14 October 2021
EMA/622203/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Edistride	dapagliflozin
Forxiga	dapagliflozin

Procedure No. EMEA/H/C/xxxx/WS/1952

Note

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

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	23 Jan 2021	23 Jan 2021
☐	CHMP Rapporteur Assessment Report	19 Mar 2021	22 Mar 2021
☐	CHMP Co-Rapporteur Assessment Report	19 Mar 2021	n/a
☐	PRAC Rapporteur Assessment Report	25 Mar 2021	22 Mar 2021
☐	PRAC members comments	29 Mar 2021	29 Mar 2021
☐	Updated PRAC Rapporteur Assessment Report	30 Mar 2021	n/a
☐	PRAC endorsed relevant sections of the assessment report[3]	09 Apr 2021	09 Apr 2021
☐	CHMP members comments	12 Apr 2021	n/a
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	15 Apr 2021	16 Apr 2021
☐	Request for supplementary information	22 Apr 2021	22 Apr 2021
☐	MAH responses by	13 Aug 2021	13 Aug 2021
☐	Re-Start of procedure	16 Aug 2021	16 Aug 2021
☐	CHMP Rapporteur Assessment Report	14 Sep 2021	14 Sep 2021
☐	PRAC Rapporteur Assessment Report	17 Sep 2021	17 Sep 2021
☐	PRAC members comments	22 Sep 2021	
☐	Updated PRAC Rapporteur Assessment Report	23 Sep 2021	23 Sep 2021
☐	PRAC endorsed relevant sections of the assessment report[3]	30 Sep 2021	30 Sep 2021
☐	CHMP members comments	04 Oct 2021	04 Oct 2021
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	07 Oct 2021	07 Oct 2021
☐	Potential Oral Explanation	n/a	n/a
☒	Opinion	14 Oct 2021	14 Oct 2021

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List of abbreviations

Abbreviation or special term	Explanation
ADA	American Diabetes Association
AE	Adverse event
ANCOVA	Analysis of covariance
AUC	Area under the concentration versus time curve
BMI	Body mass index
BOCF	Baseline observation carried forward
CI	Confidence interval
CSR	Clinical study report
DAE	Adverse event leading to discontinuation of study drug
DKA	Diabetic ketoacidosis
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
E_{max}	Maximum effect
EU	European Union
FAS	Full analysis set
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GLP-1	Glucagon-like peptide-1
HbA1c	Glycated haemoglobin
ISPAD	International Society of Pediatric and Adolescent Diabetes
LOCF	Last observation carried forward
MMRM	Mixed model for repeated measures
pcVPC	Prediction-Corrected Visual Predictive Check
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PP	Per protocol
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error of the mean
SGLT2	Sodium glucose cotransporter 2
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
UGE	Urinary glucose excretion
ULN	Upper limit of normal
UTI	Urinary tract infection

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 6 October 2020 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 for Forxiga / Edistride to include treatment of children aged 10 years and above and adolescents with T2DM based on the results from studies D1690C00016 (MB102091) and D1690C00017 (MB102138); these are paediatric studies submitted according to Article 46 of the Paediatric Regulation. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 26.3 of the RMP has also been submitted.

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 P/0086/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0086/2020 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 WSA 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 23 October 2014 (EMEA/H/SA/1012/1/FU/1/2014/PED/II). The Scientific advice pertained to clinical aspects in relation to paediatric development of the dossier.

2. Recommendations

Based on the review of the submitted data, this application regarding the following change:

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 for Forxiga / Edistride to include treatment of children aged 10 years and above and adolescents with T2DM based on the results from studies D1690C00016 (MB102091) and D1690C00017 (MB102138); these are paediatric studies submitted according to Article 46 of the Paediatric Regulation. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 26.3 of the RMP has also been submitted.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the worksharing procedure, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

3. Scientific discussion

3.1. Introduction

Dapagliflozin has been approved in Europe since November 2012. Dapagliflozin is indicated in adults from age 18 years with T2DM as an adjunct to diet and exercise to improve glycaemic control, either as monotherapy in patients for whom use of metformin is inappropriate due to intolerance, or as add-on therapy to other glucose lowering medicinal products including insulin.

The purpose of this application is to fulfil the requirement pursuant to Regulation EC No 1901/2006 for a Paediatric Investigation Plan as agreed by the Paediatric Development Committee and adopted by the European Medicines Agency, and to seek the extension of the indication for dapagliflozin in T2DM to include treatment of children aged 10 years and above.

The current application is supported by data from two clinical studies:

- Study D1690C00016 (MB102091): "A Randomized, Multi-center, Parallel Group, Single-dose, Pharmacokinetics and Pharmacodynamics Study of Dapagliflozin in Children and Adolescents Aged 10 to 17 Years with Type 2 Diabetes Mellitus"
- Study D1690C00017 (MB102138): "A 24-Week, Multicentre, Randomised, Double-Blind, Parallel Group, Phase 3 Trial with a 28-Week Long-Term Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin 10 mg in T2DM Patients Aged 10 to 24 Years"

Study D1690C00017 was designed to investigate the efficacy, safety, and tolerability of dapagliflozin versus placebo for the treatment of patients with paediatric onset T2DM. Paediatric T2DM is more prevalent in populations with low socioeconomic and educational status.

3.1.1. Problem statement

Disease or condition

The proposed extension of the indication in T2DM is:

"Forxiga/ Edistride is indicated in adults ***and children aged 10 years and above*** 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."

Epidemiology

The incidence of T2DM in children is increasing worldwide, and the main driver is the increased prevalence and degree of childhood obesity. Childhood T2DM is still relatively rare in Europe, with a prevalence of approximately 2.5 per 100 thousand.

Biologic features

As in adults, T2DM in children is characterised by hyperglycaemia driven by insulin resistance and relative insulin deficiency. The physiologic insulin resistance associated with pubertal development may

exacerbate glucose dysregulation in susceptible children. Insulin secretion is more impaired in adolescents (approximately 85% reduction) as compared to adults (approximately 50% reduction) at the time of diagnosis of T2DM. Thus, the deterioration in insulin secretion appears to be more rapid in adolescents than in adults.

Clinical presentation and prognosis

Developing T2DM at a younger age is associated with a considerably higher risk of long-term cardiovascular disease compared with those who develop T2DM in the middle age. The rapid deterioration in glucose regulation in children as compared with adults may contribute to the greater risk for micro- and macrovascular complications in children with T2DM as they develop into adults.

Management

Management of T2DM in children involves lifestyle modifications. Pharmacologic glucose-lowering treatment is often necessary and includes metformin or insulin or a combination of both. Recently, a GPL1-RA (liraglutide) has been approved for the use in children aged 10 or older.

There is a need for additional effective, well tolerated and easily administered treatments to achieve and maintain target HbA1c levels as early as possible in children with T2DM.

3.1.2. About the product

Dapagliflozin is a highly potent, selective and reversible inhibitor of SGLT2, the major transporter responsible for renal glucose reabsorption. Its mechanism of action results in the direct and insulin-independent urinary excretion of glucose and osmotic diuresis.

3.1.3. The development programme/compliance with CHMP guidance/scientific advice

The clinical development programme supporting the use of dapagliflozin in paediatric patients with T2DM includes 2 completed studies:

Study D1690C00016 (MB102091): "A Randomized, Multi-center, Parallel Group, Single-dose, Pharmacokinetics and Pharmacodynamics Study of Dapagliflozin in Children and Adolescents Aged 10 to 17 Years with Type 2 Diabetes Mellitus"

Study D1690C00017 (MB102138): "A 24-Week, Multicentre, Randomised, Double-Blind, Parallel Group, Phase 3 Trial with a 28-Week Long-Term Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin 10 mg in T2DM Patients Aged 10 to 24 Years"

As stated by the applicant, the following guidelines were referred to in the design of the clinical programme:

- EMA Guideline on Clinical Investigation of Medicinal Products in the Treatment or Prevention of Diabetes Mellitus (CPMP/EWP/1080/00) (European Medicines Agency, London, UK, 2012).
- EMA "Concept paper on extrapolation of efficacy and safety in medicine development" (EMA/129698/2012)

The applicant sought scientific advice from the EMA CHMP on study design and utilizing a partial extrapolation model to overcome recruitment difficulties in the pivotal paediatric Phase 3 clinical study D1690C00017 (Procedure No: EMEA/H/SA/1012/1/FU/1/2014/PED/II, dated 23 October 2014).

The final study design was accepted by the EMA in Procedure No: EMA/PDCO/602571/2019: EMEA-000694-PIP01-09-M08. Overall, the EMA/CHMP considered that the size of the pivotal study, as justified by the partial extrapolation modelling, could well be sufficient to draw conclusions about benefit-risk in children aged 10 years and above, given the similar disease pathophysiology in the paediatric and adult T2DM populations and the well-known mechanism of action of dapagliflozin with its low risk of off-target effects.

3.1.4. General comments on compliance with GCP

According to the applicant, the study was conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

On 12 March 2021, the MAH was informed that an investigator at one site had been indicted for fraud while serving as an investigator for a different sponsor between September 2013 and May 2016. Two patients were enrolled into the study D1690C00017 placebo group at this site in July 2016. No irregularities have been detected at this site during the conduct of study D1690C00017. However, within the principles of GCP, the MAH has exercised caution and has performed sensitivity analyses in which data from this site were retrospectively excluded. An addendum to the CSR has been provided. An initial sensitivity analysis showed that the study conclusions are not affected by removing these data from the analysis.

3.2. Non-clinical aspects

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

3.2.1. Introduction

In view of the inclusion of patients aged 10-18 the results of the previously conducted reproductive and developmental toxicity studies, in particular the juvenile toxicity studies are of special interest. The previously submitted and assessed data from the EPAR is presented below.

3.2.2. Toxicology

Reproduction toxicity (Pre- and postnatal development and juvenile toxicity)

Prenatal and postnatal development, including maternal function

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

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

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

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

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

3.2.3. Ecotoxicity/environmental risk assessment

No new data for the environmental risk assessment were included with this application. The Applicant submitted a justification of the absence of an updated ERA. Previously, the predicted environmental concentration (PEC) in surface water was calculated using the default market penetration factor (0.01). The inclusion of patients aged 10-18 years for the indication previously approved will thus not change the PEC or the previously determined ratios or conclusions.

The PEC/PNEC ratio for microorganisms was <0.1. The PEC/PNEC ratios for groundwater and surface water were <1. These risk quotients indicate that dapagliflozin is unlikely to present a risk to microorganism or the aquatic and groundwater environments. The PEC/PNEC ratio for sediment was <1, indicating that dapagliflozin is unlikely to present a risk to sediment dwelling organisms.

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

3.2.4. Discussion on non-clinical aspects

The non-clinical aspects of dapagliflozin were thoroughly evaluated during the original approval procedure for Edistride/ Forxiga. No new non-clinical studies were submitted in support of the present application. This is however acceptable.

In view of the inclusion of patients aged 10-18 the results of the previously conducted reproductive and developmental toxicity studies, in particular the juvenile toxicity studies are of special interest.

The Applicant provided a statement that the existing nonclinical data for dapagliflozin supports the use in paediatric patients down to 10 years of age. No further discussion on how the results from the juvenile toxicity study relate to the indication in adolescents was provided. This is acceptable for the current application since children younger than 10 years old are not included.

3.2.5. Conclusion on the non-clinical aspects

There are no objections from a non-clinical point of view concerning the application to the extension of the indication to include patients aged 10 years and older.

The new/extended target population does not lead to a significant increase in environmental exposure further to the use of dapagliflozin.

3.3. Clinical aspects

3.3.1. Introduction

The current application is supported by data from two clinical studies:

- Study D1690C00016 (MB102091): "A Randomized, Multi-center, Parallel Group, Single-dose, Pharmacokinetics and Pharmacodynamics Study of Dapagliflozin in Children and Adolescents Aged 10 to 17 Years With Type 2 Diabetes Mellitus"
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GCP

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

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.

