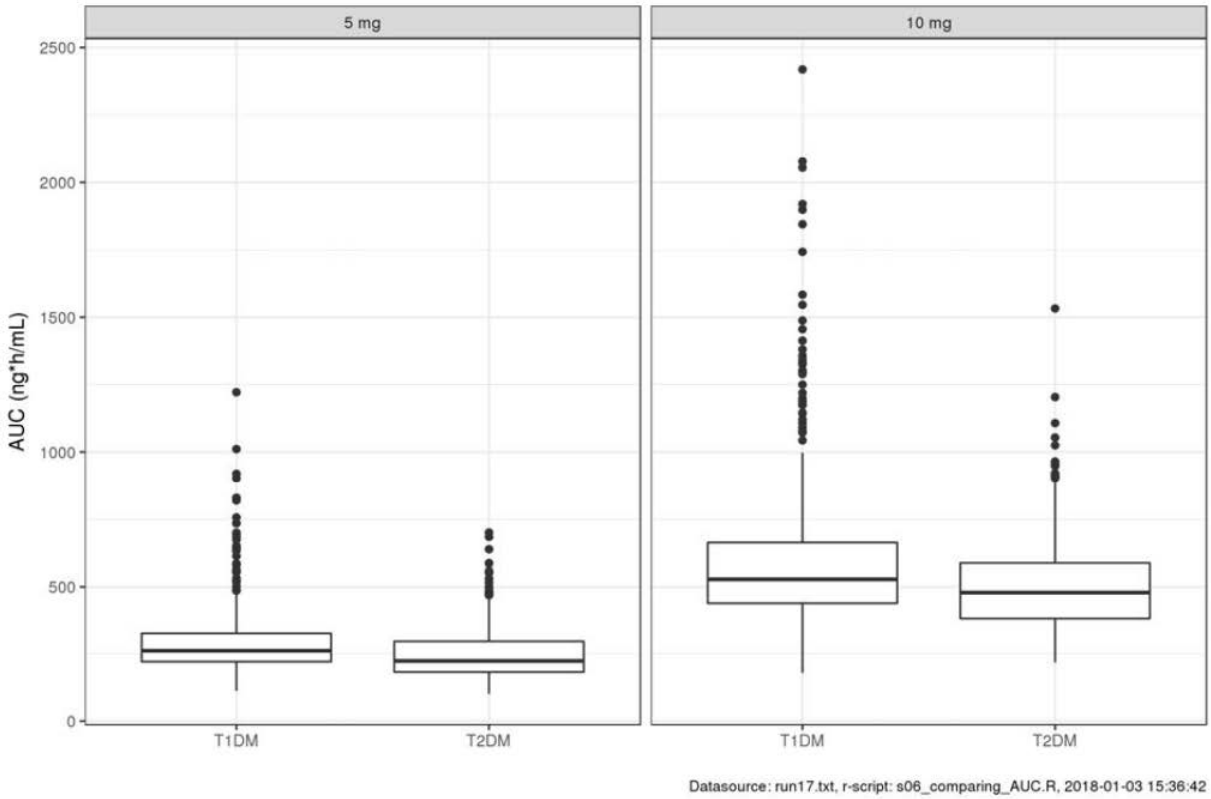


Source: PopPK Report Figure 9 in CTD Module 5.3.3.5.
The solid vertical line corresponds to the reference individual: Caucasian male with body weight of 78.7 kg and eGFR of 88.6 mL/min/1.72 m^2.
AUC in patients with lower and higher body weight were compared to the reference individual with body weight of 79 kg; AUC in patients with lower and higher eGFR were compared with AUC in the reference individual with eGFR of 88.6 mL/min/1.72 m2; AUC in female patients were compared with AUC in the reference male; AUC in Black/Afro American, Asian and other races were compared with AUC in the reference Caucasian. The symbols represent the median model predicted AUC ratio and the whiskers represent the 95% CI.
AUC area under the concentration curve; CI confidence interval; eGFR estimated glomerular filtration rate.

Comparison of dapagliflozin exposure in T1DM and T2DM patients

Model-predicted AUC for T1DM and T2DM (from previous analysis, original submission for T2DM) for 5 mg and 10 mg were extracted and compared descriptively. Apparent clearance in T1DM subjects (20.5 L/h) was similar to previous estimate in patients with T2DM and healthy subjects (22.9 L/h) which translates into similar AUC between patient populations. Boxplots for dapagliflozin AUC stratified by population and dose are displayed in **Figure 6**. The maximum plasma concentration (Cmax), area under the plasma concentration time curve (AUC), and time to reach maximum concentration (tmax) for the 2 populations are summarized in **Table 5**.

Figure 6 Comparison of predicted AUC between T1DM and T2DM



AUC: area under dapagliflizon concentration-time curve, T1DM: type 1 diabetes mellitus, T2DM; type 2 diabetes mellitus (T2DM)

Table 5 Exposure of dapagliflozin at steady-state for patients with T1DM and T2DM

Study type (study code)	Parameter	Dapa 1 mg	Dapa 2.5 mg	Dapa 5 mg	Dapa 10 mg	Dapa 20 mg	Dapa 25 mg	Dapa 100 mg
T1DM study (MB102072) Day 7	n	12	14	14	13			
	C_{max}, ng/ml median (min, max)	11.1 (3.80, 24.4)	24.9 (13.9, 39.1)	79.9 (20.6, 124)	137 (73.4, 212)			
	t_{max}, h median (min, max)	0.5 (0.4, 4.0)	1 (0.2, 3.0)	1 (0.5, 4.0)	1 (0.0, 4.0)			
	AUC, ng*h/ml median (min,max)	49.1 (31.5, 67.9)	136 (77.0, 216)	265 (159, 418)	664 (209, 1420)			
T2DM study (MB102003) Day 14	n			10			12	14
	C_{max}, ng/ml median (min, max)			71.9 (43.2, 115)			323 (106, 576)	1630 (719, 3370)
	t_{max}, h median (min, max)			1 (0.50, 2.00)			1 (1.00, 2.00)	1 (0.50, 4.00)
	AUC, ng*h/ml median (min,max)			299 (190, 463)			1490 (627, 2260)	7180 (3610, 12620)
T2DM study (MB102025) Day 14	n		9		9	9		
	C_{max}, ng/ml median (min, max)		51.4 (26.6, 72.0)		181 (112, 329)	331 (185, 484)		
	t_{max}, h median (min, max)		0.5 (0.5, 1.0)		1.0 (0.5, 1.5)	1.0 (0.50-2.0)		
	AUC, ng*h/ml median (min,max)		154 (74.0, 235)		742 (422, 987)	1252 (958, 1690)		
T2DM study (MB102007) Day 10	n					8		
	C_{max}, ng/ml median (min, max)					345 (238, 439)		
	t_{max}, h median (min, max)					1 (0.5, 1.5)		
	AUC, ng*h/ml median (min,max)					1040 (801, 1780)		

AUC Area under the concentration-time curve in 1 dosing interval; C_{max} Maximum observed plasma concentration; T1DM Type 1 diabetes mellitus; T2DM Type 2 diabetes mellitus; t_{max} time to maximum observed plasma concentration

Overall, the pharmacokinetics of dapagliflozin in T1DM patients was adequately described by the population PK model. The identified covariates in T1DM patients were similar to the covariates found in T2DM patients and healthy subjects, of which none are considered clinically relevant. Dapagliflozin systemic exposure after administration of 5 mg and 10 mg dapagliflozin once daily was dose-proportional and was comparable in adult T1DM and T2DM patients.

2.3.3. Pharmacodynamics

Mechanism of action

Dapagliflozin is a selective, and orally active inhibitor of the human renal sodium-glucose cotransporter type 2 (SGLT2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin lowers plasma glucose in an insulin-independent manner by inhibiting the renal reabsorption of glucose and promoting its urinary excretion.

Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is > 1,400 times more selective for SGLT2 versus SGLT1, the major transporter in the gut responsible for glucose absorption.

Primary and secondary pharmacology

Study MB102072

Study MB102072 was a randomised, double-blind, 5-arm, parallel-group, placebo-controlled, exploratory Phase IIa trial to evaluate the safety, tolerability, PK, and PD of dapagliflozin in subjects with T1DM who had inadequate glycaemic control (HbA1c ≥7.0% and ≤10.0%) despite insulin use. Subjects received dapagliflozin 1, 2.5, 5, or 10 mg, or matching placebo on a background of adjustable insulin for a total of 14 days and were monitored closely with regard to safety parameters, including vital signs, safety laboratory tests (including urinary ketones), and adverse events.

The primary objective was to assess the safety and tolerability of each dose of dapagliflozin. Secondary objectives were to assess the change from baseline in mean glucose based on 7-point central laboratory glucose monitoring achieved with each dapagliflozin dose versus placebo after 7 days of in-patient treatment, and to assess the PK of dapagliflozin and its major inactive metabolite, dapagliflozin 3-O-glucuronide, on Day 7.

In total, 70 subjects were randomised and treated, and 62 completed the study as planned. Mean age was 35.3 years, 57.1% of subjects were male, 88.6% of subjects were white, mean body mass index (BMI) was 24.88 kg/m^2, and mean HbA1c was 8.46%.

Pharmacodynamic results

Seven-point glucose monitoring: The 7-point glucose monitoring measured plasma glucose before and 2 hours after each meal (breakfast, lunch, dinner) and at bedtime. Mean 7-point glucose trended lower in all treatment groups compared to baseline, including the placebo group. The placebo group had a numerically higher mean value at baseline than the dapagliflozin groups. The placebo and dapagliflozin 1 mg groups tended to have progressive reductions in mean 7-point glucose values over the 7-day in-patient period. However, in the dapagliflozin 2.5, 5, and 10 mg groups, the greatest impact on mean 7-point glucose was seen at Day 1 and this effect was reduced by Day 7. There were no differences in change from baseline to Day 7 of mean of 7-point glucose measurement in any dapagliflozin treatment groups versus placebo.

Twenty-four hour (24h) UGE and inhibition of renal glucose reabsorption (IRR): The 24h UGE and percent IRR were based on 24h urine collections on Days -1, 1 and 7. UGE was higher and more variable in the placebo group at baseline, consistent with other measures suggesting a potential imbalance in overall glycaemic control at baseline in this group. The dapagliflozin groups showed a dose-dependent increase in urine glucose and a markedly higher percentage of IRR than the placebo group at Day 7. The placebo group had a change from baseline in 24h UGE at Day 7 of -21.45 g. The dapagliflozin 1 and 2.5 mg groups had changes of 41.48 and 48.09 g, respectively. Larger increases were seen in the dapagliflozin 5 mg and 10 mg groups of 71.71 and 88.02 g, respectively. The highest IRR values were reported in the dapagliflozin 5 mg and 10 mg groups.

Fasting plasma glucose (FPG): Fasting plasma glucose trended downward for all groups following administration of study drug, including the placebo group. Administration of dapagliflozin seemed to result in a numerically greater reduction in FPG at Day 1 than at Day 7.

Continuous glucose monitoring (CGM): Average daily glucose from all CGM values for a 24h period was assessed as a measure of overall glucose control. There was a trend towards improvement in the placebo group, with a change from baseline in average daily glucose derived from CGM at Day 7 of -20.25 mg/dL. Greater reductions were seen in the dapagliflozin 5 mg and 10 mg groups, with a change from baseline in average daily glucose at Day 7 of -29.55 and -41.27 mg/dL, respectively. Two different measures of glycaemic variability (standard deviation and mean amplitude of glycaemic excursions) were also assessed from CGM. Both showed little improvement in the placebo group, with more clear improvements of glycaemic variability in the dapagliflozin-treated subjects, particularly at the 5 mg and 10 mg doses.

Total daily insulin dose: Dapagliflozin treatment was associated with a 11.13% to 19.31% reduction in total daily insulin dose from baseline to Day 7: a change of -19.31% in the dapagliflozin 5 mg group and -16.17% in the 10 mg group. In the placebo group the mean percent change from baseline to Day 7 was +1.66%.

Study D1695C00001 (Part A)

Study D1695C00001 (Part A) was a Phase I study to evaluate the PK and PD of dapagliflozin in combination with insulin in Japanese subjects with T1DM who had inadequate glycaemic control. The study was a randomised, single-blind, 3-arm, parallel-group, placebo-controlled study. Subjects were randomised 1:1:1 to receive dapagliflozin 5 mg, dapagliflozin 10 mg, or placebo once daily for 7 days.

In total 62 subjects were enrolled and 42 were randomised. All subjects were recruited in Japan and were Asian. On average subjects were 38.9 years old, 161.8 cm in height, and 59.55 kg in weight with an average BMI of 22.72 kg/m^2. Approximately 24% of the subjects were obese according to Japanese criteria (BMI ≥25 kg/m2). Overall, 57.1% of the subjects were female: the placebo group was 78.6% female, the 10 mg group was 50.0% female, and the 5 mg group was 42.9% female. For all randomised subjects, the mean HbA1c at baseline was 7.98% with no substantial differences among the treatment groups. Mean baseline FPG was slightly higher in the 5 mg group than in the 10 mg group and the placebo group.

Subjects self-monitored their blood glucose at least 7 times per day (generally before and after breakfast, lunch, dinner, and bedtime) during the treatment period and contacted investigators in the event of an unusually high or low value.

Pharmacodynamic results

UGE: Similar increases of UGE from baseline to Day 7 were seen for the dapagliflozin 5 mg group (96.55 g/24h) and the 10 mg group (101.28 g/24h). During the same time interval a small decrease was seen in the placebo group with a mean change of -6.16 g/24h.

Daily insulin dose: At Day 7 the mean change from baseline in total insulin dose was -36.86%, -39.13%, and -4.97% in the 5 mg, 10 mg, and placebo groups, respectively. After Day 7 (during follow-up), a quick return to baseline was observed in both dapagliflozin groups. By Day 10, in the dapagliflozin 5 mg and 10 mg groups, the mean total insulin dose had returned to baseline.

FPG: Mean FPG was reduced in both dapagliflozin treatment groups at Day 7 compared to baseline while increases over baseline occurred for the placebo group at Day 7.

2.3.4. PK/PD modelling

Effect of dapagliflozin on UGE in subjects with T1DM compared to subjects with T2DM

Objectives

A model-based analysis was performed to characterise the relationship of dapagliflozin exposure and UGE in subjects with T1DM and compare it to data from subjects with T2DM.

Data and methods

The models were created using data from 1 study in T1DM subjects (MB102072) and data from 3 studies in T2DM subjects (MB102003, MB102007, and MB102025). Non-linear mixed effects models were developed to characterise the relationship between dapagliflozin exposure and UGE, and to evaluate the effects of baseline covariates on the UGE response. The base model also included subject type as a covariate on both E_{max} and half maximal effective concentration (EC_{50}). To evaluate the effects of baseline FPG, UGE, and eGFR, these covariates were evaluated in the final model on both E_{max} and EC_{50}. **Table 6** provides the average UGE levels (g/24h) reported in studies MB102072, MB102003, MB102007, and MB102025 across dose levels.

Table 6 Urinary glucose excretion in subjects with type 1 and type 2 diabetes

	Placebo	Dapa 1 mg	Dapa 2.5 mg	Dapa 5 mg	Dapa 10 mg	Dapa 20 mg	Dapa 25 mg	Dapa 100 mg
T1DM study (MB102072) Day 7								
n	13	12	14	14	13			
Mean (SD)	8.93 (7.45)	48.04 (20.65)	60.24 (37.82)	82.83 (47.48)	98.77 (57.53)			
T2DM study (MB102003) Day 14								
n	8			11			12	14
Mean (SD)	1.19 (2.02)			36.62 (47.20)			70.10 (35.83)	69.88 (28.76)
T2DM study (MB102025) Day 14								
n	9		9		9	9		
Mean (SD)	6.83 (11.40)		41.63 (13.4)		71.44 (11.42)	73.03 (20.82)		
T2DM study (MB102007) Day 10								
n						8		
Mean (SD)						68.35 (41.61)		

Derived from: MB102072 CSR Table 10.2-1 in CTD Module 5.3.4.2, MB102003 CSR Table S.11.3.1A, MB102025 CSR Table S 9.1.1, MB102007 CSR Table S 9.2.1 (additional calculations made).
Dapa dapagliflozin; SD standard deviation; T1DM type 1 diabetes mellitus; T2DM type 2 diabetes mellitus.

The analysis of UGE response was performed using steady-state average plasma concentration (C_{avg}) of dapagliflozin and longitudinal 24-hour UGE (Day 0 to Day 14) versus time data from T1DM subjects and T2DM subjects. Data from 160 subjects were available for this analysis: 70 with T1DM (study MB102072) and 90 with T2DM (studies MB102003 [N=46], MB102007 [N=8], and MB102025 [N=36]). Eight subjects were excluded from the analysis because of missing steady-state AUC measurements, resulting in a total of 152 subjects available for characterising the relationship between C_{avg} and change in UGE vs. time. The baseline covariates assessed in the analysis were UGE, FPG, and eGFR (**Table 7**).

Table 7 Summary of baseline covariates in analysis dataset

Baseline covariate	Mean	SD	Min, Max	5^{th}, 95^{th} percentile
T1DM				
FPG_B (mg/dL)	155	657.8	50.4, 295	69.3, 268
$eGFR_B$ (mL/min)	92.8	18.1	49.8, 145	70.5, 128
UGE_0 (g/24h)	14.2	25.2	0.0793, 194	0.182, 40.9
T2DM				
FPG_B (mg/dL)	151	34.5	95, 254	114, 222
$eGFR_B$ (mL/min)	88.9	19.1	54.6, 138	62.3, 128
UGE_0 (g/24h)	3.36	8.75	0.0264, 61.7	0.0455, 10.7

Source: Exposure-response (UGE) Report Table 4.1.1-1 in CTD Module 5.3.4.2.
$eGFR_B$ estimated glomerular filtration rate at baseline; FPG_B fasting plasma glucose at baseline; min minimum; max; maximum; SD standard deviation; T1DM type 1 diabetes mellitus; T2DM type 2 diabetes mellitus; UGE_0 urinary glucose excretion at baseline.

The MCMC Bayesian algorithm in NONMEM version 7.2 was used for model development. To evaluate convergence of three independent MCMC chains, Gelman and Rubin diagnostics were examined, and the plots of the three MCMC chains vs. iteration were visually inspected.

The structural model was defined as:

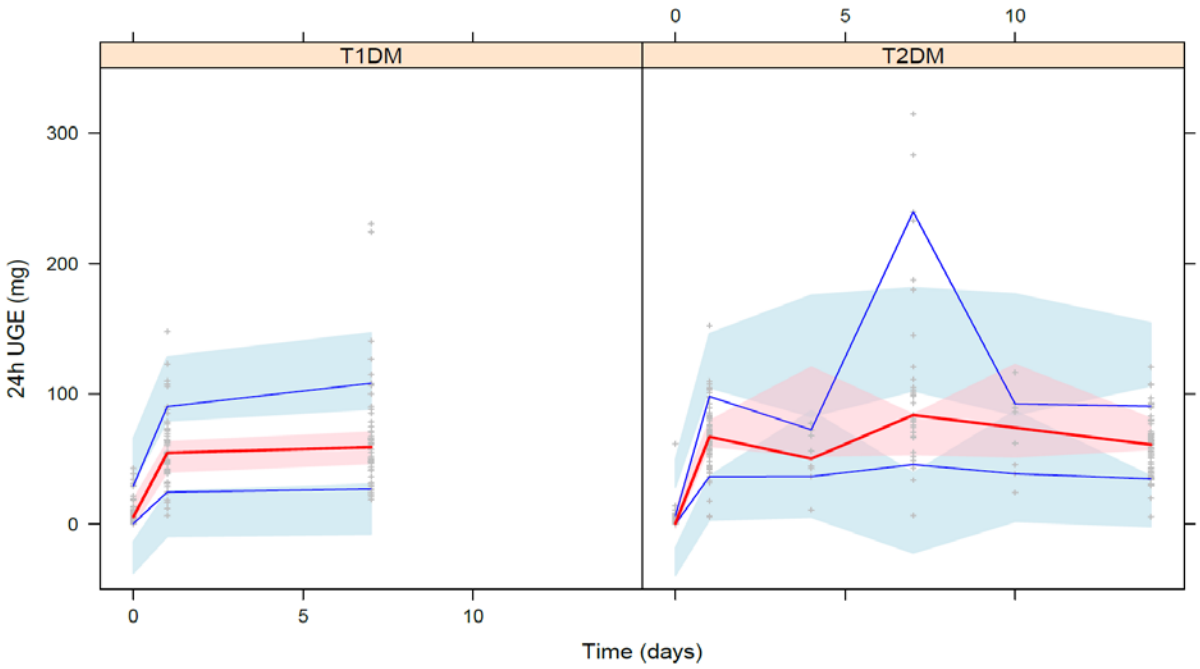
$$UGE = UGE_0 + \left[\frac{E\max \times Cavg}{EC_{50} + Cavg}\right] \bullet \left(1 - e^{(-Kdrg \bullet Day)}\right)$$

where UGE_0 is the estimated UGE at Day = 0, Emax is the maximum UGE at steady state, Cavg is the observed dapagliflozin average concentration at steady state, EC_{50} is the Cavg at which half of Emax is achieved, Kdrg is the rate constant for reaching the steady-state UGE response, and Day is the time in days. Separate population parameters were estimated for each patient type (T1DM or T2DM). Baseline covariates were evaluated on Emax and EC_{50}. An additive inter-individual (IIV) variability model was used for Emax and an exponential IIV model was tested for baseline UGE, Kdrg and EC_{50}.

Results

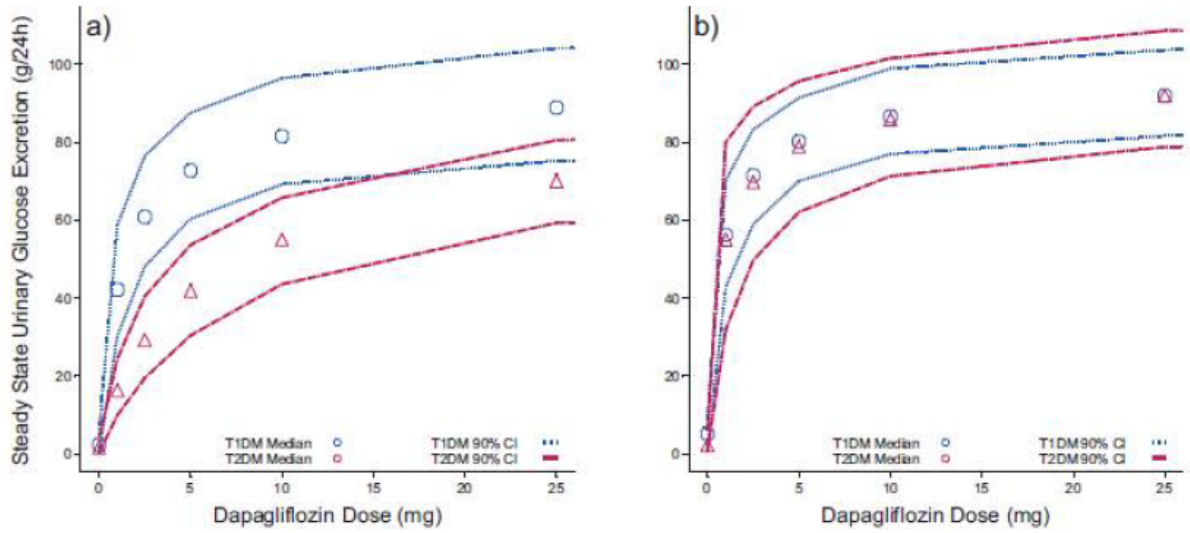
The E_{max} model described the relationship between steady-state dapagliflozin exposure and 24h UGE reasonably well although some apparent outliers are present in the T2DM population. The exposure-response relationship and model performance is visualised in **Figure 7**.

Figure 7 Prediction-corrected visual predictive check.



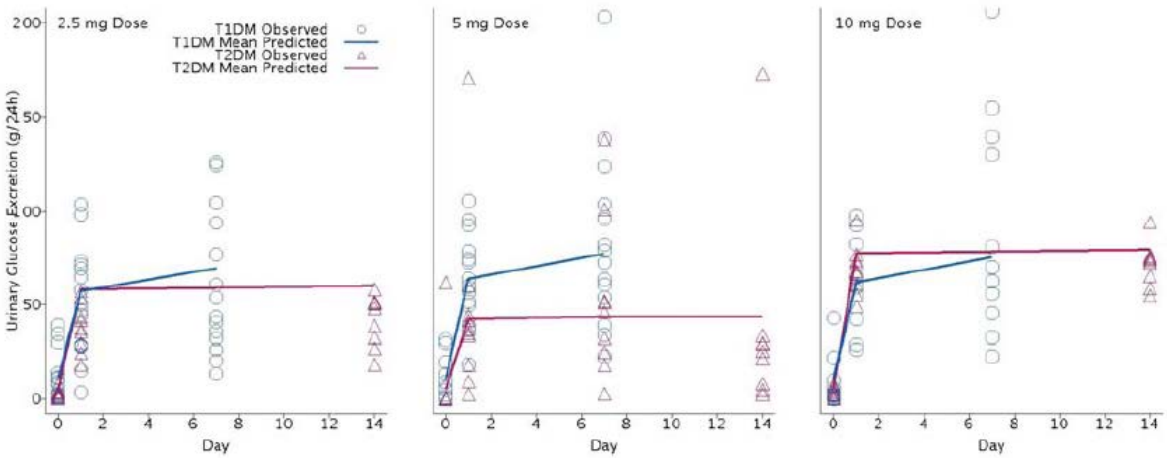
Prior to adding covariates, the potency of dapagliflozin appeared to be greater in T1DM (EC_{50} = 2.72 ng/mL) than in T2DM (EC_{50} = 12.24 ng/mL). Following normalisation for individual baseline values of FPG, eGFR and UGE, the potency of dapagliflozin was very similar in the 2 populations (T1DM EC_{50} = 8.12 ng/mL; T2DM EC_{50} = 7.75 ng/mL) (**Figure 8**), as well as the maximum effect (T1DM Emax = 71.1 g/24h; T2DM Emax = 76.8 g/24h). Whereas the rate constant to reach steady-state UGE response differs between the 2 populations (T1DM Kdrg = 2.98 1/day; T2DM Kdrg = 14.9 1/day) **(Figure 9)**.

Figure 8 Predicted dapagliflozin dose-response in subjects with T1DM and T2DM before and after normalisation for baseline covariates



Source: Exposure-response (UGE) Report Figure 5.1.3-1 in CTD Module 5.3.4.2
(a): Before normalisation
(b): After normalisation for baseline FPG, eGFR, and UGE.
Note: Dose-responses were predicted using the exposure-response model.
eGFR estimated glomerular filtration rate; FPG fasting plasma glucose; T1DM type 1 diabetes mellitus; T2DM type 2 diabetes mellitus; UGE urinary glucose excretion.

Figure 9 Observed and Final Model-Predicted Population Mean Urinary Glucose Excretion vs. Time by Dose of Dapagliflozin



Prediction of UGE response after long term treatment with dapagliflozin suggests that the 5 and 10 mg doses would be predicted to have median UGE responses of 80 g/24h (90% CI: 61-96 g/24h) and 86 g/24h (90% CI: 71 - 102 g/24h), respectively.

Overall, taking the individual baseline values UGE, FPG, and eGFR into account, the underlying exposure-response relationship is similar for subjects with T1DM and T2DM.

Effect of dapagliflozin on UGE in Japanese subjects with T1DM and non-Japanese subjects with T1DM

Objectives

The Japanese Exposure-Response Report developed a model characterising the relationship between dapagliflozin AUC and UGE in Japanese and non-Japanese T1DM subjects and evaluated the effect of covariates on this relationship.

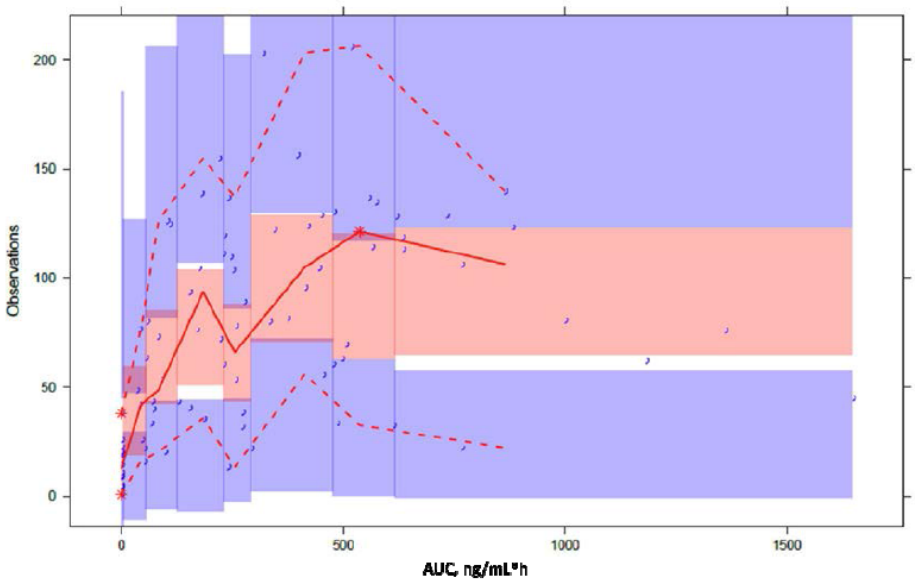
Data and methods

The model was developed using pooled Day 7 UGE data from 2 clinical studies: 1 study in Japanese T1DM subjects (D1695C00001 [Part A]) and 1 study in non-Japanese T1DM subjects (study MB102072). The final exposure-response model was designed according to data-driven decisions guided by statistical and heuristic rules. A nonlinear mixed effect modelling approach (NONMEM 7.3.0 software) was used to estimate the exposure-response parameters, their variances, and the effects of covariates. Investigated covariates included; baseline covariates age, body weight BM1, eGFR, FPG, HbA1c, total insulin and SMBG, as well as day 7 measurements of basal insulin, bolus insulin, total insulin, change from baseline SMBG, day 7 FPG and day 7 SMBG. The final model considered covariates that impact 24h UGE response: baseline eGFR, mean SMBG at Day 7, and change (%) from baseline in total insulin dose.

Results

The E_{max} model successfully described the relationship between steady-state dapagliflozin exposure and 24h UGE at Day 7. The exposure-response relationship and model performance is visualised in **Figure 10**.

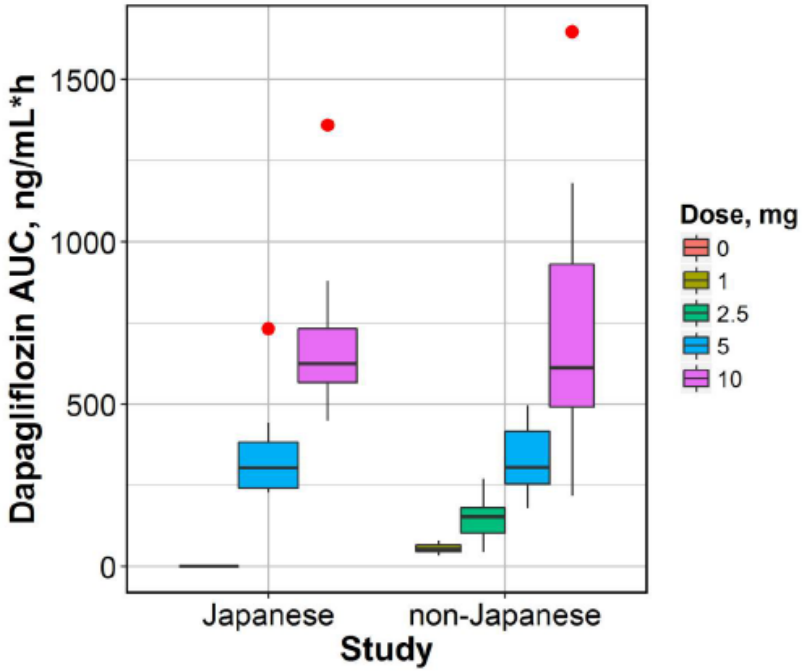
Figure 10 Visual predictive check plot, 24 hour UGE



The solid and dashed lines represent the median, 2.5th, and 97.5th percentiles of the observations; the shaded red and blue areas represent the 95% confidence interval of the median, 2.5th, and 97.5th percentiles predicted by the model.

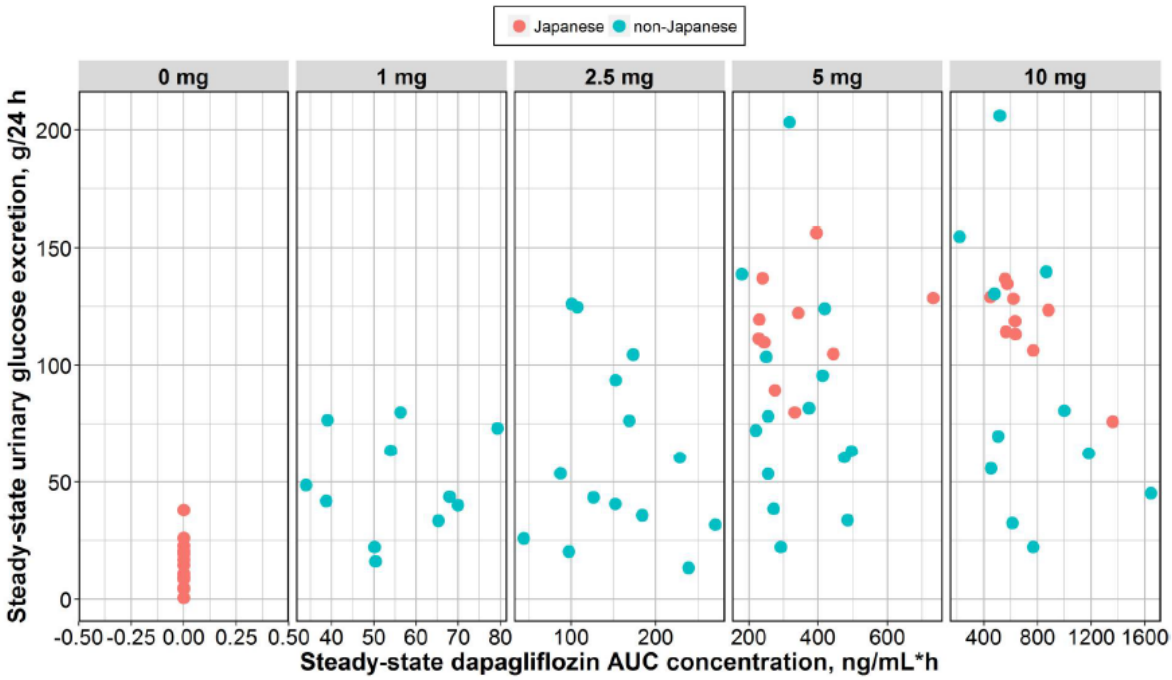
Exposure of dapagliflozin for matching doses was similar between study D1695C00001 and MB102072 (**Figure 11**). For dose-response measured by 24h UGE, the data showed a difference between the studies. In study MB102072 the average 24h UGE in the 5 mg group was 83.6 g/24h and in the 10 mg group was 90.9 g/24h. In study D1695C00001 (Part A), the difference in average 24h UGE between the 5 mg and 10 mg arms was smaller (115.9 g/24h vs 118.1 g/24h). **Figure 12** presents the exposure-response data from both studies.

Figure 11 Dapagliflozin steady-state AUC by dose in Japanese and non-Japanese subjects with T1DM



Source: Japanese Exposure-Response Report Figure 3.1-2 in CTD Module 5.3.4.2.

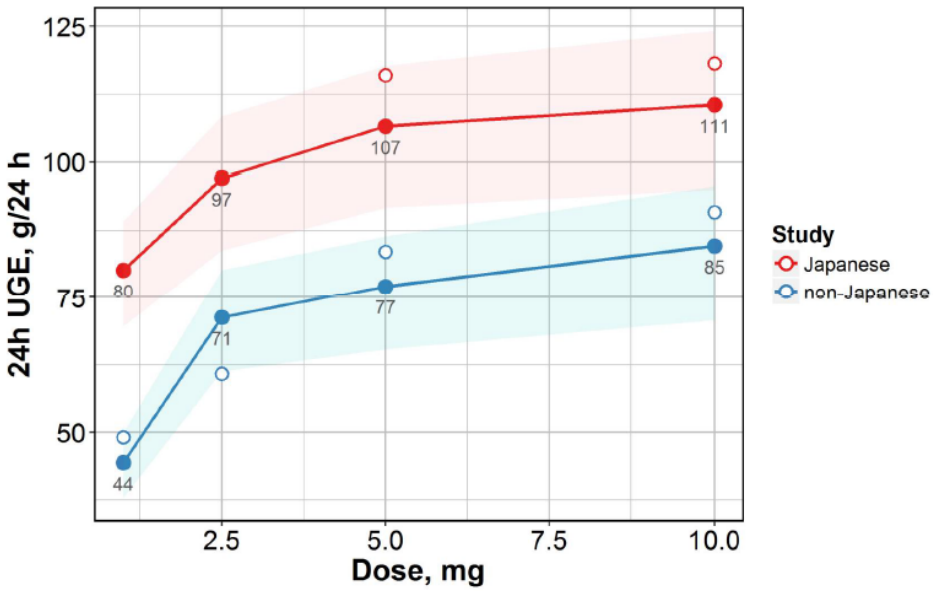
Figure 12 Dapagliflozin exposure-response in Japanese and non-Japanese subjects with T1DM



Source: Japanese Exposure-Response Report Figure 3.1-1 in CTD Module 5.3.4.2.

The modelling results indicate the apparent differences in dose-response between Japanese and non-Japanese subjects (**Figure 13**) are caused primarily by the differences in daily glycaemic control: insulin dose reductions and average SMBG levels.

Figure 13 Population dose-response (experimental values and model predictions) at Day 7 in Japanese and non-Japanese T1DM subjects



Source: Japanese Exposure-Response Report Figure 3.3-1 in CTD Module 5.3.4.2.
Filled dots = mean model predictions (final model); empty dots = mean experimental values; shaded area = simulated interquartile range; grey text = simulated 24h UGE values for each dosing group
Notes: Population characteristics were taken as median values calculated per dosing arm per study. For 1 and 2.5 mg simulated treatment in Japanese population, median AUC was taken from non-Japanese subjects and median covariate values were used from the 5 mg and 10 mg Japanese cohorts.
UGE urinary glucose excretion; T1DM type 1 diabetes mellitus.

The lack of difference in UGE between the 5 mg and 10 mg groups in the Japanese population may be explained by higher SMBG levels, likely resulting from greater insulin reductions at Day 7 in study D1695C00001. Compared with study MB102072 (average reductions: 19.31% and 16.17%), the degree of insulin dose reduction for the 5 mg and 10 mg groups was much higher in study D1695C00001 (averaging 36.86% and 39.13%, respectively).

The results from this report and the prior UGE analysis (see section on "*Effect of dapagliflozin on UGE in subjects with T1DM compared to subjects with T2DM*") are consistent in terms of predicting the effect of 5 mg and 10 mg doses of dapagliflozin from study MB102072. The UGE effect predicted by the model presented here (77 g/24h and 85 g/24h for 5 mg and 10 mg doses, respectively, see **Figure 13**) is similar to the effect predicted in the previous UGE analysis (80 g/24h and 86 g/24h for 5 mg and 10 mg doses, respectively, see also **Figure 8**).

Effect of dapagliflozin on HbA1c in subjects with T1DM

Objectives

In the Dose-Response and Exposure-Response (HbA1c) Report, pharmacometric analyses were performed to (1) graphically assess the effect of dapagliflozin on HbA1c in subjects with T1DM, (2) describe the relationships between dapagliflozin dose/exposure and HbA1c change over time and at 24 weeks, and (3) to explore the impact of covariates on those relationships.

Data and methods

These analyses included (a) graphical exploration and (b) modelling using pooled individual longitudinal HbA1c data from the short-term treatment periods of 2 Phase III studies in T1DM subjects (MB102229 and MB102230).

In both Phase III studies, HbA1c was measured at baseline and every 4 weeks thereafter during the 24-week ST treatment period. The longitudinal HbA1c data were used in the analyses. Individual AUCs were estimated for each subject from the PopPK model fitted to pooled data from studies MB102072, MB102229, and MB102230. A mixed-effect model repeated measure with dose-response and exposure-response components described with an E_{max} function was used to describe the longitudinal data in T1DM.

The following covariates were assessed during the modelling: baseline HbA1c, eGFR, reduction in total insulin dose (reduction at Week 24 relative to baseline insulin dose), age, baseline glucose levels from CGM, gender, race (Asian or non-Asian), and method of insulin administration (multiple daily injections or continuous subcutaneous insulin infusion [CSII]).

The covariates were selected base on previous exposure-response models developed for dapagliflozin in subjects with T2DM as well as exposure-response models developed for UGE in T1DM patients. Differences between the T1DM and T2DM clinical study designs precluded a robust comparison of the effect of dapagliflozin on HbA1c in the T1DM versus T2DM studies.

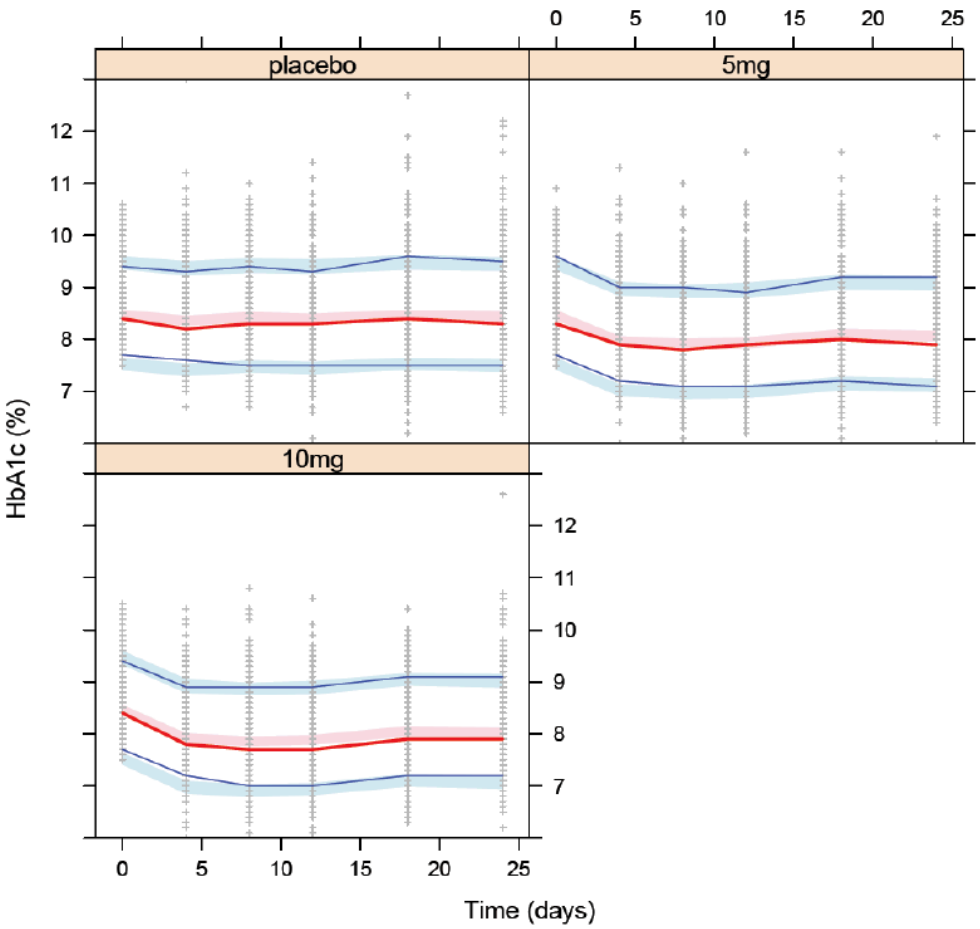
These differences included dissimilar lead-in periods (2 weeks in T2DM Phase II and III versus 8 weeks in T1DM Phase III) and varying rules on insulin dose adjustment (continuous adjustments in T1DM studies but not in T2DM studies). Therefore, the Dose-Response and Exposure-Response (HbA1c) Report does not explore a T1DM versus T2DM comparison for HbA1c response.

The software package NONMEM, version 7.3.0 was used in this analysis. PsN, version 4.2.0 and R, version 3.0 were used for the exploratory analysis and post-processing of NONMEM output, for example to assess goodness-of-fit.

Results

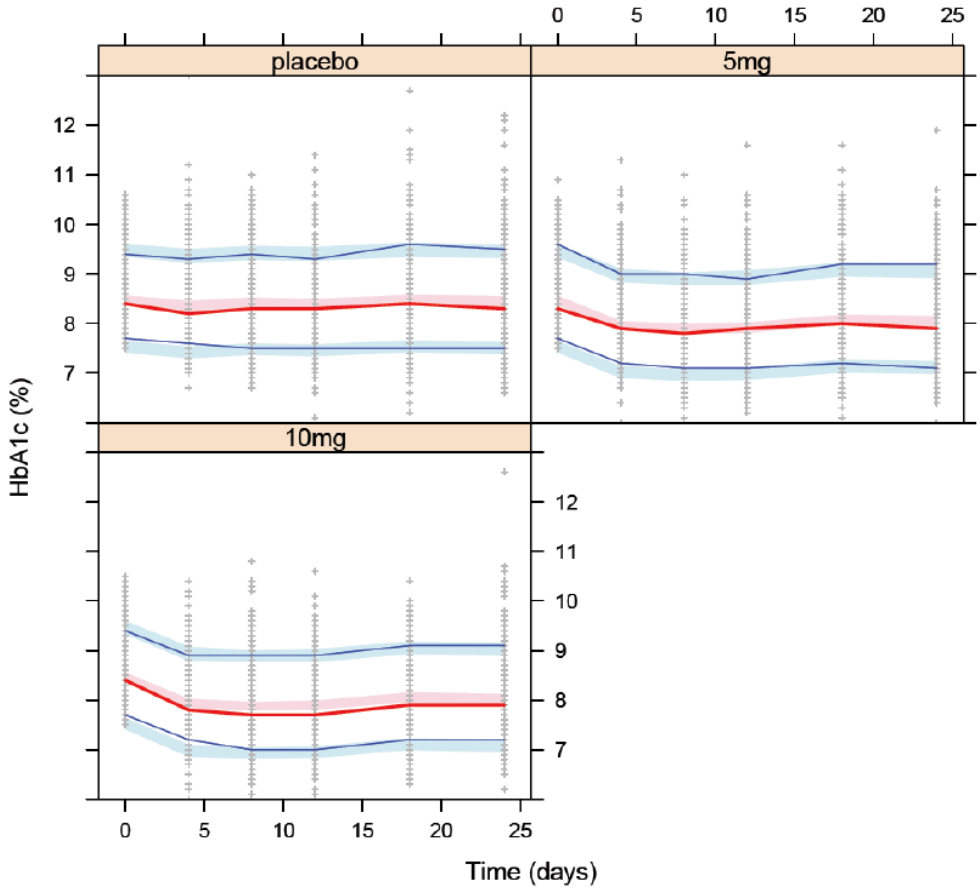
The dose-response and exposure-response models fit data from subjects with T1DM well (**Figure 14** and **Figure 15**, respectively). The mean placebo-corrected HbA1c reductions at Week 24 predicted by the dose-response model for 5 mg and 10 mg doses were -0.38% (95% CI: -0.46%, -0.30%) and -0.43% (95% CI: -0.51%, -0.35%), respectively. For exposure-response model predicted HbA1c reductions at Week 24 (placebo-corrected change from baseline) in T1DM patients were: -0.40% (95% CI -0.50, -0.31) and -0.43% (95% CI -0.53, -0.34) for 5 mg and 10 mg doses, respectively. The dose-response model and exposure response model predictions aligned well with the mean observed effects in MB102229 (-0.42% and -0.45% in the 5 mg and 10 mg groups, respectively and in MB102230 (-0.37% and -0.42%, respectively) (**Figure 16**).

Figure 14 Visual predictive check plots for the final dose-response model, stratified by dose (all T1DM data) – absolute HbA1c levels



Blue and red lines display data, light blue and pink regions display the model (mean with 10 and 90% quintiles). Datapoints correspond to the individual observations.

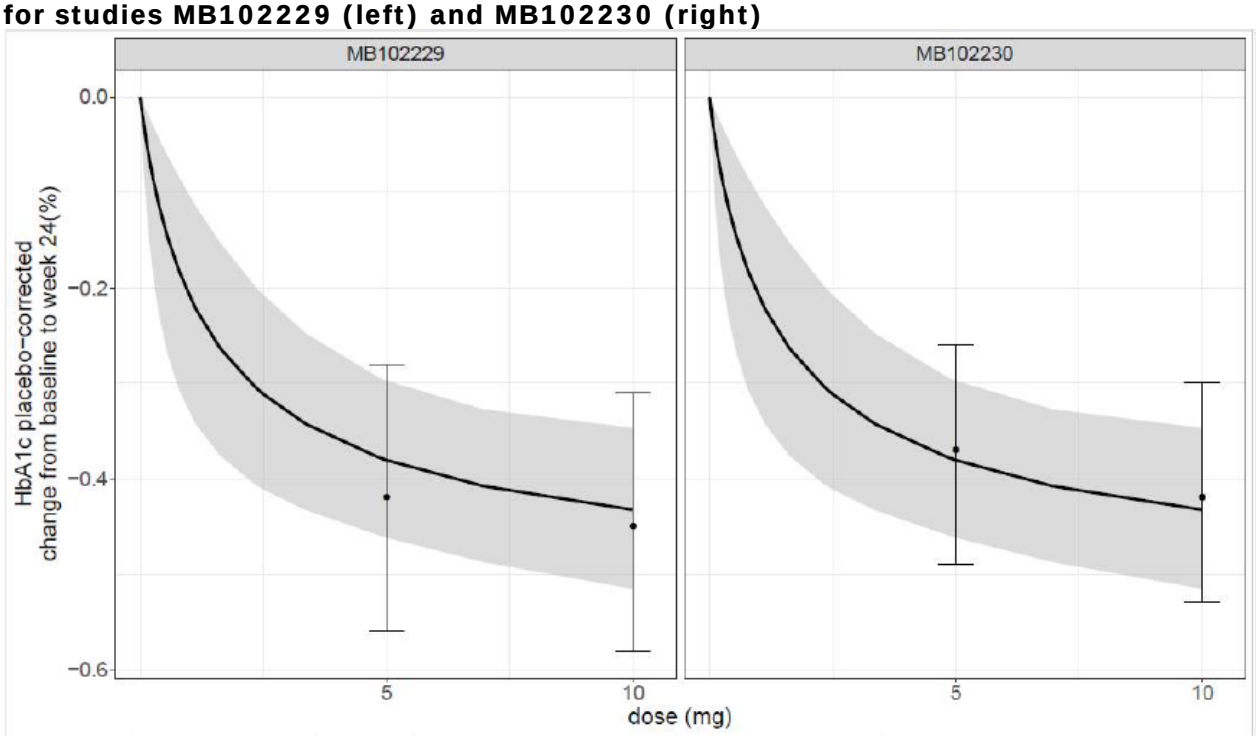
Figure 15 Visual predictive check plots for the final exposure-response model, stratified by dose - absolute HbA1c levels



Blue and red lines display data, light blue and pink regions display the model (mean with 10 and 90% quintiles). Datapoints correspond to the individual observations.

The final covariate analysis demonstrated that method of insulin administration had an impact on HbA1c reductions (patients using CSII had approximately 20% larger HbA1c reductions), however it was not deemed to be clinically relevant. None of the other covariates assessed during the modelling could be estimated with precision to have a significant impact on HbA1c response.

Figure 16 Model-predicted dose-response curves for HbA1c reduction at Week 24 for studies MB102229 (left) and MB102230 (right)



Source: Dose-Response and Exposure-Response (HbA1c) Report Figure 7 in CTD Module 5.3.4.2.
Note: The solid line and shaded area correspond to the mean model prediction with 95% confidence interval. The actual clinical data (mean with 95% confidence interval) is shown as datapoints (mean refers to mean change from baseline, based on a mixed model).

The dose- and exposure-response models adequately described HbA1c data from T1DM subjects. Model predicted HbA1c reductions for 5 mg and 10 mg dapagliflozin doses aligned well with the observed data.

2.3.5. Discussion on clinical pharmacology

Pharmacokinetics

Adequate model development and evaluation approaches have been used in the population PK analysis. Data under the limit of detection has been excluded from the analysis which is considered acceptable due to the low extent of such data. The visual predictive checks indicate that there is some model misspecification the absorption phase and description of maximum concentration, however this behaviour is considered acceptable since clearance (CL/F) is well described and it is the overall exposure (AUC or Caverage) that is more closely related to the effect. Furthermore, there is low shrinkage in the distribution of the individual Bayes estimates of CL/F which warrants for adequate prediction of individual AUC values. The provided VPCs were somewhat difficult to interpret due to low visibility in the early PK time-profile (see **Figure 4**) and the MAH is kindly asked to provide VPCs with greater detail in future applications.

Overall, the PK of dapagliflozin in T1DM patients is sufficiently described and displays no major deviation from the PK described in T2DM patients. However, the predicted distribution of exposure (AUC) is wider in the T1DM patient group, i.e. higher exposures are predicted (**Figure 6**). This result is likely due to demographic differences in the patient populations, where it is expected that the T1DM patients have a lower body weight which would lead to higher exposure.

Pharmacodynamics

No new data on the mechanism of action for dapagliflozin has been provided. This is acceptable since the mechanism of action has been adequately described in the original file supporting the MAA in the treatment of T2DM and these data may be extrapolated to the T1DM population.

In order to characterise the pharmacodynamics of dapagliflozin in patients with T1DM, data from two placebo-controlled studies (MB102072 and D1695C00001, Phase A) have been presented. The two studies were of comparable design. Study MB102072 tested four dapagliflozin doses (1 mg, 2.5 mg, 5 mg and 10 mg) in patients with T1DM. The primary objective was to assess safety and tolerability of each dose but effects on glucose, UGE and total insulin dose were also assessed. PK data was also collected. Study D1695C00001, Phase A, was designed to investigate the PK of dapagliflozin in Japanese subjects with T1DM. Effects on FPG, UGE and total insulin dose were also assessed. In contrast to study MB102072, only two dapagliflozin doses were studied (5mg and 10 mg). In both studies the insulin doses were to be adjusted at the discretion of the investigator in order to avoid hyper- or hypoglycaemias. Thus there was no titration guidance in place.

In study MB102072, the insulin dose was essentially unchanged in the placebo-treated group at Day 7 whereas a decrease in insulin doses ranging from -11% to -19% was observed in the dapagliflozin treated groups. There was no evident dose dependent change in insulin dose. In study D1695C00001, a mean change of -39.13% in total insulin dose was seen in the dapagliflozin 10 mg group and of -36.86% in the dapagliflozin 5 mg group. The mean change in the placebo group was -4.97%. Thus the reduction in total insulin dose was about twice that observed in study MB102072. Since the reduction of insulin dose was made at the discretion of the investigator, this may have affected the outcome, especially in study D1695C00001 which was single-blinded. The changes in insulin doses may affect the outcome of the endpoints such as FPG and CGM and to some extent also UGE.

A dose-dependent increase in urinary glucose excretion (UGE) was observed in both studies. An increased UGE was observed also at the lowest dose of 1 mg. The UGE was numerically higher in study D1695C00001, which only included Japanese subjects, than in study MB102072 (see modelling data). Study MB102072 also investigated the inhibition of renal glucose reabsorption (IRR) which also showed a dose dependent increase.

Both studies investigated the effect of treatment on FPG. In study MB102072, there was a greater decrease in FPG in the dapagliflozin treated groups at Day 1 compared to placebo, but this pattern was less evident at Day 7. There was no apparent dose dependent decrease. In study D1695C00001, FPG was reduced in both dapagliflozin-treated groups with no apparent dose dependency, whereas FPG had increased in the placebo-treated group. This was observed in spite of the rather large reduction in insulin doses in the dapagliflozin-treated groups.

Study MB102072 also investigated the effect of dapagliflozin on the 7-point glucose curve. Although there was a trend towards a greater reduction of the 7-point glucose curve Day 1 at the higher doses of dapagliflozin, no differences were observed at Day 7. The CGM data showed a trend towards less variability in the glucose measurements with dapagliflozin treatment compared to placebo.

The data provided support that dapagliflozin exerts a dose dependent effect on UGE in T1DM, further analysis of the data show that this effect is comparable to the effect observed in patients with T2DM. The data also indicate that, in patients with T1DM, dapagliflozin may lower blood glucose variability. The effect on FPG is difficult to assess since insulin titration was not performed in a standardised manner, but a decrease in FPG was observed with dapagliflozin across all doses compared to placebo.

PK/PD modelling

Effect of dapagliflozin on UGE in subjects with T1DM compared to subjects with T2DM

In general, the model development procedure is acceptable and the goodness-of-fit diagnostic indicate a reasonable model fit although some outliers are present in the T2DM population.

The estimated rate constant to reach steady-state UGE response (Kdrg) differs between the two patient populations. However, the calculations show that 95% of steady-state UGE is reached within the first day for both patient populations.

Effect of dapagliflozin on UGE in Japanese subjects with T1DM and non-Japanese subjects with T1DM

The model development procedure is acceptable. According to the goodness-of-fit diagnostics and visual predictive checks the model describes the data fairly well. Although the model results indicate reasonable description of data the presented model of the Japanese/non-Japanese patients display substantial differences in the covariate relationship compared to the T1DM/T2DM model. The differences are mainly due to differences in the covariate model building procedure and model parametrisation, and the differences are not deemed clinically relevant. Furthermore, in the model to compare T1DM and T2DM patients, observed Cavg was used as the exposure metric, whereas in the exposure-response model for Japanese patients AUC have been used as a driver of the effect. Although the two exposure metrics are essentially the same, the unit of the EC50 parameter will differ and for comparative reasons it is encouraged to standardise the exposure metric in future analyses exposure-UGE analyses. The MAH is encouraged to harmonise the exposure-UGE models for future applications.

Effect of dapagliflozin on HbA1c in subjects with T1DM

Standard model development and evaluation approaches have been used in the analysis of the dose/exposure-HbA1c relationships. Predicted AUC (see section on Pharmacokinetics) has been used as the exposure metric in the analysis which is acceptable. The HbA1c models describe the data well and the results are adequate to support dose selection.

2.3.6. Conclusions on clinical pharmacology

The pharmacokinetics of dapagliflozin in subjects with T1DM has been sufficiently well described. The results display no major deviation from the pharmacokinetics in subjects with T2DM, and therefore the PK findings from the T2DM development programme can therefore be applied to the T1DM population. However, a wider distribution of exposure is seen in the T1DM patients, likely due to differences in demographics between the two patient populations.

The pharmacodynamics of dapagliflozin in subjects with T1DM has been adequately described. The data show that an effect on UGE is observed across the doses investigated although a limited difference is detected in between the therapeutic doses 5 mg and 10 mg.

2.4. Clinical efficacy

2.4.1. Dose response study

No dedicated dose response study was performed. In both Phase III studies, the study treatments were either dapagliflozin 5 mg once daily, dapagliflozin 10 mg once daily, or placebo, all as add-on to insulin therapy. The 5 mg and 10 mg once daily dapagliflozin doses were chosen based on data from a Phase II T1DM study (MB102072) that showed the exposure response relationship in terms of urinary

glucose excretion is very similar in subjects with T1DM and T2DM. Dapagliflozin 5 mg has been established as the minimally effective dose in T2DM patients and dapagliflozin 5 mg and 10 mg are each approved in multiple countries worldwide for the treatment of T2DM.

2.4.2. Main studies

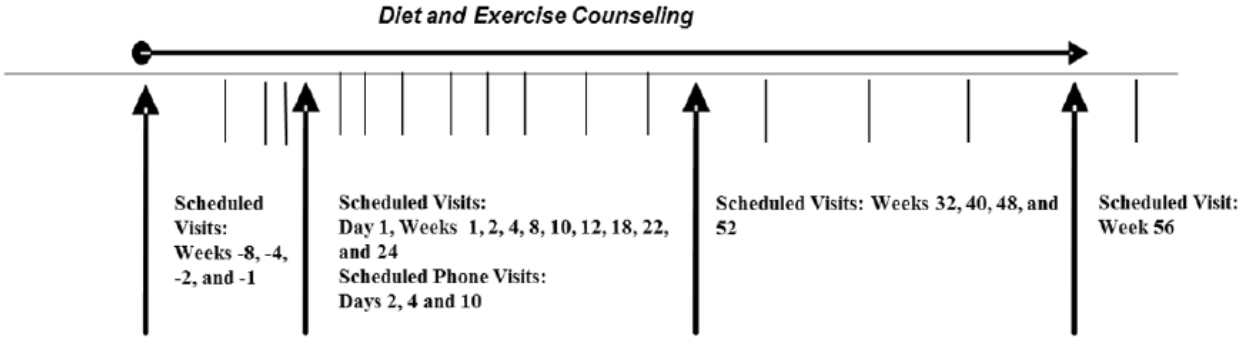
Two key Phase III efficacy studies were included in the dapagliflozin T1DM development programme: studies **MB102229** and **MB102230**.

Methods

Studies **MB102229** and **MB102230** had similar designs. Both studies were multicentre, randomised, double-blind, placebo-controlled, parallel-group, Phase III studies to evaluate the efficacy and safety of dapagliflozin when added to ongoing insulin therapy in subjects with T1DM. The studies included an 8-week lead-in period, a 24-week short-term (ST) treatment period, and a 28-week long-term (LT) extension (LT extension was still ongoing for study MB102230 at the time of submission but the data was submitted during the procedure). The primary and secondary efficacy analyses are based on the 24-week results, with selected analyses repeated for the 52-week results as exploratory analyses of LT efficacy. The safety analyses are based on the 24-week and 52-week results. The design of the 2 studies is illustrated in **Figure 17**.

Figure 17 Design of studies MB102229 and MB102230

Qualification Period ≤ 28 Days	8 Week Lead-In Period	24 Week Double-Blind Short-Term Treatment Period (1:1:1 Ratio)	28 Week Subject and Site Blinded Long-Term Treatment Period	30 day Follow-up Period
		-Dapagliflozin 5 mg + Insulin -Dapagliflozin 10 mg + Insulin -Placebo + Insulin	-Dapagliflozin 5 mg + Insulin -Dapagliflozin 10 mg + Insulin -Placebo + Insulin	



In study MB102230, the visits at Week -4, Week 2, Week 10, and Week 22 could as an option be conducted as phone visits.

During the 8-week lead-in period the diabetes management was optimised based on individual subject challenge to glycaemic control (including hyperglycaemia, hypoglycaemia, and erratic meal/exercise patterns) and the variability in blood glucose profiles and frequency of hypoglycaemic episodes at baseline was assessed.

Self-Monitored Blood Glucose (SMBG)

At the entry into the lead-in period, subjects received a glucose and ketone meter. Subjects were to self-monitor their blood glucose at least 4 times per day (generally before breakfast, lunch, dinner, and bedtime), and in the occurrence of hypoglycaemic symptoms, and to contact the Investigator in the event of an unusually high or low blood glucose value. In addition, study subjects should comply with site's instructions with regard to self-monitoring of blood glucose and insulin adjustments accordingly and should report to the site blood glucose values and/or signs and symptoms suggestive of a hypoglycaemia episode.

Self-Monitored Blood Ketone Testing and Guidance on Management and Reporting of Diabetic Ketoacidosis Episodes

Subjects were advised to measure their blood ketones when they had potential symptoms/signs of DKA, and/or during acute illness. Blood ketone test results, symptoms potentially associated with DKA and relevant risk factors (e.g. missed insulin injection, insulin pump malfunction, infection, heart attack, etc.) should be recorded in the subject diary.

Study participants

In both studies, the target population was subjects with T1DM aged ≥18 to ≤75 years who were on ongoing insulin treatment for at least 12 months and who had inadequate glycaemic control, with central laboratory HbA1c at the Week -1 visit of ≥7.5% to ≤10.5%.

Subjects were excluded from the study if they had been admitted to a hospital because of hyper- or hypoglycaemia or had experienced diabetic ketoacidosis (DKA) requiring medical intervention within 1 month of the screening visit. Subjects were also excluded from the study if they had significant concurrent disease such as cardiovascular events within the prior 6 months, malignancy within the past 5 years (with the exception of treated basal cell or squamous cell carcinoma), or renal/hepatic insufficiency.

Treatments

In both studies, the study treatments were either dapagliflozin 5 mg once daily, dapagliflozin 10 mg once daily, or placebo, all as add-on to insulin therapy.

Ongoing insulin therapy

After the first dose of study drug, it was recommended that Investigators reduce daily insulin dose by up to 20% to minimise the risk of hypoglycaemia. The timing and degree of any reduction was at the discretion of the Investigator. Insulin reductions of >20% from baseline at any time during the study were not recommended. Following any initial reduction in insulin dose, attempts were to be made to titrate insulin back to the baseline level.

Subjects were are not allowed to change their insulin administration methods (MDI or CSII) during the study unless a subject using an insulin pump needed to replace the pump, in which case the subject could temporarily use MDI but should restart CSII administration as early as feasible.

Objectives

The primary objective in both study MB102229 and MB102230 was to:

- Compare dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin for the change from baseline in HbA1c after 24 weeks of double-blinded treatment.

The secondary objectives in both study MB102229 and MB102230 were to:

1. Compare the percent change from baseline in total daily insulin dose with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment.
2. Compare the percent change from baseline in body weight with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment.
3. Compare the change from baseline in the mean value of 24-hour glucose readings obtained from continuous glucose monitoring (CGM) with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment.
4. Compare the change from baseline in mean amplitude of glucose excursion (MAGE) of 24-hour glucose readings obtained from CGM with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment.
5. Compare the change from baseline in the percent of 24-hour glucose readings obtained from CGM that falls within the target range of >70 mg/dL and ≤180 mg/dL with dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin after 24 weeks of double-blinded treatment.
6. Compare dapagliflozin 5 mg or 10 mg plus adjustable insulin versus placebo plus adjustable insulin for the proportion of subjects achieving an HbA1c reduction from baseline to Week 24 visit ≥0.5% without severe hypoglycaemia events.

The studies also included several exploratory efficacy objectives, including an objective to assess the maintenance of effect of dapagliflozin after up to 52 weeks of treatment. All efficacy analyses at/up to Week 52 were exploratory.

Outcomes/endpoints

Primary endpoint:

- Change in HbA1c from baseline to Week 24

Secondary endpoints:

- Percent change in total daily insulin dose from baseline to Week 24
- Percent change in body weight from baseline to Week 24
- Change in mean value of 24-hour glucose readings obtained from CGM from baseline to Week 24
- Change in MAGE of the 24-hour glucose readings obtained from CGM from baseline to Week 24
- Change in percentage of 24-hour glucose readings from CGMs falling within the range of >70 mg/dL to ≤180 mg/dL from baseline to Week 24

- Proportion of subjects achieving an HbA1c reduction of ≥0.5% without a severe hypoglycaemia event after 24 weeks

Sample size

To detect a difference in means of 0.35% in HbA1c at Week 24 between each dapagliflozin treatment group and placebo at the 2-sided 0.0262 significance level (based on Dunnett and Tamhane step-up procedure), and assuming a standard deviation of 1.1%, 243 subjects were needed in each treatment group in studies MB102229 and MB102230 to provide an approximately 90% power. Assuming that 5% of subjects would not have a post-baseline assessment, a total of 768 subjects (256 subjects per treatment group) were planned to be randomised in each study in a 1:1:1 ratio to each treatment group.

In study MB102229 an extra 55 patients were randomised to replace patients excluded due to a randomisation error.

Randomisation

At the screening visit each subject was assigned a unique sequential subject number by the Interactive Voice/Web Response System (IXRS). Following completion of the lead-in period, eligible subjects were randomised on Day 1 to one of the 3 double-blind treatment arms in a 1:1:1 ratio using a centralised blocked randomisation schedule.

Randomisation was stratified by the following factors to ensure equal representation across all treatment groups:

- Current use of CGM (yes or no) (ie, an unblinded/personal device being used by the subject prior to enrolment, in addition to the CGM device being introduced as part of the study)
- Method of insulin administration at baseline (multiple daily injections [MDI] defined as 3 or more injections per day versus continuous subcutaneous insulin infusion [CSII])
- Week -1 Visit (baseline) HbA1c ≥7.5% and <9.0% versus ≥9.0% and ≤10.5%

In study MB102229, an Interactive Voice Response System (IVRS) randomisation system error affected the first 55 randomised subjects. These subjects were excluded from the full analysis set prior to database lock and therefore excluded from all efficacy analyses; the subjects were, however, included in the safety analysis set and the safety analyses. The randomisation target was increased by 55 to maintain the power for the primary endpoint. Thus, the total number of subjects planned to be randomised in study MB102229 was 823.

Blinding (masking)

Blinded dapagliflozin 5 mg, 10 mg, or placebo was administered orally, once daily for the 24-week double-blinded short-term treatment period. The investigator, the MAH's personnel, and subjects remained blinded to treatment allocation throughout the short-term, double-blind treatment period. During the 28-week long-term treatment period, subjects and sites remained blinded.

Statistical methods

Study MB102229 and MB102230 are multicenter, randomized, double blind, placebo-controlled, parallel group studies.

Analysis populations

Two analysis sets were specified for efficacy, the full analysis set and the per-protocol analysis set. The efficacy analyses were based primarily on the full analysis set. The per-protocol analysis set was to be used to analyse the primary endpoint only if more than 10% of the full analysis set subjects in any treatment group had relevant protocol deviations. Safety analyses were based on the safety analysis set.

The full analysis set consists of all randomised subjects who took at least one dose of double-blind study drug during the short-term double-blind period. Subjects in the full analysis set are presented in the treatment group to which they were randomised at the start of the short-term treatment period (even if the treatment they received was different). In study MB102229 the first 55 randomized subjects were excluded from the full analysis dataset due to a randomisation error.

The per-protocol analysis set is a subset of the full analysis set consisting of subjects who did not have relevant protocol deviations that had the potential to impact the results of the primary efficacy analysis. All decisions to exclude subjects from the full analysis set were made prior to database lock.

The safety analysis set consists of all randomised subjects who received at least one dose of study drug. Any subjects receiving incorrect study drug for the entire course of their participation were summarised according to the treatment that they actually received.

Multiplicity

Treatment effects were determined through pair-wise treatment group comparisons: each dapagliflozin treatment group versus placebo. To maintain an overall Type I error rate of 5% for the endpoint, a Dunnett and Tamhane step-up procedure was used, which allowed for the correlation of 0.5 between the standard normal deviate for each comparison. Statistical significance was declared for both doses at the 2-sided 5% level if the 2-sided p-values from both pairwise comparisons were smaller than 5%. If the larger p-value among the 2 pairwise comparisons was greater than 5% and the smaller p-value was below 2.62%, then statistical significance would be declared for the latter comparison.

The primary and secondary efficacy variables were analysed and statistically tested in a stepwise fashion in the order listed under “Outcomes/endpoints” above. For comparison of each dapagliflozin group versus placebo separately, if the primary endpoint was significant, the statistical tests for the secondary efficacy endpoints were performed. The type I error rate for comparing each dapagliflozin group to placebo group for each secondary efficacy endpoint was be controlled at the 0.0262 level (two-sided). Secondary efficacy endpoints were to be tested in the order that they appear in the objectives section of the protocol and protocol synopsis. Statistical tests between each dapagliflozin group and placebo group was to be performed only performed for a given secondary endpoint if all previous sequential tests for that comparison were significant. Otherwise, the testing procedure would stop at the secondary endpoint that did not reach statistical significance. This sequential testing procedure was to be implemented independently for each dapagliflozin treatment group as it is compared to placebo.