3.3.2. Pharmacokinetics

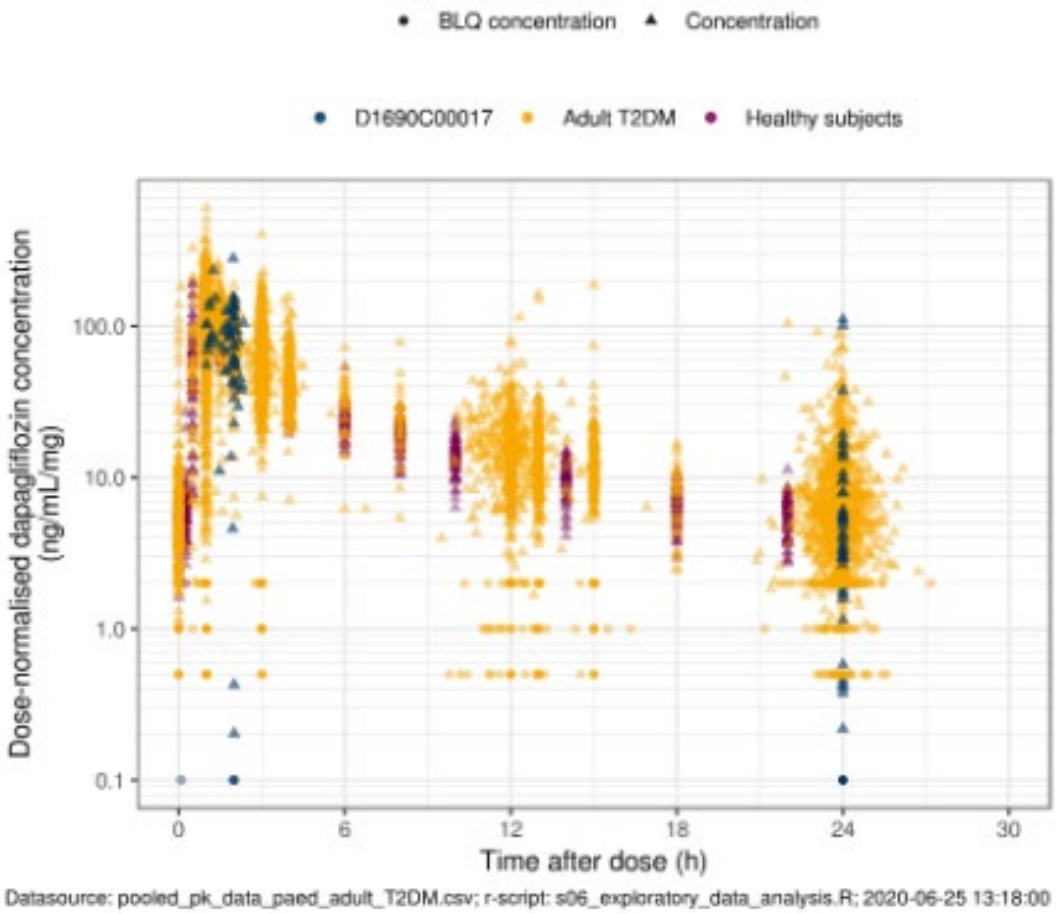
Two clinical studies were conducted that evaluated the PD and/or PK characteristics of dapagliflozin in T2DM paediatric populations. Study D1690C00016 (MB102091) was a Phase 1, single-dose, randomised, open-label study of 3 doses of dapagliflozin (2.5, 5, and 10 mg) in children and adolescents aged 10 to 17 years and with T2DM. The study included 24 randomised patients. In addition, sparse PK samples were collected from the Phase 3 study D1690C00017 (MB102138) in T2DM patients aged 10 to 24 years.

Study D1690C00016 (MB102091) showed that dapagliflozin was rapidly absorbed following oral administration, with maximum concentrations achieved within 1.5 hours after administration. Mean terminal elimination half-life ranged from 10 to 14 hours across the studied dose range (2.5, 5, and 10 mg). Systemic exposure to dapagliflozin appeared to be dose proportional following single oral doses of 2.5 to 10 mg.

Observed PK data comparison

No apparent differences between dapagliflozin plasma concentrations normalised to 10 mg were observed between D1690C00017, adult T2DM patients and healthy subjects (Figure 5).

Figure 5 Plasma dapagliflozin concentration normalised to 10 mg versus time after previous dose at steady state stratified by population (D1690D00017, adult patients with T2DM and healthy subjects). Circles: observations. Concentrations below LLOQ were set to LLOQ/2.



Population PK analysis

Objective

The analysis presented in this report does not include a full popPK model development due to the sparseness of the dapagliflozin concentrations in D1690C00017. Instead, the previously established popPK model for dapagliflozin in healthy subjects, adult and paediatric patients with T2DM (AstraZeneca 2015) was used to assess

1. whether this model could accurately describe the dapagliflozin concentrations at steady state in paediatric T2DM subjects
2. whether the exposure is similar in different patient populations, such as the T2GO study, paediatric and adult T2DM subjects.

Dataset

The popPK model was based on dapagliflozin plasma concentrations from one phase III trial D1690C00017 in subjects aged 10-24 years with T2DM, one phase I study in children and adolescents

aged 10 to 18 years with T2DM D1690C00016 (MB102091), and data from a previous T2DM submission. In total, 8347 dapagliflozin plasma concentrations from 1311 subjects were used in the analysis.

For D1690C00017, 20.6% of the PK samples were below the lower limit of quantification (BLQ) and were excluded (table below). All pre-dose samples (46, 32.6%) had missing dosing information. To assess these data, a dosing interval of 24 h was assumed and imputed.

Table 2 **Summary of data used in the population PK analysis of dapagliflozin in children and adults with type 2 diabetes mellitus (T2DM, N (%)).**

	Day 1 pre-dose conc.	Uncertain dosing info	High pre-dose conc.	Outlier	Below LLOQ	Dose time imputed	Reliable samples	Used in PK analysis
D1690C00017	0 (0)	1 (0.709)	1 (0.709)	0 (0)	29 (20.6)	46 (32.6)	64 (45.4)	110 (78)
MB102091	0 (0)	0 (0)	0 (0)	0 (0)	10 (4.24)	0 (0)	226 (95.8)	226 (95.8)
T2DM submission	412 (4.35)	2 (0.0211)	353 (3.73)	73 (0.771)	615 (6.5)	0 (0)	8011 (84.6)	8011 (84.6)
All subjects	412 (4.19)	3 (0.0305)	354 (3.6)	73 (0.742)	654 (6.64)	46 (0.467)	8301 (84.3)	8347 (84.8)

Datasource: pooled_pk_data_paed_adult_T2DM.csv; r-script: s06_exploratory_data_analysis.R; 2020-06-25 13:18:00

Abbreviations: N: Number; LLOQ: Lower limit of quantification; PK: pharmacokinetic. [a]24 of these samples were also BLQ.

Final model

The model was a two-compartment model with first-order elimination and first-order absorption. Addition of the D1690C00017 data in patients aged 10-24 had minor impact on the fixed-effects parameter estimates, which was expected due to the low number of observations in relation to the T2DM submission. The residual variability for D1690C00017 was estimated together with the D1690C00016 (MB102091), which increased the residual variability (variance) from 0.2471 to 0.356. CL/F was 23.4 L/h, which is very close to the previous estimate in paediatric T2DM patients, adult T2DM patients and healthy subjects (23 L/h). The PK parameter estimates are presented in Table 5.

Table 5 **Dapagliflozin PK model parameter estimates for final model based on D1690D00017, MB102091 and T2DM submission (Final Model – run2)**

OFV: -2383.954			
Condition number: 10			
Parameters	**Units**	**Population Mean**	**RSE (%)**
KA	(h-1)	2.96	13.5
CL/F	(L/h)	23.4	1.78
Vc/F	(L)	74.1	1.49
Vp/F	(L)	116	4.72
Q/F	(L/h)	8.87	2.98
eGFR~CL/F	(-)	0.515	9.6
SEX~CL/F	(-)	-0.182	13.2
BWT~Vc/F	(-)	0.593	11.4
EPI	(-)	0.728	3.76
Between Subject variability			
KA	(-)	8.42	7.79
CL/F	(-)	0.13	4.32
Vp/F	(-)	0.144	23.8
Residual variability			
Add Error (adults)	(-)	0.197	0.883
Prop Error (adults)	(-)	0.0978	12.6
Prop Error (pediatrics)	(-)	0.356	4.37

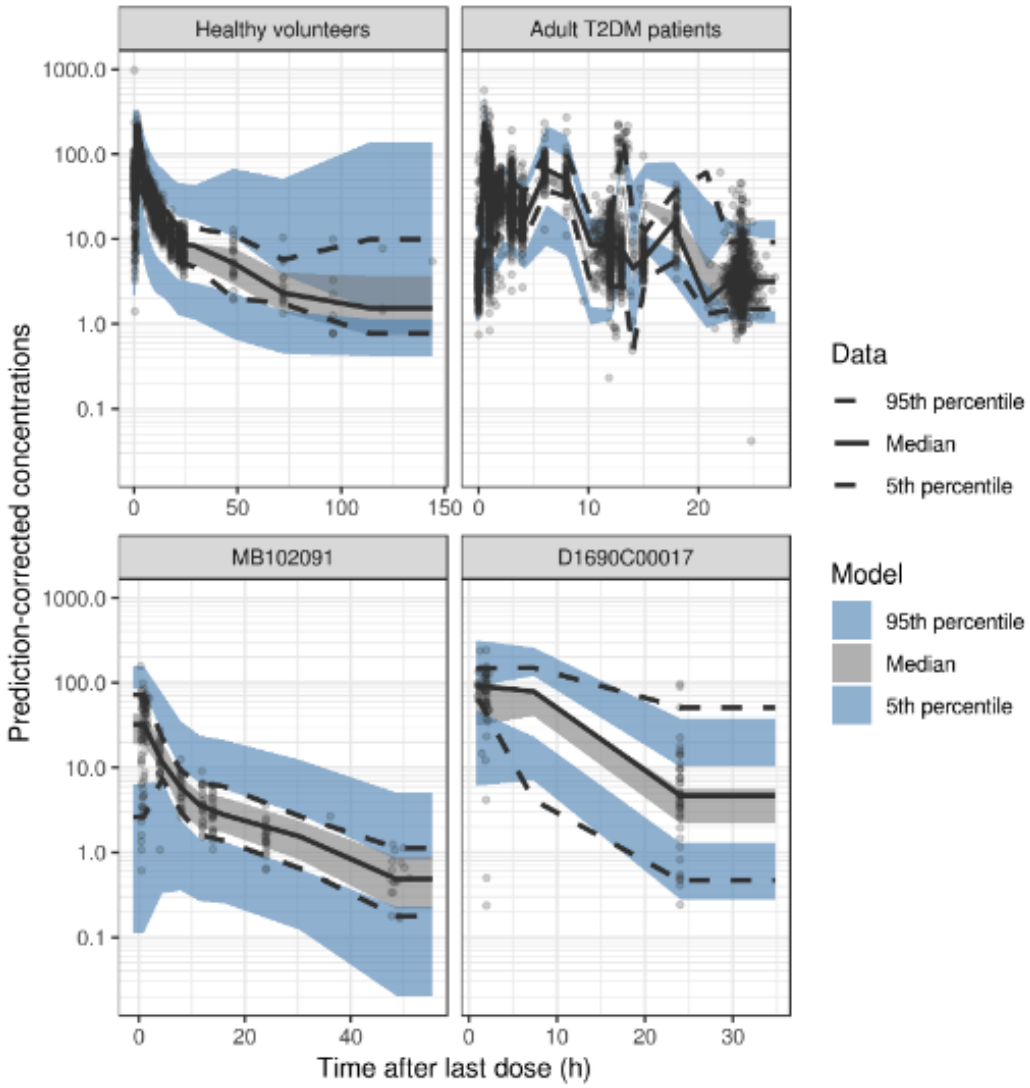
Data source: run 2, r-script: s07_PK_modelling.R, 2020-06-25 13:19:03

Abbreviations: OFV: Objective Function Value, KA: first-order absorption rate constant, CL/F: apparent clearance, Vc/F: apparent central volume of distribution, Q/F: apparent intercompartmental clearance, Vp/F: apparent peripheral volume of distribution, BWT : body weight, eGFR : estimated glomerular filtration rate , RSE: relative standard error.

VPC

The prediction-corrected visual predictive checks stratified on study are shown in Figure 6, indicated that the model could adequately describe the data. Although the median of the observed data is in the upper range, potentially due to the relatively large fraction of BLQ concentrations in the study.