P-values were calculated for all comparisons for the secondary endpoints. However, no claim is based on endpoints for which the statistical testing was not performed for the endpoint as per the testing strategy as described above. No claims are made based on these p-values.

Analysis methods

The primary analysis of the change in HbA1c from baseline to Week 24 was based on a longitudinal repeated measures analysis using 'direct likelihood'. The SAS procedure PROC MIXED was used. An unstructured matrix for the within-subject error variance-covariance was used. The denominator degrees of freedom was calculated according to the Kenward-Roger method.

Adjustment for covariates

The model for the primary analysis included the fixed categorical effects of treatment, week, randomisation stratification factor (ie, one term for each combination of all stratification factors) and treatment-by-week interaction, as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction.

Subgroup analyses

The primary efficacy endpoint of HbA1c was summarised for predefined subgroups and stratification factors: race, gender, ethnicity, baseline A1C, subject age, geographic region, method of insulin administration, use of continuous glucose monitoring (CGM) and baseline Body Mass Index. The subgroup by treatment interaction was assessed for the primary efficacy endpoint using a longitudinal repeated measures analysis model with subgroup, subgroup-by-time, and subgroup-by-time-by-treatment group interaction as 3 additional effects.

Sensitivity analyses

Sensitivity analyses of the primary efficacy variable were conducted to assess the robustness of the primary analysis. The sensitivity analyses included an estimation of the de facto (intention-to-treat) estimand for the primary efficacy variable, which had been requested by the US Food and Drug Administration, and which was included as a post-hoc analysis for study MB102229 and a pre-specified analysis for study MB102230.

Missing data

A sensitivity analyses using ANCOVA with LOCF was performed for the primary efficacy analysis. The longitudinal repeated measures model is based on a missing at random (MAR) assumption with respect to missing data. The proportion of missing data by visit was summarized and reasons (i.e. missing visit only, discontinued treatment, or discontinuation from study, including by reason for treatment or study discontinuation) was assessed to verify the validity of this assumption. If a substantial amount of missing data was observed or if imbalances occurred amongst the treatment groups, sensitivity analyses based on a missing not at random assumption (MNAR) assumption was to be conducted, as appropriate and feasible based on the observed data. Various methods such as multiple imputation, placebo-based imputation, or tipping point analysis were to be considered. For study MB102229 a tipping point analyses and a placebo based imputation were presented.

Rules for imputing the date T1DM was diagnosed if partially missing were pre-specified in the SAP.

For other analyses and summaries of efficacy, safety, outcome research measures, missing values were not imputed.

If laboratory samples were inadvertently analysed multiple times for the same test, producing multiple lab results on the same collection date and time for the same subject, the selection of laboratory result for analysis for this subject followed AZ global standard.

If the blood pressure measurements were taken at a wrong position, e.g., sitting instead of standing, then these measurements were excluded from the summary/analysis.

For listings of efficacy, safety, outcome research measures, missing values were represented as not reported.

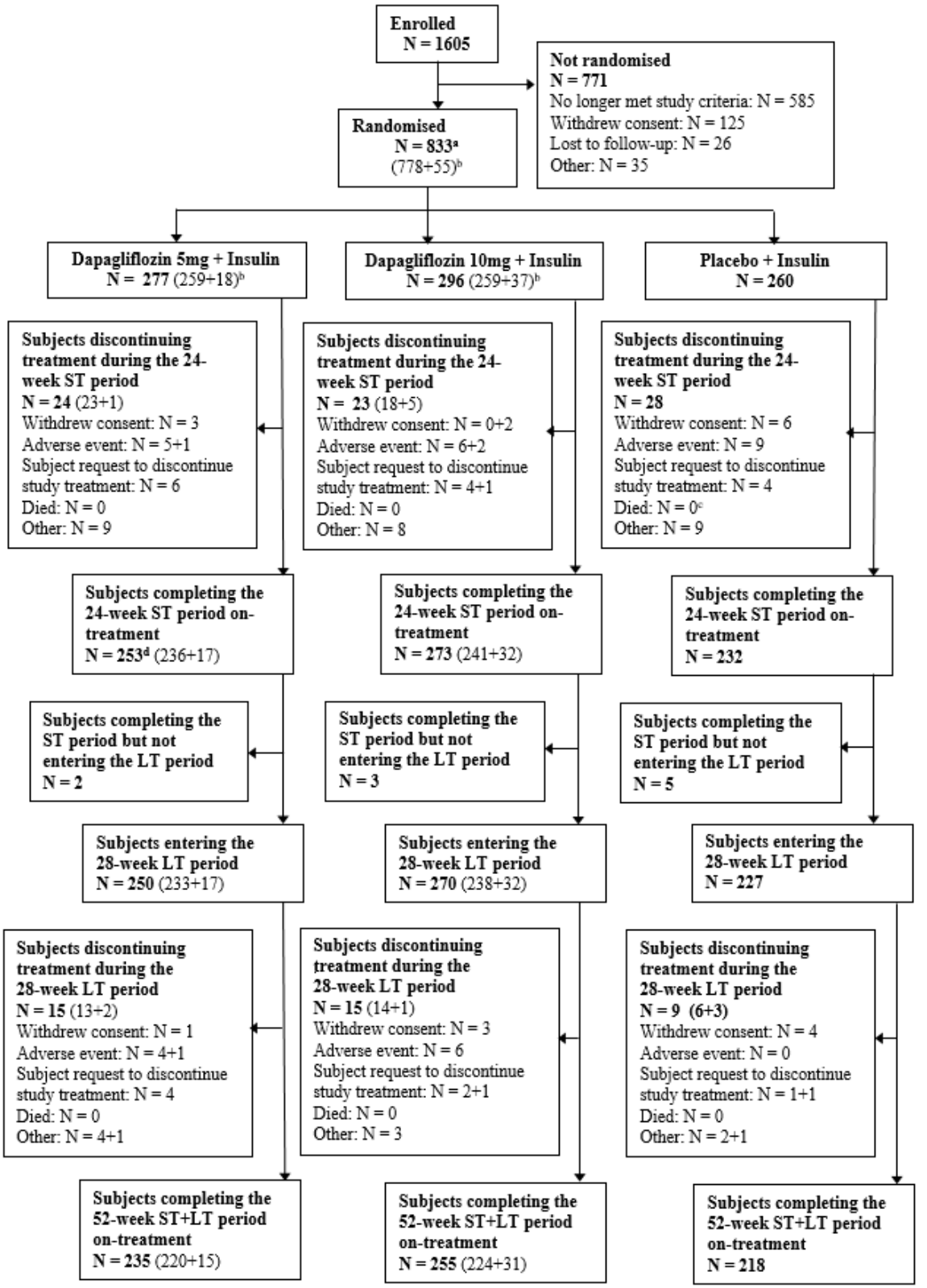
Interim analyses

No interim analyses were performed.

Results

Participant flow

Figure 18 Subject disposition in study MB102229 – enrolment to end of 52-week ST+LT treatment period



Derived from: MB102229 ST CSR and MB102229 ST+LT CSR Tables 11.1.1.1 and 11.1.1.2 in CTD Module 5.3.5.1

[a] One additional subject was randomised in error (the site randomised the subject before confirming eligibility); this subject did not receive any treatment and was removed from the full analysis set.

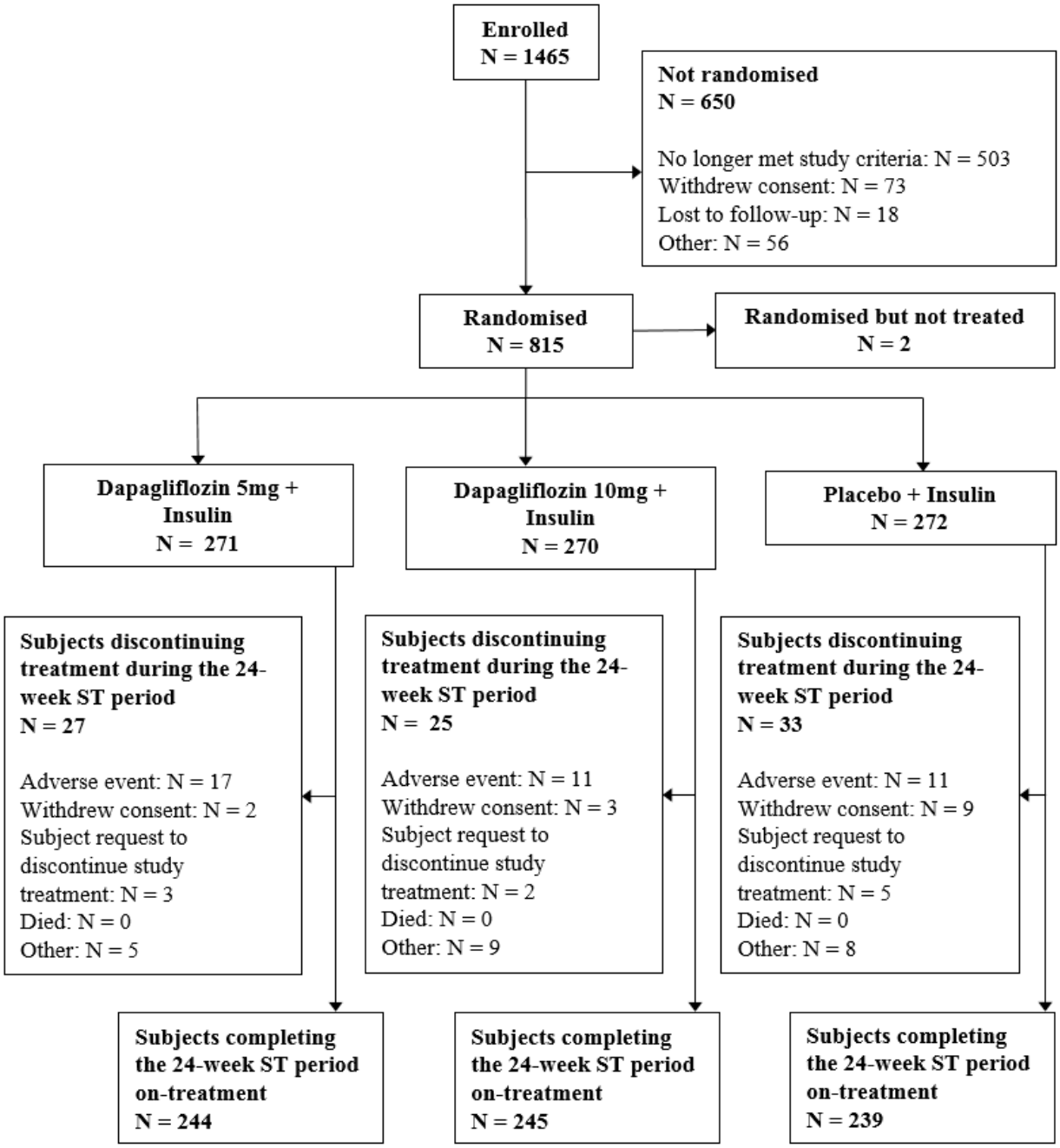
[b] There were 55 subjects randomised prior to discovery of an IVRS randomisation system error, 18 and 37 in the dapagliflozin 5 mg and dapagliflozin 10 mg treatment groups, respectively.

[c] One patient in the placebo group died during the short-term treatment period; the patient had previously discontinued study drug due to an AE of hypoglycaemia.

[d] There is a discrepancy in the subject status summary tables for the ST and the ST+LT treatment periods (see Table 11.1.1.1 in the ST CSR and Table 11.1.1.1 in the ST+LT CSR). In raw.stat at ST DBL, subject 0164-00443 was recorded as completing the ST period on-treatment. This status was changed to "no" the raw.stat at ST+LT DBL. Accordingly, the data in this figure matches the data in the ST CSR and the ST Table 11.1.1.1 (N = 253), but not the data in the ST+LT Table 11.1.1.1 (N = 252).

AE adverse event; CTD Common Technical Document; DBL database lock; IVRS Interactive Voice Response System; LT long-term; N number of subjects; ST short-term

Figure 19 Subject disposition in study MB102230 – enrolment to end of 24-week ST
treatment period



Recruitment

MB102229

Subjects were randomised at 138 participating sites in 17 countries: Australia, Austria, Belgium, Canada, Germany, Denmark, Finland, France, Hungary, Israel, Italy, Mexico, Romania, Spain, Sweden, United Kingdom, and United States (US).

First subject enrolled: 11 November 2014
Last subject completed 24w treatment period: 04 January 2017
Last subject completed 52w treatment period: 25 August 2017

MB102230

Subjects were enrolled at 148 participating sites in 13 countries: Argentina, Belgium, Canada, Chile, Germany, Japan, Netherlands, Poland, Russian Federation, Sweden, Switzerland, United Kingdom, and United States.

First subject enrolled: 08 July 2015
Last subject completed 24w treatment period: 02 September 2017
Last subject completed 52w treatment period: 18 April 2018

Conduct of the study

Amendments

MB102229

Five amendments, two of which were country-specific, were made to the protocol. The first amendment was made before first subject enrolled, and all amendments were made before last subject completed. The most important changes are provided in the following.

Amendment #3 (May 2015) concerned the removal of exclusion criteria stating that HbA1c may not drop more than 0.5% during the lead-in phase after consultation with EMA/SAWP (EMA/248307/2015) since the requirement does not reflect clinical practice and had resulted in feasibility issues.

With amendment #5 (May 2016), the randomisation target was increased by 55 subjects due to the IVRS randomisation system error. In addition, recommendations on insulin reductions and other measures to avoid hypoglycaemia and DKA were clarified.

MB102230

Five amendments, two of which were country-specific, were made to the protocol. All but one amendment (#5) were made before first subject enrolled, and all amendments were made before last subject completed. The most important changes are provided in the following.

Amendment #3 (May 2015) concerned the removal of exclusion criteria stating that HbA1c may not drop more than 0.5% during the lead-in phase after consultation with EMA/SAWP (EMA/248307/2015) since the requirement does not reflect clinical practice and had resulted in feasibility issues.

With amendment #5 (May 2016), recommendations on insulin reductions and other measures to avoid hypoglycaemia and DKA were clarified.

Protocol deviations

In study MB102229, few subjects (33 [4.2%]) who were included in the full analysis set had a relevant protocol deviation during the 24-week treatment period. In addition, 55 subjects that were affected by an IVRS error were excluded from the full analysis set. The most common protocol deviation was randomised subjects who did not take any study drug for ≥2 consecutive weeks. Per-protocol analysis was not conducted due to the small number of protocol deviations.

In study MB102230, few subjects (42 [5.2%] overall) in the full analysis set had a relevant protocol deviation during the 24-week treatment period. The most common protocol deviation was randomised

subjects who did not take any study drug for ≥2 consecutive weeks. Per-protocol analysis was not conducted due to the small number of protocol deviations.

Baseline data

Demographic characteristics were generally balanced between treatment groups within studies MB102229 and MB102230 (**Table 8**). In study MB102229, most subjects were white (95.6%) and randomised at study sites in Europe (59.3%). In study MB102230, 78.4% of subjects were white and 19.7% of subjects were Asian; most were randomised at study sites in North America or Europe (34.6% and 33.5%, respectively).

Common diabetes complications were as expected for subjects with this T1DM disease duration.

Table 8 Demographics and diabetes-related baseline characteristics in studies MB102229/MB102230 (full analysis set) (abbreviated)

	Study MB102229				Study MB102230			
	DAPA 5 mg + INS (N=259)	DAPA 10 mg + INS (N=259)	PLA + INS (N=260)	Total (N=778)	DAPA 5 mg + INS (N=271)	DAPA 10 mg + INS (N=270)	PLA + INS (N=272)	Total (N=813)
Age (years, mean [SD])	41.9 (14.08)	42.7 (14.11)	42.7 (13.57)	42.5 (13.91)	42.7 (13.35)	42.4 (12.80)	43.0 (13.73)	42.7 (13.29)
Sex (n [%])								
Male	111 (42.9)	130 (50.2)	132 (50.8)	373 (47.9)	118 (43.5)	121 (44.8)	119 (43.8)	358 (44.0)
Female	148 (57.1)	129 (49.8)	128 (49.2)	405 (52.1)	153 (56.5)	149 (55.2)	153 (56.3)	455 (56.0)
Body weight (kg, mean [SD])	80.97 (18.369)	82.08 (17.418)	84.36 (18.332)	82.47 (18.078)	78.74 (17.384)	80.06 (18.302)	78.88 (18.867)	79.22 (18.183)
BMI (kg/m^2, mean [SD])	28.36 (5.804)	28.15 (5.152)	28.62 (5.251)	28.38 (5.406)	27.27 (5.128)	27.80 (5.525)	27.62 (5.414)	27.56 (5.357)
Duration of T1DM (years, mean [SD])	19.69 (12.035)	19.87 (11.056)	21.23 (12.190)	20.27 (11.776)	19.35 (11.785)	19.45 (11.896)	18.98 (11.653)	19.26 (11.766)
Total baseline insulin (IU, mean [SD])	62.134 (44.1578)	59.440 (28.1955)	63.133 (29.2737)	61.574 (34.6415)	58.188 (27.9293)	58.678 (28.2647)	56.574 (25.2281)	57.812 (27.1547)
HbA1c (%, mean [SD])	8.53 (0.711)	8.52 (0.639)	8.53 (0.672)	8.53 (0.674)	8.45 (0.693)	8.43 (0.694)	8.43 (0.645)	8.43 (0.677)
HbA1c (n [%])								
<8%	66 (25.5)	51 (19.7)	62 (23.8)	179 (23.0)	69 (25.5)	79 (29.3)	76 (27.9)	224 (27.6)
≥8% and <9%	126 (48.6)	146 (56.4)	131 (50.4)	403 (51.8)	142 (52.4)	131 (48.5)	135 (49.6)	408 (50.2)
≥9%	67 (25.9)	62 (23.9)	67 (25.8)	196 (25.2)	60 (22.1)	60 (22.2)	61 (22.4)	181 (22.3)
Fasting C-peptide (number [%])								
<Lower limit of detection	217 (83.8)	219 (84.6)	224 (86.2)	217 (83.8)	228 (84.1)	218 (80.7)	221 (81.3)	667 (82.0)
≥0.05 ng/mL	40 (15.4)	34 (13.1)	30 (11.5)	40 (15.4)	38 (14.0)	50 (18.5)	50 (18.4)	138 (17.0)
Not reported	2 (0.8)	6 (2.3)	6 (2.3)	14 (1.8)	5 (1.8)	2 (0.7)	1 (0.4)	8 (1.0)
Method of insulin administration								
MDI	162 (62.5)	165 (63.7)	165 (63.5)	492 (63.2)	179 (66.1)	178 (65.9)	180 (66.2)	537 (66.1)
CSII	97 (37.5)	94 (36.3)	95 (36.5)	286 (36.8)	92 (33.9)	92 (34.1)	92 (33.8)	276 (33.9)

GFR (mL/min /1.73 m^2)								
<60	10 (3.9)	6 (2.3)	16 (6.2)	32 (4.1)	9 (3.3)	10 (3.7)	6 (2.2)	25 (3.1)
≥60 and <90	129 (49.8)	123 (47.5)	112 (43.1)	364 (46.8)	127 (46.9)	136 (50.4)	127 (46.7)	390 (48.0)
≥90	120 (46.3)	130 (50.2)	132 (50.8)	382 (49.1)	135 (49.8)	124 (45.9)	139 (51.1)	398 (49.0)

Derived from: MB102229 24w CSR Tables 11.1.4.1 and 11.1.9.1 and MB102230 24w CSR Tables 11.1.4.1 and 11.1.9.1 in CTD Module 5.3.5.1
This table includes all subjects who are in the full analysis dataset.
Percentages reported are based on the total number of subjects in each treatment group.
GFR is calculated using the Modification in Diet and Renal Disease formula.
The race subgroup of other includes subjects with reported race of American Indian/Alaska Native; Native Hawaiian/Other Pacific Islander; or Other.
Adj adjusted; BMI body mass index; CSII continuous subcutaneous insulin infusion; CTD Common Technical Document; DAPA dapagliflozin; GFR glomerular filtration rate; HbA1C Haemoglobin A1c; INS insulin; IU international units; MDI multiple daily injections; N number of subjects; PLA placebo; SD standard deviation; T1DM type 1 diabetes mellitus

Numbers analysed

MB102229

Table 9 Analysis sets summary

	DAPA 5 mg + INS	DAPA 10 mg + INS	PLA + INS	Total
Subjects in full analysis set[a]	259	259	260	778
Subjects in safety analysis set[b]	277	296	260	833
Subjects in short-term completers analysis set[c]	235	241	232	708

Source: Table 11.1.3
[a] Full analysis set consists of all randomised subjects who took at least one dose of study drug during the short-term treatment period, excluding the first 55 randomised subjects due to the presence of an IVRS randomisation system error.
[b] Subjects who took at least one dose of study drug in the treatment group to which they were randomised unless subjects have never received the study drug they were randomised. In which case subjects will be included in the treatment group based on the first treatment received.
[c] Full analysis set subjects who completed the ST period on study drug.
DAPA dapagliflozin; INS insulin; IVRS Interactive Voice Response System; PLA placebo; ST short-term

MB102230

Table 10 Analysis sets summary

	DAPA 5 mg + INS	DAPA 10 mg + INS	PLA + INS	Total
Subjects in full analysis set[a]	271	270	272	813
Subjects in per-protocol analysis set[b]	262	266	269	797
Subjects in safety analysis set[c]	271	270	272	813

Source: Table 11.1.3
[a] Full analysis set consists of all randomised subjects who took at least one dose of study drug during the short-term treatment period.
[b] Full analysis set without a relevant protocol deviation.
[c] Subjects who took at least 1 dose of study drug in the treatment group to which they were randomised unless subjects have never received the study drug they were randomised. In which case subjects will be included in the treatment group based on the first treatment received.
DAPA dapagliflozin; INS insulin; PLA placebo

Outcomes and estimation

Primary efficacy variable: change in HbA1c from baseline to Week 24

The primary analysis demonstrated statistically significant reductions in HbA1c with dapagliflozin 5 mg and 10 mg compared with placebo following 24 weeks of treatment in both study MB102229 and MB102230 (**Table 11**).

The de facto (intention-to-treat) estimand for the primary efficacy variable was estimated as a sensitivity analysis in both studies. In study MB102229, the de facto estimand for the adjusted mean change compared with placebo in HbA1c from baseline to Week 24 was -0.41% for dapagliflozin 5 mg (95% CI: -0.55, -0.28) and -0.39% (95% CI: -0.53, -0.26) for dapagliflozin 10 mg. In study MB102230, the de facto estimand for the adjusted mean change compared with placebo in HbA1c from baseline to Week 24 was -0.32% for dapagliflozin 5 mg (95% CI: -0.45, -0.19) and -0.39% (95% CI: -0.52, -0.25) for dapagliflozin 10 mg.

Table 11 Primary efficacy variable in studies MB102229 / MB102230: HbA1c at Week 24 (full analysis set)

	Study MB102229			Study MB102230		
	DAPA 5 mg + INS (N=259)	DAPA 10 mg + INS (N=259)	PLA + INS (N=260)	DAPA 5 mg + INS (N=271)	DAPA 10 mg + INS (N=270)	PLA + INS (N=272)
HbA1c (%) at Week 24[a]						
N[b]	254	254	257	266	267	267
Baseline mean (SD)	8.52 (0.716)	8.50 (0.622)	8.50 (0.666)	8.45 (0.685)	8.39 (0.670)	8.40 (0.630)
Week 24 mean (SD)	8.04 (0.902)	8.04 (0.826)	8.43 (0.924)	8.09 (0.843)	7.99 (0.762)	8.43 (0.858)
Mean change from baseline (SD)	-0.48 (0.790)	-0.46 (0.753)	-0.06 (0.831)	-0.36 (0.634)	-0.40 (0.710)	0.03 (0.668)
Adjusted mean change from baseline (SE)	-0.45 (0.0537)	-0.47 (0.0538)	-0.03 (0.0540)	-0.34 (0.0452)	-0.39 (0.0450)	0.03 (0.0453)
95% CI for adj. mean change from baseline	(-0.55, -0.34)	(-0.58, -0.37)	(-0.13, 0.08)	(-0.43, -0.25)	(-0.48, -0.30)	(-0.06, 0.12)
Difference from placebo (SE)	-0.42 (0.0697)	-0.45 (0.0696)		-0.37 (0.0579)	-0.42 (0.0578)	
95% CI for difference from placebo	(-0.56, -0.28)	(-0.58, -0.31)		(-0.49, -0.26)	(-0.53, -0.30)	
P-value vs. placebo[c]	<0.0001	<0.0001		<0.0001	<0.0001	

Derived from: MB102229 24w CSR Table 11.2.1.1 in CTD Module 5.3.5.1 and MB102230 24w CSR Table 11.2.1.1 in CTD Module 5.3.5.1

[a] Mixed model: change from baseline = baseline treatment week stratum week*treatment week*baseline

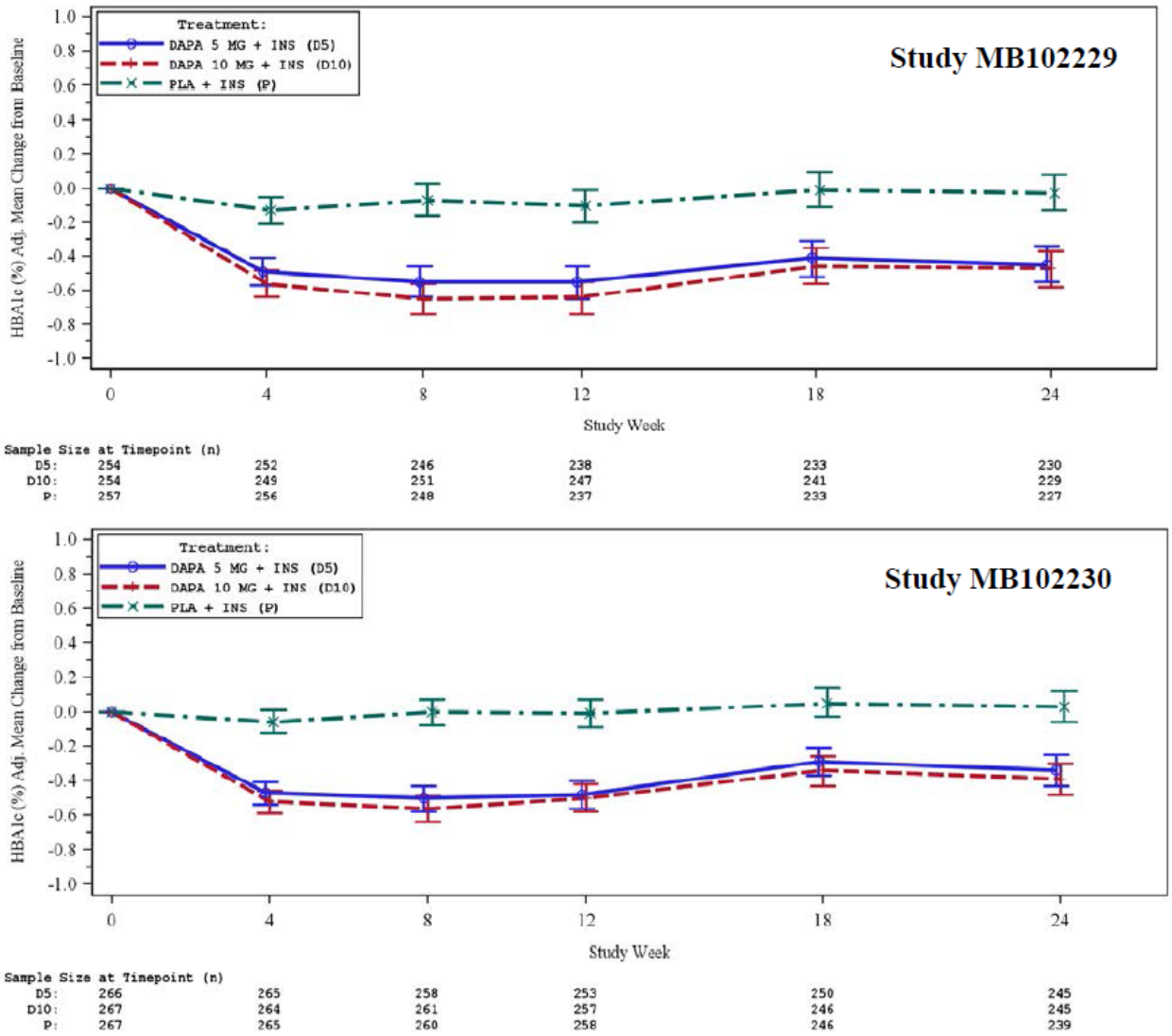
[b] Number of subjects in full analysis dataset with non-missing baseline and at least one post-baseline value.

[c] Nominal p-value.

Adj adjusted; CI confidence interval; CTD Common Technical Document; DAPA dapagliflozin; INS insulin; PLA placebo; SD standard deviation; SE standard error

In both studies, most of the reduction in HbA1c in the dapagliflozin treatment groups occurred over the first 4 weeks of treatment and was maintained for the duration of the ST treatment period (**Figure 20**). The reduction of HbA1c appeared to be maintained up to Week 52 in the LT extension of study MB102229; see section “Ancillary analysis” for a detailed discussion of the ST+LT efficacy results.

Figure 20 Change in HbA1c from baseline over time – 24-week ST treatment period in studies MB102229 and MB102230 (full analysis set)



Source: Figure 11.2.2.3 in MB102229 24w CSR and Figure 11.2.2.3 MB102230 24w CSR in CTD Module 5.3.5.1

Full analysis dataset consists of all randomised subjects who took at least one dose of double-blind study drug during the short-term double-blind period and had at least one post-baseline value, excluding the first 55 randomised subjects in study MB102229 due to the presence of an IVRS randomisation system error.

Mean refers to mean change from baseline based on a mixed model with treatment, baseline value, week, week-by-treatment interaction, week-by-baseline interaction and stratum (one term for each combination of all stratification factors) as independent variables.

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

Treatment symbols shifted horizontally to prevent error bar overlapping.

CTD Common Technical Document; D5 dapagliflozin 5 mg; D10 dapagliflozin 10 mg; DAPA dapagliflozin; INS insulin; P placebo; ST short-term

Secondary efficacy variables

Percent change in total daily insulin dose

Statistically significant reductions in total daily insulin dose were demonstrated for each of the dapagliflozin doses compared with placebo at Week 24 in both study MB102229 and MB102230 **(Table 12).**

In both studies, the reductions in each dapagliflozin group occurred during the first 2 weeks of treatment and the effect was maintained for the duration of the ST treatment period (**Figure 21**).

Figure 21 Change from baseline in total daily insulin over time – 24-week short-term treatment period (full analysis set) – top panel study MB102229 and bottom panel study MB102230

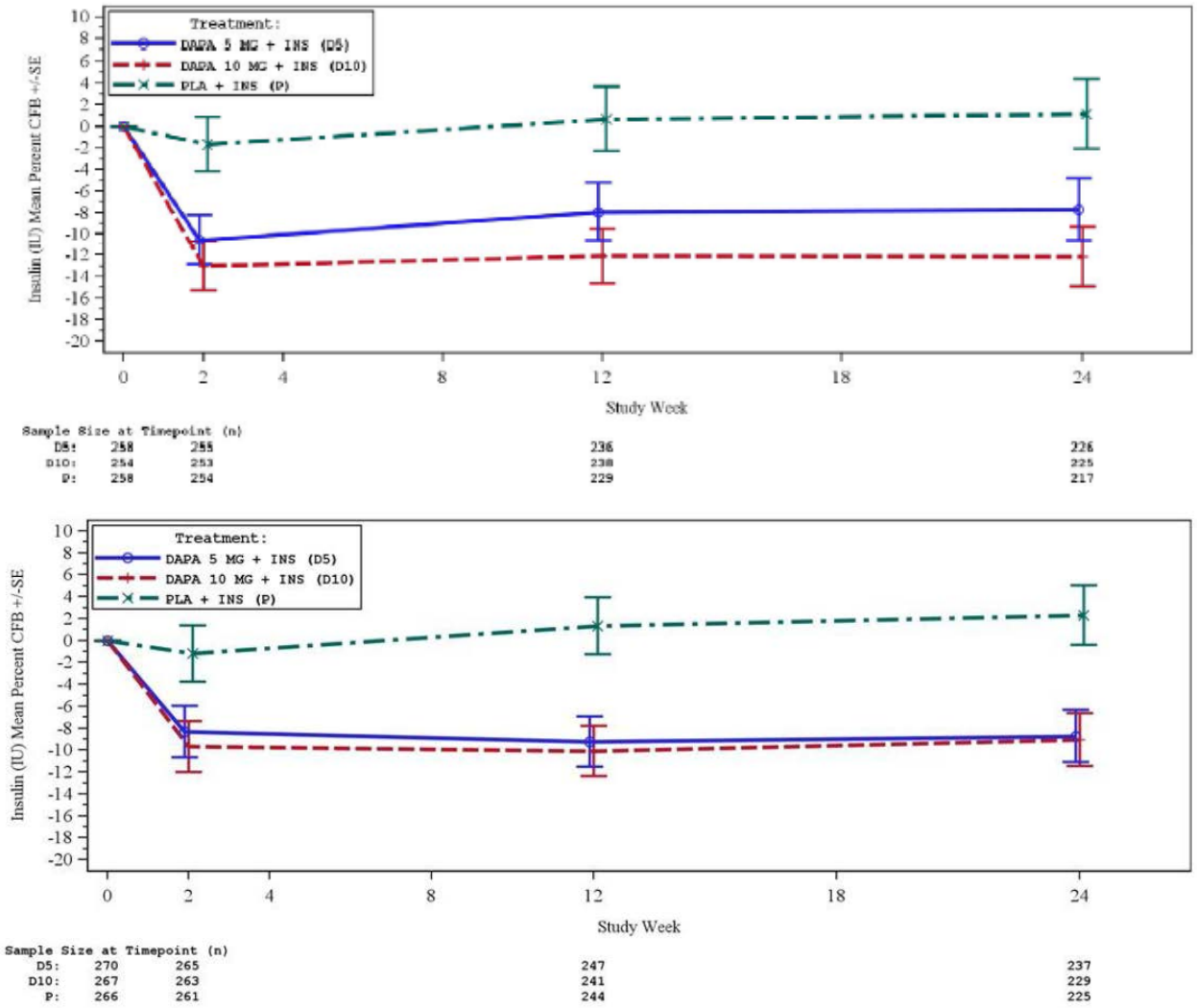


Table 12 Secondary efficacy variable in studies MB102229 / MB102230: total daily insulin dose at Week 24 (full analysis set)

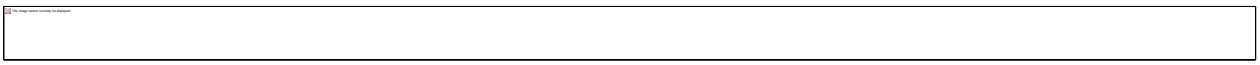
	Study MB102229			Study MB102230		
	DAPA 5 mg + INS (N=259)	DAPA 10 mg + INS (N=259)	PLA + INS (N=260)	DAPA 5 mg + INS (N=271)	DAPA 10 mg + INS (N=270)	PLA + INS (N=272)
Total daily insulin dose (IU) at Week 24[a]						
N[b]	258	254	258	270	267	266
Baseline mean (SD)	62.91 (46.157)	59.59 (28.203)	61.74 (26.557)	59.09 (28.051)	59.28 (28.210)	56.45 (25.225)
Week 24 mean (SD)	56.12 (30.750)	52.35 (27.379)	62.13 (27.406)	53.60 (27.040)	53.79 (29.535)	56.98 (28.120)
Mean percent change from baseline (SD)	-7.00 (221.615)	-10.67 (22.916)	2.29 (22.300)	-8.68 (17.292)	-9.20 (20.812)	1.54 (17.763)
Adj. mean percent change from baseline (SE)	-7.74 (1.4881)	-12.16 (1.4326)	1.16 (1.6593)	-8.73 (1.2158)	-9.05 (1.2309)	2.29 (1.3919)
95% CI for adj. mean % change from baseline	(-10.61, -4.77)	(-14.92, -9.30)	(-2.04, 4.47)	(-11.09, -6.31)	(-11.43, -6.60)	(-0.41, 5.06)
Difference from placebo (SE)	-8.80 (1.9555)	-13.17 (1.8643)		-10.78 (1.5291)	-11.08 (1.5331)	
95% CI for difference from placebo	(-12.56, -4.88)	(-16.75, -9.43)		(-13.73, -7.72)	(-14.04, -8.02)	
P-value vs. placebo[c]	<0.0001	<0.0001		<0.0001	<0.0001	

Derived from: MB102229 24w CSR Table 11.2.1.1 and MB102230 24w CSR Table 11.2.1.1 in CTD Module 5.3.5.1

[a] Mixed model: ln(post)-ln(baseline) = ln(baseline) treatment week stratum week*treatment week*ln(baseline). Mean percent change from baseline calculated using the geometric mean back-transformed from the results calculated under the logarithm transformation. Stratum includes one term for each combination of all stratification factors.

[b] Number of subjects in full analysis dataset with non-missing baseline and at least one post-baseline value.

[c] Nominal p-value.



In study MB102229, the proportional reductions seen for basal and bolus insulin individually were similar to the proportional reduction in total insulin (dapagliflozin 5 mg group, basal -12% and bolus -14%; dapagliflozin 10 mg group, basal -14% and bolus -18%; placebo group, basal -0.6% and bolus -4.6%).

In study MB102230, the proportional reductions seen for basal and bolus insulin individually were similar in the dapagliflozin 5 mg group (-11% and -12%) whereas in the dapagliflozin 10 mg group there was a greater reduction in basal insulin than in bolus insulin (-17% and -8%). There was no net change in the placebo group (1.5% and -2.6%).

Percent change in body weight

Statistically significant reductions in body weight were demonstrated for each of the dapagliflozin doses compared with placebo at Week 24 in both study MB102229 and MB102230 (**Table 13**).

Each dapagliflozin group in the 2 studies exhibited continuous weight loss over the 24-week ST treatment periods (**Figure 22** and **Figure 23**).

Table 13 Secondary efficacy variable in studies MB102229 / MB102230: percent change in body weight at Week 24 (full analysis set)

	Study MB102229			Study MB102230		
	DAPA 5 mg + INS (N=259)	DAPA 10 mg + INS (N=259)	PLA + INS (N=260)	DAPA 5 mg + INS (N=271)	DAPA 10 mg + INS (N=270)	PLA + INS (N=272)
Body weight (kg) at Week 24[a]						
N[b]	259	258	259	269	269	272
Baseline mean (SD)	81.85 (18.582)	81.76 (16.493)	84.42 (18.506)	79.22 (17.214)	80.39 (18.510)	79.03 (19.052)
Week 24 mean (SD)	79.38 (18.152)	78.72 (15.906)	84.50 (18.752)	76.74 (16.957)	77.54 (18.553)	79.15 (19.339)
Mean percent change from baseline (SD)	-3.00 (3.704)	-3.65 (3.716)	0.08 (3.210)	-3.15 (3.339)	-3.67 (3.558)	0.20 (4.560)
Adj. mean percent change from baseline (SE)	-3.00 (0.2330)	-3.67 (0.2299)	0.05 (0.2407)	-3.22 (0.2731)	-3.76 (0.2721)	-0.02 (0.2844)
95% CI for adj. mean % change from baseline	(-3.45, -2.54)	(-4.12, -3.22)	(-0.42, 0.52)	(-3.76, -2.69)	(-4.29, -3.22)	(-0.57, 0.54)
Difference from placebo (SE)	-3.05 (0.3251)	-3.72 (0.3213)		-3.21 (0.3829)	-3.74 (0.3812)	
95% CI for difference from placebo	(-3.68, -2.41)	(-4.34, -3.08)		(-3.96, -2.45)	(-4.49, -2.99)	
P-value vs. placebo[c]	<0.0001	<0.0001		<0.0001	<0.0001	

Derived from: MB102229 24w CSR Table 11.2.1.1 and MB102230 24w CSR Table 11.2.1.1 in CTD Module 5.3.5.1

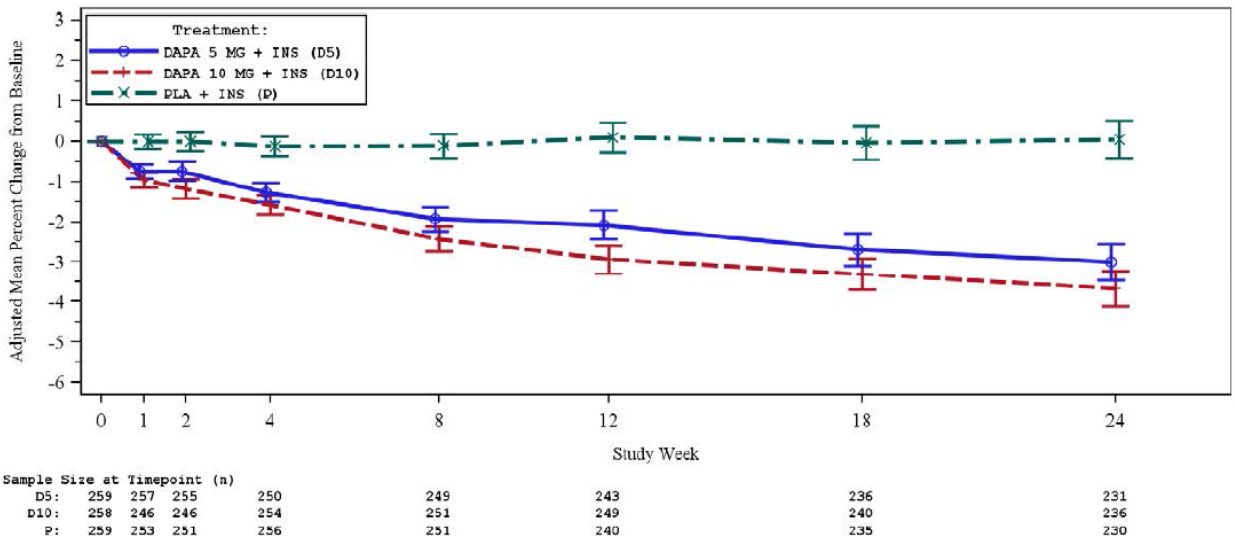
[a] Mixed model: ln(post)-ln(baseline) = ln(baseline) treatment week stratum week*treatment week*ln(baseline). Mean percent change from baseline calculated using the geometric mean back-transformed from the results calculated under the logarithm transformation. Stratum includes one term for each combination of all stratification factors.

[b] Number of subjects in full analysis dataset with non-missing baseline and at least one post-baseline value.

[c] Nominal p-value.

Adj adjusted; CI confidence interval; CTD Common Technical Document; DAPA dapagliflozin; INS insulin; PLA placebo; SD standard deviation; SE standard error

Figure 22 Change from baseline in total body weight over time – 24-week short-term treatment period (full analysis set) - study MB102229



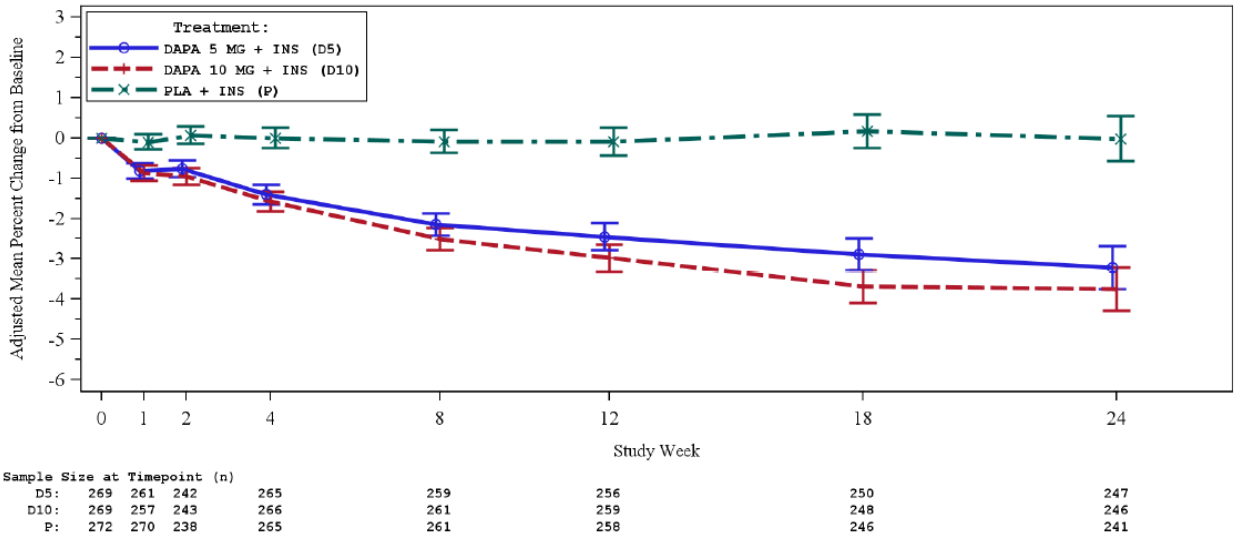
Source: Figure 11.2.4.2

Mean refers to mean percent change from baseline based on a mixed model with treatment, ln(baseline) value, week, week-by-treatment interaction, week-by-ln (baseline) interaction and stratum (1 term for each combination of all stratification factors) as independent variables.

Error bars represent 95% confidence intervals for the adjusted mean percent change from baseline. Treatment symbols shifted horizontally to prevent error bar overlapping.

BL baseline; D5 dapagliflozin 5 mg; D10 dapagliflozin 10 mg; DAPA dapagliflozin; INS insulin; n number of subjects; P placebo; PLA placebo; W week

Figure 23 Change from baseline in total body weight over time – 24-week short-term treatment period (full analysis set) - study MB102230



Source: Figure 11.2.4.2

Mean refers to mean percent change from baseline based on a mixed model with treatment, ln(baseline) value, week, week-by-treatment interaction, week-by-ln (baseline) interaction and stratum (1 term for each combination of all stratification factors) as independent variables.

Error bars represent 95% confidence intervals for the adjusted mean percent change from baseline. Treatment symbols shifted horizontally to prevent error bar overlapping.

BL baseline; D5 dapagliflozin 5 mg; D10 dapagliflozin 10 mg; DAPA dapagliflozin; INS insulin; n number of subjects; P placebo; PLA placebo; W week

Change in mean value of 24-hour glucose readings

Statistically significant reductions in mean CGM readings were demonstrated for each of the dapagliflozin doses compared with placebo at Week 24 in both study MB102229 and MB102230 (**Table 14**).

In both studies, the effect was similar at Weeks 12 and 24.

Table 14 Secondary efficacy variable in studies MB102229 / MB102230: change in mean value of 24-hour glucose readings at Week 24 (full analysis set)

	Study MB102229			Study MB102230		
	DAPA 5 mg + INS (N=259)	DAPA 10 mg + INS (N=259)	PLA + INS (N=260)	DAPA 5 mg + INS (N=271)	DAPA 10 mg + INS (N=270)	PLA + INS (N=272)
24-hour CGM mean value (mg/dL) at Week 24[a]						
N[b]	238	239	234	252	255	257
Baseline mean (SD)	192.91 (29.866)	189.40 (27.257)	191.35 (29.613)	192.67 (28.677)	191.53 (28.092)	190.89 (28.945)
Week 24 mean (SD)	178.29 (31.845)	173.60 (26.671)	192.87 (34.230)	181.49 (32.931)	176.01 (26.517)	195.73 (31.035)
Mean change from baseline (SD)	-14.62 (29.073)	-15.80 (28.602)	1.52 (33.501)	-11.18 (29.607)	-15.52 (26.717)	4.84 (30.079)
Adj. mean change from baseline (SE)	-10.28 (1.8862)	-12.97 (1.9231)	5.06 (1.9320)	-6.46 (1.8274)	-10.54 (1.8348)	9.20 (1.8504)
95% CI for adj. mean change from baseline	(-13.99, -6.58)	(-16.75, -9.20)	(1.27, 8.85)	(-10.04, -2.87)	(-14.14, -6.94)	(5.57, 12.83)
Difference from placebo (SE)	-15.34 (2.4859)	-18.03 (2.5050)		-15.66 (2.3468)	-19.74 (2.3419)	
95% CI for difference from placebo	(-20.22, -10.46)	(-22.95, -13.11)		(-20.26, -11.05)	(-24.34, -15.14)	
P-value vs. placebo[c]	<0.0001	<0.0001		<0.0001	<0.0001	

Derived from: MB102229 24w CSR Table 11.2.1.1 and MB102230 24w CSR Table 11.2.1.1 in CTD Module 5.3.5.1

[a] Mixed model: change from baseline = baseline treatment week stratum week*treatment week*baseline.

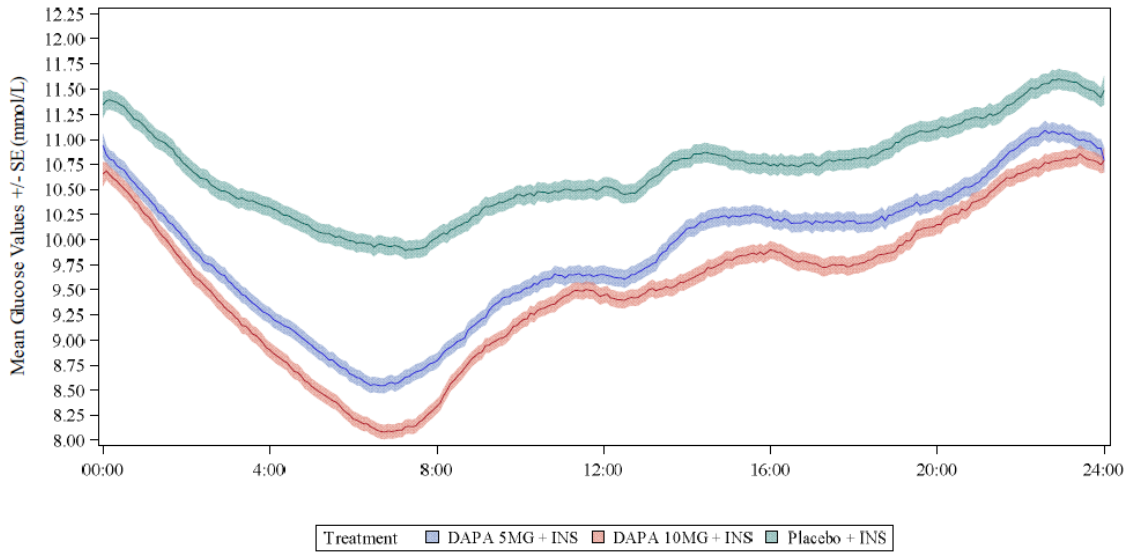
[b] Number of subjects in full analysis dataset with non-missing baseline and at least one post-baseline value.

[c] Nominal p-value.

Adj adjusted; CGM continuous glucose monitoring; CI confidence interval; CTD Common Technical Document; DAPA dapagliflozin; INS insulin; PLA placebo; SD standard deviation; SE standard error.

Figure 24 presents mean interstitial glucose and standard error during the 24-hour period from midnight to midnight at Week 24 (study MB102229), illustrating the reduction in mean glucose seen with dapagliflozin over the course of a day. A similar pattern was observed in study MB102230.

Figure 24 Continuous glucose monitoring at Week 24 – 24-week short-term treatment period (full analysis set) – study MB102229



Change in mean amplitude of glucose excursions

Statistically significant reductions in MAGE were demonstrated for each of the dapagliflozin doses compared with placebo at Week 24 in both study MB102229 and MB102230 (**Table 15**). The reductions in the dapagliflozin groups compared with placebo were greater in study MB102229 than in

MB102230.

The effect was similar at Weeks 12 and 24.

Table 15 Secondary efficacy variable in studies MB102229/MB102230: change in mean amplitude of glucose excursions at Week 24 (full analysis set)

	Study MB102229			Study MB102230		
	DAPA 5 mg + INS (N=259)	DAPA 10 mg + INS (N=259)	PLA + INS (N=260)	DAPA 5 mg + INS (N=271)	DAPA 10 mg + INS (N=270)	PLA + INS (N=272)
24-hour CGM MAGE (mg/dL) at Week 24[a]						
N[b]	238	239	234	252	255	257
Baseline mean (SD)	170.66 (31.114)	170.97 (31.398)	169.09 (34.269)	169.35 (29.604)	171.02 (29.854)	168.38 (29.288)
Week 24 mean (SD)	152.23 (34.448)	150.49 (32.802)	168.13 (34.892)	156.98 (33.887)	158.17 (35.687)	165.82 (28.223)
Mean change from baseline (SD)	-18.43 (29.361)	-20.48 (31.338)	-0.96 (31.927)	-12.37 (30.515)	-12.85 (28.671)	-2.56 (27.462)
Adj. mean change from baseline (SE)	-14.92 (1.9915)	-16.55 (2.0419)	2.38 (2.0477)	-10.17 (1.8980)	-9.68 (1.9135)	-0.33 (1.9316)
95% CI for adj. mean change from baseline	(-18.83, -11.01)	(-20.56, -12.55)	(-1.64, 6.40)	(-13.90, -6.45)	(-13.44, -5.93)	(-4.12, 3.46)
Difference from placebo (SE)	-17.30 (2.6273)	-18.93 (2.6482)		-9.85 (2.4519)	-9.36 (2.4487)	
95% CI for difference from placebo	(-22.46, -12.14)	(-24.13, -13.73)		(-14.66, -5.03)	(-14.16, -4.55)	
P-value vs. placebo[c]	<0.0001	<0.0001		<0.0001	0.0001	

Derived from: MB102229 24w CSR Table 11.2.1.1 and MB102230 24w CSR Table 11.2.1.1 in CTD Module 5.3.5.1

[a] Mixed model: change from baseline = baseline treatment week stratum week*treatment week*baseline.

[b] Number of subjects in full analysis dataset with non-missing baseline and at least one post-baseline value.

[c] Nominal p-value.

Adj adjusted; CGM continuous glucose monitoring; CI confidence interval; CTD Common Technical Document; DAPA dapagliflozin; INS insulin; MAGE mean amplitude of glucose excursion; PLA placebo; SD standard deviation; SE standard error

Change in percentage of 24-hour glucose readings falling within the range of >70 mg/dL to ≤180 mg/dL

Statistically significant increases in the percentage of glucose readings falling within the range of >70 mg/dL to ≤180 mg/dL were demonstrated for each of the dapagliflozin doses compared with placebo at Week 24 in both study MB102229 and MB102230 (**Table 16**).

The increase in the percentage of readings >70 mg/dL to ≤180 mg/dL seen with dapagliflozin was not accompanied by any clinically relevant increase in the percentage of readings ≤70 mg/dL at Week 24. In study MB102229, there was a small numerical decrease in the percentage of readings ≤70 mg/dL in both dapagliflozin groups; adjusted mean change compared with placebo from baseline to Week 24 was -0.43% (95% CI: -1.24, -0.38) for dapagliflozin 5 mg and -0.47% (95% CI: -1.28, -0.34) for dapagliflozin 10 mg. In study MB102230, there were no relevant changes in the percentage of readings ≤70 mg/dL in the dapagliflozin groups; adjusted mean change compared with placebo from baseline to Week 24 was +0.46% (95% CI: -0.23, 1.16) for dapagliflozin 5 mg and +0.70% (95% CI: 0.00, 1.39) for dapagliflozin 10 mg.

Table 16 Secondary efficacy variable in studies MB102229/MB102230: change in percentage of 24-hour glucose readings falling within the range of >70 mg/dL to ≤180 mg/dL at Week 24 (full analysis set)

	Study MB102229			Study MB102230		
	DAPA 5 mg + INS (N=259)	DAPA 10 mg + INS (N=259)	PLA + INS (N=260)	DAPA 5 mg + INS (N=271)	DAPA 10 mg + INS (N=270)	PLA + INS (N=272)
24-hour CGM values >70 mg/dL and ≤180 mg/dL(%) at Week 24[a]						
N[b]	238	239	234	252	255	257
Baseline mean (SD)	43.19 (12.368)	44.57 (12.374)	44.42 (12.893)	43.50 (12.434)	43.68 (11.826)	43.53 (12.548)
Week 24 mean (SD)	52.29 (14.840)	54.64 (13.101)	43.84 (14.717)	51.12 (14.152)	53.22 (13.392)	42.40 (13.226)
Mean change from Baseline (SD)	9.10 (13.477)	10.07 (14.149)	-0.58 (14.018)	7.62 (12.771)	9.53 (12.602)	-1.13 (11.975)
Adj. mean change from baseline (SE)	6.98 (0.8824)	8.52 (0.9000)	-2.13 (0.9032)	5.92 (0.8169)	7.60 (0.8225)	-3.10 (0.8318)
95% CI for adj. mean change from baseline	(5.25, 8.71)	(6.75, 10.29)	(-3.90, -0.35)	(4.32, 7.52)	(5.98, 9.21)	(-4.73, -1.47)
Difference from placebo (SE)	9.11 (1.1611)	10.65 (1.1689)		9.02 (1.0415)	10.70 (1.0396)	
95% CI for difference from placebo	(6.83, 11.39)	(8.35, 12.94)		(6.97, 11.06)	(8.66, 12.74)	
P-value vs. placebo[c]	<0.0001	<0.0001		<0.0001	<0.0001	

Derived from: MB102229 24w CSR Table 11.2.1.1 and MB102230 24w CSR Table 11.2.1.1 in CTD Module 5.3.5.1

[a] Mixed model: change from baseline = baseline treatment week stratum week*treatment week*baseline.

[b] Number of subjects in full analysis dataset with non-missing baseline and at least one post-baseline value.

[c] Nominal p-value.

Adj adjusted; CGM continuous glucose monitoring; CI confidence interval; CTD Common Technical Document; DAPA dapagliflozin; INS insulin; PLA placebo; SD standard deviation; SE standard error

Proportion of subjects achieving an HbA1c reduction of ≥0.5% without severe hypoglycaemia events

Statistically significant increases in the proportion of subjects achieving ≥0.5% reductions in HbA1c without severe hypoglycaemia events were demonstrated for each of the dapagliflozin doses compared with placebo at Week 24 in both study MB102229 and MB102230. In both studies, approximately twice as many patients experienced a ≥0.5% reduction in HbA1c without severe hypoglycaemia events in the dapagliflozin groups compared with the placebo group.

In study MB102229, the proportions of subjects experiencing a ≥0.5% reduction in HbA1c without severe hypoglycaemia events were 49.6% and 50.8% in the dapagliflozin 5 mg and 10 mg groups, respectively, compared with 25.3% in the placebo group. In study MB102230, the proportions of subjects experiencing a ≥0.5% reduction in HbA1c without severe hypoglycaemia events were 39.5% and 41.6% in the dapagliflozin 5 mg and 10 mg groups, respectively, compared with 20.1% in the placebo group.

Ancillary analyses

Long-term data

Studies MB102229 and MB102230 both have 24-week ST treatment periods and LT extension periods of 28 weeks. The primary and secondary efficacy objectives procedure comprised variables at Week 24. The efficacy analyses at Week 52 were exploratory, and no p-values were calculated for comparisons at Week 52.

In study **MB102229**, a total of 747 subjects entered the LT extension period of the study. Similar proportions of subjects in each treatment group completed the 52-week ST+LT treatment period: 84.8%, 86.1%, and 83.8% of the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively. The median number of days of exposure to dapagliflozin 5 mg, dapagliflozin 10 mg, or placebo was 364.0 days at Week 52.

The effect of dapagliflozin observed on the primary variable at Week 24 appeared to be maintained at Week 52 (**Table 17**).

Table 17 HbA1c at Week 52 in study MB102229 (full analysis set)

	DAPA 5 mg + INS (N=259)	DAPA 10 mg + INS (N=259)	PLA + INS (N=260)
HbA1c (%) at Week 52[a]			
N[a]	254	254	257
Baseline mean (SD)	8.53 (0.710)	8.52 (0.634)	8.53 (0.669)
N[b]	211	211	206
Week 52 mean (SD)	8.22 (1.014)	8.15 (0.961)	8.53 (1.078)
Mean change from baseline (SD)	-0.32 (0.822)	-0.33 (0.878)	0.02 (0.993)
Adj. mean change from baseline (SE)	-0.27 (0.0622)	-0.31 (0.0621)	0.06 (0.0628)
95% CI for adj. mean change from baseline	(-0.40, -0.15)	(-0.43, -0.19)	(-0.07, 0.18)
Difference from placebo (SE)	-0.33 (0.0830)	-0.36 (0.0828)	
95% CI for difference from placebo	(-0.49, -0.17)	(-0.53, -0.20)	

Derived from: MB102229 52w CSR Table 11.2.1.1 in CTD Module 5.3.5.1

[a] Number of subjects in full analysis dataset with non-missing baseline and at least one post-baseline value.

[b] Number of subjects in full analysis dataset with non-missing baseline and Week 52 values.

Data included for mixed model is up to 8 days post last dose of short-term plus long-term treatment period.

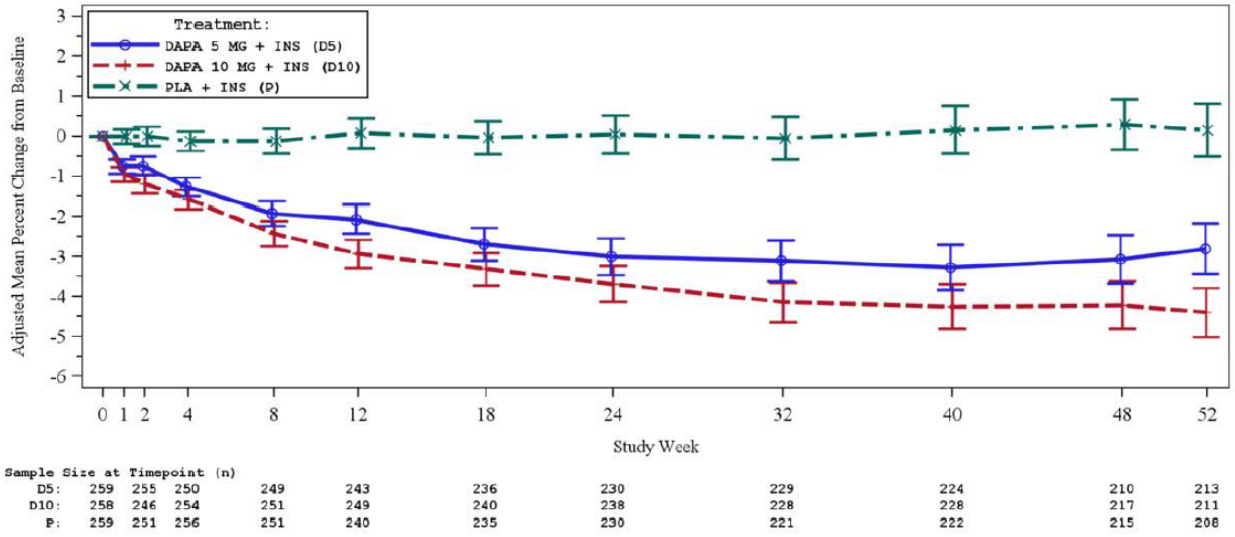
Mixed model: change from baseline = baseline treatment week stratum week*treatment week*baseline

Stratum includes one term for each combination of all stratification factors.

Adj adjusted; CI confidence interval; CTD Common Technical Document; DAPA dapagliflozin; HbA1c glycated haemoglobin; INS insulin; PLA placebo; SD standard deviation; SE standard error

The secondary variables body weight and proportion of subjects achieving ≥0.5% reductions in HbA1c without severe hypoglycaemia events were re-analysed at Week 52 in an exploratory manner. The adjusted mean change compared with placebo in body weight from baseline to Week 52 was -2.95% (95% CI: -3.83%, -2.06%) for dapagliflozin 5 mg and -4.54% (95% CI: -5.40%, -3.66%) for dapagliflozin 10 mg (**Figure 25**). The proportion of subjects achieving ≥0.5% reductions in HbA1c without severe hypoglycaemia events from baseline to Week 52 was 40.2%, 42.1%, and 23.7% for the dapagliflozin 5 mg group, the dapagliflozin 10 mg group, and the placebo group, respectively.

Figure 25 Change from baseline in total body weight over time – 52-week short-term plus long-term treatment period (full analysis set)



Source: Figure 11.2.3.2

Mean refers to mean percent change from baseline based on a mixed model with treatment, ln(baseline) value, week, week-by-treatment interaction, week-by-ln (baseline) interaction and stratum (one term for each combination of all stratification factors) as independent variables.

Error bars represent 95% confidence intervals for the adjusted mean percent change from baseline. Treatment symbols shifted horizontally to prevent error bar overlapping.

BL baseline; D5 dapagliflozin 5 mg; D10 dapagliflozin 10 mg; DAPA dapagliflozin; INS insulin; P placebo; PLA placebo; W week

Insulin dose during the LT extension was recorded on a weekly basis, and the reduction in insulin dose observed at Week 24 appeared to be maintained at Week 52. Since study CGM was not used after Week 24, the Week 52 analyses did not include mean value of 24-hour glucose readings, mean amplitude of glucose excursions, or percentage of 24-hour glucose readings falling within the range of >70 mg/dL to ≤180 mg/dL.

In **study MB102230**, a total of 717 subjects entered the LT extension period of the study. Similar proportions of subjects in each treatment group completed the 52-week ST+LT treatment period: 85.2%, 83.7%, and 79.4% for the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively. The median number of days of exposure to dapagliflozin 5 mg, dapagliflozin 10 mg, or placebo was 365.0 days at Week 52.

The adjusted mean change in HbA1c from baseline to Week 52 was -0.11%, -0.16%, and 0.09% for the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively, corresponding to a mean change versus placebo of -0.20% (95% CI: -0.34%, -0.06%) for dapagliflozin 5 mg and -0.25% (95% CI: -0.38%, -0.11%) for dapagliflozin 10 mg.

The secondary variables body weight and proportion of subjects achieving ≥0.5% reductions in HbA1c without severe hypoglycaemia events were re-analysed at Week 52 in an exploratory manner. The adjusted mean change compared with placebo in body weight from baseline to Week 52 was -4.42% (95% CI: -5.19%, -3.64%) for dapagliflozin 5 mg and -4.86% (95% CI: -5.63%, -4.08%) for dapagliflozin 10 mg. The proportion of subjects experiencing a ≥0.5% reduction in HbA1c without severe hypoglycaemia events was 32.7% and 32.2% in the dapagliflozin 5 mg and dapagliflozin 10 mg groups, respectively, compared with 20.8% in the placebo group.

Insulin dose during the LT extension was recorded on a weekly basis, and the reduction in insulin dose observed at Week 24 appeared to be maintained at Week 52.