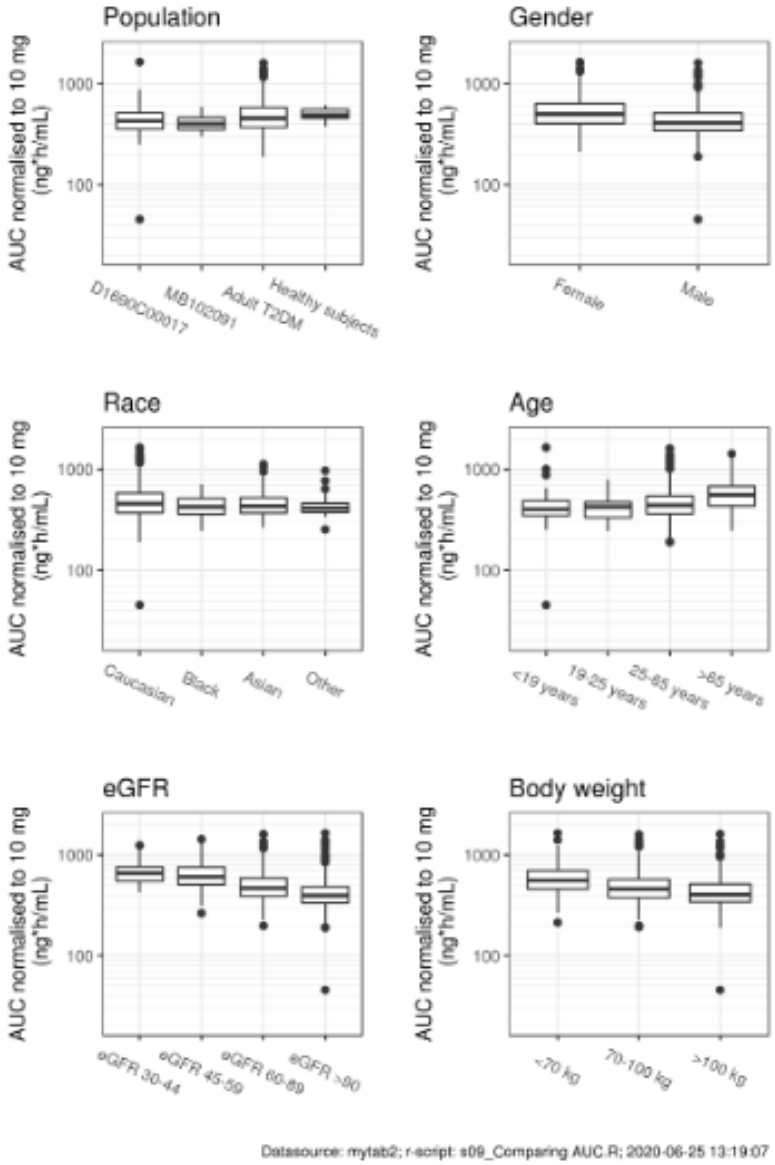
Figure 6 **Prediction-corrected visual predictive check of time after last dose of the final dapagliflozin PK model based on D1690C00017, MB102091, adult T2DM submission, stratified by population**



Model predicted exposure

Model-predicted AUC normalised to 10 mg for dapagliflozin stratified on population, sex, race, age-group, renal function, and body weight is presented in Figure 7

Figure 7 **Dapagliflozin AUC normalised to 10 mg stratified on different covariates.**



AUC: area under dapagliflozin concentration-time profile, eGFR: estimated glomerular filtration rate

WSA conclusion popPK analysis

Model-predicted AUC normalised to 10 mg was similar between studies D1690C00017 (MB102138), D1690C00016 (MB102091) and adult T2DM patients. Small and not clinically meaningful differences may have been due to slightly higher eGFR in paediatric patients.

3.3.3. Pharmacodynamics

Following administration of a single oral dose of 2.5 to 10 mg of dapagliflozin to paediatric patients with T2DM, the 24-hour UGE increased in a dose-related manner. The FPG concentration was lower for dapagliflozin panels 2.5, 5, and 10 mg on Day 2 versus pre-dose on Day 1. The population-based exposure-response analysis was performed to compare the paediatric and adult T2DM populations.

Integrated data from 3 clinical studies: 1 paediatric study in T2DM patients (MB102091) and 2 studies performed in adults with T2DM (MB102003 and MB102025) was used. Data from a total of 83 patients were analysed (20 paediatrics and 63 adults), which had AUC_{24} and 24h-UGE data available and were collected following single dose of dapagliflozin. A sigmoidal E_{max} model accurately described the relationship between dapagliflozin exposure (AUC_{24}) and response (24-hour UGE) after a single dose in adult and paediatric patients with T2DM. Baseline eGFR, FPG and gender were identified as covariates that have a significant impact on dapagliflozin E_{max} in both patient populations. Patients with a higher baseline eGFR and FPG are expected to have a greater UGE effect, and females are expected to have a lower UGE effect, compared with male patients. The effect of sex on dapagliflozin efficacy was previously observed when FPG was used as a PD endpoint. However, it was not considered to be clinically meaningful, and no dose adjustment was recommended. Paediatric and adult T2DM patients had similar exposure-response relationship following single doses of dapagliflozin after accounting for differences in covariates.

3.3.4. Discussion on clinical pharmacology

Efficacy and safety were studied in the paediatric phase 3 trial here (see clinical sections below), and the D1690C00017 study was not designed as an extrapolation of efficacy and safety from adults to paediatric population based on PK.
However, there are questions regarding efficacy in the D1690C00017 study. With PK/PD relationship considered similar between adults and paediatric patients a similar PK profile and exposure for paediatric patients 10-17 years compared to adults would provide reassurance on the adequacy of efficacy and the chosen dose in 10-17 years-old patients.

The applicant concludes that PK of dapagliflozin was not meaningfully different between the paediatric and adult patients and that small and not clinically meaningful differences may have been due to slightly higher eGFR in paediatric patients. The applicant supported their conclusion with a popPK analysis.

The observed data plot supports that exposure profile is similar with data overlapping. The popPK does not describe variability in healthy subject adequately. Some slight model misspecification can also be seen for both adult patients and the paediatric patients from the D1690C00017 study, but the model is generally able to predict the median. The D1690C00017 study included paediatric patients and young adults. Stratified pcVPCs on age (i.e., 10-13, 14-17 and 18-25 years for the D1690C00017) study were provided in the 2nd round and are deemed satisfactory. Overall, the popPK analysis support a PK bridge (extrapolation of efficacy from adults to paediatric patients).

In the box plots derived from the popPK model, exposures are largely overlapping. Low body weight patients have slightly higher exposure. Lower age patients have slightly lower exposure, potentially due to higher eGFR. The current popPK analysis provides support that the 10 mg dose is adequate in 10–17 years old patients.

The exposure-response analysis did not include the phase 3 trial data. Paediatric and adult T2DM patients had similar exposure-response relationship following single doses of dapagliflozin after accounting for differences in covariates. This would support a PK bridge strategy extrapolating efficacy from adults to paediatric patients.

3.3.5. Conclusions on clinical pharmacology

The applicant concludes that exposure of dapagliflozin was not meaningfully different between the paediatric and adult patients and this is agreed with. Similar exposure for paediatric patients 10-17 years compared to adults allows for extrapolation of efficacy from adult to paediatric patients.

3.4. Clinical efficacy

3.4.1. Main study - D1690C00017 (MB102138)

Title of Study

A 24-Week, Multicentre, Randomised, Double-Blind, Parallel Group, Phase 3 Trial with a 28-Week Long-Term Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin 10 mg in T2DM Patients Aged 10 to 24 Years

Methods

This was a prospective, multicentre, 24-week, placebo-controlled, double-blind, randomised study (ST period) with a 28-week open-label active treatment extension (LT period), which included patients ≥10 years and < 25 years of age, with confirmed diagnosis of T2DM, who were being treated with diet and exercise and a stable dose of metformin IR or XR, or a stable dose of insulin for a minimum, or a stable combination of metformin and insulin.

Consented patients meeting screening criteria entered a 4-week placebo lead-in period. Patients were instructed to follow a diet and exercise programme (in accordance with the ADA or similar national guidelines) for the duration of the study. Patients were to maintain their baseline types of diabetic therapy throughout the study. The study design is shown in Figure 1.

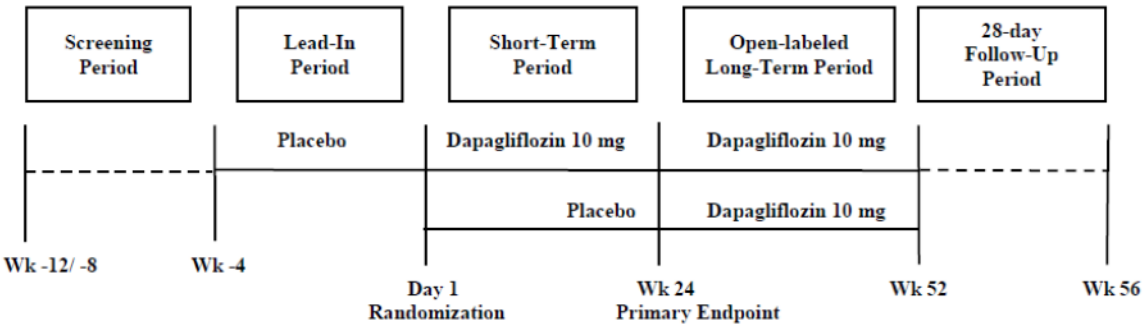
Recruitment (randomisation) of patients ≥ 18 and < 25 years old was limited to be less than 40% of patients. Recruitment (randomisation) of patients ≥ 10 and ≤ 15 years old was to include at least 20% of patients.

After the lead-in period, at least 66 patients with HbA1c ≥ 6.5% and ≤ 11% at screening who met all the inclusion criteria and none of the exclusion criteria were planned to be randomised 1:1 to receive oral dapagliflozin 10 mg or placebo in a double-blind manner. After completion of the 24-week double-blind ST treatment period, patients were eligible to enter a 28-week open-label LT safety extension period for safety monitoring. All patients received open-label dapagliflozin 10 mg for the duration of the LT period. This was followed by a 4-week post-treatment safety follow-up period, during which patients did not receive study drug, and ended at the completion of a phone visit performed to assess AEs and medications.

Patients who permanently discontinued study drug before the end of the study treatment period entered a non-treatment, follow-up phase, in which patients followed their visit schedules with modified assessments until study completion. Discontinued patients were not replaced.

Glycaemic rescue was permitted in the study. Rescued patients were to continue treatment on study drug.

Figure 1: Flow Chart of Study Design



Study participants

Patients were ≥ 10 years and < 25 years-of-age, with confirmed diagnosis of T2DM, and were being treated with diet and exercise and a stable dose of metformin (at least 1000 mg daily) for a minimum of 8 weeks prior to screening, or a stable dose of insulin for a minimum of 8 weeks prior to screening, or a stable combination of metformin and insulin for a minimum of 8 weeks prior to screening.

Recruitment (randomisation) of patients aged ≥ 18 and < 25 years was limited to be less than 40% of patients. Recruitment (randomisation) of patients ≥ 10 and ≤ 15 years old was to include at least 20% of patients.

Relevant inclusion criteria

1. Previously diagnosed with T2DM by WHO/ADA diagnostic criteria
2. HbA1c ≥ 6.5% and ≤ 11% obtained at screening visit
3. Currently on diet and exercise and a stable dose of metformin (at least 1000 mg daily) for a minimum of 8 weeks, or stable dose of insulin for a minimum of 8 weeks, or a stable combination of metformin (at least 1000 mg daily) and insulin for a minimum of 8 weeks prior to screening
4. FPG ≤ 255 mg/dL (≤ 14.2 mmol/L) obtained at screening visit
5. Patient re-enrolment: This study permitted the re-enrolment of a patient who had discontinued the study as a pre-treatment failure (i.e. patient had not been randomised/had not been treated).

Relevant exclusion criteria

Target disease exceptions

1. Previous diagnosis of type 1 diabetes
2. Previous diagnosis of monogenic aetiology of T2DM such MODY, genetic disorders with strong associations with insulin resistance/diabetes and/or obesity such as Turner's Syndrome and Prader-Willi, or secondary diabetes (steroid use, Cushing's disease, acromegaly)
3. DKA within 6 months of screening
4. Current use of the following medications for the treatment of diabetes, or use within the specified timeframe prior to screening for the main study:

a. Eight weeks: sulfonylureas, alpha glucosidase inhibitors, metiglinide, oral or injectable incretins or incretin mimetics or other diabetic medications not otherwise specified

b. Sixteen weeks: thiazolidinediones

c. Any previous history or current use of an SGLT2 inhibitor, including dapagliflozin

5. Initiation or discontinuation of prescription or non-prescription weight loss drugs within 8 weeks of screening. Use of prescription or non-prescription weight loss drugs had to be stable during the study.

Medical history and concurrent diseases

6. History of unstable or rapidly progressive renal disease
7. History of unresolved vesico-ureteral reflux

Treatments

Study drug was either dapagliflozin or matching placebo:

Dapagliflozin: Film-coated tablets containing placebo matching dapagliflozin 10 mg.

Placebo: Film-coated tablets containing placebo matching dapagliflozin 10 mg.

Background medication

Patients were expected to be on background medication of metformin (IR or XR) and/or insulin.

Rescue medication

During the course of the trial, patients may have required the addition of open-label rescue medication to their blinded treatment regimen in order to treat ongoing hyperglycaemia. Insulin was initiated or up-titrated for glycaemic rescue. Rescue medication was not provided by the Sponsor in this study.

Prespecified rescue criteria (Table 1) were established during the treatment period, starting at Day 1, and up to the Week 52 visit, to determine eligibility for open-label rescue medication. For patients on baseline insulin, persistently increased doses of insulin 20% or more above baseline dose, despite advice and counsel to keep the insulin dose stable, could be considered another potential manifestation of poor glycaemic control, and were to be evaluated for rescue. Any permanent changes in dose of basal insulin were to be made after evaluation of rescue criteria, including both SMBG and central laboratory FPG values.

Table 1: Lack of Glycaemic Control Criteria for Initiation of Rescue Medication

Study week	Rescue criterion
From Day 1 visit up to and including Week 24 visit	FPG > 13.3 mmol/L (240 mg/dL) based on SMBG for 3 consecutive days followed by a confirmatory central laboratory FPG or Single central laboratory FPG followed by a confirmatory central laboratory FPG
Following Week 24 visit up to and not including Week 52 visit	FPG > 10 mmol/L (180 mg/dL) based on SMBG for 3 consecutive days followed by a confirmatory central laboratory FPG or Single central laboratory FPG followed by a central laboratory FPG or HbA1c > 8.0%

Objectives

The primary and secondary efficacy objectives and their associated endpoints for the initial double-blind, 24-week treatment period are summarised in Table 2.

The primary objective was to compare the mean change from baseline in HbA1c achieved with dapagliflozin against the mean achieved with placebo after 24 weeks of double-blind add-on treatment in patients aged 10 to less than 25 years with T2DM who have inadequate glycaemic control on diet and exercise with metformin or insulin ± metformin.

Outcomes/endpoints

The primary and secondary efficacy objectives were assessed at Week 24, but also exploratively at Week 52, to assess the long-term trend of glycaemic control with dapagliflozin.

Table 2: Efficacy Objectives and Endpoints

Objective	Endpoint / variable
Primary objective: • To compare the mean change from baseline in HbA1c achieved with dapagliflozin against the mean achieved with placebo after 24 weeks of double-blind add-on treatment in patients aged 10 to less than 25 years with T2DM who have inadequate glycaemic control on diet and exercise with metformin or insulin ± metformin	• Change from baseline in HbA1c at Week 24
Secondary objectives: • To compare the mean change from baseline in FPG achieved with dapagliflozin against the mean achieved with placebo after 24 weeks of double-blind add-on treatment in patients aged 10 to less than 25 years with T2DM who have inadequate glycaemic control on diet and exercise with metformin or insulin ± metformin • To compare the percentage of patients who require glycaemic rescue or discontinuation due to lack of glycaemic control with dapagliflozin against the percentage with placebo over the 24-weeks of double-blind add-on treatment in patients aged 10 to less than 25 years with T2DM who have inadequate glycaemic control on diet and exercise with metformin, or insulin ± metformin • To compare the percentage of patients with baseline HbA1c > 7% who achieve a HbA1c level < 7% with dapagliflozin against the percentage achieved with placebo after 24 weeks of double-blind add-on treatment in patients aged 10 to less than 25 years with T2DM who have inadequate glycaemic control on diet and exercise with metformin, or insulin ± metformin	• The change from baseline in FPG at Week 24 • The percentage of patients who required glycaemic rescue medication or who permanently discontinued treatment due to lack of glycaemic control over the 24-week double-blind treatment period • The percentage of patients with baseline HbA1c ≥ 7% who achieved HbA1c level < 7% at Week 24

Sample size

Given the anticipated challenges to recruitment with this population, a partial extrapolation from adult data was used to better inform the sample size determination. Simulation was used to estimate the difference versus placebo for the Week 24 change from baseline in HbA1c, and was -0.78% for dapagliflozin. Based on an estimated treatment difference of 0.78% and assuming a SD of 0.9% for change from baseline in HbA1c at Week 24, a sample size of 25 per treatment group would provide 85% statistical power to demonstrate the superiority of dapagliflozin to placebo (where superiority was defined as a difference in placebo-corrected mean HbA1c at 24 weeks indicating improvement that is statistically significant) at a 2-sided alpha level of 5%. To ensure that at least 50 patients would have Week 24 assessments while on treatment, at least 66 patients (33 patients per treatment group) were planned to be randomised (Protocol Amendment 3).

Randomisation

Subjects were randomly assigned to 1 of 2 blinded treatment groups by the IWRS in a 1:1 ratio. Randomisation was stratified by gender, age (< 18 vs. ≥ 18 years and ≤ 15 years vs. > 15 to < 18 years) and baseline medication (metformin alone vs. insulin ± metformin).

Blinding

Methods used to ensure blinding included

- Investigational product was labelled using a unique material kit ID, which is linked to the randomization code.
- The IWRS assigned the bottle of study material to be dispensed to each patient.
- The study had a double-blind design, wherein each patient received either the active drug or matching placebo, being both active drug and placebo tablets identical and presented in identical packaging to ensure blinding of the medication.

Statistical methods

A database lock of the 24-week data occurred on 02 April 2020 and the data were unblinded. A review of the results revealed that some relevant protocol deviations related to treatment compliance had not been correctly captured. Therefore, the 24-week ST database was unlocked on 08 May 2020 to correct the protocol deviations and subsequently re-locked on 11 May 2020. The updates were made only on the system that holds the protocol deviations, whereas the Week 24 data in the clinical data management system were not unlocked for this update. The final database lock was on 18 May 2020.

A comprehensive SAP was prepared prior to first patient randomised and any subsequent amendments were documented, with final amendments completed prior to the 24-week database lock.

Analysis sets

The Full analysis subjects data set (FAS) consisted of all patients who were randomised and assigned to a treatment group through the IXRS. This data set was used for efficacy analysis. Whenever using the FAS, patients are presented in the treatment group to which they were randomised.

The Per protocol (PP) subjects data set was a subset of the FAS, with all data points collected after relevant protocol deviations were excluded from the data set. This data set was used for sensitivity

analyses of the primary efficacy endpoint when > 10% of patients in either treatment group had relevant protocol deviations that led to complete exclusion from efficacy analyses. Whenever using the PP subjects data set, the patients are presented using the randomised treatment group.

Efficacy analysis methods

The main research hypothesis was: dapagliflozin results in a greater mean reduction from baseline in HbA1c compared with placebo after 24 weeks of double-blind add-on treatment in patients aged ≥ 10 to < 25 years with T2DM who had inadequate glycaemic control on diet and exercise with metformin or insulin ± metformin.

The primary analysis of the primary variable was based on a MMRM, as described in the SAP, including all scheduled time points following randomisation up to and including Week 24. This model included patients in the FAS (see Section 9.8.2.3) who had a baseline measurement and at least one post-baseline measurement. The primary analysis only included measurements prior to the administration of rescue medication or permanent discontinuation from study drug. Point estimates and 95% CIs for the least square mean change in HbA1c for each treatment group, as well as the difference in the estimated mean change between the dapagliflozin treatment group and placebo, were calculated. The p-value of the difference in Week 24 estimates between dapagliflozin and placebo was presented.

Sensitivity analyses

To assess the robustness of the primary efficacy analysis for the change in HbA1c from baseline to Week 24, additional sensitivity analyses were carried out using the following approaches:

- A longitudinal repeated measures analysis, similar to the primary analysis, but using all available data, ie, regardless of rescue therapy initiation or discontinuation from the study drug.
- If at least 10 percent of patients in either treatment group had relevant protocol deviations leading to complete data exclusion from the ST period, then a longitudinal repeated measures analysis similar to the primary analysis were to be performed using the Per Protocol Subjects Data Set.
- Multiple imputation based on "copy to reference" method were to be performed. This method included all subjects from the FAS.
- Tipping point analysis including all subjects from the FAS. All the observations were to be included regardless of rescue therapy initiation or permanent discontinuation from study drug.
- ANCOVA analysis including all subjects from the FAS who have a baseline assessment. Week 24 observations were to be imputed using LOCF or BOCF methodology as appropriate.

Post hoc analyses were performed which repeated the primary efficacy analysis after excluding a single change from baseline value from HbA1c analyses that corresponded to the Week 16 assessment from one patient.

Type I error control

The family-wise Type I error level related to the primary and secondary efficacy endpoints was controlled at the 2-sided 0.05 level by using a hierarchical closed testing procedure.

For comparison of dapagliflozin versus placebo, if the primary variable was significant, the statistical tests for the secondary efficacy endpoints were to be performed in the following order; the change from

baseline in FPG at Week 24; the percentage of patients who required glycaemic rescue medication or who permanently discontinued treatment due to lack of glycaemic control over 24 weeks of double-blind treatment period; the percentage of patients with baseline HbA1c ≥ 7% who achieved HbA1c level < 7% at Week 24.

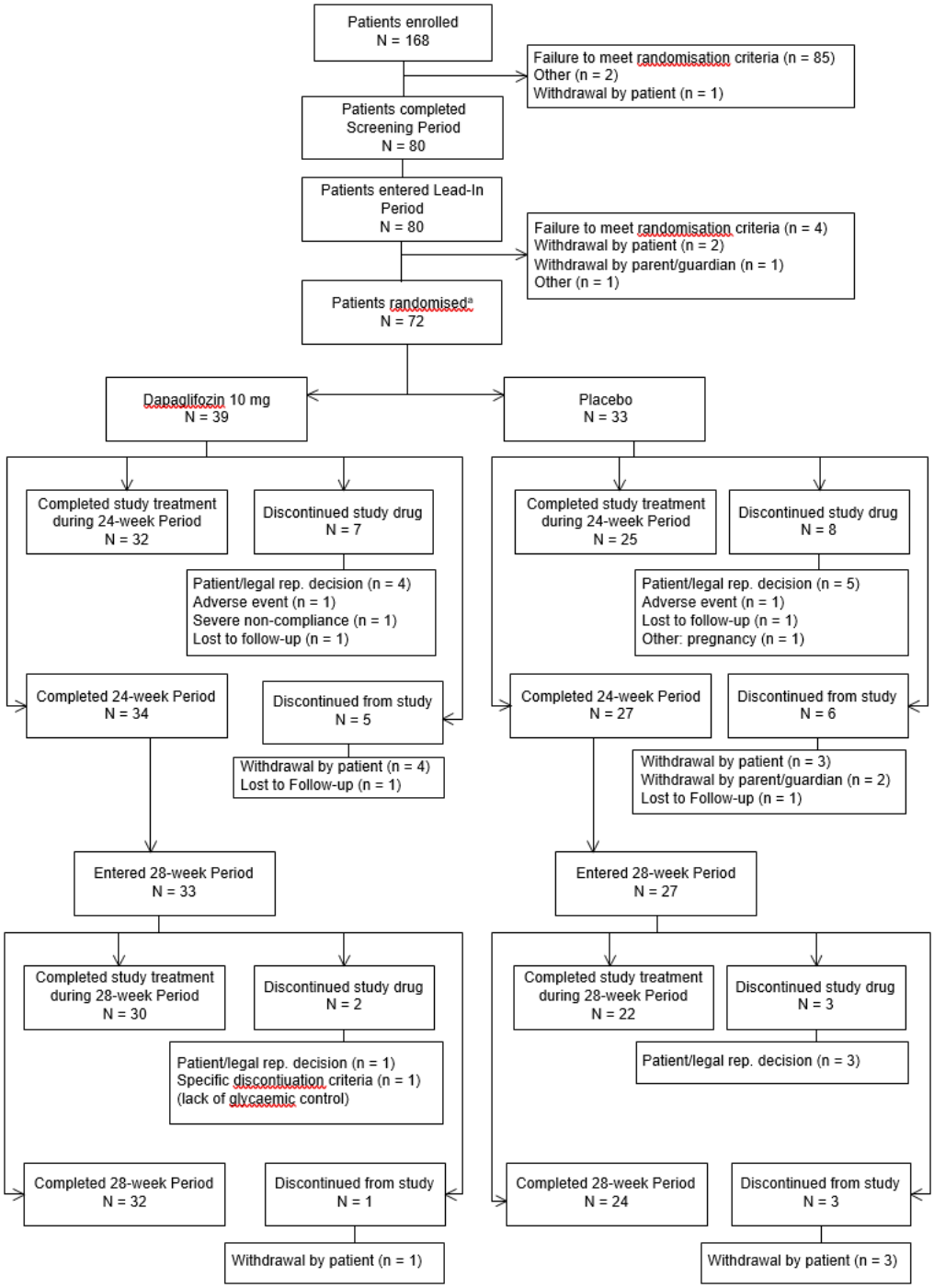
For exploratory endpoints no multiplicity procedure was used, and no claims were to be made. Although all patients received open-label dapagliflozin during the LT period, results are presented by randomised treatment assigned.

Results

Participant flow

The disposition of the patients in this study is summarised in Figure 2.

Figure 2: Patient Disposition (Full Analysis Subjects Set)



[a] Randomised patients were those assigned treatment by Interactive Web/Voice Response System (IXRS).
Derived from: Table 14.1.1.1, Table 14.1.1.2, and Table 14.1.1.3

All randomised patients received study drug, and 82.1% (32/39) and 75.8% (25/33) patients in the dapagliflozin and placebo groups, respectively, remained on study drug throughout the ST period. It is noted that 1 patient in the dapagliflozin group and 2 patients in the placebo group discontinued study drug during the ST period, but entered the LT period.

There were no imbalances between treatments with regards to permanent discontinuations from study drug or withdrawal from study that were considered to have a potential influence on the results or their interpretation.

Recruitment

The study was conducted from 22 June 2016 (first patient enrolled) to 06 Apr 2020 (last patient last visit) in Hungary, Israel, Mexico, Romania, Russia, United Kingdom and US. A total of 168 patients (with 13 re-screened patients) were enrolled and 72 were randomised: 39 patients in the dapagliflozin group and 33 patients in the placebo group.

By region, 32 (44.4%) patients were randomised in North America (US), 24 (33.3%) patients in Europe (including Israel with 13 patients, 9 in Russia, and 2 in Hungary), and 16 (22.2%) patients in Latin America (Mexico).

Conduct of the study

Protocol amendments

Three important amendments were made to the original study protocol.