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 18 Summary of Efficacy for trial MB102229

Title: A Multicentre, Randomised, Double-Blind, Placebo-controlled, Parallel Group, Phase 3 Study to Evaluate the Efficacy and Safety of Dapagliflozin as an Add-on to Insulin Therapy in Subjects with Type 1 Diabetes Mellitus				
Study identifier	MB102229			
Design	This was a randomised, double-blinded, 3-arm, parallel-group, placebo-controlled, multicentre Phase III study with a 24-week short-term treatment period, followed by a 28-week long-term subject- and site-blinded treatment period, to evaluate the efficacy and safety of dapagliflozin 5 mg and 10 mg as add-on therapy to insulin in adult subjects with T1DM and inadequate glycaemic control (defined as HbA1c ≥7.5%).			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks 8 weeks 28 weeks		
Hypothesis	Superiority			
Treatments groups	Dapagliflozin 5 mg	259 randomised		
	Dapagliflozin 10 mg	259 randomised		
	Placebo	260 randomised		
Endpoints and definitions	Primary endpoint	HbA1c (%)	Change in HbA1c from baseline at week 24	
	Secondary endpoint	Body weight (%)	Percent change in body weight at week 24	
	Secondary endpoint	MAGE (mg/dL)	Change in mean amplitude of glucose excursions at week 24	
	Secondary endpoint	Responders (%)	Proportion of subjects achieving an HbA1c reduction of ≥0.5% without severe hypoglycaemia events	
Database lock	21 February 2017			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat (full analysis set)			
Descriptive statistics and estimate variability	Treatment group	Dapagliflozin 5 mg	Dapagliflozin 10 mg	Placebo
	Number of subject	259	259	260
	HbA1c (adj mean change)	-0.45	-0.47	-0.03
	95% CI	(-0.55, -0.34)	(-0.58, -0.37)	(-0.13,0.08)
	Body weight (adj mean % change)	-3.00	-3.67	0.05
	95% CI	(-3.45, -2.54)	(-4.12,-3.22)	(-0.42, 0.52)
	MAGE (mg/dL)	-14.9	-16.6	2.4
	95% CI	(-18.8, -11.0)	(-20.6, -12.6)	(-1.6, 6.4)
	Responders (%)	49.6	50.8	25.3
Effect estimate per comparison		Comparison groups	Dapagliflozin 5mg vs placebo	Dapagliflozin 10mg vs placebo

	Primary endpoint: HbA1c (%)	Difference in adj means	-0.42	-0.45
		(95% CI)	(-0.56, -0.28)	(-0.58, -0.31)
		P-value	< 0.0001	< 0.0001
	Secondary endpoint: Body weight (%)	Difference in adj means	-3.05	-3.72
		(95% CI)	(-3.68, -2.41)	(-4.34, -3.08)
		P-value	< 0.0001	< 0.0001
	Secondary endpoint: MAGE (mg/dL)	Difference in adj means	-17.3	-18.9
		(95% CI)	(-22.5, -12.1)	(-24.1, -13.7)
		P-value	< 0.0001	< 0.0001
	Secondary endpoint: Responders (%)	Odds ratio	3.09	3.29
		(95% CI)	(2.10, 4.56)	(2.23, 4.85)
		P-value	< 0.0001	< 0.0001

Table 19 Summary of Efficacy for trial MB102230

Title: A Multicentre, Randomised, Double-Blind, Placebo-controlled, Parallel Group, Phase 3 Study to Evaluate the Efficacy and Safety of Dapagliflozin as an Add-on to Insulin Therapy in Subjects with Type 1 Diabetes Mellitus			
Study identifier	MB102230		
Design	This was a randomised, double-blinded, 3-arm, parallel-group, placebo-controlled, multicentre Phase III study with a 24-week short-term treatment period, followed by a 28-week long-term subject- and site-blinded treatment period, to evaluate the efficacy and safety of dapagliflozin 5 mg and 10 mg as add-on therapy to insulin in adult subjects with T1DM and inadequate glycaemic control (defined as HbA1c ≥7.5%).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks 8 weeks 28 weeks	
Hypothesis	Superiority		
Treatments groups	Dapagliflozin 5 mg	271 randomised	
	Dapagliflozin 10 mg	270 randomised	
	Placebo	272 randomised	
Endpoints and definitions	Primary endpoint	HbA1c (%)	Change in HbA1c from baseline at week 24
	Secondary endpoint	Body weight (%)	Percent change in body weight at week 24
	Secondary endpoint	MAGE (mg/dL)	Change in mean amplitude of glucose excursions at week 24
	Secondary endpoint	Responders (%)	Proportion of subjects achieving an HbA1c reduction of ≥0.5% without severe hypoglycaemia events
Database lock	25 October 2017		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat (full analysis set)			
Descriptive statistics and estimate variability	Treatment group	Dapagliflozin 5 mg	Dapagliflozin 10 mg	Placebo
	Number of subject	271	270	272
	HbA1c (adj mean change)	-0.34	-0.39	0.03

	95% CI	(-0.43, -0.25)	(-0.48, -0.30)	(-0.06, 0.12)
	Body weight (adj mean % change)	-3.22	-3.76	-0.02
	95% CI	(-3.76, -2.69)	(-4.29,-3.22)	(-0.57, 0.54)
	MAGE (mg/dL)	-10.2	-9.7	-0.3
	95% CI	(-13.9, -6.4)	(-13.4, -5.9)	(-4.1, 3.5)
	Responders (%)	39.5	41.6	20.1

Effect estimate per comparison		Comparison groups	Dapagliflozin 5mg vs placebo	Dapagliflozin 10mg vs placebo
	Primary endpoint: HbA1c (%)	Difference in adj means	-0.37	-0.42
		(95% CI)	(-0.49, -0.26)	(-0.53, -0.30)
		P-value	< 0.0001	< 0.0001
	Secondary endpoint: Body weight (%)	Difference in adj means	-3.21	-3.74
		(95% CI)	(-3.96, -2.45)	(-4.49, -2.99)
		P-value	< 0.0001	< 0.0001
	Secondary endpoint: MAGE (mg/dL)	Difference in adj means	-9.9	-9.4
		(95% CI)	(-14.7, -5.0)	(-14.2, -4.6)
		P-value	< 0.0001	< 0.0001
	Secondary endpoint: Responders (%)	Odds ratio	2.71	3.07
		(95% CI)	(1.81, 4.06)	(2.05, 4.60)
		P-value	< 0.0001	< 0.0001

Analysis performed across trials (pooled analyses)

Comparison of results in sub-populations

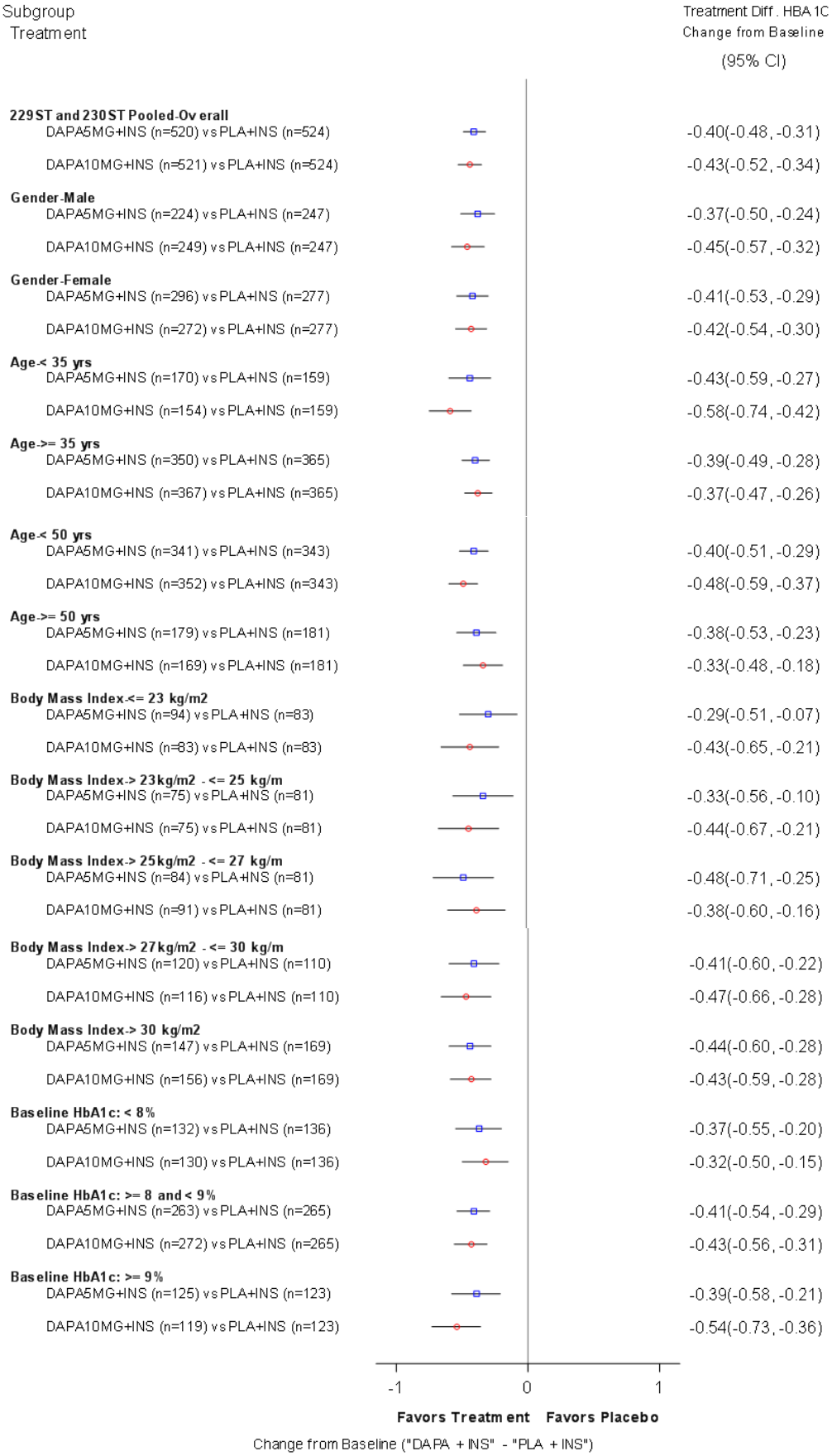
Subgroup analyses were conducted to evaluate the consistency of the treatment effect across subgroups for change in HbA1c from baseline to Week 24. The prespecified subgroup categories in studies MB102229 and MB102230 were sex, race, ethnicity, baseline HbA1c, age, geographic region, method of insulin administration, use of CGM, and baseline BMI.

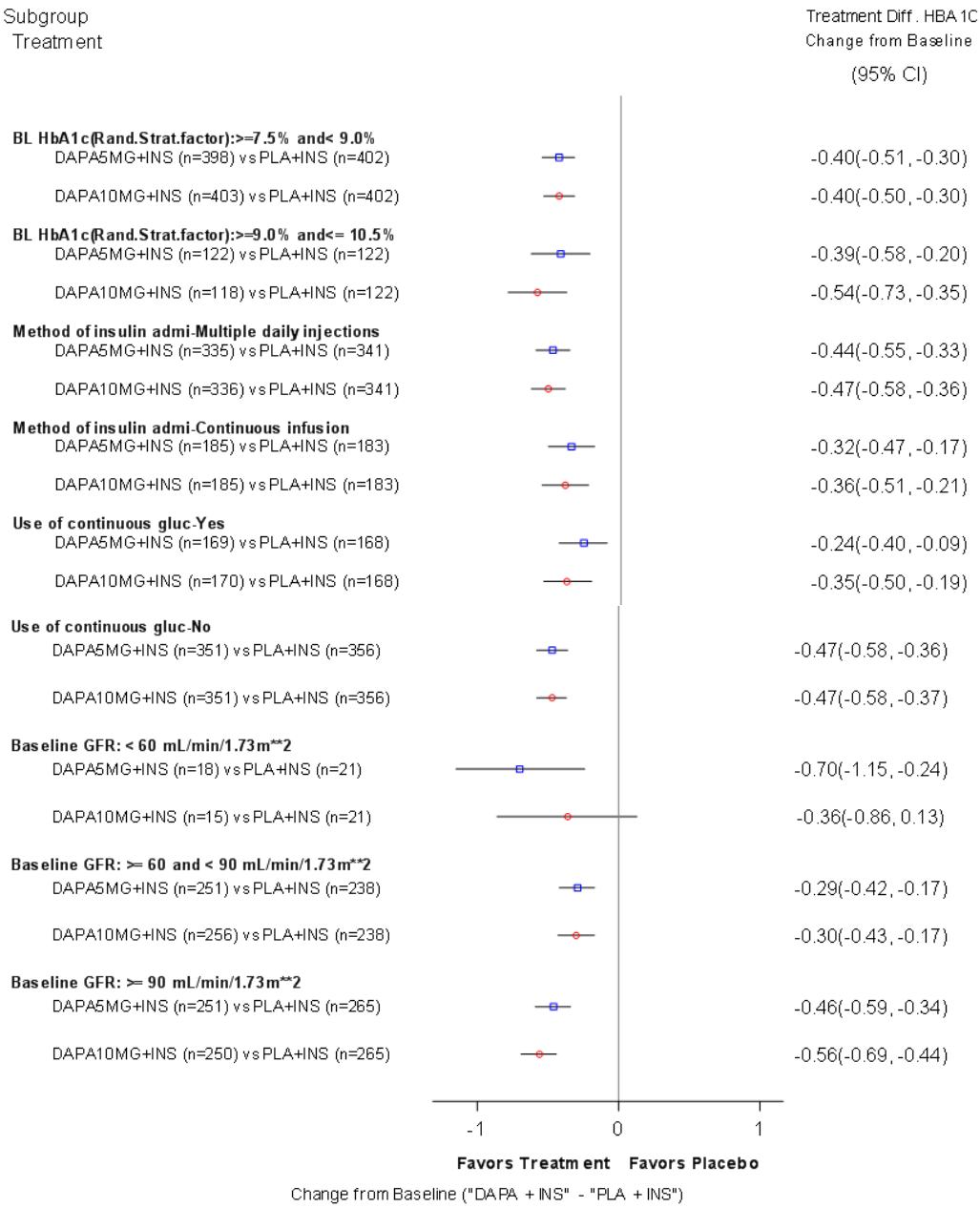
Data from studies MB102229 and MB102230 were pooled to provide greater sensitivity to detect variations in treatment effect across subgroups. Overall, the effect on HbA1c from baseline to Week 24 was consistent across the subgroups evaluated (**Figure 26**).

The effect on HbA1c from baseline to Week 24 was also consistent across subgroups when evaluated individually for each study.

Analyses of secondary efficacy endpoints that included only subjects randomised to US study sites were conducted in studies MB102229 and MB102230. The results of these US-specific analyses were generally consistent with the overall analyses.

Figure 26 Forest plot of change from baseline in HbA1c at Week 24 by subgroup in studies MB102229 and MB102230 (pooled) (full analysis set)





2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical study program supporting the use of dapagliflozin in T1DM patients consists of two Phase III studies of similar design, MB102229 and MB102230. Both were randomised, double-blind, placebo-controlled, parallel-group studies. The duration of the run-in (8 weeks) and treatment phases (24 weeks and 28 weeks, short- and long-term respectively) were accepted by the CHMP in scientific advice given. Study MB102229 had been finalised at the time of submission, whereas data for the 28 week extension of study MB102230 was provided with the responses to the 1st RSI.

No formal dose finding study was performed; instead the doses chosen for the Phase III studies were selected based on the data obtained from study MB102072 as well as from the data in T2DM. In T2DM, 5 mg and 10 mg has been established as the minimally effective doses. The rationale for dose selection is adequate from an efficacy perspective. Both the 5 mg and 10 mg dose was investigated in the studies.

The inclusion and exclusion criteria are considered adequate. Although patients with frequent hypoglycaemias and highly variable blood glucose may be a target population for treatment, it was accepted to exclude this population for safety reasons. Patients were to be on a total insulin dose of ≥0.3 U/kg/day in order to reduce the risk of ketoacidosis in lean patients. Subjects were also excluded if they had been admitted to a hospital because of hyper- or hypoglycaemia or had experienced diabetic ketoacidosis (DKA) requiring medical intervention within 1 month of the screening visit. Study MB102229 initially included an eligibility criterion excluding subjects whose HbA1c changed ≥0.5% between enrolment and randomisation. Because this criterion accounted for approximately 80% of subjects being ineligible for randomisation after completing the lead-in period and did not reflect clinical practice, the MAH amended the study protocol to remove the criterion after consultation with the CHMP.

Comparison with placebo was accepted by the CHMP and justified by the fact that the insulin dose of a subject could be up- or down-titrated as deemed appropriate to be consistent with good medical practice. Furthermore, no other medicinal products than insulin are available for the treatment of T1DM.

No fixed titration schedules were used in the study. Insulin doses could be adjusted as deemed appropriate to be consistent with good medical practice according to SMBG readings, local guidance and individual circumstances. Recommendations were given on dose reductions in order to avoid hypoglycaemia after the first dose of study drug. Insulin dose reductions of > 20% from baseline were not recommended in order to avoid DKA. In case of hypoglycaemias in spite of a 20 % reduction of the insulin dose, the patients were recommended to increase their carbohydrate intake.

The primary objective was to compare the effect of dapagliflozin 5 mg and 10 mg versus placebo on the change from baseline in HbA1c in patients on an optimised and adjustable insulin treatment. Secondary objectives compared the effect on change in total insulin dose and body weight, but also on the effect on blood glucose variability when measured by CGM. To investigate the effect on hypoglycaemias in relation to HbA1c reduction, the proportion of subjects achieving an HbA1c reduction ≥0.5% without severe hypoglycaemic events was included as a secondary endpoint. The objectives and endpoints were adequate and as agreed in SA.

The sample sizes calculations were adequate. A randomisation error affected the first 55 patients in study MB102229. The choice to exclude these patients from the efficacy analyses is endorsed. With these patients excluded the randomisation error is unlikely to affect the efficacy analyses.

The study was double-blinded although it may be questioned whether the subjects could have identified that they were on active therapy due to effects on blood glucose and urinary volume. However, there is no indication in the pattern of study discontinuation that treatment group was known to the subjects. In summary, the blinding is considered adequately handled.

In summary the statistical methodology for both trials (MB102229 and MB102230) are generally considered acceptable.

The primary endpoint is change of HbA1c after 24 weeks analysed using a mixed model for repeated measures analysis (MMRM) and targeting a treatment effect as if patients adhered to treatment until week 24.

Missing data are a minor problem for the two pivotal studies with less (Study 29) and around 10% (Study 30) withdrawals and similar withdrawal patterns between the treatment arms. The primary efficacy analysis is based on a MAR assumption and it is not possible to know if this assumption is applicable. There is some indication that missing data is associated with an increased HBA1C-level before drop out (figure 12.1.9.5 study MB102229) and other methods, such as placebo based imputation, may be considered giving more adequate estimates of efficacy. Results from the placebo based imputation analysis presented for study MB102229 and MB102230 does however show very similar point estimates to the primary efficacy analysis. The LOCF sensitivity analysis did also give consistent results.

While the primary efficacy target of estimation, or estimand, and type of analysis was common standard in studies for antidiabetic drugs in recent years, current discussions could suggest that other targets of estimation could be preferable. These could be targets of estimation using data regardless of treatment discontinuation or analyses with (multiple) imputations based on observations from patients of the same treatment arm discontinuing treatment, but not withdrawing from the trial.

The Applicant adequately addressed the issue by including the analyses described above, partly addressing different targets of estimation. While these analyses might not be considered sensitivity analysis in the sense of the draft ICH E9 addendum, they demonstrate that the different effect estimates result in very comparable results. They also suggest that analyses for secondary endpoints, which are using an analysis close to the defined primary analysis, are interpretable in the same way and should allow robust conclusions.

Statistical methods for secondary and exploratory endpoints are considered acceptable. Extending the additional “sensitivity analysis” for the primary analysis to the secondary endpoints would have been welcomed. However, as results of the different analyses for the primary endpoint, partly targeting a different target of estimation, are very similar and the secondary analyses close to the primary analysis method, one may indirectly conclude that “sensitivity analysis” for the secondary endpoints using an analysis close to the primary analysis would also have similar results.

For the responder endpoint “proportion of subjects achieving an HbA1c reduction from baseline to Week 24 of ≥0.5% without severe hypoglycaemia events”, a logistic regression model using LOCF week 24 data was applied. While the LOCF single imputation approach is not considered to have acceptable properties and a multiple imputation approach similar to the “de-facto estimand” for the primary analysis would have been preferred, it is considered most unlikely that conclusions from an analysis using a different imputation approach would change conclusions due to the large observed effect compared to placebo.

The control of the type I error is considered acceptable. The primary and secondary efficacy variables were analysed and statistically tested in a pre-specified stepwise procedure. The pivotal studies use a standard parallel group design with two active doses compared to placebo. A Dunnett and Tamhane step-up procedure was chosen to control the type I error with regards to testing of the two doses. The Dunnett and Tamhane step-up procedure needs some assumptions about correlation and data structure in the two dose arms, but these are most likely fulfilled in a study setting with two doses like in the pivotal trial and therefore the primary analysis is acceptable. Although no interim analyses were performed, study MB102229 was divided into two parts, a 24 week follow up and a 52 week follow up with un-blinding at 24 weeks. The efficacy endpoints were however defined for the 24 week time point so this is not considered to inflate the type I error rate.

The methodology for subgroups analyses to assess the homogeneity of results is considered appropriate. Tests for interaction to assess heterogeneity are considered informative, but there is no

commonly accepted statistical method to assess homogeneity of heterogeneity of results. Exploratory subgroup analyses are acceptable and are considered more important than interaction tests.

In study MB102229, there were two amendments made (#3 and #5) that could potentially influence the outcome and interpretation of the data. With amendment #3 the change in exclusion criteria was introduced as discussed above. This may have resulted in a change in the characteristics of the patients included after the amendment. This amendment came into effect 6 month after the enrolment of the first patient. Amendment #5 was introduced one year later. With this amendment the number of patients to be enrolled was increased by 55 to compensate for the exclusion of the patients enrolled before the error in the IVRS randomisation system was discovered. The MAH has clarified that only 121 out of 778 patients were included before amendment #3 and included in the final analysis, thus the characteristics of the population is not expected to be affected to any greater extent.

Both amendments were also made to the protocol for study MB102230, but only amendment #5 came into effect after the inclusion of the first patient in this study. Amendment #5 also included clarifications on how to change the insulin doses. The MAH has clarified that in study MB102229, six out of 778 patients, and in study MB102230, 315 out of 815 patients were included after amendment #5. Thus, the majority of patients in both studies were not exposed to the new recommendations at study start. This may have implications for the interpretation of the efficacy of the recommendations as a means for avoiding DKA but is not considered to have affected the outcome of the study.

In both studies, protocol deviations were few and evenly distributed between treatment groups. There are no concerns with regards to the general conduct of the studies.

Efficacy data and additional analyses

In study MB10229, 91.3%, 92.2%, and 89.2% in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively, completed the ST period. For the 52-week ST+LT treatment period: 84.8%, 86.1%, and 83.8% in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups completed the study. The corresponding figures for the ST period in study MB102230 were 90.0%, 90.7%, and 87.9% for the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups. For the 52-week ST+LT treatment period: 85.2%, 83.7%, and 79.4% in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups completed the study. Thus in both studies, discontinuation rates were generally low and balanced between groups. In the ST period, withdrawals due to adverse events were rather balanced between groups. In the LT period, discontinuations due to adverse events were only observed in the dapagliflozin treated groups.

Baseline demographic characteristics were generally balanced both between treatment groups and between studies. Mean HbA1c was comparable in both studies (8.53% and 8.43% in study MB102229 and MB102230, respectively). Mean BMI was rather high (about 28 kg/m^2) in both studies compared with what is typical for the T1DM patient population in European countries (approximately 25 kg/m^2, [Stadler et al., Diabetes Obes Metab. 2017;19:1171–1178]). About 35% of subjects in both studies used CSII. GFR <60 mL/min/1.73 m^2 was reported for about 4.1% and 3.1% of subjects in study MB102229 and MB102230, respectively. In study MB102229, 59% of subjects were recruited in Europe and in study MB102230, 34% of subjects were European. Study MB102230 also included 19% Japanese subjects.

In both studies, a statistically significant but modest decrease in HbA1c from baseline was observed for both dapagliflozin doses. The outcome was comparable between studies and there was no apparent difference in between the doses. Sensitivity analyses confirmed the result. In study MB102229, the adjusted mean change compared with placebo in HbA1c from baseline to Week 24 was -0.42% (95%

CI: 0.56, -0.28; p<0.0001) for dapagliflozin 5 mg and -0.45% (95% CI: -0.58, -0.31; p<0.0001) for dapagliflozin 10 mg. In study MB102230, the adjusted mean change compared with placebo in HbA1c from baseline to Week 24 was -0.37% (95% CI: -0.49, -0.26; p<0.0001) for dapagliflozin 5 mg and -0.42% (95% CI: -0.53, -0.30; p<0.0001) for dapagliflozin 10 mg. The lowest HbA1c was observed between week 4 and week 12, after which a slight increase was observed at week 18. From week 18 and up to week 24, the HbA1c remained stable. It should be noted that, although the improvement in glycaemic control was small, it was achieved despite a concomitant reduction in insulin requirements.

While reduction in insulin dose is not a recognized benefit in itself, it may reduce risk of hypoglycaemia and weight gain. In both studies, the total daily insulin dose was significantly decreased with both dapagliflozin doses compared to placebo. In spite of high HbA1c at inclusion (mean of about 8.5%), no increase in total insulin dose was observed in the placebo treated groups. This may be explained by the fact that insulin doses were increased during insulin therapy optimisation during lead-in and a further change (increase) in insulin dose has not necessarily to be expected during the course of the study. Numerically, there was almost no difference in the change in total insulin dose between dapagliflozin doses or between studies, the percent change from baseline ranging from -9% to -13%. It should be noted that more detailed recommendations on how to reduce the insulin dose was introduced during the course of the studies through amendment #5 of the protocol; this potentially affected more patients in study MB102230. There was however no apparent difference in the outcome between studies. In general, the proportional reductions seen for basal and bolus insulin individually were similar to the proportional reduction in total insulin, thus both basal and bolus insulin were reduced to the same extent.

In study MB102229, the adjusted mean change compared with placebo in body weight from baseline to Week 24 was -3.05% in the dapagliflozin 5 mg group and -3.72% for dapagliflozin 10 mg. In study MB102230, the adjusted mean change compared with placebo in body weight from baseline to Week 24 was -3.21% for dapagliflozin 5 mg and -3.74% for dapagliflozin 10 mg. A small part of this reduction is probably due to the diuretic effect of dapagliflozin but a reduction in fat mass has been clearly shown in the usually overweight patients with T2DM and can be attributed to nutrient loss through glucose excretion. While weight (fat) loss is not relevant and not desirable in normal weight patients, it can be considered beneficial in overweight/obese patients; similar to the general population, overweight/obesity is an increasing problem also in patients with T1DM. In the two phase 3 studies presented here, most of the participants were overweight or obese. In absolute terms, the placebo-corrected weight loss was around 2 kg in the normal weight group and was up to 3.65 kg in obese patients receiving 10 mg dapagliflozin. In all subsets the weight loss was lower with 5 mg dapagliflozin than with 10 mg dapagliflozin, indicating a dose-dependent effect.

There was a comparable and significant decrease in mean value of 24-hour glucose readings (CGM) in both studies. The difference from placebo was larger for the 10 mg dose compared to the 5 mg dose in both studies (-15 vs -18 in study MB102229 and -16 vs -20 in study MB102230). This is in line with the observed decrease in HbA1c. Surprisingly, the most profound glucose-lowering effect of dapagliflozin in combination with insulin compared to insulin alone was found to occur during the early morning hours. It can only be speculated that dapagliflozin counteracts what is called the dawn phenomenon by increasing urinary glucose excretion in response to rising blood glucose levels. Another possible explanation could be that renal glucose excretion continues during the night. As no food intake compensates for this glucose loss, blood glucose steadily decreases.

In T1DM patients, a decreased variability in blood glucose is an important treatment target in order to allow optimisation of the insulin therapy. Therefore, the following secondary endpoints investigating the effect on blood glucose variability are considered important. The mean amplitude of glucose

excursions decreased significantly for both dapagliflozin doses in both studies. The decrease was more pronounced in study MB102229 compared to study MB102230. The percentage of 24-hour glucose readings falling within the range of >70 mg/dL to ≤180 mg/dL increased with both doses of dapagliflozin compared to placebo, with a numerically larger increase with the higher dose (9% vs 11%). The outcome was comparable in both studies. This was achieved without any relevant change in the percentage of readings ≤70 mg/dL in the dapagliflozin groups in either of the studies (about ±0.5%). Together these two secondary endpoints indicate that the variability in glucose decreased with dapagliflozin treatment. In order to assess whether this effect was driven by the method of insulin administration subgroup analyses of these two endpoints by method of administration, i.e. injections and CSII, was provided. The data provided does not indicate that the outcome with regards to glucose variability was driven by the method of administration.

The proportion of patients achieving an HbA1c reduction of ≥0.5% without severe hypoglycaemia events was twice as high in the dapagliflozin treated groups compared to placebo. There was no relevant difference between dapagliflozin doses but the proportions were higher in study MB102229 (49.6% and 50.8% for 5 mg and 10 mg, respectively, 25.3% for placebo) than in study MB102230 (39.5% and 41.6% for 5 mg and 10 mg, respectively, 20.1% for placebo). It is known that (the fear of) hypoglycaemia is the main obstacle to improving glycaemic control in this patient population. Therefore, this finding may be clinically relevant. HbA1c reductions of this magnitude, if maintained, are expected to translate into some reduction of microvascular complications.

Exploratory data from the finalised 28 week extension phase of study MB102229 show that the placebo-adjusted change from baseline in HbA1c was largely maintained up to 52 weeks (-0.33% at 52 weeks vs -0.42% at 24 weeks with dapagliflozin 5 mg and -0.36% at 52 weeks vs -0.45% at 24 weeks with dapagliflozin 10 mg). A similar pattern was observed in study MB102230 (-0.20% at 52 weeks vs -0.37% at 24 weeks with dapagliflozin 5 mg and -0.25% at 52 weeks vs -0.42% at 24 weeks with dapagliflozin 10 mg), although the attenuation of the glycaemic effect was slightly larger in this study. Reduction of body weight was maintained, but there did not appear to be any further decline in body weight after week 32. The weight reduction was more pronounced in patients treated with the 10 mg dose. Similar results were observed in both studies. There was a decrease in the proportion of patients achieving ≥0.5% reductions in HbA1c without severe hypoglycaemia events in the dapagliflozin treated groups at week 52 compared to week 24. The decrease ranged from 6.8% to 9.4% in the dapagliflozin treated groups and whereas the proportion remained more stable in the placebo treated groups (-1.6% and +0.7%, MB102229 and MB102230, respectively). The difference versus placebo was however maintained. Overall the long-term data was consistent across the two studies.

A subgroup analysis was performed on pooled data from studies MB102229 and MB102230. The subgroups selected were adequate. The analysis showed consistent outcomes in all subgroups with regards to the primary endpoint, including analysis by age and BMI. The subgroup of patients with GFR<60 was small and showed wide CIs. The subgroup with GFR<60 and treated with dapagliflozin 10 mg was the only subgroup for which the 95% CI included 0.

The MAH made efforts to identify a population which could have a higher benefit than average from dapagliflozin addition and to identify patients who are at particular risk for developing DKA. According to the analyses provided, overweight/obese type 1 diabetic patients with a high basal insulin need may benefit from dapagliflozin treatment. In addition, patients with highly variable blood glucose levels (measured as MAGE) could theoretically benefit from dapagliflozin treatment.

2.4.4. Conclusions on the clinical efficacy

The application is supported by two Phase III studies of similar design. The outcomes of the studies are consistent and show that treatment with both doses of dapagliflozin (5 mg and 10 mg) results in a modest reduction in HbA1c, without an increased risk of hypoglycaemia. In addition, a weight reduction is observed and also a decrease in blood glucose variability. The outcome of the studies appears robust. The effect seems to be similar in different subgroups, but patients with overweight/obesity are expected to benefit more from the combined effect on CV risk factors also considering that further increase of the insulin dose may not be adequate in these patients since that would lead to additional weight gain.

There is virtually no difference in the extent of HbA1c reduction between the 5 mg and 10 mg dapagliflozin group. This finding was consistent in both pivotal studies. Therefore, only the 5 mg dose is recommended for use in the T1DM population.

2.5. Clinical safety

Introduction

Dapagliflozin, human renal SGLT2 inhibitor, inhibits the renal reabsorption of glucose, causing glucose to be excreted in the urine and thereby lowering plasma glucose levels in an insulin-independent manner. The amount of glucose excreted depends on the amount of glucose filtered by the kidney, which in turn depends on the plasma glucose concentration and the glomerular filtration rate (GFR).

The safety and tolerability of dapagliflozin were thoroughly investigated and documented in the original submission for approval of dapagliflozin for treatment of type 2 diabetes mellitus (T2DM). The original T2DM submission has been supplemented over time with updated information on the safety and tolerability of dapagliflozin, notably with data from a 30-month update cut-off relative to the original data cut and with extensive post-marketing data.

The safety profile of dapagliflozin is characterised by an increased risk of urogenital infections and volume depletions related adverse reactions due to the mechanism of action which results in increased excretion of glucose in the urine and increased urinary volume. The inherent risk of hypoglycaemia with dapagliflozin is low and rather related to the background therapy used, i.e. SU or insulin. Post-marketing, an increased risk of (euglycaemic) diabetes ketoacidosis (DKA) has been observed.

New data

With this application, information on the safety and tolerability of dapagliflozin in patients with type 1 diabetes mellitus (T1DM) is provided and compared with the known safety profile of dapagliflozin. Data primarily come from 2 Phase III global studies of dapagliflozin as add-on to insulin therapy in subjects with T1DM: studies MB102229 and MB102230. Data from a United States (US) Phase IIa pilot study, MB102072, and from a Japanese Phase I/III study, D1695C00001, are briefly summarised but are generally not included in the overall discussion of adverse events (AEs) or clinical laboratory evaluations due to one or more of their short duration, small study size, or lack of placebo control.

Pooling strategy

To detect potential imbalances in less common AEs and to provide an overview of the experience with dapagliflozin in subjects with T1DM, ST data from studies MB1020229 and MB102230 were pooled (the 'ST placebo-controlled Phase III pool'). Data from studies MB102072 and D1695C00001 (Part A) were not included in the ST placebo-controlled Phase III pool due to their short treatment periods and

limited number of subjects. Data from study D1695C00001 (Part B) were not included in the pool as this part of the study was not placebo-controlled. Long-term data from studies MB102229, MB102230 and D1695C00001 (Part B) are presented separately.

Safety variables collected and methods of evaluation

Safety assessments in the dapagliflozin T1DM studies included the adjudication of certain events by blinded independent adjudication committees:

- Diabetic Ketoacidosis (DKA) Adjudication Committee (DKAAC). Potential DKA events sent to adjudication were identified based on recorded ketone test results, symptoms potentially associated with DKA, and relevant risk factors in the subject diary. Over 20000 ketone (beta-hydroxybutyrate) readings were recorded.
- Cardiovascular Adjudication Committee.
- Hepatic Adjudication Committee

The safety analysis set for each of the dapagliflozin T1DM studies consisted of all randomised subjects who received at least one dose of study drug. Any subjects receiving incorrect study drug for the entire course of their participation were assessed according to the treatment that they actually received.

Studies MB102229 and MB102230

The following AEs of special interest were assessed in studies MB102229 and MB102230: hypoglycaemia, DKA, cardiovascular AEs, hepatobiliary AEs, genital infections, urinary tract infections, volume depletion, fractures, worsening renal function, and hypersensitivity. Each of these AEs of special interest is discussed individually in subsequent sections.

Events of hypoglycaemia, hypoglycaemic episodes, and discontinuation due to hypoglycaemia were recorded separately from other AEs on electronic Case Report Form (eCRF) pages for hypoglycaemia.

Investigators reported all potential DKA events to a blinded and independent adjudication committee. The assessment of DKA events was based on the adjudicated outcomes.

The assessments of the remaining AEs of special interest were primarily based pre-specified lists of preferred terms (PTs), coded for this SCS according to Medical Dictionary for Regulatory Activities (MedDRA) version 20.0.

Cardiovascular events and liver-related abnormalities were also subject to blinded and independent adjudication. The adjudicated outcomes for cardiovascular events and liver-related abnormalities supplemented the overall assessment of cardiovascular and hepatobiliary AEs based on pre-specified PTs.

Studies MB102072 and D1695C00001 (Part A & Part B)

The collection and assessment of safety variables was similar in studies MB102072 and D1695C00001 (Part A and Part B) to that for studies MB102229 and MB102230, with the exception that there was no adjudication of potential DKA events in study MB102072.

Patient exposure

There were 1797 subjects randomised in the T1DM Phase III studies, of whom 1265 were treated with dapagliflozin. A total of 1155 subjects completed 24 weeks of treatment with dapagliflozin. The long-term extensions of studies MB102229 and D1695C00001 (Part B) are complete: 562 subjects were

treated with dapagliflozin for >360 days. Cumulative exposure to dapagliflozin across the T1DM Phase III studies is 906.8 patient-years.

Table 20 summarises the extent of exposure to study drug in the ST placebo-controlled Phase III pool. Mean exposure was similar across all treatment groups. Cumulative exposure to study drug was greater in the dapagliflozin treatment groups than in placebo, which was primarily due to the higher numbers of subjects in the dapagliflozin groups as a result of the randomisation system error in study MB102229.

Table 20 Summary of extent of exposure to double-blind study drug – ST placebo-controlled Phase III pool (safety analysis set)

	Number of subjects (%)		
Duration (days)	**DAPA 5 MG + INS (N=548)**	**DAPA 10 MG + INS (N=566)**	**PLA + INS (N=532)**
1-7	3 (0.5)	3 (0.5)	4 (0.8)
8-30	10 (1.8)	6 (1.1)	8 (1.5)
31-60	9 (1.6)	8 (1.4)	11 (2.1)
61-90	12 (2.2)	11 (1.9)	13 (2.4)
91-120	4 (0.7)	8 (1.4)	6 (1.1)
121-180	491 (89.6)	505 (89.2)	473 (88.9)
>180	19 (3.5)	25 (4.4)	17 (3.2)
Summary Statistics			
Mean	161.1	162.8	159.9
Median	169.0	169.0	169.0
Min, Max	2, 201	1, 224	1, 190
Standard Deviation	32.40	28.97	32.76
Cumulative exposure (patient-years)	241.6	252.3	232.9

Source: Table 8.3.1.1
This table includes all subjects in safety analysis set. Percentages reported are based on the total number of subjects in each treatment group. The extent of exposure to study drug during the short-term double-blind period is defined as the difference between the last and the first dose of study drug of the short-term double-blind treatment period plus 1 day. Cumulative exposure is calculated as the sum of the exposure to study drug of all subjects (in years) in a treatment group.
The ST placebo-controlled Phase III pool consists of all study MB102229 and MB102230 data included in the safety analysis set for the 24-week short-term treatment period.
DAPA dapagliflozin; INS insulin; PLA placebo

Demographic and other characteristics of study population

In the ST placebo-controlled Phase III pooled population, the treatment groups were generally balanced with respect to demographic, disease, and baseline characteristics. Table 21 summarises key characteristics.