Amendment made before the start of patient recruitment:

1. Protocol Amendment 01 (15 January 2016) was made to incorporate new safety information related to DKA.

Amendments made after the start of patient recruitment:

2. With Protocol Amendment 02 (13 February 2017), the protocol was amended to reflect the end of Bristol-Myers Squibb's role in the study as of 31 December 2016. The duration of the screening period was extended, and details relating to the masking of spot urine glucose, the study weeks relating to lack of glycaemic control criteria for initiation of rescue medication, and the use of third-party vendors for lost to follow-up patients were clarified.
3. With Protocol Amendment 03 (20 September 2017), the number of patients randomised in the study was increased to ensure that at least 50 patients would complete the 24-week double-blind ST period on study drug and the Week 24 assessment.

Changes to the planned analyses

Changes to the planned analyses are shown in Table 3. This table indicates when any changes were made in relation to the unblinding of study data.

Table 3: Changes to the planned analyses

Key details of change (Section of this report affected)	Reason for change	Person(s)/ group(s) responsible for change
Changes made before unblinding of study data		
Odds ratios were presented instead of differences in proportions between dapagliflozin and placebo (as specified in the protocol) for comparison of the percentage of patients with baseline HbA1c ≥ 7% who achieved a HbA1c level < 7.0% requiring rescue medication or discontinuing study drug due to lack of glycaemic control (Section 11.1)	Logistic regression reports odds ratios, not differences in proportions	AstraZeneca

Naming and definition of some of the analysis sets, ie, the CSP-defined randomised subjects data set is named and defined as the FAS in the SAP, and the CSP-defined evaluable subjects data set is named and defined as the PP subjects data set in the SAP. In addition, the lead-in subjects data set was not defined in the CSP, but it is in the SAP (Section 9.8.2)	Primary and secondary endpoints, as well as sensitivity analyses on primary variable and FPG, using an ITT estimand are analysed using the FAS	AstraZeneca
Changes made after unblinding of study data		
Post hoc analyses were performed which repeated the primary efficacy analysis after excluding a single change from baseline value from HbA1c analyses that corresponded to the Week 16 assessment from one patient (Sections 10.3 and 11.1.1.2): • Primary analysis - Change from baseline in HbA1c (%) at Week 24 excluding values after rescue medication initiation or discontinuation from study drug (FAS) • Change from baseline in HbA1c (%) at Week 24 - ANCOVA LOCF/BOCF excluding values after rescue medication initiation or discontinuation from study drug (FAS) • Change from baseline in HbA1c (%) during the 24-week double-blind ST period - Multiple imputation wash-out method at Week 24 including all values regardless of rescue medication initiation or discontinuation from study drug (FAS) • Change from baseline in HbA1c (%) at Week 24 - Tipping-point analysis regardless of rescue medication initiation or discontinuation from study drug (FAS)	A patient was found to have a severe deviation from the protocol at the Week 16 assessment. Post hoc analyses were performed excluding the Week 16 assessment data. See further details in Section 10.2.	AstraZeneca

Protocol deviations

Of the 72 patients who received randomised treatment, 16.7% (12/72) of patients had at least one relevant deviation during the ST period, which led to complete data exclusion from the analyses based on the PP subjects set: 12.8% (5/39) of patients in the dapagliflozin group and 21.2% (7/33) of patients in the placebo group. The most common reason for complete exclusion was low treatment compliance (< 80%): 12.8% (5/39) of patients in the dapagliflozin group and 18.2% (6/33) patients in the placebo group. In the placebo group, 1/33 patients (3.0%) had a relevant deviation leading to complete exclusion for not satisfying the target population baseline anti-hyperglycaemic therapy requirement.

During the 56-week study, important protocol deviations were reported in 95.8% (69/72) of patients: 94.9% (37/39) of patients in the dapagliflozin/dapagliflozin group and 97.0% (32/33) in the placebo/dapagliflozin group. The most common protocol deviation categories were again safety assessment (91.7% [66/72]) followed by study drug (38.9% [28/72]) and informed consent (37.5% [27/72])

Upon review of the data after unblinding of the 24-week data, one patient in the dapagliflozin group was found with a severe protocol deviation and should have been assigned to discontinuation from study drug, which would have resulted in an omission of a single change from baseline value from the primary analysis. The primary efficacy analysis was repeated post hoc with the exclusion of the single post-baseline (Week 16) HbA1c value for this patient. According to the narrative, the patient had been off study drug for at least 6 weeks, although treatment compliance is unknown because the patient did not return the tablet bottles. A pre-dose PK sample at week 16 showed a non-detectable level of dapagliflozin, confirming that the patient was off study drug at the visit.

Treatment compliance

Overall mean (SD) compliance during the ST period was 94.03% (17.34) and median compliance was 98.85%, ranging from 4.2% to 140.0%. The majority of the patients (83.3% [60/72]) had compliance between 80% and 120%, and this percentage was higher for dapagliflozin (87.2% [34/39] of patients) than for placebo (78.8% [26/33] of patients).

Relevant protocol deviations of low treatment compliance (< 80%) that resulted in complete exclusion from the PP efficacy analysis were reported in 15.3% (11/72) of patients (see above).

Overall mean (SD) compliance during the ST + LT periods was 91.89% (17.25) and median compliance was 97.35%, ranging from 4.2% to 140.0%. The majority of the patients (77.8% [56/72]) had compliance between 80% and 120%, and this was higher among patients who received dapagliflozin/dapagliflozin during the ST + LT periods (82.1% [32/39] of patients) than among those who received placebo/dapagliflozin (72.7% [24/33] of patients).

Baseline data

Demographic characteristics

The demographic characteristics of study patients are summarised in Table 4. Overall mean age was 16.1 years (ranging from 11 to 24 years), with the majority (73.6%) of patients being 10 to 17 years of age. There were more female (59.7%) than male patients (40.3%).

Overall, there were more patients from the non-Europe regions (44.4% from North America and 22.2% from Latin America) than from the Europe region (33.3%), and the proportion of patients from the Europe region was higher in the dapagliflozin group (41.0%) than in the placebo group (24.2%).

Table 4: Demographic Characteristics (Full Analysis Subjects Set)

Demographic characteristic		Dapagliflozin 10 mg (N=39)	Placebo (N=33)	Total (N=72)
Age (years)	n	39	33	72
	Mean	16.1	16.2	16.1
	SD	3.3	3.6	3.4
	Median	16.0	16.0	16.0
	Min	11	11	11
	Max	23	24	24
Age group (years) n (%)	≥ 10 and ≤ 15	16 (41.0)	14 (42.4)	30 (41.7)
	> 15 and < 18	13 (33.3)	10 (30.3)	23 (31.9)

Demographic characteristic		Dapagliflozin 10 mg (N=39)	Placebo (N=33)	Total (N=72)
	≥ 18 and < 25	10 (25.6)	9 (27.3)	19 (26.4)
	Total	39 (100)	33 (100)	72 (100)
Sex n (%)	Male	15 (38.5)	14 (42.4)	29 (40.3)
	Female	24 (61.5)	19 (57.6)	43 (59.7)
	Total	39 (100)	33 (100)	72 (100)
Race n (%)	White	28 (71.8)	16 (48.5)	44 (61.1)
	Black or African American	8 (20.5)	10 (30.3)	18 (25.0)
	Asian	0	1 (3.0)	1 (1.4)
	Native Hawaiian or other Pacific Islander	1 (2.6)	0	1 (1.4)
	American Indian or Alaska Native	2 (5.1)	3 (9.1)	5 (6.9)
	Other	0	3 (9.1)	3 (4.2)
	Total	39 (100)	33 (100)	72 (100)
Ethnic group n (%)	Hispanic or Latino	12 (30.8)	12 (36.4)	24 (33.3)
	Not Hispanic or Latino	26 (66.7)	21 (63.6)	47 (65.3)
	Total	38 (97.4)	33 (100)	71 (98.6)

Patient characteristics

The baseline patient characteristics are summarised in Table 5. Mean measured baseline BMI was 32.38 kg/m^2, and most patients (62.5%) had a baseline BMI ≥ 30 kg/m^2. Mean standardised baseline BMI (z-score) was 1.756, with the majority of patients (62.5%) assessed as obese according to the 2000 CDC growth charts.

Clinical data for the 9 patients with low BMI (< 25 mg/kg^2) were reviewed by the Medical Monitors for confirmation of correct diagnosis of T2DM.

Table 5: Patient Characteristics (Full Analysis Subjects Set)

Patient characteristic		Dapagliflozin 10 mg (N=39)	Placebo (N=33)	Total (N=72)
Baseline height (cm)	n	39	33	72
	Mean	167.94	164.16	166.21
	SD	9.78	11.28	10.59
	Min	137.0	141.0	137.0
	1st quartile	160.00	157.00	159.20
	Median	169.00	166.00	167.25

Patient characteristic		Dapagliflozin 10 mg (N=39)	Placebo (N=33)	Total (N=72)
	3rd quartile	174.50	173.00	174.00
	Max	185.4	182.0	185.4
Standardised baseline height (z-score) [a]	n	39	33	72
	Mean	0.456	-0.082	0.209
	SD	0.984	1.072	1.053
	Min	-1.60	-2.74	-2.74
	1st quartile	-0.460	-0.770	-0.630
	Median	0.760	0.060	0.425
	3rd quartile	1.170	0.630	0.970
	Max	2.02	2.10	2.10
Baseline weight (kg)	n	39	33	72
	Mean	89.23	92.47	90.71
	SD	25.69	31.87	28.52
	Min	41.6	31.2	31.2
	1st quartile	73.90	67.40	71.55
	Median	84.40	91.70	88.35
	3rd quartile	101.90	108.50	102.20
	Max	148.6	165.2	165.2
Standardised baseline weight (z-score) [a]	n	39	33	72
	Mean	1.824	1.801	1.813
	SD	0.964	1.208	1.075
	Min	-0.87	-2.31	-2.31
	1st quartile	1.170	1.490	1.365
	Median	1.890	1.950	1.930
	3rd quartile	2.500	2.260	2.475
	Max	3.42	3.56	3.56
Baseline BMI (kg/m^2)	n	39	33	72
	Mean	31.38	33.55	32.38
	SD	7.51	8.81	8.14
	Min	17.2	14.2	14.2
	1st quartile	26.10	29.20	26.75
	Median	30.50	32.20	31.50
	3rd quartile	36.10	37.20	36.25

Patient characteristic		Dapagliflozin 10 mg (N=39)	Placebo (N=33)	Total (N=72)
	Max	50.6	50.0	50.6
Standardised baseline BMI (z-score) [a]	n	39	33	72
	Mean	1.685	1.841	1.756
	SD	0.905	1.078	0.984
	Min	-1.92	-2.70	-2.70
	1st quartile	1.310	1.590	1.410
	Median	1.940	2.020	1.960
	3rd quartile	2.370	2.540	2.380
	Max	2.77	3.17	3.17
Baseline BMI group (kg/m^2) n (%)	< 25 kg/m^2	6 (15.4)	3 (9.1)	9 (12.5)
	≥ 25 kg/m^2	33 (84.6)	30 (90.9)	63 (87.5)
	≥ 27 kg/m^2	26 (66.7)	27 (81.8)	53 (73.6)
	≥ 30 kg/m^2	22 (56.4)	23 (69.7)	45 (62.5)
	Total	39 (100)	33 (100)	72 (100)
Baseline BMI group (kg/m^2) n (%)	< 30 kg/m^2	17 (43.6)	10 (30.3)	27 (37.5)
	≥ 30 kg/m^2	22 (56.4)	23 (69.7)	45 (62.5)
	Total	39 (100)	33 (100)	72 (100)
Standardised baseline BMI group (percentile) [b]	≥ 95th	22 (56.4)	23 (69.7)	45 (62.5)
	≥ 85th and < 95th	11 (28.2)	7 (21.2)	18 (25.0)
	≥ 5th and < 85th	5 (12.8)	2 (6.1)	7 (9.7)
	< 5th	1 (2.6)	1 (3.0)	2 (2.8)
	Total	39 (100)	33 (100)	72 (100)

Disease characteristics

Diabetes-related characteristics are summarised in Table 6. Mean duration of T2DM at screening was 3.12 (0.2 – 12 years). In the majority of patients (59.7%), the duration was < 3 years.

HbA1c at screening was between 6.5% and 11% in all randomised patients, with a mean value of 8.06%. At baseline 9.7% of patients had HbA1c values < 6.5% and 2.8% patients had HbA1c values 11%. The majority of patients (61.1%) had baseline HbA1c values < 8%, and the mean baseline HbA1c was 7.90%.

FPG at screening was ≤14.2 mmol/L (≤255 mg/dL) in all randomised patients, with a mean value of 8.23 mmol/L. At baseline 8.3% of patients had FPG values > 14.2 mmol/L. Mean baseline FPG was 8.94 mmol/L.

Background diabetic medication was metformin alone for the majority of patients (51.4%), followed by insulin + metformin (31.9% of patients). The proportion of patients with metformin alone was lower in the dapagliflozin group (43.6%) compared with the placebo group (60.6%), whereas the proportion of patients with insulin + metformin was higher in the dapagliflozin group (38.5%) compared with the placebo group (24.2%). Insulin alone was the background diabetic medication in 16.7% of patients overall, with a similar percentage in the treatment groups.

Table 6: Diabetes-related Characteristics at Screening (Full Analysis Subjects Set)

Characteristic		Dapagliflozin 10 mg (N=39)	Placebo (N=33)	Total (N=72)
Duration of type 2 diabetes (years)	n	39	33	72
	Mean	3.10	3.15	3.12
	SD	2.67	3.05	2.83
	Min	0.2	0.2	0.2
	1st quartile	1.06	0.96	0.97
	Median	2.16	2.17	2.17
	3rd quartile	4.11	4.68	4.31
	Max	11.1	12.0	12.0
Duration of type 2 diabetes (years) n (%)	< 3	22 (56.4)	21 (63.6)	43 (59.7)
	≥ 3 and ≤ 10	15 (38.5)	10 (30.3)	25 (34.7)
	> 10	2 (5.1)	2 (6.1)	4 (5.6)
	Total	39 (100)	33 (100)	72 (100)
Screening HbA1c (%)	n	39	33	72
	Mean	8.09	8.02	8.06
	SD	1.36	1.06	1.22
	Median	7.70	7.70	7.70
	Min	6.6	6.5	6.5
	Max	11.0	10.5	11.0
Screening HbA1c (%) n (%)	< 6.5%	0	0	0
	≥ 6.5% and ≤ 11%	39 (100)	33 (100)	72 (100)
	> 11%	0	0	0
	Total	39 (100)	33 (100)	72 (100)
Baseline HbA1c (%)	n	39	33	72
	Mean	7.95	7.85	7.90
	SD	1.59	1.19	1.41
	Median	7.60	7.70	7.60

Characteristic		Dapagliflozin 10 mg (N=39)	Placebo (N=33)	Total (N=72)
	Min	5.4	5.3	5.3
	Max	12.4	10.5	12.4
Baseline HbA1c (%) n (%)	< 6.5%	5 (12.8)	2 (6.1)	7 (9.7)
	≥ 6.5% and < 9%	25 (64.1)	24 (72.7)	49 (68.1)
	≥ 9% and ≤ 11%	7 (17.9)	7 (21.2)	14 (19.4)
	> 11%	2 (5.1)	0	2 (2.8)
	Total	39 (100)	33 (100)	72 (100)
Baseline HbA1c (%) n (%)	< 8%	25 (64.1)	19 (57.6)	44 (61.1)
	≥ 8%	14 (35.9)	14 (42.4)	28 (38.9)
	Total	39 (100)	33 (100)	72 (100)
Screening FPG (mmol/L)	n	39	33	72
	Mean	7.71	8.85	8.23
	SD	2.10	2.86	2.52
	Median	7.30	8.05	7.52
	Min	4.8	4.7	4.7
	Max	12.8	14.1	14.1
Screening FPG (mmol/L) n (%)	≤ 14.2	39 (100)	33 (100)	72 (100)
	> 14.2	0	0	0
	Total	39 (100)	33 (100)	72 (100)
Baseline FPG (mmol/L)	n	39	33	72
	Mean	8.66	9.27	8.94
	SD	3.09	3.51	3.28
	Median	7.40	8.40	7.89
	Min	5.3	4.7	4.7
	Max	16.4	20.0	20.0
Baseline FPG (mmol/L) n (%)	≤ 14.2	36 (92.3)	30 (90.9)	66 (91.7)
	> 14.2	3 (7.7)	3 (9.1)	6 (8.3)
	Total	39 (100)	33 (100)	72 (100)
Background diabetic medication n (%)[a]	Metformin	17 (43.6)	20 (60.6)	37 (51.4)
	Insulin	7 (17.9)	5 (15.2)	12 (16.7)

Characteristic		Dapagliflozin 10 mg (N=39)	Placebo (N=33)	Total (N=72)
	Insulin + metformin	15 (38.5)	8 (24.2)	23 (31.9)
	Total	39 (100)	33 (100)	72 (100)
Metformin diabetic background medication-Total daily dose (mg) [a]	n	32	28	60
	Mean	1665.6	1625.0	1646.7
	SD	431.3	565.4	494.4
	Median	1700.0	1600.0	1700.0
	Min	1000	1000	1000
	Max	2550	2550	2550
Insulin diabetic background medication-Total daily dose (Insulin unit) [a]	n	22	13	35
	Mean	58.0	57.2	57.7
	SD	42.7	48.1	44.1
	Median	44.5	38.0	40.0
	Min	5	3	3
	Max	170	170	170

[a] As collected in CRF background metformin page and background insulin dosing page.

Mean eGFR at baseline (Table 7) was 118 mL/min/1.73 m2, irrespective of age category (< or > 18 years of age) and study group. At baseline, 50.9% (27/53) of patients < 18 years of age had an eGFR value ≥ 90 and < 120 mL/min/1.73 m2, and 39.6% (21/53) of patients < 18 years of age had an eGFR value ≥ 120 mL/min/1.73 m2.

Table 7: Renal baseline Characteristics in Patients < 18 Years Old (Full Analysis Subjects Set)

Characteristic		Dapagliflozin 10 mg (N=29)	Placebo (N=24)	Total (N=53)
Screening eGFR (mL/min/1.73 m^2)	n	28	24	52
	Mean	120.0	116.5	118.4
	SD	24.8	25.4	24.9
	Median	115.5	114.0	114.5
	Min	84	82	82
	Max	171	175	175
Screening eGFR (mL/min/1.73 m^2) n (%)	< 60	0	0	0
	≥ 60 and < 80	0	0	0
	≥ 80	28 (96.6)	24 (100)	52 (98.1)

	Total	28 (96.6)	24 (100)	52 (98.1)
Baseline eGFR (mL/min/1.73 m^2)	n	29	24	53
	Mean	119.3	116.6	118.1
	SD	23.0	22.3	22.5
	Median	116.0	110.5	116.0
	Min	81	88	81
	Max	166	175	175
Baseline eGFR (mL/min/1.73 m^2) n (%)	< 60	0	0	0
	≥ 60 and < 90	3 (10.3)	2 (8.3)	5 (9.4)
	≥ 90 and < 120	14 (48.3)	13 (54.2)	27 (50.9)
	≥ 120	12 (41.4)	9 (37.5)	21 (39.6)
	Total	29 (100)	24 (100)	53 (100)

Concomitant medication

Concomitant medications during the ST period are summarised in Table 8. The treatment groups were well balanced regarding the use of current medications, which were reported for all patients in the treated subjects set. Apart from metformin and insulins and analogues, that are described below, the most common current medications were vitamin D and analogues (19.4% [14/72] of patients).

Table 8: Concomitant Antihypertensive, Antipsychotic, and Antihyperlipidemic Medication During the 24-week Double-blind Short-term Period (Treated Subjects Set)

ATC classification / Generic term	Number (%) of patients		
	Dapagliflozin 10 mg (N=39)	Placebo (N=33)	Total (N=72)
Number of patients with concomitant medication	39 (100)	33 (100)	72 (100)
Antihypertensive medication			
ACE INHIBITORS, PLAIN	4 (10.3)	4 (12.1)	8 (11.1)
ENALAPRIL	2 (5.1)	2 (6.1)	4 (5.6)
ENALAPRIL MALEATE	1 (2.6)	0	1 (1.4)
LISINOPRIL	0	2 (6.1)	2 (2.8)
TRITACE	1 (2.6)	0	1 (1.4)
BETA BLOCKING AGENTS, SELECTIVE	0	3 (9.1)	3 (4.2)
METOPROLOL	0	2 (6.1)	2 (2.8)
NORMITEN	0	1 (3.0)	1 (1.4)
Antipsychotic medication			
OTHER ANXIOLYTICS	2 (5.1)	2 (6.1)	4 (5.6)
ESCITALOPRAM	1 (2.6)	1 (3.0)	2 (2.8)
FLUOXETIN	0	1 (3.0)	1 (1.4)
PROZAC	0	1 (3.0)	1 (1.4)
ZOLOFT	1 (2.6)	0	1 (1.4)

ATC classification / Generic term	Number (%) of patients		
	Dapagliflozin 10 mg (N=39)	Placebo (N=33)	Total (N=72)
CENTRALLY ACTING SYMPATHOMIMETICS	1 (2.6)	0	1 (1.4)
DEXMETHYLPHENIDATE HYDROCHLORIDE	1 (2.6)	0	1 (1.4)
OTHER ANTIEPILEPTICS	1 (2.6)	0	1 (1.4)
LAMOTRIGINE	1 (2.6)	0	1 (1.4)
SELECTIVE SEROTONIN (5HT1) AGONISTS	1 (2.6)	0	1 (1.4)
RIZATRIPTAN	1 (2.6)	0	1 (1.4)
Antihyperlipidemic medication			
HMG COA REDUCTASE INHIBITORS	2 (5.1)	1 (3.0)	3 (4.2)
ATORVASTATIN	1 (2.6)	0	1 (1.4)
LIPITOR	0	1 (3.0)	1 (1.4)
SIMVASTATIN	1 (2.6)	0	1 (1.4)
FIBRATES	1 (2.6)	2 (6.1)	3 (4.2)
BEZAFIBRATE	0	2 (6.1)	2 (2.8)
GEMFIBROZIL	1 (2.6)	0	1 (1.4)

Concomitant insulin and non-insulin diabetic medication use at randomisation are summarised in Table 9 and Table 10, respectively.

The number of patients with concomitant insulin treatment was higher in the dapagliflozin group (56.4% [22/39] of patients) compared with the placebo group (42.4% [14/33] of patients). Overall, the most commonly used insulin was long-acting insulins (33.3% [24/72] of patients) followed by rapid-acting insulin (29.2% [21/72] of patients). Rapid-acting insulin was more commonly used in the dapagliflozin group (35.9% [14/39] of patients) than in the placebo group (21.2% [7/33] of patients); no remarkable differences between the treatment groups were observed in the use of long-acting insulin.

The use of background metformin was balanced between the treatment groups.

Table 9: Concomitant Insulin Diabetic Medications Ongoing or Initiated at Randomisation (Treated Subjects Set)

ATC classification / Generic term	Number (%) of patients		
	Dapagliflozin 10 mg (N=39)	Placebo (N=33)	Total (N=72)
Number of patients with concomitant insulin diabetic medication ongoing or initiated at randomisation	22 (56.4)	14 (42.4)	36 (50.0)
INSULINS AND ANALOGUES FOR INJECTION, FAST-ACTING	14 (35.9)	7 (21.2)	21 (29.2)
ACTRAPID [INSULIN HUMAN]	1 (2.6)	0	1 (1.4)
ADMELOG	1 (2.6)	1 (3.0)	2 (2.8)
HUMALOG	6 (15.4)	3 (9.1)	9 (12.5)
INSULIN ASPART	1 (2.6)	0	1 (1.4)
INSULIN LISPRO	0	1 (3.0)	1 (1.4)

ATC classification / Generic term	Number (%) of patients		
	Dapagliflozin 10 mg (N=39)	Placebo (N=33)	Total (N=72)
LISPRO INSULIN	1 (2.6)	0	1 (1.4)
NOVOLIN 30R [INSULIN]	2 (5.1)	1 (3.0)	3 (4.2)
NOVOLOG	2 (5.1)	1 (3.0)	3 (4.2)
NOVORAPID	0	1 (3.0)	1 (1.4)
INSULINS AND ANALOGUES FOR INJECTION, INTERMEDIATE- OR LONG-ACTING COMBINED WITH FAST-ACTING	3 (7.7)	2 (6.1)	5 (6.9)
HUMALOG MIX	2 (5.1)	2 (6.1)	4 (5.6)
NOVOMIX	1 (2.6)	0	1 (1.4)
INSULINS AND ANALOGUES FOR INJECTION, INTERMEDIATE-ACTING	4 (10.3)	1 (3.0)	5 (6.9)
HUMULINE	1 (2.6)	0	1 (1.4)
INSULATARD HUMAN	1 (2.6)	0	1 (1.4)
INSUMAN BASAL	1 (2.6)	0	1 (1.4)
NPH INSULIN	1 (2.6)	1 (3.0)	2 (2.8)
INSULINS AND ANALOGUES FOR INJECTION, LONG-ACTING	12 (30.8)	12 (36.4)	24 (33.3)
BASAGLAR	1 (2.6)	3 (9.1)	4 (5.6)
INSULIN GLARGINE	2 (5.1)	1 (3.0)	3 (4.2)
LANTUS	7 (17.9)	7 (21.2)	14 (19.4)
LEVEMIR	2 (5.1)	0	2 (2.8)
TRESIBA	0	2 (6.1)	2 (2.8)

Table 10: Concomitant Non-insulin Diabetic Medication Ongoing or Initiated at Randomisation (Treated Subjects Set)

ATC classification / Generic term	Number (%) of patients		
	Dapagliflozin 10 mg (N=39)	Placebo (N=33)	Total (N=72)
Number of patients with concomitant non-insulin diabetic medication ongoing or initiated at randomisation	32 (82.1)	28 (84.8)	60 (83.3)
BIGUANIDES	32 (82.1)	28 (84.8)	60 (83.3)
METFORMIN	32 (82.1)	28 (84.8)	60 (83.3)

Numbers analysed

The analysis sets and the number of patients in each analysis set are summarised in Table 11. All decisions on the inclusion or exclusion of patients from analyses were to be made while the data were still blinded before database lock. However, corrections on protocol deviations that impacted the PP subjects set were made after unblinding. A total of 72 patients were randomised and received at least one dose of study drug and were, therefore, included in the FAS and in the treated subjects set: 39 patients in the dapagliflozin group and 33 patients in the placebo group.