Table 21 Demographics and diabetes-related baseline characteristics – ST placebo controlled Phase III pool (safety analysis set)

	DAPA 5 mg + INS	DAPA 10 mg + INS	PLA + INS	Total
	N=548	N=566	N=532	N=1646
Age (years, mean [SD])	42.4 (13.65)	42.9 (13.38)	42.9 (13.64)	42.7 (13.55)
Sex (n [%])				
Male	237 (43.2)	273 (48.2)	251 (47.2)	761 (46.2)
Female	311 (56.8)	293 (51.8)	281 (52.8)	885 (53.8)
Race (n [%])				
White	474 (86.5)	501 (88.5)	457 (85.9)	1432 (87.0)
Black or African-American	9 (1.6)	14 (2.5)	4 (0.8)	27 (1.6)
Asian	59 (10.8)	44 (7.8)	60 (11.3)	163 (9.9)
Other	6 (1.1)	7 (1.2)	11 (2.1)	24 (1.5)
BMI (kg/m^2, mean [SD])	27.86 (5.457)	28.16 (5.377)	28.11 (5.354)	28.04 (5.395)
Duration of T1DM (years, mean [SD])	19.52 (11.900)	19.66 (11.480)	20.10 (11.965)	19.76 (11.778)
HbA1c (%, mean [SD])	8.49 (0.703)	8.47 (0.669)	8.48 (0.659)	8.48 (0.677)
GFR (n [%])				
<60 mL/min/1.73 m^2	19 (3.6)	16 (3.0)	22 (4.1)	57 (3.6)
≥60 and <90 mL/min/1.73 m^2	256 (48.3)	259 (49.0)	239 (44.9)	754 (47.4)
≥90 mL/min/1.73 m^2	255 (48.1)	254 (48.0)	271 (50.9)	780 (49.0)

Derived from: Table 8.1.4.2 and 8.1.9.1
GFR is calculated using the Modification in Diet and Renal Disease (MDRD) formula.
The race subgroup of other includes subjects with reported race of American Indian/Alaska Native; Native Hawaiian/Other Pacific Islander; or Other.
The ST placebo-controlled Phase III pool consists of all study MB102229 and MB102230 data included in the safety analysis set for the 24-week short-term treatment period.
BMI body mass index; DAPA dapagliflozin; GFR Glomerular Filtration Rate; HbA1c glycated haemoglobin; INS insulin; PLA placebo; SD standard deviation; ST short-term; T1DM type 1 diabetes mellitus

Adverse events

The primary presentations in this section are of data from the ST placebo-controlled Phase III pool. These data are discussed in the context of the known safety profile of dapagliflozin, as derived from the dapagliflozin T2DM clinical programme, and any differences from this known safety profile of dapagliflozin are addressed in detail. Long-term data from studies MB102229 and D1695C00001 (Part B) are also discussed. Only death and DKA data from studies MB102072 and D1695C00001 (Part A) are presented in the following.

Overall adverse events

Table 22 is an overall AE summary for the ST placebo-controlled Phase III pool. The proportion of subjects with any AE was higher in the dapagliflozin treatment groups than the placebo group. The slightly higher rates of events in the dapagliflozin treatment groups were mainly driven by known side effects of dapagliflozin, such as genital infections and increased urinary frequency/output. Ketone-related events were also more frequent in the dapagliflozin treatment groups. Note that **Table 22** only

includes hypoglycaemia and DKA events reported as SAEs; hypoglycaemia and DKA events are discussed under “Adverse events of special interest”.

Table 22 Overall adverse events summary – ST placebo-controlled Phase III pool (safety analysis set)

	Number of subjects (%)		
	DAPA 5 mg + INS (N=548)	DAPA 10 mg + INS (N=566)	PLA + INS (N=532)
At least one adverse event	384 (70.1)	388 (68.6)	332 (62.4)
At least one related adverse event	157 (28.6)	153 (27.0)	63 (11.8)
Death	0	0	1 (0.2)
At least one SAE	37 (6.8)	31 (5.5)	20 (3.8)
At least one related SAE	18 (3.3)	12 (2.1)	3 (0.6)
SAE leading to discontinuation of study drug	15 (2.7)	7 (1.2)	6 (1.1)
AE leading to discontinuation of study drug	23 (4.2)	20 (3.5)	20 (3.8)

Source: Table 8.3.2.1
MedDRA Version: 20.0
Includes non-serious adverse events with onset on or after the first date/time of double-blind treatment and on or prior to the last day of short-term double-blind treatment plus 4 days or up to the start date of the long-term period if earlier. Includes serious adverse events with onset on or after the first date/time of double-blind treatment and on or prior to the last day of short-term double-blind treatment plus 30 days or up to the start date of the long-term period if earlier. Only hypoglycaemia and DKA events reported as SAEs are included in the AE, related AE, SAE, related SAE, and AE leading to discontinuation summary lines.
The ST placebo-controlled Phase III pool consists of all study MB102229 and MB102230 data included in the safety analysis set for the 24-week short-term treatment period.
AE adverse event; DAPA dapagliflozin; INS insulin; PLA placebo; SAE serious adverse event

Overall AE analyses for the ST+LT treatment period of study MB102229 were consistent with the data from the ST treatment period of study MB102229. Analyses of AE data from the LT period of study MB102229 and from study D1695C00001 (Part B) did not identify any safety concerns.

Adverse events by system organ class and preferred term

The most common AEs by system organ class (SOC) in the ST placebo-controlled Phase III pool were Infections and infestations and Gastrointestinal disorders.

The higher proportion of AEs in the dapagliflozin treatment groups (70.1% and 68.6% in the dapagliflozin 5 mg and 10 mg groups, respectively) compared to placebo (62.4%) can primarily be attributed to differences in the SOCs of Infections and infestations (43.1%, 41.5%, and 36.5% in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo treatment groups, respectively) and Renal and urinary disorders (10.0%, 11.0%, and 4.5%, respectively). Genital infections and urinary tract infections are discussed under “Adverse events of special interest”. Increased urinary frequency/output, a known side effect of dapagliflozin, accounted for the majority of events in the Renal and urinary disorders SOC; none of these events were recorded as serious SAEs and these events are not discussed further in this SCS.

The distribution of AEs by SOC and PT in the ST placebo-controlled Phase III pool is considered consistent with the known safety profile of dapagliflozin after taking into account the differing background rates of certain AEs between study populations, including the higher overall rate of genital infections in those with T1DM than T2DM (de Leon et al 2002). **Table 23** presents the most common AEs by PT.

Table 23 Adverse event summary: adverse events by Preferred Term, ≥2% in any treatment group – 24-week short-term period – ST placebo-controlled Phase III pool (safety analysis set)

Preferred term (%)	DAPA 5 mg + INS (N=548)	DAPA 10 mg + INS (N=566)	PLA + INS (N=532)
Total subjects with an event	**384 (70.1)**	**388 (68.6)**	**332 (62.4)**
Viral upper respiratory tract infection	78 (14.2)	77 (13.6)	80 (15.0)
Headache	22 (4.0)	32 (5.7)	21 (3.9)
Upper respiratory tract infection	31 (5.7)	27 (4.8)	23 (4.3)
Pollakiuria	31 (5.7)	26 (4.6)	14 (2.6)
Thirst	11 (2.0)	23 (4.1)	3 (0.6)
Nausea	24 (4.4)	22 (3.9)	13 (2.4)
Diarrhoea	17 (3.1)	19 (3.4)	14 (2.6)
Polyuria	11 (2.0)	18 (3.2)	4 (0.8)
Vulvovaginal mycotic infection	16 (2.9)	18 (3.2)	6 (1.1)
Influenza	17 (3.1)	17 (3.0)	15 (2.8)
Gastroenteritis	14 (2.6)	14 (2.5)	11 (2.1)
Vomiting	18 (3.3)	14 (2.5)	9 (1.7)
Pain in extremity	9 (1.6)	14 (2.5)	10 (1.9)
Urinary tract infection	28 (5.1)	13 (2.3)	22 (4.1)
Pharyngitis	11 (2.0)	13 (2.3)	7 (1.3)
Back pain	13 (2.4)	12 (2.1)	10 (1.9)
Genital infection fungal	17 (3.1)	11 (1.9)	0
Sinusitis	5 (0.9)	11 (1.9)	12 (2.3)
Bronchitis	5 (0.9)	10 (1.8)	12 (2.3)
Fatigue	12 (2.2)	9 (1.6)	8 (1.5)

Derived from: Table 8.3.2.2.1
MedDRA Version 20.0
Includes only PTs occurring in ≥2% of subjects in any treatment group
Table ordered by descending total frequency in the dapagliflozin 10 mg treatment group
Includes non-serious adverse events with onset on or after the first date/time of double-blind treatment and on or prior to the last day of short-term double-blind treatment plus 4 days or up to the start date of the long-term period if earlier. Includes serious adverse events with onset on or after the first date/time of double-blind treatment and on or prior to the last day of short-term double-blind treatment plus 30 days or up to the start date of the long-term period if earlier. Only hypoglycaemia and DKA events reported as SAEs are included.
The ST placebo-controlled Phase III pool consists of all study MB102229 and MB102230 data included in the safety analysis set for the 24-week short-term treatment period.
DAPA dapagliflozin; INS insulin; PLA placebo

Most AEs reported in the ST placebo-controlled Phase III pool were of mild intensity. Few subjects experienced an AE assessed as very severe in intensity: 2, 4, and 3 in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo treatment groups, respectively.

There were more AEs assessed by the Investigator as related to study drug in the dapagliflozin treatment groups than the placebo group: 28.6%, 27.0%, and 11.8% in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively. As with the overall AEs, the difference can primarily be attributed to events associated with genital infections and increased urinary frequency/output.

Data on AEs by SOC and PT from the ST+LT period of study MB102229 and from study D1695C00001 (Part B) were consistent with the ST placebo-controlled Phase III pool.

Serious adverse event

Table 24 is a summary of SAEs by SOC for the ST placebo-controlled Phase III pool. SAEs were reported in 6.8%, 5.5%, and 3.8% of subjects in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo treatment groups, respectively.

SAEs were most frequently reported in the SOC Metabolism and nutrition disorders and were primarily ketone-related. DKA events are discussed under "Adverse events of special interest". There were few SAEs in any other SOC and they generally occurred in similar proportions across all treatment groups.

Table 24 Adverse event summary: serious adverse events by System Organ Class, ≥2 subjects in any treatment group – 24-week short-term period – ST placebo-controlled Phase III pool (safety analysis set)

System organ class (%)	DAPA 5 mg + INS (N=548)	DAPA 10 mg + INS (N=566)	PLA + INS (N=532)
Total subjects with an event	37 (6.8)	31 (5.5)	20 (3.8)
Metabolism and nutrition disorders	17 (3.1)	13 (2.3)	5 (0.9)
Injury, poisoning and procedural complications	4 (0.7)	5 (0.9)	4 (0.8)
Infections and infestations	6 (1.1)	2 (0.4)	3 (0.6)
Nervous system disorders	4 (0.7)	3 (0.5)	2 (0.4)
Gastrointestinal disorders	1 (0.2)	4 (0.7)	0
Cardiac disorders	1 (0.2)	3 (0.5)	1 (0.2)
Musculoskeletal and connective tissue disorders	1 (0.2)	1 (0.2)	2 (0.4)
General disorders and administration site conditions	0	3 (0.5)	1 (0.2)
Eye disorders	2 (0.4)	0	0
Renal and urinary disorders	2 (0.4)	0	0

Derived from: Table 8.3.2.4.1
MedDRA Version 20.0
Includes only SOCs with ≥2 subjects in any treatment group
Table ordered by descending total frequency
Includes serious adverse events with onset on or after the first date/time of treatment and on or prior to the last day of short-term treatment plus 30 days or up to the start date of the long-term period if earlier. Includes serious adverse events of hypoglycaemia and DKA.
The ST placebo-controlled Phase III pool consists of all study MB102229 and MB102230 data included in the safety analysis set for the 24-week short-term treatment period.
DAPA dapagliflozin; INS insulin; PLA placebo

The distribution of SAEs in the pooled T1DM studies was consistent with the known safety profile of dapagliflozin, except that there were more ketone-related SAEs in the pooled T1DM studies than were observed in T2DM studies.

SAE data from the ST+LT period of study MB102229 and from study D1695C00001 (Part B) were consistent with the ST placebo-controlled Phase III pool.

Deaths

There was 1 death, in a placebo-group subject, in the ST placebo-controlled Phase III pool. There were no deaths in studies MB102072 or D1695C00001 or in the LT period of study MB102229. One additional subject in study MB102230 died after enrolment but before the start of the lead-in period.

The death in the ST placebo-controlled Phase III pool occurred during study Week 7 in a placebo-group subject in study MB102229 who had previously discontinued study drug. The subject died during the night due to suspected hypoglycaemia.

Adverse events of special interest

The following event categories were included as predefined AEs of special interest in studies MB102229 and MB102230: hypoglycaemia, DKA, cardiovascular AEs, hepatobiliary AEs, genital infections, urinary tract infections, volume depletion, fractures, worsening renal function, and hypersensitivity. Potential DKA events, and cardiovascular and hepatobiliary AEs, were adjudicated.

Hypoglycaemia

In studies MB102229 and MB102230, events of hypoglycaemia, hypoglycaemic episodes, or discontinuation due to hypoglycaemia were recorded and analysed separately from other AEs on eCRF pages for hypoglycaemia and categorised according to ADA recommendations (ADA 2005). Subjects were specifically asked to report symptoms of hypoglycaemia at each visit and a diary for documenting symptoms of hypoglycaemia was used. The Investigator had to determine whether symptoms reported by the subject met the clinical definition of hypoglycaemia. Only symptoms or blood glucose values deemed by the Investigator to meet the definition of hypoglycaemia were to be reported on the hypoglycaemia eCRF pages.

The incidence of overall hypoglycaemia events and severe hypoglycaemia events in the ST placebo-controlled Phase III pool were similar across all treatment groups (**Table 25**).

Table 25 Summary of recurrent hypoglycaemia events – ST placebo-controlled Phase III pool (safety analysis set)

	DAPA 5 mg + INS (N=548) (P-Y=241.6)	DAPA 10 mg + INS (N=566) (P-Y=252.3)	PLA + INS (N=532) (P-Y=232.9)
Total number of hypoglycaemic events	**8912**	**9667**	**8851**
Total number (%) of subjects experiencing:			
At least 1 event[a]	443 (80.8)	466 (82.3)	441 (82.9)
1-5 events[a]	120 (21.9)	121 (21.4)	119 (22.4)
6-9 events[a]	62 (11.3)	54 (9.5)	55 (10.3)
≥10 events[a]	261 (47.6)	291 (51.4)	267 (50.2)
Exposure adjusted incidence rate (IR/100P-Y)[c]	3688.05	3832.16	3800.33
ADA categorisation			
Severe hypoglycaemia			
Total number of events[b]	89 (1.0)	94 (1.0)	105 (1.2)
Total number (%) of subjects experiencing:			
At least 1 event[a]	38 (6.9)	42 (7.4)	40 (7.5)
1 event[a]	30 (5.5)	25 (4.4)	23 (4.3)
2 events[a]	4 (0.7)	7 (1.2)	6 (1.1)
≥3 events[a]	4 (0.7)	10 (1.8)	11 (2.1)
Exposure adjusted incidence rate (IR/100P-Y)[c]	36.83	37.26	45.08

Derived from: Table 8.3.2.6.5.1

[a] Percentages are based on the total number of subjects in safety analysis set.

[b] Percentages are based on the total number of events.

[c] Exposure adjusted incidence rate per 100 person-years of exposure (IR/100P-Y) = events count*100/person-years of exposure

Includes hypoglycaemia events with onset on or after the first date/time of double-blind treatment and on or prior to the last day of short-term double-blind treatment plus 4 days or up to the start of the long-term if earlier.

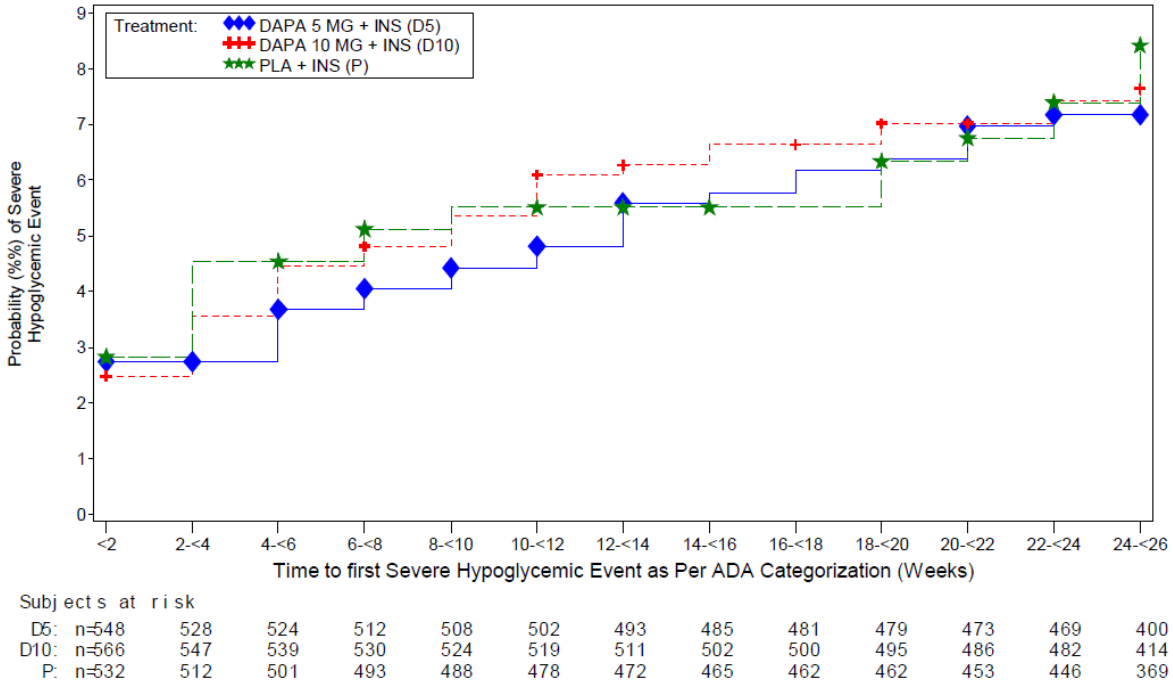
The ST placebo-controlled Phase III pool consists of all study MB102229 and MB102230 data included in the safety analysis set for the 24-week short-term treatment period.

ADA categories as per the criteria described in ADA 2005.

ADA American Diabetes Association; DAPA dapagliflozin; INS insulin; IR incidence rate; N number of subjects; PLA placebo; P-Y person-years of exposure

Figure 27 is a Kaplan-Meier plot of time to severe hypoglycaemia AE as per ADA categorisation for the ST placebo-controlled Phase III pool. There were 38, 42, and 40 subjects in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively, who experienced a severe hypoglycaemic event, corresponding to Kaplan-Meier percentages at Week 24 of 7.2%, 7.4%, and 7.4% respectively. Only 4 subjects, 3 in the dapagliflozin 5 mg group and 1 in the placebo group, discontinued study drug due to hypoglycaemia.

Figure 27 Kaplan-Meier plot of time to first severe hypoglycaemia event as per ADA categorisation – ST placebo-controlled Phase III pool (safety analysis set)



Source: Figure 8.3.2.6.5.11

Symbols represent censored observations. Week is not scheduled visit week but actual days from the first dose of double-blind study drug divided by 7. Number of subjects at risk is the number of subjects at risk at the beginning of the period. The results beyond Week 24 should be interpreted with caution as the number of subjects at risk might be limited. Includes events with onset on or after the first date/time of double-blind treatment.

The ST placebo-controlled Phase III pool consists of all study MB102229 and MB102230 data included in the safety analysis set for the 24-week short-term treatment period.

ADA American Diabetes Association; D5 dapagliflozin 5 mg; D10 dapagliflozin 10 mg; DAPA dapagliflozin; INS insulin; n number of subjects at risk at the beginning of each period; P placebo; PLA placebo

The incidence of hypoglycaemia events decreased over time. During the ST+LT treatment period in study MB102229 there were 29, 25, and 30 subjects in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively, who experienced a severe hypoglycaemic event, corresponding to Kaplan-Meier percentages at Week 52 of 10.7%, 8.9%, and 12.6% respectively.

Diabetic ketoacidosis

Identification and assessment of diabetic ketoacidosis events

Study subjects were advised on how to identify potential signs/symptoms of DKA (e.g., excessive thirst, nausea and vomiting, fruity scented breath, and weakness or fatigue) and were provided with blood ketone meters (ketones were measured by daily urine ketone testing in study MB102072) and instructions for use. Subjects were to record symptoms potentially associated with DKA, blood ketone test results, and relevant risk factors in a diary and to contact the study site if their self-measured blood ketone reading was ≥0.6 mmol/L.

Investigators were to identify potential DKA events based on recorded ketone test results, symptoms potentially associated with DKA, and relevant risk factors in the subject diary. Potential events were to be recorded on the DKA eCRF pages (including ketone test results and symptoms, and risk factors). Additionally, Investigators were asked to evaluate if AEs identified by a prespecified list PTs could be potential DKA events. If 'yes', then these events were also to be sent for adjudication.

DKA Adjudication Committees, blinded to treatment allocation, independently adjudicated all events identified by Investigators as potential DKA events. Potential DKA events were adjudicated as 'definite', 'possible', or 'unlikely'. The DKAAC Charter specified criteria, based on the ADA consensus

statement (Kitabchi et al 2009), to be applied when ascertaining 'definite' DKA events. The 'definite' DKA criteria included venous pH <7.3, HCO3 ≤18 mEq/L [≤18 mmol/L], and at least one of the following symptoms: hyperventilation, dehydration, or depressed consciousness/confusion. Events adjudicated as not being DKA were to be categorised as 'possible' or 'unlikely' DKA at the Adjudicators' discretion. No criteria were specified for distinguishing between 'possible' and 'unlikely' events. For events adjudicated as 'definite' DKA, Adjudicators were to assess severity according to the ADA consensus statement and to identify a primary cause and contributing factors. For completeness, both those potential DKA events adjudicated as DKA (i.e., 'definite' DKA events) as well as those adjudicated as not DKA (i.e., 'possible' and 'unlikely' DKA events) are presented below.

Overview of diabetic ketoacidosis events

Data presentations in the following sections include ST placebo-controlled Phase III pool data, followed by ST+LT data from studies MB102229 and D1695C00001 (Part B).

The MAH considers DKA events adjudicated as 'definite' DKA events to be clinically confirmed DKA events; the presentations following this overview section will therefore focus on these events.

Table 26 presents an overview of adjudication outcomes in the ST placebo-controlled Phase III pool. Overall, there were more events sent for adjudication in the dapagliflozin groups than in the placebo group.

In the ST placebo-controlled Phase III pool, 11 (2.0%), 11 (1.9%) and 3 (0.6%) subjects in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively, had an event adjudicated as a 'definite' DKA event (see **Table 26**).

Table 26 Summary of subjects with adjudicated diabetic ketoacidosis events – ST placebo-controlled Phase III pool (safety analysis set)

	DAPA 5 MG + INS (N=548)	DAPA 10 MG + INS (N=566)	PLA + INS (N=532)
During short-term treatment period			
Number (%) of subjects with event adjudicated as definite DKA	11 (2.0)	11 (1.9)	3 (0.6)
Number (%) of subjects with event adjudicated as possible DKA	11 (2.0)	11 (1.9)	3 (0.6)
Number (%) of subjects with event adjudicated as unlikely DKA	16 (2.9)	12 (2.1)	10 (1.9)
Total number (%) of subjects with an event sent for adjudication	36 (6.6)	33 (5.8)	15 (2.8)

Derived from: Table 8.3.2.6.4.1
Includes all subjects with an onset from Day 1 of the short-term treatment period up to and including 4 days after the last dose date in the short-term treatment period (or up to the start date of the long-term treatment, whichever comes first).
Percentages are based on the total number of subjects in safety analysis set.
Subjects can be in the different categories.
The ST placebo-controlled Phase III pool consists of all study MB102229 and MB102230 data included in the safety analysis set for the 24-week short-term treatment period.
DAPA Dapagliflozin; DKA diabetic ketoacidosis; INS insulin; N number of subjects; PLA placebo

In the ST+LT period of MB102229, 11 (4.0%), 10 (3.4%) and 5 (1.9%) subjects in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively, had an event adjudicated as a 'definite' DKA event (**Table 27**).

Table 27 Summary of subjects with adjudicated diabetic ketoacidosis events – MB102229 52-week ST+LT treatment period (safety analysis set)

	DAPA 5 MG + INS (N=277)	DAPA 10 MG + INS (N=296)	PLA + INS (N=260)
During short-term + long-term treatment period			
Number (%) of subjects with event adjudicated as definite DKA	11 (4.0)	10 (3.4)	5 (1.9)
Number (%) of subjects with event adjudicated as possible DKA	8 (2.9)	9 (3.0)	2 (0.8)
Number (%) of subjects with event adjudicated as unlikely DKA	9 (3.2)	11 (3.7)	3 (1.2)
Total number (%) of subjects with an event sent for adjudication	24 (8.7)	28 (9.5)	9 (3.5)

Derived from: MB102229 52w CSR Table 11.3.2.6.4.1 in CTD Module 5.3.5.1
Includes all subjects who have events that are not reported and reported as serious adverse events with an onset from Day 1 of the short-term double-blind treatment period up to and including 4 days and 30 days respectively, after the last dose date in the short-term plus long-term treatment period.).
Percentages are based on the total number of subjects in safety analysis set.
Subjects can be in the different categories.
DAPA Dapagliflozin; DKA diabetic ketoacidosis; INS insulin; N number of subjects; PLA placebo

In the ST+LT period of MB102230, 11 (4.1%), 10 (3.7%) and 1 (0.4%) subjects in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively, had an event adjudicated as a 'definite' DKA event (**Table 28**).

Table 28 Summary of subjects with adjudicated diabetic ketoacidosis events – MB102230 52-week ST+LT treatment period (safety analysis set)

	DAPA 5 MG + INS (N=271)	DAPA 10 MG + INS (N=270)	PLA + INS (N=272)
During ST+LT treatment period[a]			
Number (%) of subjects with event adjudicated as definite DKA	11 (4.1)	10 (3.7)	1 (0.4)
Number (%) of subjects with event adjudicated as possible DKA	8 (3.0)	4 (1.5)	2 (0.7)
Number (%) of subjects with event adjudicated as unlikely DKA	10 (3.7)	10 (3.7)	9 (3.3)
Total number (%) of subjects with an event sent for adjudication	27 (10.0)	23 (8.5)	11 (4.0)

Source: Table 11.3.2.6.4.1

[a] Includes all subjects who have events that are not reported and reported as serious adverse events with an onset from Day 1 of the short-term double-blind treatment period up to and including 4 days and 30 days respectively, after the last dose date in the short-term plus long-term treatment period.

DAPA Dapagliflozin; DKA diabetic ketoacidosis; INS insulin; N number of subjects; PLA placebo; ST short-term; LT long-term

There were no potential DKA events reported in studies MB102072 or D1695C00001 (Part A). In the non-placebo controlled study D1695C00001 (Part B) there were 3 'definite' DKA events in 2 subjects in the dapagliflozin 5 mg group and 1 subject in the dapagliflozin 10 mg group. There was also 1 'possible' DKA event in a subject in the dapagliflozin 5 mg group.

Diabetic ketoacidosis events adjudicated as 'definite'

In the ST placebo-controlled Phase III pool, 11 (2.0%), 11 (1.9%) and 3 (0.6%) subjects in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively, had an event adjudicated as

a ‘definite’ DKA event. Study drug was discontinued in 14 subjects, 9 in the dapagliflozin 5 mg treatment group and 5 in the dapagliflozin 10 mg treatment group, due to AEs of ketoacidosis or diabetic ketoacidosis. No subject experienced more than 1 ‘definite’ DKA event. Adjudicators classified 19 of the 25 events as either mild or moderate severity.

Treatment consistent with standard practice (i.e., insulin and intravenous fluids) was documented for 18 of the 25 events, while most of the remaining events were treated with additional insulin. All subjects recovered.

In the ST placebo-controlled Phase III pool, missed insulin dose and insulin pump failure were the most common primary causes and occurred in 15 of the 25 cases (Table 29). In 5 cases there was no primary cause identified. Alcohol was a factor in 6 of the events. More events occurred in subjects using insulin pumps (16 in subjects using continuous subcutaneous insulin infusion and 9 in subjects using MDI); this observation applied both to the dapagliflozin treatment groups and to the placebo group. For 5 of the ‘definite’ events, 2 in the dapagliflozin 5 mg treatment group and 3 in the dapagliflozin 10 mg treatment group, there were recorded glucose values in the euglycaemic range (p-glucose <250 mg/dL [<13.875 mmol/L]).

Table 29 Summary of primary cause, contributing factors, and risk factors associated with diabetic ketoacidosis events adjudicated as 'definite' – ST placebo-controlled Phase III pool (safety analysis set)

	DAPA 5 MG + INS (N=548)	DAPA 10 MG + INS (N=566)	PLA + INS (N=532)
Total number of definite DKA events	**11**	**11**	**3**
Incidence rate per 100 patient-years	4.55	4.36	1.29
Primary cause on final adjudication forms			
Insulin pump failure[a]	3 (27.3)	3 (27.3)	1 (33.3)
Missed insulin dose[a]	3 (27.3)	4 (36.4)	1 (33.3)
Severe illness[a]	0	0	0
Not identified[a]	5 (45.5)	0	0
Other[a]	0	4 (36.4)	1 (33.3)
Contributing factors on final adjudication forms			
Insulin pump failure[a]	3 (27.3)	3 (27.3)	1 (33.3)
Missed insulin dose[a]	3 (27.3)	4 (36.4)	1 (33.3)
Severe illness[a]	0	0	0
Not identified[a]	4 (36.4)	0	0
Other[a]	1 (9.1)	7 (63.6)	2 (66.7)
Number of subjects experiencing event with			
At least 1 contributing factor[b]	7 (1.3)	10 (1.8)	3 (0.6)
1 contributing factor[b]	7 (1.3)	6 (1.1)	2 (0.4)
2 contributing factors[b]	0	4 (0.7)	1 (0.2)
≥3 contributing factors[b]	0	0	0

Derived from: Tables 8.3.2.6.4.3 and 8.3.2.6.4.5

[a] Percentages are based on the total number of events

[b] Includes all contributing factors except for 'not identified'. Percentages are based on the total number of subjects in safety analysis set

Includes all events with an onset from Day 1 of the short-term treatment period up to and including 4 days after the last dose in the short-term treatment period (or up to the start date of the long-term treatment period, whichever comes first).

The ST placebo-controlled Phase III pool consists of all study MB102229 and MB102230 data included in the safety analysis set for the 24-week short-term treatment period.

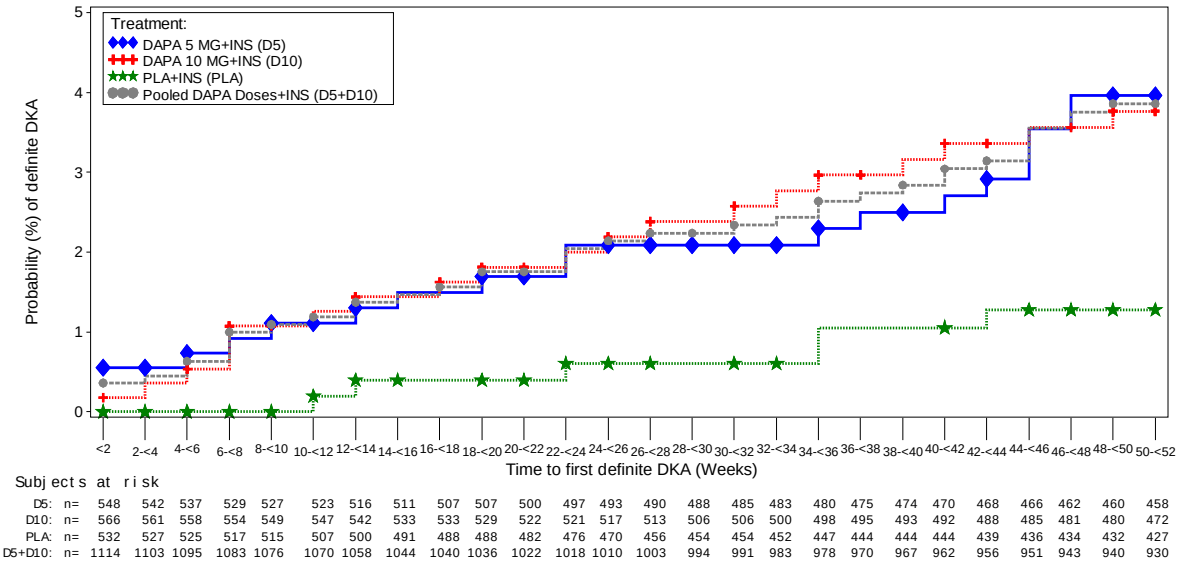
DAPA dapagliflozin; DKA diabetic ketoacidosis; INS insulin; N number of subjects; PLA placebo; ST short-term

The 'definite' DKA events in the LT studies had similar characteristics to those in the ST placebo-controlled Phase III pool. Compared to the ST pool, the incidence rate per 100 patient-years was increased (9.87, 7.58 and 4.40 for dapagliflozin 5 mg, dapagliflozin 10 mg and placebo respectively), based on a total of 27 events. Across the entire programme, most events in all treatment groups were precipitated by a temporary insufficiency in insulin, whether accidental (e.g., missed dose or pump failure) or due to situational increased insulin demand (i.e., some subjects showed signs of infection or other serious disease, or had alcohol intake in association with the DKA event). One subject in the LT period of study MB102229 had a recurrent 'definite DKA' event.

A thorough review of individual events with a focus on identifying potential risk factors for DKA associated with use of dapagliflozin did not identify any clear factors (e.g., baseline HbA1c, baseline insulin dose per kilogram, insulin dose changes during the study, insulin administration method, region) that could prospectively identify those at higher risk of DKA when treated with dapagliflozin.

Pooled data for the ST+LT periods of studies MB102229 and MB102230 (**Figure 28**), show that the occurrence of 'definite' DKA events was evenly distributed over time, and no time point could be identified as being of particular risk for the occurrence of DKA.

Figure 28 Time to first diabetic ketoacidosis event adjudicated as "definite", Kaplan-Meier estimate in the pooled ST+LT MB102229 and MB102230 studies (safety analysis set)



DDAPA Dapagliflozin; DKA Diabetic ketoacidosis; INS Insulin; LT Long-term; PLA Placebo; ST Short-term

Diabetic ketoacidosis events adjudicated as 'possible'

Events adjudicated as 'possible' DKAs did not qualify as DKAs based on the ADA criteria. There was no confirmed acidosis in any of the 'possible' cases. Of the 31 'possible' events, 7 events resulted in visits to a medical facility, and of these, 3 events resulted in documented treatment for DKA consistent with standard practice.

Risk of DKA in subgroups

The risk of DKA was analysed by different cut-offs for baseline BMI and baseline total insulin dose. In the overall ST+LT population the risk difference vs placebo was 2.64%. In patients with BMI ≥25kg/m^2, the risk difference was 1.88% and in patients with a total insulin dose of ≥0.6IU/kg, the risk difference was 1.91%.

Cardiovascular events

There were few cardiovascular events in the ST placebo-controlled Phase III pool: 2 (0.4%), 5 (0.9%), and 2 (0.4%) in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively, none of which resulted in death. There were no cardiovascular DAEs. The incidence of cardiovascular AEs in LT studies was similar to that in the ST placebo-controlled Phase III pool.

Hepatobiliary

There were few hepatic AEs in any treatment group in the ST placebo-controlled Phase III pool: 7 (1.3%), 8 (1.4%), and 9 (1.7%) in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups,

respectively. The incidence of hepatic AEs in LT studies was similar to that in the ST placebo-controlled Phase III pool.

There were 3 subjects with adjudicated liver-related abnormalities in the ST placebo-controlled Phase III pool. Two dapagliflozin 10 mg-treated subjects in study MB102229 had aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >10X upper limit of normal (ULN) and the events were adjudicated as having a 'possible' causal relationship to study drug. In both of these cases other aetiologies were considered likely: alcoholic liver disease in 1 case and association with a 'definite DKA event' in the other case. There was 1 placebo-treated subject in study MB102230 with adjudicated liver-related abnormalities during the short-term treatment period. This subject had 2 events of elevated liver tests sent for adjudication; both events were adjudicated as having 'unlikely' causal relationship to study drug.

There were no subjects in the LT extension of study MB102229 with adjudicated liver-related abnormalities. There was 1 subject in study D1695C00001 (Part B) with an adjudicated liver-related abnormality: an event of AST >10X ULN in a dapagliflozin 5 mg-treated subject was adjudicated as having 'unlikely' causal relationship to study drug.

Genital infections

Genital infection AEs were more frequent in the dapagliflozin treatment groups than the placebo group in the ST placebo-controlled Phase III pool: 11.1%, 9.5%, and 2.3% in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively.

A similar proportion of subjects in each treatment group with AEs of genital infection received antimicrobial treatment. Few subjects had recurrent events, though more frequently in the dapagliflozin treatment groups than the placebo group. However, a lower proportion of subjects with events in the dapagliflozin treatment groups than in the placebo group needed additional treatment due to inadequate response to the initial course.

Genital infection AEs were more common in women than men: 15.8% versus 5.1% in the dapagliflozin 5 mg group, 14.3% versus 4.4% in the dapagliflozin 10 mg group, and 4.3% versus 0% in the placebo group.

Most genital infections were of mild intensity and no genital infection SAEs were reported in any of the treatment groups. There were few genital infection DAEs: 3 due to genital infection fungal in the dapagliflozin 10 mg group, 2 due to genitourinary tract infection (1 in each of the dapagliflozin 5 mg and placebo groups), and 1 due to vulvovaginitis in the placebo group.

As expected, given the observed higher colonisation rate (odds ratio: 3.4) of Candida species in those with T1DM compared to those with T2DM (de Leon et al 2002), the overall proportion of subjects with AEs of genital infection was higher in all treatment groups than has been previously observed in dapagliflozin studies in subjects with T2DM. However, the relative ratio of genital infection in dapagliflozin-treated subjects to those receiving placebo was similar to previous dapagliflozin experience in T2DM.

The incidence of genital infection AEs in the LT studies was similar to that in the ST placebo-controlled Phase III pool, though with somewhat fewer events.

Urinary tract infections

The greatest proportion of subjects with AEs of urinary tract infection (including kidney infections) in the ST placebo-controlled Phase III pool was in the dapagliflozin 5 mg group and the lowest proportion in the dapagliflozin 10 mg group: 6.8%, 3.7%, and 4.7% in the dapagliflozin 5 mg, dapagliflozin 10

mg, and placebo groups, respectively. There were no meaningful differences in the proportions of subjects in each treatment group with AEs of urinary tract infection having recurrent events, though more subjects in the dapagliflozin treatment groups received antimicrobial treatment and received additional treatment due to inadequate response to the initial course.

Urinary tract infection AEs were more common in women than men: 11.3% versus 0.8% in the dapagliflozin 5 mg group, 6.5% versus 0.7% in the dapagliflozin 10 mg group, and 7.8% versus 1.2% in the placebo group.

There were 4 urinary tract infection SAEs reported (1 pyelonephritis and 3 urinary tract infections): 3 in the dapagliflozin 5 mg group and 1 in the dapagliflozin 10 mg group. There were 6 urinary tract infection DAEs: 3, 1, and 2 in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively.

The incidence of urinary tract infection AEs in LT studies was similar to that in the ST placebo-controlled Phase III pool.

Volume depletion

There were few AEs of volume depletion in the ST placebo-controlled Phase III pool: 8 (1.5%), 3 (0.5%), and 4 (0.8%) in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo treatment groups, respectively. There were no SAEs or DAEs of volume depletion. The incidence of AEs of volume depletion in LT studies was similar to that in the ST placebo-controlled Phase III pool.

Renal impairment/failure

Worsening renal function was investigated based on a prespecified list of PTs relating to renal impairment and renal failure. There were few AEs of renal impairment and renal failure in the ST placebo-controlled Phase III pool: 6 (1.1%), 2 (0.4%), and 0 in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo treatment groups, respectively. Of these 8 AEs, 6 were assessed as mild intensity and the remaining 2 were reported as SAEs: 1 was obstructive uropathy (reported as an SAE) and 1 was acute prerenal failure (reported as an SAE and DAE and resolved following fluid resuscitation). The incidence of worsening renal function in LT studies was similar to that in the ST placebo-controlled Phase III pool. There were no events of renal impairment or failure in study D1695C00001 (Part B).

Fractures

There were few AEs of fracture in the ST placebo-controlled Phase III pool: 8 (1.5%), 6 (1.1%), and 5 (0.9%) in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively. The incidence of fracture AEs in LT studies was similar to that in the ST placebo-controlled Phase III pool with 4, 6, and 8 events in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively.

Hypersensitivity

Potential hypersensitivity events in the ST placebo-controlled Phase III pool were investigated based on a prespecified list of PTs. These AEs occurred in 30 (5.5%), 23 (4.1%), and 19 (3.6%) of subjects in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively. None of these AEs were recorded as SAEs; the majority were mild, skin-related events such as rash, dermatitis, and eczema. The incidence of AEs related to hypersensitivity in LT studies was similar to that in the ST placebo-controlled Phase III pool.

Laboratory findings

The section presents data from the ST placebo-controlled Phase III pool. Clinical laboratory data from the ST+LT period of study MB102229 and from study D1695C00001 (Part B) were consistent with the ST placebo-controlled Phase III pool.

Marked abnormalities

Overall, marked abnormalities (MAs) and elevated liver tests were rare in the ST placebo-controlled Phase III pool.

Key findings with regards to the proportions of subjects with MAs of laboratory values (except liver tests) in the ST placebo-controlled Phase III pool are summarised below:

- High haematocrit (>0.55 vol) levels were reported in 2.2%, 1.3%, and 0.6% of subjects in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively.
- High creatinine (≥1.5 baseline) was reported in 1.5%, 1.8%, and 1.0% of subjects in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively.
- Few subjects had MAs of serum electrolytes, with similar proportions across the treatment groups.

Key findings with regards to the proportions of subjects with elevated liver tests during the ST period of the pooled studies are summarised below:

- Elevated liver tests were observed in 3.3%, 3.9%, and 4.5% of subjects in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively.
- There were no subjects with ALT or AST >3X ULN and total bilirubin >1.5X ULN within 14 days on or after ALT/AST elevation.

Changes in clinical laboratory evaluations over time

Overall, there were no meaningful changes in clinical laboratory parameters from baseline to Week 24 in the ST placebo-controlled Phase III pool, with the exception of urinary glucose which, as expected, was increased in the dapagliflozin treatment groups.

Vital signs and electrocardiograms

The section presents data from the ST placebo-controlled Phase III pool. Data from the LT treatment period of study MB102229 and from Part B of study D1695C00001 were consistent with the data from the ST placebo-controlled Phase III pool.

Vital signs

The mean change from baseline at Week 24 in seated SBP in the pooled studies was -3.8 mmHg, -2.8 mmHg, and -0.5 mmHg in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively. The mean change from baseline at Week 24 in seated DBP was -1.5 mmHg, -1.4 mmHg, and 0.1 mmHg, respectively.

A small decrease in mean seated heart rate from baseline to Week 24 was noted in the dapagliflozin treatment groups in the pooled studies: -0.3, -0.8, and 1.6 beats per minute in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively.

Electrocardiograms

For most subjects in the ST placebo-controlled Phase III pool, the ECG assessment did not change from baseline to Week 24 (LOCF). Proportions of subjects with a change in ECG assessment from normal to abnormal and from abnormal to normal were balanced across all treatment groups.

Safety in special populations

Age

In the ST placebo-controlled Phase III pool the proportion of subjects with at least 1 AE increased in all treatment groups with increased age. In the <35 years age group 65.7%, 65.0%, and 59.9% of subjects in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively, experienced an AE whereas in the ≥50 years group the respective proportions were 72.3%, 70.4%, and 65.8%. The overall analysis of AEs by age did not reveal any relevant findings.

Gender

There was a larger proportion of AEs in female subjects (71.1%, 72.7%, and 65.5% in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively) than male subjects (68.8%, 64.1%, and 59.0%, respectively), again primarily driven by AEs in the SOC Infections and infestations and genital infections in particular. The overall analysis of AEs by sex did not reveal any relevant findings.

Race

There was a larger proportion of AEs in Asian subjects across all treatment groups (74.6%, 79.5%, and 70.0% in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively) than in white subjects (69.6%, 67.3%, and 61.7%, respectively). There were too few subjects of other races to allow for meaningful comparisons and therefore these data should be interpreted with caution. The overall analysis of AEs by race did not reveal any relevant findings.

Pregnancy and lactation

Dapagliflozin has not been studied in pregnant women or nursing mothers. Pregnancies and breast feeding were rare during the T2DM clinical programme and in postmarketing experience. This limited experience has not given rise to any safety concerns.

Pregnant subjects were excluded from participation in the T1DM studies. There were 6 pregnancies identified during the ST periods of studies MB102229 and MB102230, of which 3 were in subjects treated with dapagliflozin and 3 with placebo, and 2 in the LT period of study MB102229, both in subjects treated with dapagliflozin. Study drug was discontinued in the event of pregnancy.

Table 30 lists the pregnancies reported in subjects treated with dapagliflozin. Subject MB102- 229-0035-00826 had a premature delivery (Week 36) and the baby was born with respiratory depression, poor perfusion, jaundice, ankyloglossia, as well as a clavicle fracture due to birth trauma.

Table 30 Pregnancies reported in subjects treated with dapagliflozin

Subject number	Age (years)	Dose	Estimated exposure to dapagliflozin during pregnancy	Outcome
MB102229-0035-00826	30	5 mg	4 weeks	Unhealthy baby
MB102229-0045-01568	31	5 mg	5 weeks	Elective abortion
MB102229-0123-01209	20	5 mg	7 weeks	Spontaneous abortion
MB102229-0096-00976	23	10 mg	9 weeks	Unknown
MB102229-0151-00562	38	10 mg	3 weeks	Unknown

Estimated exposure and outcome are derived from AstraZeneca's safety database.

Safety related to drug-drug interactions and other interactions

Interactions between dapagliflozin and other drugs or food were addressed in the original dapagliflozin T2DM clinical programme. No new information is available on the potential impact on safety of such interactions in subjects with T1DM.

Discontinuation due to adverse events

Table 31 is a summary of DAEs by PT for the ST placebo-controlled Phase III pool.

Discontinuations due to AEs occurred in 4.2%, 3.5%, and 3.8% of subjects in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo treatment groups, respectively.

Table 31 Adverse event summary: adverse events leading to discontinuation of study drug, ≥2 subjects across all treatment groups – 24-week short-term period – ST placebo-controlled Phase III pool (safety analysis set)

Preferred Term (%)	DAPA 5 mg + INS (N=548)	DAPA 10 mg + INS (N=566)	PLA + INS (N=532)
Total subjects with an event	23 (4.2)	20 (3.5)	20 (3.8)
Diabetic ketoacidosis	8 (1.5)	3 (0.5)	3 (0.6)
Genital infection fungal	0	3 (0.5)	0
Ketoacidosis	1 (0.2)	2 (0.4)	0
Headache	1 (0.2)	2 (0.4)	0
Ketosis	0	2 (0.4)	0
Nausea	0	2 (0.4)	0
Hypoglycaemic seizure	2 (0.4)	0	0
Hypoglycaemia	1 (0.2)	0	1 (0.2)
Urinary tract infection	1 (0.2)	1 (0.2)	0
Asthenia	1 (0.2)	1 (0.2)	0
Back pain	1 (0.2)	1 (0.2)	0

Derived from: Table 8.3.2.5
MedDRA Version: 20.0
Includes only PTs with ≥2 subjects across all treatment groups
Table ordered by descending total frequency
Includes adverse events (serious and non-serious) with an onset on or after the first date/time of treatment and on or prior to the start date of the long-term treatment period. Includes discontinuations due to hypoglycaemia and DKA only if reported as a serious adverse event.
The ST placebo-controlled Phase III pool consists of all study MB102229 and MB102230 data included in the safety analysis set for the 24-week short-term treatment period.
DAPA dapagliflozin; INS insulin; PLA placebo

DAE data from the ST+LT period of study MB102229 and from study D1695C00001 (Part B) were consistent with the ST placebo-controlled Phase III pool.

Post marketing experience

Dapagliflozin was first approved for treatment of patients with T2DM in Australia on 05 October 2012 and it is currently approved in over 90 countries. The most recent PBRER, with a data lock of 04 October 2017 and including approximately 2 995 081 patient-years of post-marketing exposure, concluded that a comprehensive review of clinical studies and post-marketing experience revealed no new information to alter the overall positive benefit-risk profile for dapagliflozin in the approved indication (T2DM).

2.5.1. Discussion on clinical safety

With this application, information on the safety and tolerability of dapagliflozin in patients with type 1 diabetes mellitus (T1DM) is provided and compared with the known safety profile of dapagliflozin. Data

primarily come from 2 Phase III global studies of dapagliflozin as add-on to insulin therapy in subjects with T1DM: studies MB102229 and MB102230. Data from the Phase IIa pilot study, MB102072, and from a Japanese Phase I/III study, D1695C00001, are briefly summarised but are generally not included in the overall discussion of adverse events (AEs) or clinical laboratory evaluations due to one or more of their short duration, small study size, or lack of placebo control.

The pooling strategy is adequate and acceptable. The selection of AEs of special interest is considered relevant based on the knowledge of the safety profile of dapagliflozin in T2DM as well as knowledge of the mechanism of action. The methods of evaluation were adequate. Notably adjudication committees were in place for DKA, CV-events and hepatic events.

The ST-pool provides 24 week data in about 1 000 T1DM patients exposed to dapagliflozin. The extent of exposure to randomised study drug is considered adequate to characterise the general safety profile of dapagliflozin in T1DM, taking into consideration that the safety profile of dapagliflozin has been well characterised in patients with T2DM. The differences in exposure data between treatment groups are small. In addition, 52 week data is available for 490 patients in study MB102229 and 457 patients in study MB102230.

In the pooled ST-data set, demographic characteristics were well balanced between treatment groups.

More patients in the dapagliflozin-treated groups reported AEs (70%, 69% for the 5 mg and 10 mg dose respectively) than in the placebo-treated group (62%). The imbalance in AEs between dapagliflozin treated groups and placebo is attributable to a higher reporting of AEs related to the known safety profile of dapagliflozin, i.e. pollakiuria, thirst, nausea, polyuria, vulvovaginal and genital (genital infections only reported for dapagliflozin) mycotic infections. Notably, urinary tract infections were reported at a similar rate in all treatment groups. Further analysis of the higher reporting of GI events in the dapagliflozin treated groups could not relate these events to developing ketoacidosis.

Most AEs were of mild intensity; severe AEs were few and reported at a similar rate in all treatment groups. AEs considered related to treatment were more than twice as common in the dapagliflozin treated groups compared to placebo (28.6%, 27.0%, and 11.8% in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively). There were no apparent differences in the LT data compared to the ST data.

SAEs were reported in 6.8%, 5.5%, and 3.8% of subjects in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo treatment groups, respectively. Out of these, 2.7% and 2.1% vs 0.6% were deemed as related to treatment in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively. SAEs were most frequently reported in the SOC Metabolism and nutrition disorders and were primarily ketone-related. SAEs in SOCs GI, Eye and Renal/Urinary disorders were only reported in the dapagliflozin treated groups. Except for metabolic events, most SAEs were few, thus imbalances are difficult to interpret. The distribution of SAEs in the pooled T1DM studies was consistent with the known safety profile of dapagliflozin, except that there were more ketone-related SAEs in the pooled T1DM studies than were observed in T2DM studies.

There was 1 death, in a placebo-group subject, in the ST placebo-controlled Phase III pool. The subject had previously discontinued study drug and died during the night due to suspected hypoglycaemia.

Numerically, no difference in the rate of hypoglycaemic events or severe hypoglycaemic events was observed between treatment groups. Kaplan-Meier plot show no apparent difference in the time to first severe hypoglycaemia between groups, with Kaplan-Meier percentages at Week 24 of 7.2%, 7.4%, and 7.4% for dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo, respectively. Only 4 subjects, 3 in the dapagliflozin 5 mg group and 1 in the placebo group, discontinued study drug due to

hypoglycaemia. The incidence of hypoglycaemia events decreased over time with Kaplan-Meier percentages at Week 52 of 10.7%, 8.9%, and 12.6% respectively.

The major safety issue with the use of dapagliflozin in T1DM patients is the risk of DKA. In the Art 20 referral procedure on SGLT2-inhibitors and DKA (EMA/PRAC/50218/2016) the occurrence of DKA in predominantly T2DM patients was assessed and the procedure resulted in the introduction of warnings and recommendations in the SmPCs for all SGLT2-inhibitors. The data available in the referral could not clarify whether there was and actual increase in the risk but rather a different presentation of the DKA (euglycaemic DKA) since the background incidence is not known for T2DM. There are however plausible theories which indicate that treatment with SGLT2-inhibitors could precipitate DKA through its mechanism of action. Therefore, DKA was specifically investigated in the studies and measures were taken to reduce the risk. In both studies, patients were repeatedly educated on the symptoms of DKA and were provided with blood ketone meters. The patients were also told to record symptoms and contact the study site if their self-measured blood ketone reading was ≥0.6 mmol/L.

In the ST placebo-controlled Phase III pool, 11 (2.0%), 11 (1.9%) and 3 (0.6%) subjects in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively, had an event adjudicated as a 'definite' DKA event. In 18 of the 25 cases, treatment with insulin and intravenous fluids was documented, i.e. the patients would have been treated in hospital. In the ST+LT placebo-controlled Phase III pool, 22 (4.0%), 20 (3.5%) and 6 (1.1%) subjects in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively, had an event adjudicated as a 'definite' DKA event.

In the ST pool, the incidence rate of DKA was about three times higher in the dapagliflozin treated groups (4.55 and 4.36 per 100 PYs) compared to placebo (1.29 per 100 PYs). The incidence rate in the placebo-treated group was considerably lower than reported in the literature (5-7% annual rate). In the ST+LT data the incidence rate per 100 PY was twice as high as in the ST pool (9.87 and 7.58 per 100 PYs) and the placebo-treated group showed an incidence rate closer to that reported in the literature (4.4 per 100 PYs). The occurrence of 'definite' DKA events was evenly distributed over time in the ST+LT pool, and no time point could be identified as being of particular risk for the occurrence of DKA. There was no major difference between the two doses.

Well known precipitating factors such as pump failure or missed insulin dose, were equally common in all groups (about 30% each). However, in about 30% of cases either no cause could be identified or the event was related to "other" causes.

In addition to the DKA events adjudicated as definite, 31 possible events were identified. The distribution between treatment groups was similar to that observed for definite events.

Analyses made by the MAH could not identify any potential risk factors for DKA that could prospectively identify patients at higher risk of DKA when treated with dapagliflozin. However, the reduction in insulin dose after addition of dapagliflozin was more pronounced in the patients experiencing DKA than in subjects not developing DKA. Thus, a marked reduction in insulin dose after addition of dapagliflozin could indicate an increased risk for DKA, and a recommendation to reduce the insulin dose with caution (when dose reduction would be needed to prevent hypoglycaemia) has been included in the SmPC.

Factors such as age, diabetes duration, baseline HbA1c, HbA1c prior to the event or change in insulin dose prior to the event, were not found to be associated with an increased risk of DKA while on dapagliflozin treatment.

In contrast, for baseline insulin dose there was a clear accumulation of DKA cases in patients receiving low insulin doses at baseline. Particularly in the 5 mg dapagliflozin group it became obvious that nearly all dapagliflozin cases had an insulin need at baseline below the study population mean (around 0.75

IU/kg); only in two patients with DKA the insulin need was slightly above the population mean. When the risk of DKA was analysed by different cut-offs for total insulin dose, the risk difference versus placebo was decreased from 2.64% (overall population) to 1.91% when a cut-off of ≥0.6 IU/kg was applied.

A similar phenomenon was observed for BMI: most DKA cases occurred in patients whose BMI was below the population mean. This finding is plausible since higher BMI is correlated with insulin resistance and hence with higher insulin need. When the risk of DKA was analysed by different cut-offs for BMI, the risk difference versus placebo was decreased from 2.64% (overall population) to 1.88% when a cut-off of ≥25 kg/m^2 was applied.

It is biologically highly plausible that patients with low insulin need at baseline are vulnerable to DKA. Low insulin doses mean that there is virtually no insulin resistance and that the amount of injected insulin can be considered essential substitution therapy. Under these circumstances there is little room for insulin dose reduction, and any attempts to save insulin by addition of dapagliflozin can lead to insulin deficiency which manifests itself as DKA. The SmPC includes recommendations not to use dapagliflozin in patients with low insulin need.

Monitoring of blood ketone levels may be a valuable RMM tool, especially in the presence of other risk factors. As a measure to prevent DKA, the MAH employed blood ketone self-measurement. However, no actions to be taken were defined in case a high ketone reading was reported by the patient. A problem is that it is not known which patients with ketosis actually develop DKA. For precaution, actions could be taken in all patients with marked ketosis, e.g. administration of an additional insulin dose (together with carbohydrates if needed) and interruption of dapagliflozin treatment. The MAH has provided a treatment algorithm which is included in the SmPC and the educational material. This algorithm is based on current knowledge on DKA associated with the use of SGLT2i and is deemed adequate.

Genital infection AEs were among the AEs of special interest. Genital infections were more frequent in the dapagliflozin treatment groups than the placebo group in the ST placebo-controlled Phase III pool: 11.1%, 9.5%, and 2.3% in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively. The overall proportion of subjects with AEs of genital infection was higher in all treatment groups than has been previously observed in dapagliflozin studies in subjects with T2DM. However, the relative ratio of genital infection in dapagliflozin-treated subjects to those receiving placebo was similar to previous dapagliflozin experience in T2DM.

UTI was most common in the 5 mg dapagliflozin treated group and least common in the 10 mg dapagliflozin treated group; 6.8%, 3.7%, and 4.7% in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively. As may be expected, UTI was more common in women. There were no meaningful differences in the proportions of subjects in each treatment group with AEs of urinary tract infection having recurrent events, though more subjects in the dapagliflozin treatment groups received antimicrobial treatment and received additional treatment due to inadequate response to the initial course, showing that the UTI in the dapagliflozin treated groups were more difficult to treat. There was also an overrepresentation of UTI SAEs in the dapagliflozin treated groups (4 events vs none in the placebo treated group).

AEs related to worsening of renal function/renal impairment were only reported in the dapagliflozin treated groups (1.1% and 0.4% for 5 mg and 10 mg, respectively). The two SAEs reported appears, however, not to have been directly related to treatment. One case of obstructive uropathy may have been worsened/precipitated by increased urine volumes. The other case reported prerenal failure and was hospitalized due to progressive nausea and vomiting, but the information on the case is limited.

AEs of volume depletion were few and only slightly overrepresented in the dapagliflozin treated group (1.5% and 0.5% vs 0.8%). In this context it should be remembered that the mean age in the study population was lower than in the T2DM population, thus patients may be less sensitive to volume depletion.

Cardiovascular events were few in the ST placebo-controlled Phase III pool and although the events were not evenly distributed, no safety concerns arise. Hepatic events were also few and but evenly distributed across treatment groups. There was a slight imbalance in the number of fractures with the highest rate reported in the 5 mg dapagliflozin group. The majority of fractures in all treatment groups were foot/ankle fractures. There was a slight imbalance in the number of events due to potential hypersensitivity with the highest rate reported in the 5 mg dapagliflozin group. The majority of events were mild and skin-related. High haematocrit and high creatinine was reported at a higher rate in dapagliflozin treated patients compared to placebo, in line with the mechanism of action of dapagliflozin and with previous observations in patients with T2DM. There was no difference in the reporting rate of elevated liver tests between active treatment and placebo and no patient showed a concomitant increase in ALT or AST and total bilirubin within 14 days on or after ALT/AST elevation. There were no meaningful changes in clinical laboratory parameters from baseline to Week 24 in the ST placebo-controlled Phase III pool, with the exception of urinary glucose. This is consistent with the known safety profile of dapagliflozin.

A decrease in both SBP (-3.8 mmHg, -2.8 mmHg, and -0.5 mmHg in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively) and DBP (-1.5 mmHg, -1.4 mmHg, and 0.1 mmHg, respectively) was observed in the dapagliflozin treated groups, whereas the blood pressure remained unchanged in the placebo treated group. There was also a small decrease in mean seated heart rate, less than 1 beat per minute, in the dapagliflozin treated groups, while the heart rate increased slightly in the placebo treated group. There were no relevant changes in the ECG assessment.

The mean age in the study population was lower than in previous studies with T2DM patients. The age of the patients included ranged from 18 to 75 years, and only 5% of subjects were older than 65 years. In spite of this, the duration of disease ranged from 0 to 66 years. When using an age cut-off of ≥50 years, a higher reporting of AEs was observed compared to patients <35 years age. This increase was balanced between all treatment groups and possibly reflects a higher co-morbidity/vulnerability in the older age group. AEs were more common reported by female patients than by male patients. This was mainly driven by a higher reporting of genital infections. Notably the pattern was comparable for all treatment groups. Across treatment groups, there was a higher reporting of AEs in Asian patients compared to white patients.

Pregnancies have been rare in the T2DM population, possibly due to the age distribution in this population. Notably 6 pregnancies were identified in the T1DM program. The outcome is not known in 2 of the cases. In one case, an unhealthy baby was born; however, the description of the condition is compatible with the complications known to occur in babies born to diabetic mothers. In 2 of the cases the pregnancy was either terminated early or resulted in a spontaneous abortion. Should the use of dapagliflozin be approved for the T1DM population, there will probably be an increased risk of exposure during pregnancies. The SmPC however includes adequate information, and dapagliflozin is not recommended for use in the second and third trimester based on non-clinical findings.

No new data regarding interactions have been provided. This is acceptable since the T1DM and T2DM are not considered different in this respect. Thus, the data concerning interactions in T2DM subjects may be extrapolated to the T1DM population.

Discontinuations due to AEs were evenly distributed between groups (4.2% and 3.5% vs 3.8), whereas SAEs leading to discontinuations were twice as common in the 5 mg group (2.7%) compared to both the 10 mg group (1.2%) and placebo (1.1%). DKA was the most common cause for discontinuation in the study with 8 events in the 5 mg dapagliflozin treated group and 3 events in both the 10 mg dapagliflozin treated group and in the placebo group. In addition, 5 patients in the dapagliflozin treated groups discontinued due to ketoacidosis/ketosis (none in the placebo group). Discontinuations due to genital or urinary tract infections were only observed in the dapagliflozin treated groups (5 patients). Not different in the ST+LT data.

Post-marketing experience in T2DM patients is by now rather extensive with almost 3 million PYs of exposure. The safety profile in this population is well known.

Report from the Ad Hoc expert Group (AHEG) meeting held on 21 November 2018

CHMP requested an ad hoc expert meeting to obtain the opinion of experts in the field of endocrinology and diabetology, as well as from patient representatives, on the issues of clinical relevance of observed treatment effects, risk of diabetic ketoacidosis (DKA), and a potential target population of patients with T1DM that could benefit from treatment with dapagliflozin. Questions were addressed to the ad hoc expert group. The corresponding answers are presented below:

Question 1

What is the AHEG opinion on the clinical relevance of the treatment effects observed with dapagliflozin, esp. with regard to reduction of HbA1c, insulin doses, body weight and glucose variability?

Efficacy outcomes from studies MB102229 and MB102230 were presented to the experts. With regard to individual aspects they had the following view:

The absolute reductions of HbA1c in the treatment groups by 0.36 to 0.48 % (mean absolute change from baseline) were seen as positive and by several experts also as clinical relevant, although the majority of the experts with unrestricted participation considered the reduction only of borderline clinical relevance.

The experts did not see an obvious benefit in the observed reduction of the average insulin doses (both basal and post prandial); one expert pointed out that insulin treatment in patients with type 1 diabetes mellitus (T1DM) is a hormone replacement therapy, therefore, conceptually, a lowering of the insulin dose may not be a goal at all (at least in non-overweight patients).

The reduction of body weight by 3.00 to 3.65% (mean absolute percent change from baseline) was considered of minor benefit, but nevertheless was considered to be beneficial for some patients, according to some of the experts.

The studies also demonstrated a reduction of the variability of plasma glucose. This was seen by the experts in general as a relevant goal, in particular as it did not result in an increase of hypoglycaemic events. The company was asked whether benefits of a reduction in glucose variability were reflected by improvements of patient reported outcomes, which was not the case (no data to support this), however it was acknowledged by the experts that this might be difficult to capture. Another benefit, mentioned by patients, is that such an improvement helps to simplify insulin dose calculations.

The AHEG had a split view whether the totality of the efficacy outcomes demonstrated in studies MB102229 and MB102230 would represent a clinically important benefit overall for patients with T1DM.

The majority of the experts with unrestricted participation were of the view that this add-on treatment may provide only a small benefit.

Considering this to be a potentially lifelong treatment for T1DM, some experts and patients suggested the need for the generation of more data with long-term treatment, such as renal outcomes, and safety outcomes in general.

Question 2

The risk of DKA was considerably higher in the dapagliflozin treated groups compared to placebo despite careful information to patients and monitoring including measurements of ketones.

a. Please discuss the acceptability of this risk in clinical practice

All experts agreed that DKA represents a substantial and important risk. The experts also noted that the incidence of DKA in the real world is considerably higher than the incidence seen in the control group of the studies, presumably due to the measures implemented during the trial to mitigate this risk. Nevertheless, the experts noted that cases of DKA where reported with similar frequency at all time points during the studies.

The experts stated that education and awareness of the problem, including the occurrence of DKA with only slightly elevated plasma glucose levels, is of foremost importance to reduce the risk.

The AHEG had split views on the acceptability of this risk. A majority of experts considered that the risk might be manageable in a restricted subpopulation (in particular in patients well trained and well-educated in treatment of T1DM). The majority of experts with unrestricted participation were of the opinion that the expected extent of DKA could constitute an unacceptable risk in clinical practice.

The risk of DKA with the use of dapagliflozin maybe different in different health care systems as, according to experts, once available, the product could be expected to be prescribed also by less well-trained generalists in some member states.

b. Risk minimisation measures such as a guide for health care professionals and patients, as well as a Patient Alert Card have been proposed in order to mitigate the risks. What is the AHEG view on the appropriateness and effectiveness of the proposed measures in clinical practice?

The experts, including the 2 patients, raised some concerns with regard to the suitability of the proposed materials for a broad spectrum of health care professionals and patients, intended to mitigate the risk of DKA: Some experts found that the material for doctors might not be very user friendly, would be demanding (e.g. to “establish a personal action plan” for the patient etc.), and may not address sufficiently risks such as patients not complying with ketone testing or the situation of insulin pump users. Patients felt it would put quite a high responsibility on them, and may, to some degree, over-burden them.

c. Please discuss any additional potential measures that could be introduced to decrease the risk of DKA.

As the product information recommends that patients should be able to monitor blood ketone levels themselves, ketone measurements were discussed extensively. It was acknowledged that ketone measurements by patients could represent an important contribution to the safe use of the product. It was pointed out, however, that this was not easily available in some member states, and even if this was the case, whether this was practical to measure on a frequent base and would achieve high acceptance by patients was questioned. Also, experience with this seems to indicate that slight

increases for various causes (e.g. diet) may cause frequent follow-ups by health care professionals. From the patients' perspective the acceptance of another frequently to be self-measured laboratory parameter beyond glucose was questioned.

The AHEG emphasized that general awareness and education of DKA (in particular also euglycaemic DKA), both with patients and health care professionals, is of high importance to reduce the risk. There was also the unanimous view that to mitigate the risk treatment and prescription of this therapy should be exclusively by specialists.

The experts had no further proposals for risk mitigation.

Question 3

Please discuss which patients, if any, with T1DM could relevantly benefit from treatment with dapagliflozin, i.e. what could be a potential target population in clinical practice? Could restrictions with respect to BMI and insulin requirements be of relevance?

The experts found any benefit in patients with T1DM could be expected to be most relevant in patients who are overweight, who are well educated and trained in T1DM, and who have large glucose variability. While it was acknowledged that the risk of DKA seemingly is higher in patients treated with insulin pump therapy, it was also said that those patients may particularly benefit as often suffering from high glucose variability in the first place, and in any case represent an increasing and important proportion of the T1DM population.

The experts were asked to discuss possible parameters indicative of an improved benefit/risk ratio. The total daily insulin dose as one possible parameter was discussed. While it was acknowledged that patients with low insulin requirements may be of somewhat increased risk of DKA, the experts were sceptical of a specific cut off value for treatment (e.g. to treat only patients with a total daily insulin dose > 0.6 IU/kg), as under some circumstances even patients with low insulin requirements may benefit, a cut off value would be very difficult to define based on available data, and because insulin requirements may be the consequence of other underlying circumstances which should be taken into account. The experts thought that a low HbA1c value should not constitute an exclusion criterion per se, but that highly elevated HbA1c should, also considering that the latter may reflect a low degree of patient compliance. The experts also thought that body weight could be a relevant parameter, as the safety profile would improve with a higher BMI. One expert emphasized the importance of C-peptide levels, as an important marker of residual beta-cell function relevant for definition of the most appropriate target population to define an indication.

The experts agreed that the general T1DM population is in any case a too broad target population. They further agreed that proper patient education and compliance is very essential and, if approved for T1DM, the product should exclusively be prescribed in specialist centres, or at least by specialists, i.e. diabetologists or endocrinologists.

2.5.2. Conclusions on clinical safety

The general safety profile of dapagliflozin when used in patients with T1DM does not differ when compared to what is known from the use of dapagliflozin in patients with T2DM. However, treatment with dapagliflozin was associated with an increased risk of DKA in spite of repeated education of the patients and monitoring of ketones. There was no apparent difference in the risk by dose of dapagliflozin and the DKA events increase steadily over time, suggesting that DKA risk is not limited e.g. to treatment initiation but unrelievedly present throughout SGLT2 therapy. Considering that DKA

is a serious condition, additional measures to minimise this risk are considered necessary and warnings and recommendations have been included in the SmPC.

2.5.3. PSUR cycle

Based on the inclusion of a new population (T1DM) at a higher risk of DKA in the indication, the CHMP is of the opinion that the already existing entry in the EURD list for dapagliflozin needs to be amended as follows: The frequency of PSUR submission should be revised to 6 months. The next PSUR should cover the period from 05 October 2018 to 04 October 2019 and be submitted within 70 days of the data lock point. The following PSUR should cover the period from 05 October 2019 to 04 April 2020 and be submitted within 70 days of the data lock point in accordance with the updated list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

3. Risk management plan

The MAH submitted an updated RMP version 16 and subsequent versions up to 16.7 within this procedure.