In total, 60 (83.3%) patients were included in the PP subjects set: 34 (87.2%) patients in the dapagliflozin group and 26 (78.8%) patients in the placebo group; reasons for exclusion were relevant protocol deviations.

Of the 39 patients treated with dapagliflozin, 35 were included in the PK data set, and the 4 patients that were excluded did not contribute at least one PK sample (3 patients discontinued the study before Week 16 and 1 patient missed the Week 16 visit and discontinued before Week 24).

Table 11: Analysis sets

	Number of patients	
	Dapagliflozin 10 mg	**Placebo**
Full analysis subjects set	39	33
Patients excluded from the FAS [a]	0	0
Per protocol subjects set	34	26
Patients excluded from the PP subjects set [a]	5	7
Treated subjects set	39	33
Patients excluded from the treated subjects set [a]	0	0
Pharmacokinetic analysis set	35	0
Patients excluded from PK analysis set [a]	4	33

[a] An individual subject could have been excluded for more than 1 reason. The Full analysis subjects set will consist of all randomized subjects randomized by IXRS.
The Per Protocol subjects set will be a subset of the Full analysis subjects set, excluding subjects with relevant protocol deviations that lead to a complete exclusion.
The Treated subjects set will consist of all subjects who receive at least one dose of study medication during the treatment period.
The pharmacokinetic analysis set will include all patients who received a dapagliflozin dose and have collected at least 1 PK sample.

Outcomes and estimation

Primary Efficacy Endpoint: change from baseline in HbA1c at Week 24

A summary of the change from baseline in HbA1c at Week 24 is presented in Table 12. A line plot of the adjusted mean change from baseline in HbA1c over the ST period for each treatment is displayed in Figure 3.

At Week 24, the adjusted mean change from baseline (LS mean) in HbA1c was -0.25% and 0.50% in the dapagliflozin and placebo groups, respectively, resulting in a difference of -0.75% (SE 0.45; 95% CI -1.65 to 0.15)

Table 12: Change from Baseline in HbA1c (%) at Week 24 - Longitudinal Repeated Measures Analysis Excluding Values after Rescue Medication Initiation or Discontinuation from Study Drug (Full Analysis Subjects Set)

Efficacy Endpoint Statistic	Dapagliflozin 10 mg (N=39)	Placebo (N=33)
Baseline HbA1c (%) N#	37	29
Mean (SD)	7.94 (1.63)	7.79 (1.18)
HbA1c (%) at Week 24 N##	31	23
Mean (SD)	7.15 (1.71)	8.20 (2.21)
Mean change from baseline (SD)	-0.48 (1.63)	0.45 (1.82)
Adjusted mean change from baseline LS mean (SE)	-0.25 (0.30)	0.50 (0.34)
95% CI	-0.85, 0.34	-0.18, 1.17
Difference from Placebo LS mean (SE)	-0.75 (0.45)	
95% CI	-1.65, 0.15	
p-value	0.101	

Figure 3 shows the adjusted mean HbA1c values for each treatment with time. The difference in HbA1c was present at 4 weeks and was sustained through Week 24. Values after rescue medication initiation or premature treatment discontinuation were excluded. The separation from placebo was maintained during this period but the 95% CI became wider over time.

Figure 3: HbA1c (%) - Adjusted Mean Change from Baseline over Time During the 24-week Double-blind Short-term Period, Excluding Values after Rescue Medication Initiation or Discontinuation from Study Drug, Repeated Measures Model, LS mean (95% CI) (Full Analysis Subjects Set)

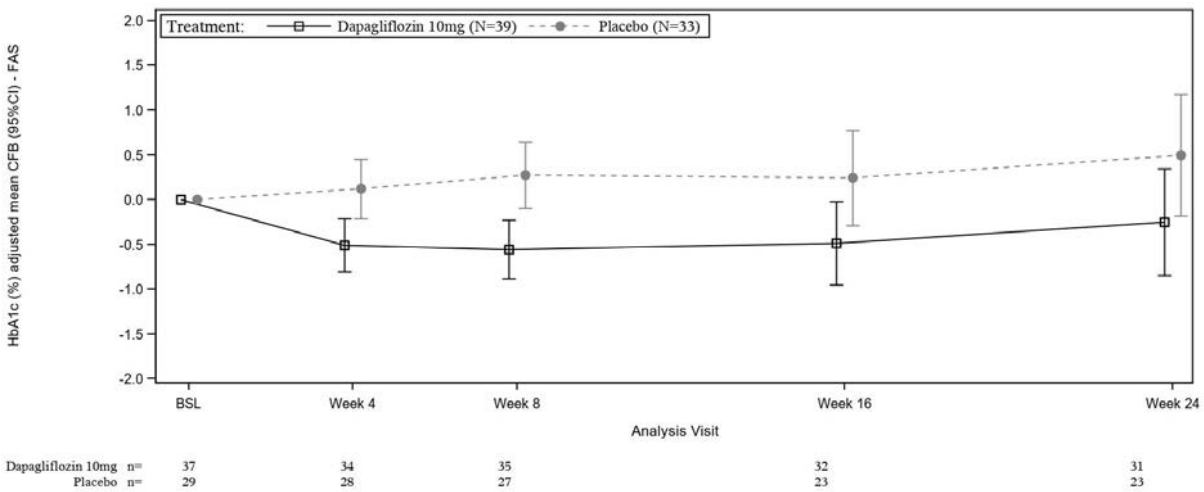


Table 13: Sensitivity and Post Hoc Analyses of the Change from Baseline in HbA1c (%) at Week 24

Variable	Type of estimate	Dapagliflozin 10 mg (N=39) [n]	Placebo (N=33) [n]	Comparison between groups	95% CI	p-value
Longitudinal repeated measures analysis excluding values after rescue medication initiation or discontinuation from study drug (PP set)	LS mean (SE)	[33] -0.51 (0.28)	[24] 0.62 (0.33)	-1.13 (0.43)	(-1.99, -0.26)	0.012
Longitudinal repeated measures analysis regardless of rescue medication initiation or discontinuation from study drug (FAS)	LS mean (SE)	[35] -0.24 (0.30)	[27] 0.42 (0.34)	-0.66 (0.45)	(-1.57, -0.24)	0.146
ANCOVA LOCF/BOCF excluding values after rescue medication initiation or discontinuation from study drug (FAS)	LS mean (SE)	[39] -0.39 (0.25)	[33] 0.40 (0.27)	-0.79 (0.37)	(-1.52, -0.06)	0.035
Multiple imputation wash-out method including all values regardless of rescue medication initiation or discontinuation from study drug (FAS)	Combined LS mean (SE)	[39] -0.48 (0.31)	[33] 0.35 (0.34)	-0.82 (0.46)	(-1.73, 0.08)	0.075
Tipping-point analysis regardless of rescue medication initiation or discontinuation from study drug, delta = 0 (FAS)	Combined LS mean (SE)	[39] -0.29 (0.30)	[33] 0.40 (0.34)	-0.70 (0.45)	(-1.57, 0.18)	0.120
Post hoc analyses excluding one change from baseline value (Week 16 assessment)						
Longitudinal repeated measures analysis excluding values after rescue medication initiation or discontinuation from study drug (FAS)	LS mean (SE)	[36] -0.41 (0.27)	[29] 0.51 (0.31)	-0.92 (0.42)	(-1.75, -0.08)	0.031

ANCOVA analysis of covariance; BOCF baseline observation carried forward; CI confidence interval; FAS full analysis subjects set; HbA1c glycated haemoglobin; LOCF last observation carried forward; LS least square; N number of subjects in the treatment group; n number of subjects with baseline value; PP per protocol; SE standard error of the mean

Derived from: Table 14.2.1.2.1, Table 14.2.1.2.2, Table 14.2.1.2.7, Table 14.2.1.2.8, Table 14.2.1.2.9, and Table 14.2.1.2.10

Secondary Variables

Table 14: Secondary Efficacy Variables, Overview of Key Results - 24-week Double-blind Short-term Period (Full Analysis Subjects Set)

Type of estimate	Dapagliflozin 10 mg (N = 39)	Placebo (N = 33)	Comparison between groups	95% CI	Nominal p-value
Change from baseline in FPG (mmol/L) at Week 24, MMRM, 24-week ST period [a]					
LS mean (SE) 95% CI	-0.07 (0.53) (-1.13, 1.00)	0.72 (0.61) (-0.51, 1.95)	-0.78 (0.81)	(-2.42, 0.85)	0.340
Proportion of patients discontinued due to lack of glycaemic control or rescued at or prior to Week 24[b,c]					
Risk difference	2/39 (5.1%)	3/33 (9.1%)	-3.96%	(-20.11, 9.62)	0.655
Proportion of patients with baseline HbA1c ≥ 7% who achieve HbA1c < 7% at Week 24 [b,c]					
Risk difference	7/28 (25.0%)	1/24 (4.2%)	20.83%	(0.50, 41.11)	0.056

Change from baseline in FPG at Week 24

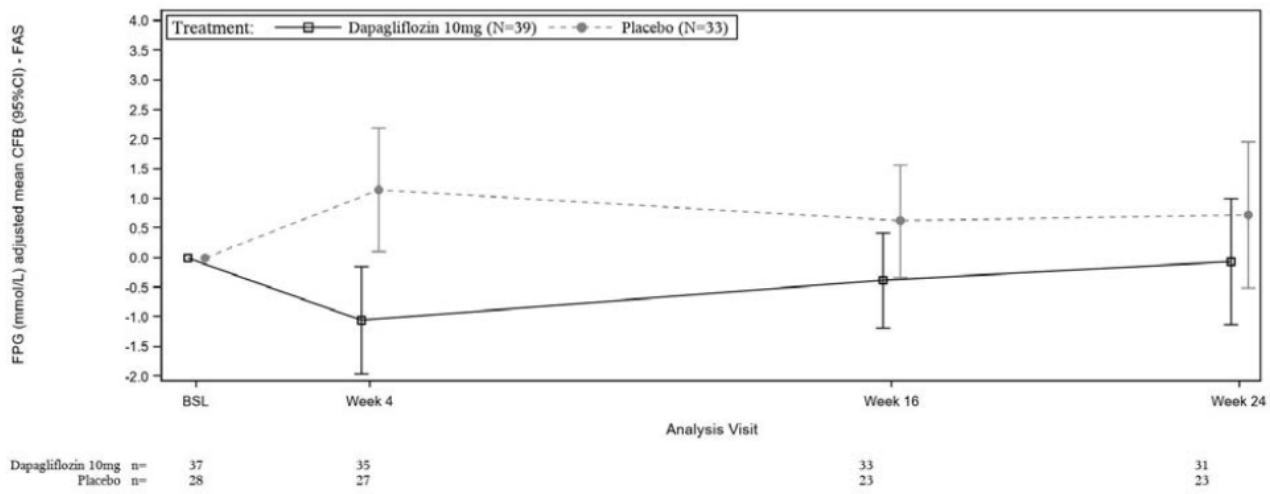
A summary of the change from baseline in FPG at Week 24 is presented in Table 15. A line plot of the adjusted mean change from baseline in FPG during the ST period is displayed in Figure 4.

A numerical reduction from baseline in FPG after 24 weeks of double-blind add-on treatment was observed in the dapagliflozin group compared with a numerical increase in the placebo group (LS mean of -0.07% and 0.72%, respectively; LS mean [SE] difference: -0.78% [0.81]; 95% CI -2.42 to 0.85; p = 0.340).

Table 15: Change from Baseline in FPG (mmol/L) at Week 24 - Longitudinal Repeated Measures Analysis Excluding Values after Rescue Medication Initiation or Discontinuation from Study Drug (Full Analysis Subjects Set)

Efficacy Endpoint Statistic	Dapagliflozin 10 mg (N=39)	Placebo (N=33)
Baseline FPG (mmol/L) N#	37	28
Mean (SD)	8.61 (3.09)	8.92 (2.95)
FPG (mmol/L) at Week 24 N##	31	23
Mean (SD)	8.26 (3.41)	9.06 (3.32)
Mean change from baseline (SD)	0.05 (2.47)	0.50 (3.82)
Adjusted mean change from baseline LS mean (SE)	-0.07 (0.53)	0.72 (0.61)
95% CI	-1.13, 1.00	-0.51, 1.95
Difference from Placebo LS mean (SE)	-0.78 (0.81)	
95% CI	-2.42, 0.85	
p-value	0.340	

Figure 4 FPG (mmol/L) - Adjusted Mean Change from Baseline over Time During the 24-week Double-blind Short-term Period Repeated Measures Model, LS mean (95% CI) (Full Analysis Subjects Set)



Glycaemic rescue medication or permanent treatment discontinuation due to lack of glycaemic control during the 24-week double-blind short-term treatment period

The proportion of patients who required glycaemic rescue or permanent treatment discontinuation due to lack of glycaemic control over the 24 weeks of double-blind add-on treatment was numerically smaller in the dapagliflozin group (5.1% [2/39] of patients) compared with placebo (9.1% [3/33] of patients), and was quantified in their difference (difference in proportion -3.96%; 95% CI -20.11 to 9.62)

Patients with baseline HbA1c ≥ 7% who achieved HbA1c level < 7% at Week 24

The proportion of patients with baseline HbA1c ≥ 7% who achieved HbA1c level < 7% at Week 24 was larger in the dapagliflozin group (25.0% [7/28] of patients) than that in the placebo group (4.2% [1/24] of patients), and was quantified in their difference (difference in proportion 20.83%; 95% CI 0.50 to 41.11; nominal p value = 0.056). Despite the low number of patients, the proportion of patients with baseline HbA1c ≥ 7% achieving HbA1c < 7% at Week 24 was 5 times higher with dapagliflozin than placebo.