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

The PRAC considered that the risk management plan version 16.7 is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 16.7 with the following content:

Safety concerns

Summary of safety concerns

Important identified risks	Urinary tract infection
	Renal impairment
	Diabetic Ketoacidosis including events with atypical presentation
Important potential risks	Volume depletion
	Clinical consequences of increased haematocrit
	Bone fracture
	Serious hypersensitivity reactions
	Liver injury
	Bladder cancer
	Breast cancer
	Prostate cancer
	Lower limb amputation
	Pancreatitis
Missing information	None

Pharmacovigilance plan

Ongoing and planned additional pharmacovigilance activities

Study (study short name, and title) Status (planned/ongoing)	Summary of objectives	Safety concerns addressed	Milestones (required by regulators)	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Retrospective Cohort Study on the Risk of Diabetic Ketoacidosis (DKA). (planned)	Determine the effectiveness of additional risk minimization measures in place for DKA in Europe by assessing the impact of the RMMs on the risk of DKA in T1DM patients who are treated with dapagliflozin in Europe.	diabetic ketoacidosis in T1DM	Protocol submission Feasibility assessment Populations size update Submission of interim report(s) Submission of final data	May 15, 2019 May 15, 2019 Annual Q4 2023 (estimated) Q4 2025 (estimated) Q4 2026 (estimated)
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
MB102103 (D1690R00008)- Observational study: Complications of UTI in Patients on Dapagliflozin Ongoing	Assess the incidence of hospitalization or emergency department visit for severe complications of UTI among new users of dapagliflozin compared to those who are new users of certain other antidiabetic drugs.	Severe complications of UTI	Submission of interim data Submission of final data	2016, 2019 2020
MB102104 (D1690R00005) - Observational study: Acute Liver Injury in Patients on Dapagliflozin Ongoing	To assess the incidence of hospitalization for ALI among new users of dapagliflozin compared to those who are new users of certain other antidiabetic drugs.	Risk of acute hepatic failure	Submission of Interim data Submission of final data	2016, 2019 2020
MB102110 (D1690R00004) - Observational study: Acute Kidney Injury in Patients on Dapagliflozin and Other Antidiabetic	To assess the incidence of hospitalization for AKI among new users of dapagliflozin compared to those who are new users of	Risk of AKI	Submission of Interim data Submission	2016, 2019 2020

Ongoing and planned additional pharmacovigilance activities

Study (study short name, and title) Status (planned / ongoing)	Summary of objectives	Safety concerns addressed	Milestones (required by regulators)	Due dates
Medications Ongoing	certain other antidiabetic drugs.		of final data	
MB102118 (D1690R00007) - Observational study: Cancer in Patients on Dapagliflozin and Other Antidiabetic Treatment Ongoing	To assess the incidence of breast and bladder cancer among new users of dapagliflozin compared to those who are new users of certain other antidiabetic drugs.	Risk of cancer	Submission of Interim data Submission of final data	2016, 2019, 2021, 2023 2025
D1693C00001 (DECLARE) - Interventional: Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events Ongoing	To assess the estimated risk ratio of the composite endpoint of CV death, myocardial infarction or ischaemic stroke, in patients with T2DM with either established CV disease or at least 2 CV risk factors in addition to T2DM, treated with dapagliflozin compared to placebo.	Clinical consequences of increased haematocrit, Renal impairment, Bone fracture, Liver injury, Serious hypersensitivity reactions, Bladder cancer, Breast cancer, Prostate cancer	Submission of final data	2020
Nonclinical mechanistic model studies - Postdoc project Ongoing	Studies aimed to elucidate the metabolic adaptations in term of glucose flux, lipolysis, and ketogenesis following insulin withdrawal in subjects with diabetes mellitus and absolute or relative endogenous insulin deficiency, when treated with dapagliflozin.	Ketoacidosis	Submission of final data	When available
Meta-analysis across studies D1690C00018, D1690C00019, and D1693C00001 (DECLARE). Planned	Determine the incidence of amputation and relevant preceding AEs over time by showing the cumulative proportion of subjects with events and numbers of subjects at risk at relevant time points.	Lower limb amputation	Protocol submission Submission of final data	Q1 2018 Q3 2020

Risk minimisation measures

Summary table of risk minimisation activities by safety concern

Safety concern	Risk minimisation measures
Important identified risks	
Urinary tract infection	Routine risk minimisation measures: SmPC section: 4.4, 4.8 PL section: 4 Direction on how to detect symptoms of UTI (PL section 2). Instructions on when to stop taking Forxiga and see a doctor as soon as possible (ie, signs of a severe infection of the urinary tract) (PL Section 2).
Diabetic Ketoacidosis including events with atypical presentation	Routine risk minimisation measures: SmPC sections 4.4, 4.8 PL section 4 Information includes that dapagliflozin should be interrupted in relation to major surgical procedures or acute serious medical illnesses, or if DKA is suspected (SmPC section 4.4, PL section 2). Before initiating dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered (SmPC section 4.4). Additional risk minimisation for T1DM included for Forxiga 5 mg only: Information included that T1DM patients will be informed of the risk of DKA, risk factors, signs and symptoms, and that DKA may occur even if blood glucose levels are not elevated, in a mandatory education session. Recommendation on education about use of blood ketone monitoring, including directions to seek prompt medical attention in case of suspected ketoacidosis (SmPC section 4.4, PL section 2). Information on how to detect symptoms of DKA and instructions to seek prompt medical attention (PL section 2, 4). Recommendation that T1DM patients with BMI < 27 kg/m^2 should not be initiated on dapagliflozin. Additional risk minimisation measures: Educational materials for HCPs and patients/carers.

Summary table of risk minimisation activities by safety concern

Safety concern	Risk minimisation measures
Renal impairment	Routine risk minimisation measures: SmPC section 4.8 PL section 4 Guidance is provided on monitoring renal function (SmPC section 4.4 and PL section 2).
Volume depletion	Routine risk minimisation measures: SmPC section: 4.2, 4.8 PL section 4 In SmPC section 4.4 it is stated that: Monitoring of volume status in at-risk patients is recommended. Not recommended in patients on loop diuretics or volume depleted. Use caution in patients for whom dapagliflozin-induced reduction in blood pressure could pose a risk (PL sections 2, 4).
Clinical consequences of increased haematocrit	Routine risk minimisation measures: SmPC section 4.8 PL section 4 Recommendation to use dapagliflozin with caution in patients with already elevated haematocrit (SmPC section 4.4). Direction to consult health care professional at any time before or during treatment in the event red blood cells are increased (PL section 4).
Bone fracture	No risk minimisation measures.
Liver injury	No risk minimisation measures.
Serious hypersensitivity reactions	Routine risk minimisation measures: SmPC section 4.3 PL section 2
Bladder cancer	Routine risk minimisation measures: SmPC section 4.8 Recommendation not to use dapagliflozin in patients on concomitant pioglitazone (SmPC section 4.4).
Breast cancer	Routine risk minimisation measures: SmPC section 4.8

Summary table of risk minimisation activities by safety concern

Safety concern	Risk minimisation measures
Prostate cancer	Routine risk minimisation measures: SmPC section 4.8
Pancreatitis	No risk minimisation measures.
Lower limb amputation	Routine risk minimisation measures: Recommendation on counselling patients on routine preventative foot care (SmPC section 4.4) and guidance for patients on routine/directed foot care (PL section 2).

4. Changes to the Product Information

As a result of this variation, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated to include information on the use of dapagliflozin in T1DM. The Package Leaflet is updated in accordance.

Please refer to Attachment 1 which includes all proposed changes to the Product Information (SmPC, Annex II, Labelling and Package Leaflet (changes highlighted) of Forxiga 5mg film-coated tablet, as a relevant example with changes highlighted as adopted by the CHMP on 31 January 2019).

4.1.1. User consultation

The WSA has submitted the results of a user consultation with target patient groups on the package leaflet that meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human. The user test report is considered acceptable. For detailed evaluation, see appendix 3.

5. Benefit-Risk Balance

5.1. Therapeutic Context

5.1.1. Disease or condition

The current application seeks to extend the indication of dapagliflozin to also include treatment of patients with T1DM:

"Forxiga / Edistride is indicated in adults for the treatment of insufficiently controlled

- type 2 diabetes mellitus as an adjunct to diet and exercise
  - as monotherapy when metformin is considered inappropriate due to intolerance
  - in addition to other medicinal products for the treatment of type 2 diabetes.
- ***type 1 diabetes mellitus as an adjunct to insulin in patients with BMI ≥ 27 kg/m^2 , when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.***

For clinical trial results with respect to populations studied, effects on glycaemic control and combinations with other medicinal products see sections 4.4, 4.5 and 5.1."

In patients with T1DM, SGLT2 inhibition by dapagliflozin is expected to produce glucose-lowering effects, as well as modest reductions in body weight, blood pressure, and, potentially, glycaemic variability, as the amount of glucose excreted following dapagliflozin treatment is dependent on the plasma glucose concentration and independent of insulin.

5.1.2. Available therapies and unmet medical need

Patients with T1DM require lifelong insulin therapy due to their inability to produce enough endogenous insulin. However, a large proportion of the T1DM population is unable to achieve recommended glycaemic levels with insulin alone.

There are currently no approved adjunct treatments to insulin for patients with T1DM in the EU.

While insulin treatment is lifesaving in patients with T1DM, many patients suffer from hypoglycaemic events as a result of the treatment, which negatively impact their daily lives and can, conversely, be life-threatening. Unwanted increase of body weight may also be a problem when insulin doses are increased. The glycaemic variability associated with insulin treatment also negatively impacts patients' quality of life. Reducing swings in glucose levels is therefore of importance to prevent insulin-induced hypoglycaemia/hyperglycaemia as well as to improve the quality of life in patients with T1DM. Another risk associated with suboptimal insulin use is DKA.

5.1.3. Main clinical studies

Two key Phase III efficacy studies were included in the dapagliflozin T1DM development programme: studies **MB102229** and **MB102230**.

Both studies were multicentre, randomised, double-blind, placebo-controlled, parallel-group, Phase III studies to evaluate the efficacy and safety of dapagliflozin 5 mg and 10 mg when added to ongoing insulin therapy in subjects with T1DM. The studies included an 8-week lead-in period, a 24-week short-term (ST) treatment period, and a 28-week long-term (LT) extension (LT extension ongoing for study MB102230). The primary and secondary efficacy analyses are based on the 24-week results, with selected analyses repeated for the 52-week results as exploratory analyses of LT efficacy. The safety analyses are based on the 24-week and 52-week results.

The target population was subjects with T1DM aged ≥18 to ≤75 years who were on ongoing insulin treatment for at least 12 months and who had inadequate glycaemic control, with central laboratory HbA1c at the Week -1 visit of ≥7.5% to ≤10.5%.

In total, 1591 patients were randomised 1:1:1 and included in the primary analysis. The ST-pool from these studies provides 24 week safety data in about 1 000 T1DM patients exposed to dapagliflozin. In addition, 52 week safety data is available for 490 patients in study MB102229 and 457 patients in study MB102230.

5.2. Favourable effects

Primary efficacy variable was change in HbA1c from baseline to Week 24. In study MB102229, the adjusted mean change compared with placebo in HbA1c from baseline to Week 24 was -0.42% (95% CI: -0.56, -0.28; p<0.0001) for dapagliflozin 5 mg and -0.45% (95% CI: -0.58, -0.31; p<0.0001) for dapagliflozin 10 mg. In study MB102230, the adjusted mean change compared with placebo in HbA1c from baseline to Week 24 was -0.37% (95% CI: -0.49, -0.26; <0.0001) for dapagliflozin 5 mg and -0.42% (95% CI: - 0.53, -0.30; <0.0001) for dapagliflozin 10 mg. This was supported by a significant

decrease in the adjusted mean change compared with placebo in 24-hour CGM values from baseline to Week 24 in both studies.

In both studies, most of the reduction in HbA1c in the dapagliflozin treatment groups occurred over the first 4 weeks of treatment and was maintained for the duration of the ST treatment period.

The percent change in total daily insulin dose was a secondary endpoint. In study MB102229, the adjusted mean change compared with placebo in total daily insulin dose from baseline to Week 24 was -8.80% for dapagliflozin 5 mg and -13.17% for dapagliflozin 10 mg. In study MB102230, the adjusted mean change compared with placebo in total daily insulin dose from baseline to Week 24 was -10.78% for dapagliflozin 5 mg and -11.08% for dapagliflozin 10 mg. In general, the proportional reductions seen for basal and bolus insulin individually were similar to the proportional reduction in total insulin, thus both basal and bolus insulin were reduced to the same extent.

In study MB102229, the adjusted mean change compared with placebo in body weight from baseline to Week 24 was -3.05% in the dapagliflozin 5 mg group and -3.72% for dapagliflozin 10 mg. In study MB102230, the adjusted mean change compared with placebo in body weight from baseline to Week 24 was -3.21% for dapagliflozin 5 mg and -3.74% for dapagliflozin 10 mg.

The effect on blood glucose variability was investigated by two secondary endpoint, 1) change in mean value of 24-hour glucose readings (MAGE) and 2) change in percentage of 24-hour glucose readings falling within the range of >70 mg/dL to ≤180 mg/dL.

In study MB102229, the adjusted mean change compared with placebo inMAGE from baseline to Week 24 was -17.30 mg/dL in the dapagliflozin 5 mg group and -18.93 mg/dL for dapagliflozin 10 mg. In study MB102230, the adjusted mean change compared with placebo in MAGE from baseline to Week 24 was -9.85 mg/dL for dapagliflozin 5 mg and -9.36 mg/dL for dapagliflozin 10 mg.

In study MB102229, the adjusted mean change compared with placebo in the percentage of glucose readings falling between >70 mg/dL and ≤180 mg/dL from baseline to Week 24 was 9.11% in the dapagliflozin 5 mg group and 10.65% for dapagliflozin 10 mg. In study MB102230, the adjusted mean change compared with placebo in the percentage of glucose readings falling between >70 mg/dL and ≤180 mg/dL from baseline to Week 24 was 9.02% for dapagliflozin 5 mg and 10.70% for dapagliflozin 10 mg.

In study MB102229, the proportions of subjects experiencing a ≥0.5% reduction in HbA1c without severe hypoglycaemia events were 49.6% and 50.8% in the dapagliflozin 5 mg and 10 mg groups, respectively, compared with 25.3% in the placebo group. In study MB102230, the proportions of subjects experiencing a ≥0.5% reduction in HbA1c without severe hypoglycaemia events were 39.5% and 41.6% in the dapagliflozin 5 mg and 10 mg groups, respectively, compared with 20.1% in the placebo group.

A decrease in both SBP (-3.8 mmHg and 2.8 mmHg) and DBP (-1.5 mmHg and -1.4 mmHg) was observed in the dapagliflozin treated groups, whereas the blood pressure remained unchanged in the placebo treated group.

Subgroups analyses showed consistent outcomes in all subgroups with regards to the primary endpoint.

Long-term treatment up to 52 weeks shows a slight attenuation of the effect on HbA1c compared to the outcome at week 24, whereas the effect on body weight is maintained. The findings in both Phase III studies were consistent.

Since there were only marginal differences in efficacy between the two doses, only the lower dose of 5 mg is acceptable as a precautionary measure.

5.3. Uncertainties and limitations about favourable effects

The outcome of the two Phase III studies showed consistent results and there are no important uncertainties with regards to the favourable effects.

Regarding the potential mechanisms by which dapagliflozin might improve glycaemic control, it can be assumed that the SGLT2 inhibitor blunts the post-prandial glucose excursion since a higher blood glucose level will lead to a higher glucose excretion. However, a clear effect of dapagliflozin on postprandial blood glucose was not observed, which suggests that dapagliflozin does not exert an additional effect to prandial insulin. Instead, dapagliflozin on top of insulin lead to markedly decreased blood glucose levels during the night, especially in the early morning hours. Therefore, dapagliflozin may counteract the so-called “dawn-phenomenon”.

Data from the DCCT trial has shown that a decrease in HbA1c is correlated with a decrease in mortality in patients with T1DM. However, the long-term effect of stabilised blood glucose levels is less well documented, thus the clinical significance of the decrease in the glucose variability observed in the studies is uncertain.

5.4. Unfavourable effects

More patients in the dapagliflozin-treated groups reported AEs (70%, 69% for the 5 mg and 10 mg dose respectively) than in the placebo-treated group (62%). The imbalance in AEs between dapagliflozin treated groups and placebo is attributable to a higher reporting of AEs related to the known safety profile of dapagliflozin, i.e. pollakiuria, thirst, nausea, polyuria, vulvovaginal and genital mycotic infections.

SAEs were reported in 6.8%, 5.5%, and 3.8% of subjects in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo treatment groups, respectively. Out of these, 2.7% and 2.1% vs 0.6% were deemed as related to treatment in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively. The distribution of SAEs in the pooled T1DM studies was consistent with the known safety profile of dapagliflozin, except that there were more ketone-related SAEs in the pooled T1DM studies than were observed in T2DM studies.

Genital infections were more frequent in the dapagliflozin treatment groups than the placebo group: 11.1%, 9.5%, and 2.3% in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively. The overall proportion of subjects with AEs of genital infection was higher in all treatment groups than has been previously observed in dapagliflozin studies in subjects with T2DM. However, the relative ratio of genital infection in dapagliflozin-treated subjects to those receiving placebo was similar to previous dapagliflozin experience in T2DM.

UTI was most common in the 5 mg dapagliflozin treated group and least common in the 10 mg dapagliflozin treated group; 6.8%, 3.7%, and 4.7% in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively. As may be expected, UTI was more common in women. There was an overrepresentation of UTI SAEs in the dapagliflozin treated groups (4 events vs none in the placebo treated group).

AEs related to worsening of renal function/renal impairment were only reported in the dapagliflozin treated groups (1.1% and 0.4% for 5 mg and 10 mg, respectively).

Numerically, no difference in the rate of hypoglycaemic events or severe hypoglycaemic events was observed between treatment groups. Kaplan-Meier plot show no apparent difference in the time to first severe hypoglycaemia between groups, with Kaplan-Meier percentages at Week 24 of 7.2%, 7.4%, and 7.4% for dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo, respectively. The incidence of hypoglycaemia events decreased over time with Kaplan-Meier percentages at Week 52 of 10.7%, 8.9%, and 12.6% respectively.

Other AEs of special interest such as cardiovascular events, hepatic events, volume depletion, fractures and events due to potential hypersensitivity were few and although there were some imbalances, no new safety concerns arise from these data. High haematocrit and high creatinine was reported at a higher rate in dapagliflozin treated patients compared to placebo, in line with the mechanism of action of dapagliflozin and with previous observations in patients with T2DM.

Most AEs were of mild intensity; severe AEs were few and reported at a similar rate in all treatment groups. AEs considered related to treatment were more than twice as common in the dapagliflozin treated groups compared to placebo (28.6%, 27.0%, and 11.8% in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively). There were no apparent differences in the LT data compared to the ST data.

The major safety issue with the use of dapagliflozin in T1DM patients is the risk of diabetic ketoacidosis (DKA). In the Art 20 referral procedure on SGLT2-inhibitors and DKA (EMA/PRAC/50218/2016) the occurrence of DKA in predominantly T2DM patients was assessed and the procedure resulted in the introduction of warnings and recommendations in the SmPCs for all SGLT2-inhibitors. DKA was specifically investigated in the studies and measures were taken to reduce the risk.

In the short term pooled data, 11 (2.0%), 11 (1.9%) and 3 (0.6%) subjects in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively, had an event adjudicated as a ‘definite’ DKA event. In the short term+long term placebo-controlled Phase III pool, 22 (4.0%), 20 (3.5%) and 6 (1.1%) subjects in the dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo groups, respectively, had an event adjudicated as a ‘definite’ DKA event.

The occurrence of ‘definite’ DKA events was evenly distributed over time in the ST+LT pool, and no time point could be identified as being of particular risk for the occurrence of DKA. There was no major difference between the two doses.

Well known precipitating factors such as pump failure or missed insulin dose, were equally common in all groups (about 30% each). However, in about 30% of cases either no cause could be identified, or the event was related to “other” causes.

Attempts have been made to identify patients with an increased risk of DKA. However, the reliability of those analyses is questioned due to few events. There was however a higher number of DKA cases in patients receiving low insulin doses at baseline. When the risk of DKA was analysed by different cut-offs for total insulin dose, the risk difference versus placebo was decreased from 2.9% (overall pooled phase 3 population receiving 5 mg dapagliflozin) to 1.6% when a cut-off of ≥0.6 IU/kg was applied in this population. A similar phenomenon was observed for BMI: most DKA cases occurred in patients whose BMI was below the population mean. When the risk of DKA was analysed by different cut-offs for BMI, the risk difference versus placebo was decreased from 2.9% (overall population) to 0.7% when a cut-off of ≥27 kg/m^2 was applied. However, all subgroup analyses concerning risk of DKA should be interpreted with caution due to low number of events.

5.5. Uncertainties and limitations about unfavourable effects

Treatment with dapagliflozin was associated with an increased risk of DKA in spite of repeated education of the patients and monitoring of ketones.

Despite confirmation of ketosis in the study, development of ketoacidosis obviously could not always be prevented. The SmPC now includes detailed warnings and recommendations and additional risk minimisation measures will be provided in the form of an educational material. Compared to the clinical studies, risk minimisation measures have been strengthened. Therefore, a post-approval safety study will be conducted in order to evaluate the effectiveness of the measures taken.

The mean age in the study population was lower than in previous studies with T2DM patients. The age of the patients included ranged from 18 to 75 years, and only 5% of subjects were older than 65 years. In spite of this, the duration of disease ranged from 0 to 66 years. When using an age cut-off of ≥50 years, a higher reporting of AEs was observed compared to patients <35 years age. AEs were more commonly reported by female patients than by male patients. This was mainly driven by a higher reporting of genital infections. Notably the pattern was comparable for all treatment groups.

Pregnancies have been rare in the T2DM population, possibly due to the age distribution in this population. Notably 6 pregnancies were identified in the T1DM program. The SmPC includes adequate warnings.

5.6. Effects Table

Table 1. Effects Table for Forxiga / Edistride in the treatment of T1DM

Effect	Short description	Unit	Dapa-gliflozin	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
HbA1c	Change in HbA1c from baseline week 24	%	5 mg: -0.45/-0.34 10 mg: -0.47/-0.39	-0.03/0.03	The difference from placebo was statistically significant for both doses in both studies; p<0.0001	Studies MB102229/ MB102230
Weight	Percent change in body weight by week 24	%	5 mg: -3.00/-3.22 10 mg: -3.67/-3.76	0.05/-0.02	As above	Studies MB102229/ MB102230
MAGE	Change in mean amplitude glucose excursions	mg/dL	5 mg: -14.9/-10.2 10 mg: -16.6/-9.7	2.4/-0.3	As above	Studies MB102229/ MB102230
Re-sponders	Proportion with ≥0.5% HbA1c reduction without severe hypo	%	5 mg: 49.6/39.5 10 mg: 50.8/41.6	25.3/20.1	As above	Studies MB102229/ MB102230

Effect	Short description	Unit	Dapa-gliflozin	Placebo	Uncertainties / Strength of evidence	References
Unfavourable Effects						
Hypo-glycaemia	Total number (%) of subjects with at least 1 event	n (%)	5 mg: 443 (80.8) 10 mg: 466 (82.3)	441 (82.9)	No difference between treatment groups	ST-pool
Hypo-glycaemia	Exposure adjusted incidence rate	IR/100 PY	5 mg: 3688.05 10 mg: 3832.16	3800.33	Total exposure about 250 patient-years per treatment group	ST-pool
Diabetic Keto-acidosis	Number (%) of subjects with definite DKA	n (%)	5 mg: 11 (2.0) 10 mg: 11 (1.9)	3 (0.6)		ST-pool
Diabetic Keto-acidosis	Incidence rate per 100 patient-years	IR/100 PY	5 mg: 4.55 10 mg: 4.36	1.29	Annual rate of DKA in T1DM reported in the literature to be 5-7%	ST-pool

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

T1DM is characterised by insulin deficiency due to destruction of the insulin-producing cells. Insulin treatment aims at normalising blood glucose levels in order to avoid acute symptoms of hyperglycaemia and to minimise the risk of long-term microvascular and macrovascular complications. Optimal treatment requires that the patient monitors blood glucose levels and make insulin dose adjustments on a daily basis. Thus, the management of T1DM has a large impact on the patient's daily life. Currently only insulin is approved for the treatment of T1DM in the EU. In spite of improvements in insulins, methods of administration and monitoring of blood glucose, normalisation of glucose levels is difficult, and the treatment is associated with hypo- and hyperglycaemia as well as weight increase. Thus, there is a need for new therapies as an adjunct to insulin therapy, in order to alleviate the negative effects of insulin treatment in order to reach treatment targets. However, it should be acknowledged that treatment of T1DM carries an inherent risk of DKA since interruption of treatment or an excessive increase in insulin need will result in the development of DKA.

The data provided with this application show that dapagliflozin, when added to optimised insulin therapy, results in a moderate decrease in HbA1c without a subsequent increase in the risk of hypoglycaemias compared to placebo. In addition, decrease of body weight and blood pressure was documented and blood glucose measurements were less variable. Previous knowledge from the DCCT trial show that a decrease in HbA1c has beneficial effects on morbidity and mortality, whereas the long-term benefits of stabilisation of blood glucose are less well documented.

The general safety profile of dapagliflozin is well known and most of these issues such as urogenital infections are easily identified and can be handled. The safety profile is not different in the T1DM population compared to the T2DM population with one important exception which is the increased risk of DKA observed in the studies.

In 2015, an Art 20 referral procedure on SGLT2-inhibitors and DKA (EMA/PRAC/50218/2016) was initiated due to an increased reporting of DKA in T2DM patients. At the time of the procedure data was not sufficient to conclude whether SGLT2-inhibitors increased the risk of DKA. However, based on the knowledge about the pharmacodynamic effect of SGLT2-inhibition, it is plausible that treatment with SGLT2-inhibitors could promote DKA development.

The data presented with this application did indeed show that, in spite of the precautionary measures taken, there was a considerable increase in the risk of DKA compared to placebo in T1DM patients. This lends support to a direct promoting effect of dapagliflozin on the development of DKA. The increased risk is of concern, taking into consideration that DKA is a condition which is potentially life-threatening.

The CHMP has taken the position that the benefit risk balance is negative when considering the total study population (type 1 diabetes mellitus,which would also include lean and slightly overweight patients), as well as when considering T1D patients with a BMI above 25 (proposal for a restricted target population as presented during the oral explanation). Therefore, the MAH made further efforts to identify a subgroup with a potentially positive benefit/risk balance based on the results from the pivotal studies. However, it should be emphasized that general knowledge about the pathophysiology of the disease and DKA by the patient are also of relevance in such an exercise. The subsequently proposed target population consisted of patients with BMI ≥27 kg/m^2 and total daily insulin dose ≥0.7 IU/kg. This subgroup constitutes almost 30% of the overall study population (145/548).

The main benefit of treatment with dapagliflozin in patients with type 1 diabetes is a combined effect on glycaemic control, weight reduction and effects on blood pressure. One additional benefit that was emphasised by some members of the ad hoc expert group was the reduced glucose variability. Based on study data, the benefits of treatment in the proposed target population seem to be rather similar to the total population. However, the unmet need in patients with high overweight/obesity is very different compared to patients with normal weight considering that the alternative treatment, i.e. increase of insulin dose, will lead to additional weight gain which subsequently may increase the risk of cardiovascular disease. Therefore, the expected benefit is higher in the target population (overweight or obese) compared to the total type 1 diabetes population.

Since no remarkable gain in efficacy parameters was observed with the 10mg daily administration, only the 5mg strength is granted approval for use in type1 diabetes ; the recommended dose in this indication is 5mg once daily.

When considering the risk of DKA, the incidence rate in the proposed target population with BMI ≥27 kg/m^2 and total daily insulin dose ≥0.7 IU/kg was comparable to the corresponding subgroup on placebo treatment. Since this population is rather limited and the DKA events are few, these analyses are uncertain. In addition, the CHMP was concerned that the inclusion of total daily insulin (IU) in the indication could create confusion, since patient´s insulin doses may change, sometimes on a daily basis. Finally, during the January CHMP discussion, the indication wording was agreed as follows: “Forxiga / Edistride is indicated in adults for the treatment of insufficiently controlled type 1 diabetes mellitus as an adjunct to insulin in patients with BMI ≥ 27 kg/m^2, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy”. However, since there are indications that a low insulin dose indeed may increase the risk of DKA, this information is included in the warning section of the SmPC.

The MAH has proposed a comprehensive risk minimisation plan which includes the provision of additional risk minimisation measures (educational materials) as such: healthcare professionals guide including a prescriber’s guide, patient’s/carer’s guide and a patient alert card. The objectives of these additional risk minimisation measures are:

- to provide healthcare professionals with specific guidance on the signs, symptoms, risks and treatment of DKA including events with atypical presentation in patients prescribed dapagliflozin for type 1 diabetes.
- To provide specific guidance to patients/carers being prescribed dapagliflozin for type 1 diabetes on the signs, symptoms and risks of DKA including events with atypical presentation.

The Patient Alert Card, which the patients will be carried at all times, will ensure that patients/carer hold at all times information about dapagliflozin and the signs, symptoms and risk of DKA. The information can be made available to relevant healthcare professionals (e.g., emergency room physicians) when needed.

Moreover, in order to estimate the incidence of DKA in T1DM dapagliflozin users following implementation of risk minimisation measures in Europe and assess their effectiveness, the MAH will conduct and submit the results from an imposed category 1 observational cohort study using existing data sources in European countries where dapagliflozin will be launched for T1DM.

To minimise the risk of DKA, dapagliflozin use will be restricted for initiation and supervision by specialists in type 1 diabetes only, and it is of outmost importance that only motivated and educated type 1 diabetes patients are identified for treatment with dapagliflozin. In addition to being overweight/obese and having an inadequate glycaemic control, the patient should be able and committed to monitor their ketones levels and have a close contact with a specialist doctor or nurse. Patients should be educated on how to recognise DKA risk factors, signs or symptoms, and how and when to monitor ketone levels and what actions to take when elevated ketone readings occur. As such an educational session by the specialist in type 1 diabetes with the patient will take place prior initiation of treatment, in which the educational materials will be given to patients. It will also be important that insulin dose reduction during treatment should only be done when needed to prevent hypoglycaemia and should be done cautiously to avoid ketosis and DKA. Marked reductions of insulin should be avoided; when necessary, this should prompt discontinuation of dapagliflozin. It should be noted that overall these actions are more stringent than the risk minimisation measures that were used in the pivotal studies submitted for this application.

Thus, dapagliflozin will be a treatment alternative only for a limited number of patients with type 1 diabetes, but in some patients, e.g. those with substantial problems with glucose variability and for those where an increase of the insulin dose would not be appropriate, it would be a valuable addition to insulin treatment.

5.7.2. Balance of benefits and risks

The benefit-risk balance of Forxiga/Edistride in the proposed indication " *type 1 diabetes mellitus as an adjunct to insulin in patients with BMI ≥ 27 kg/m^2 , when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy",* is considered as positive since the benefits are considered to outweigh the risks.

5.7.3. Additional considerations on the benefit-risk balance

An AHEG meeting was held on 21 November 2018. The discussions from this meeting are present in the section 2.5.1 of this report.

5.8. Conclusions

The overall B/R of Forxiga/Edistride in the proposed indication "type 1 diabetes mellitus as an adjunct to insulin, in patients with BMI ≥ 27 kg/m^2 , when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy" is considered as positive since the benefits are considered to outweigh the risks.

6. Recommendations

Outcome

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

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

Extension of Indication to include new indication for the treatment of insufficiently controlled type 1 diabetes mellitus as an adjunct to insulin, when insulin alone does not provide adequate glycaemic control, for Forxiga and Edistride 5 mg film-coated tablets; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The Annex II and Package Leaflet are updated accordingly. The RMP has also been updated to version 16.7.
In addition, the Worksharing applicant (WSA) took the opportunity to introduce minor editorial changes to SmPC, Labelling and Package Leaflet.

The worksharing procedure leads to amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

This CHMP recommendation is subject to the following amended conditions:

Conditions or restrictions regarding supply and use

Forxiga 5 mg Tablets
Type 1 diabetes: Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).
Type 2 diabetes: Medicinal product subject to medical prescription

Forxiga 10 mg Tablets
Type 2 diabetes: Medicinal product subject to medical prescription

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

Risk management plan (RMP)

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

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

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

Additional risk minimisation measures

Prior to launch of the new adult indication for dapagliflozin, for the treatment of insufficiently controlled type 1 diabetes mellitus as an adjunct to insulin in patients with BMI ≥ 27 kg/m^2, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy, in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational materials, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational materials are aimed at providing guidance on how to manage risk of diabetic ketoacidosis (DKA) in patients with type 1 diabetes.

The MAH shall ensure that in each Member State where dapagliflozin is marketed for type 1 diabetes, all healthcare professionals and patients/carers who are expected to prescribe, dispense or use the product have access to:

- Guide for Health Care Professionals including a prescriber's checklist
- Patient's/Carer's Guide
- Patient Alert Card

The guide for healthcare professionals including the prescriber's checklist should contain the following key elements:

- Dapagliflozin is not a substitute for insulin (and does not alter insulin-sensitivity).
- The risk of DKA is increased with dapagliflozin treatment.

- If treated with dapagliflozin, glucose levels will not adequately reflect insulin needs, and DKA may occur in patients treated with dapagliflozin even if blood glucose levels are below 14 mmol/l (250 mg/dl). Therefore, glucose monitoring must be supplemented by ketone monitoring.
- Patients with euglycaemic DKA may need glucose in addition to standard of care treatment for DKA and dapagliflozin should be discontinued if DKA occurs.
- Guidance to the physician for assessing whether the patient is eligible for dapagliflozin prescription, e.g. patient selection criteria including adherence to insulin treatment and insulin thresholds, patient's beta-hydroxybutyrate (BHB) < 0.6 mmol/L or urine ketones < 1+, BMI ≥ 27 kg/m^2, absence of DKA risk factors.
- Guidance to the physician for assessing whether the patient is prepared and engaged to perform self-ketone testing before and during therapy.
- Summary of the recommendations for patients, particularly regarding blood ketone measurement and managing sick days.
- For pump users: restrict dapagliflozin prescription to patients experienced in pump use, common trouble-shooting strategies when interruptions of insulin delivery via pump occur in case of pump failure.
- Counsel the patient and evaluate their adherence to ketone monitoring while establishing their baseline ketone level 1 to 2 weeks before treatment initiation and ensure the patient:
  - Has received education/training in ketone testing, and interpreting/acting upon test results
  - Is willing/able to perform ketone testing as prescribed
  - Is adequately informed about managing sick days
- Ensure the patient is on optimal insulin therapy prior to initiation of dapagliflozin treatment.
- Dapagliflozin treatment should be temporarily stopped before surgical procedures or in case of hospitalisation for acute serious illness.
- If addition of dapagliflozin leads to marked reduction of insulin need, discontinuation of dapagliflozin should be considered to avoid high risk of DKA.

The patient's/carer's guide should contain the following key elements:

- Dapagliflozin is not a substitute for insulin
- DKA may occur in patients treated with dapagliflozin even if blood glucose levels are below 14 mmol/l (250 mg/dl), i.e. an explanation of the concept of euglycaemic DKA
- Signs/symptoms of DKA - if not adequately managed DKA can be severe and fatal.
- How to measure ketones, how to interpret the results and what to do in case of hyperketonaemia/DKA (contact HCP immediately if BHB > 0.6 mmol/L with symptoms or if BHB > 1.5 mmol/L with or without symptoms)
- Insulin dose reduction during treatment should only be done when needed to prevent hypoglycaemia and should be done cautiously to avoid ketosis and DKA
- Do not start caloric restriction or carbohydrate restriction while treated

The patient alert card should contain the following key elements:

- The Patient Alert Card should be presented to any HCP consulted.
- DKA may occur in patients treated with dapagliflozin even if blood glucose levels are below 14 mmol/l (250 mg/dl).
- Signs/symptoms of DKA.
- Patients with euglycaemic DKA should receive glucose, insulin and fluids for DKA, dapagliflozin should be discontinued.
- Dapagliflozin should be temporarily stopped before surgical procedures or hospitalisation for acute serious illness.
- Contact details of the dapagliflozin prescriber' and 'Name of patient'.

Obligation to conduct post-authorisation measures:

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Non-interventional PASS: In order to estimate the incidence of DKA in T1DM	31/12/2026

Description	Due date
dapagliflozin users following implementation of RMMs in Europe, the MAH should conduct and submit the results from an observational cohort study using existing data sources in European countries where dapagliflozin will be launched for T1DM.	

7. EPAR changes

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

Scope

Extension of Indication to include new indication for the treatment of insufficiently controlled type 1 diabetes mellitus as an adjunct to insulin, when insulin alone does not provide adequate glycaemic control, for Forxiga and Edistride 5 mg film-coated tablets; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The Annex II and Package Leaflet are updated accordingly. The RMP has also been updated to version 16.7.
In addition, the Worksharing applicant (WSA) took the opportunity to introduce minor editorial changes to SmPC, Labelling and Package Leaflet.

Summary

Please refer to the Scientific Discussion (EMEA/H/C/WS1344) .