Exploratory variables

Change from baseline in HbA1c at Week 52

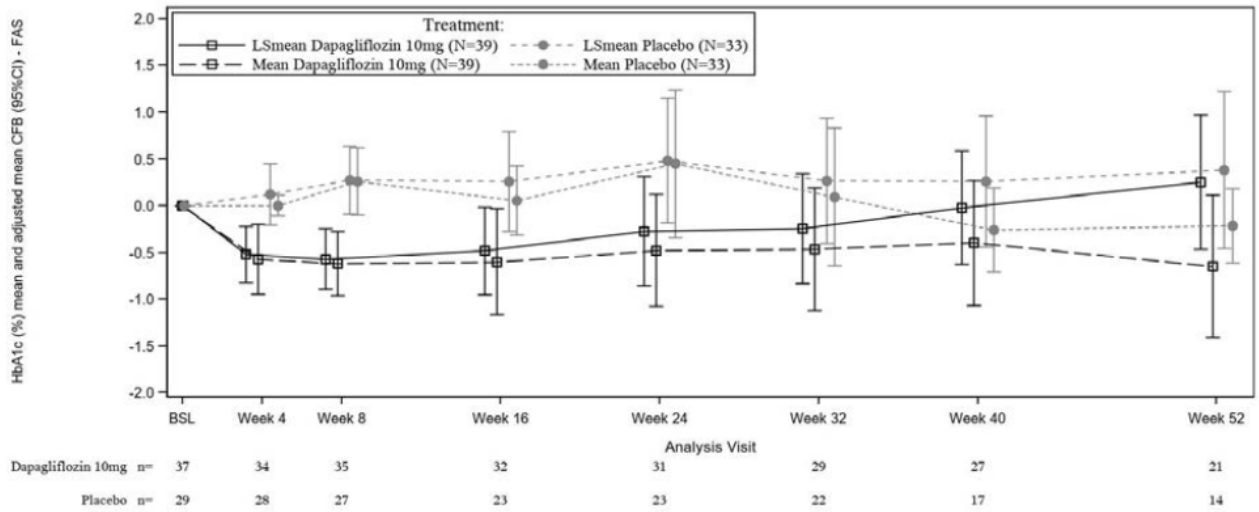
A summary of the change from baseline in HbA1c at Week 52 is presented in Table 16. A line plot of the adjusted mean change from baseline in HbA1c during the 52-week ST + LT period is displayed in Figure 5.

An increase from baseline in HbA1c after 52 weeks of treatment was observed in the both dapagliflozin/dapagliflozin and placebo/dapagliflozin groups (adjusted mean changes from baseline to Week 52 (LS mean) 0.25% and 0.38%, respectively).

Table 16: Change from Baseline in HbA1c (%) at Week 52 - Longitudinal Repeated Measures Analysis Excluding Values after Rescue Medication Initiation or Discontinuation from Study Drug (Full Analysis Subjects Set)

Efficacy endpoint statistic	Dapagliflozin 10 mg / Dapagliflozin 10 mg (N=39)	Placebo / Dapagliflozin 10 mg (N=33)
Baseline HbA1c (%) N#	37	29
Mean (SD)	7.94 (1.63)	7.79 (1.18)
HbA1c (%) at Week 52 N##	21	14
Mean (SD)	6.81 (1.88)	7.51 (0.97)
Mean change from baseline (SD)	-0.65 (1.68)	-0.21 (0.68)
Adjusted mean change from baseline LS mean (SE)	0.25 (0.35)	0.38 (0.41)
95% CI	-0.47, 0.97	-0.46, 1.22
Difference from Placebo LS mean (SE)	-0.13 (0.54)	
95% CI	-1.24, 0.97	

Figure 5 HbA1c (%) – Mean and Adjusted Mean Change from Baseline over Time During the 52-week Short-term plus Long-term Period, Excluding Values after Rescue Medication Initiation or Discontinuation from Study Drug, Repeated Measures Model, LS mean (95% CI) (Full Analysis Subjects Set)



Change from baseline in FPG at Week 52

A summary of the change from baseline in FPG at Week 52 is presented in Table 17. A line plot of the adjusted mean change from baseline in FPG during the ST + LT periods is displayed in Figure 6.

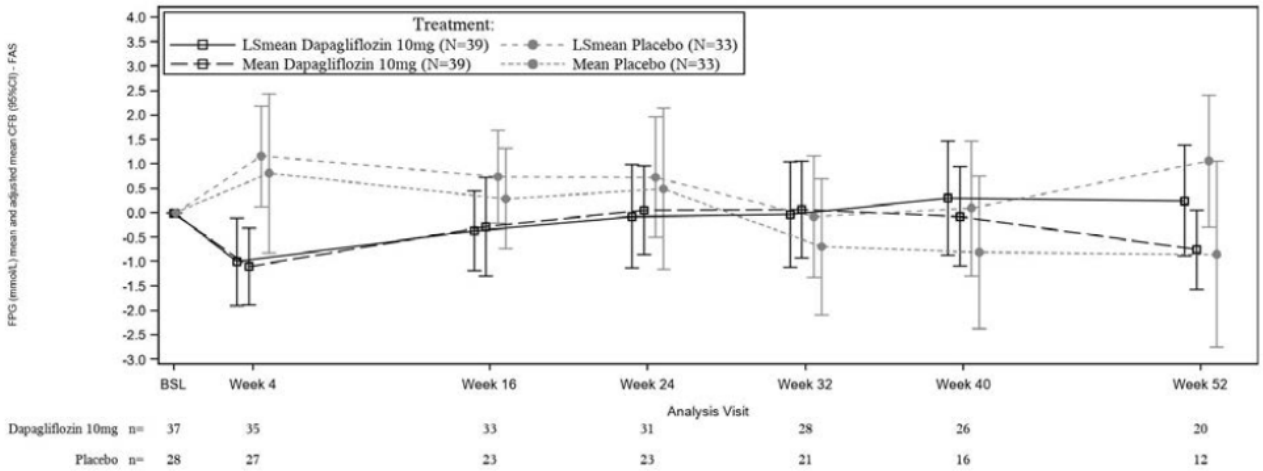
An increase from baseline in FPG after 52 weeks of treatment was observed in both dapagliflozin/dapagliflozin and placebo/dapagliflozin groups (adjusted mean changes from baseline to Week 52 (LS mean) 0.25% and 1.06%, respectively).

Table 17: Change from Baseline in FPG (mmol/L) at Week 52 - Longitudinal Repeated Measures Analysis Excluding Values after Rescue Medication Initiation or Discontinuation from Study Drug (FAS)

Efficacy endpoint statistic	Dapagliflozin 10 mg / Dapagliflozin 10 mg (N=39)	Placebo / Dapagliflozin 10 mg (N=33)
Baseline FPG (mmol/L) N#	37	28
Mean (SD)	8.61 (3.09)	8.92 (2.95)
FPG (mmol/L) at Week 52 N##	20	12
Mean (SD)	6.87 (2.21)	8.43 (2.31)
Mean change from baseline (SD)	-0.75 (1.72)	-0.85 (3.00)
Adjusted mean change from baseline LS mean (SE)	0.25 (0.55)	1.06 (0.66)
95% CI	-0.88, 1.38	-0.29, 2.41

Difference from Placebo LS mean (SE)	-0.81 (0.87)	
95% CI	-2.59, 0.97	

Figure 6 FPG (mmol/L) – Mean and Adjusted Mean Change from Baseline over Time During the 52-week Short-term plus Long-term Period, Excluding Values after Rescue Medication Initiation or Discontinuation from Study Drug, Repeated Measures Model, LS mean (95% CI) (Full Analysis Subjects Set)

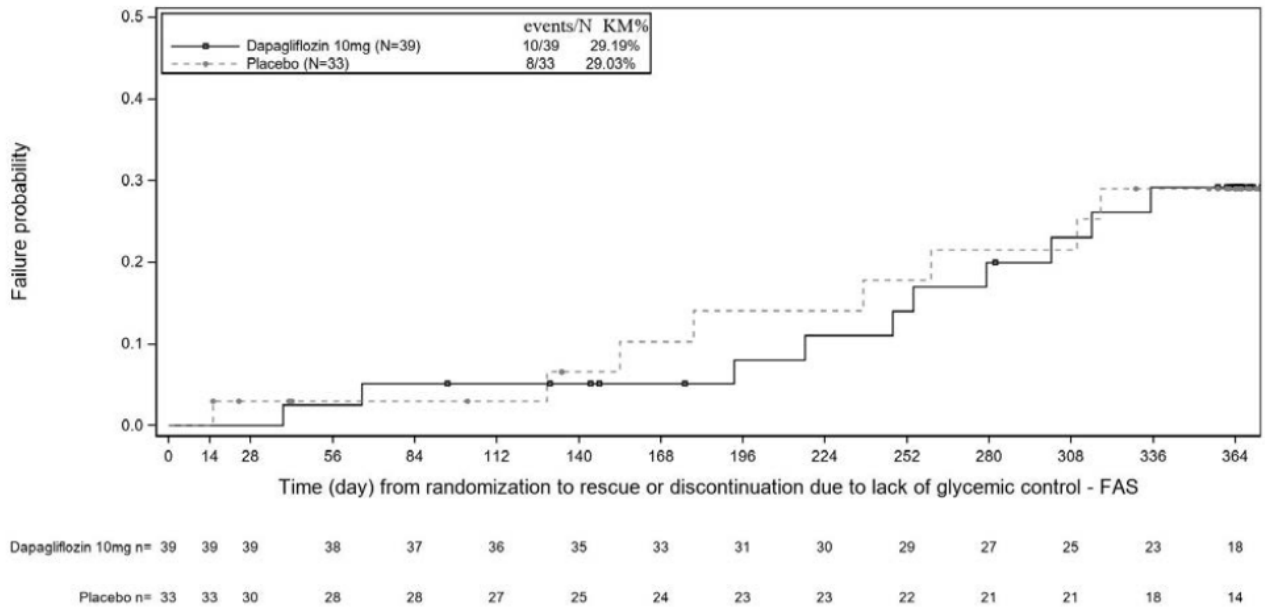


Glycaemic rescue medication or permanent treatment discontinuation due to lack of glycaemic control during the 52-week short-term plus long-term period

The proportion of patients who required glycaemic rescue or permanent treatment discontinuation due to lack of glycaemic control over the ST + LT periods were similar for the dapagliflozin/dapagliflozin and placebo/dapagliflozin groups (adjusted proportion 21.32% and 22.67%; odds ratio 0.92; 95% CI 0.28 to 3.03).

A Kaplan-Meier plot of the time to rescue therapy initiation or discontinuation from the study drug due to lack of glycaemic control during the ST + LT periods is displayed in Figure 7.

Figure 7 Time to Rescue Therapy Initiation or Discontinuation from Study Drug due to Lack of Glycaemic Control During the 52-week Short-term plus Long-term Period, Kaplan-Meier Estimates (Full Analysis Subjects Set)



Patients with baseline HbA1c ≥ 7% who achieved HbA1c level < 7% at Week 52

At Week 52, the proportion of patients with baseline HbA1c ≥ 7% who achieved HbA1c level < 7% was 17.9% (5/28) among patients who received dapagliflozin/dapagliflozin during the 52-week ST +LT period, compared with 0/24 among those who received placebo/dapagliflozin (Table 27).

When the analysis was performed independently of baseline HbA1c values, the proportion of patients who achieved HbA1c level < 7% at Week 52 was greater for those who received dapagliflozin/dapagliflozin during the ST +LT period (35.9% [14/39]) than for those who received placebo/dapagliflozin (9.1% [3/33]).

Ancillary analyses

Subgroup analyses of the primary variable

Forest plots with the adjusted mean changes from baseline in HbA1c at Week 24 by subgroup are displayed in Figure 8. A numerical improvement in dapagliflozin-treated patients over placebo in HbA1c was consistent across race, sex, baseline HbA1c, and background medication subgroups.

Figure 8: Adjusted Mean Change from Baseline in HbA1c (%) at Week 24 – MMRM by Subgroup Analysis (Full Analysis Subjects Set)

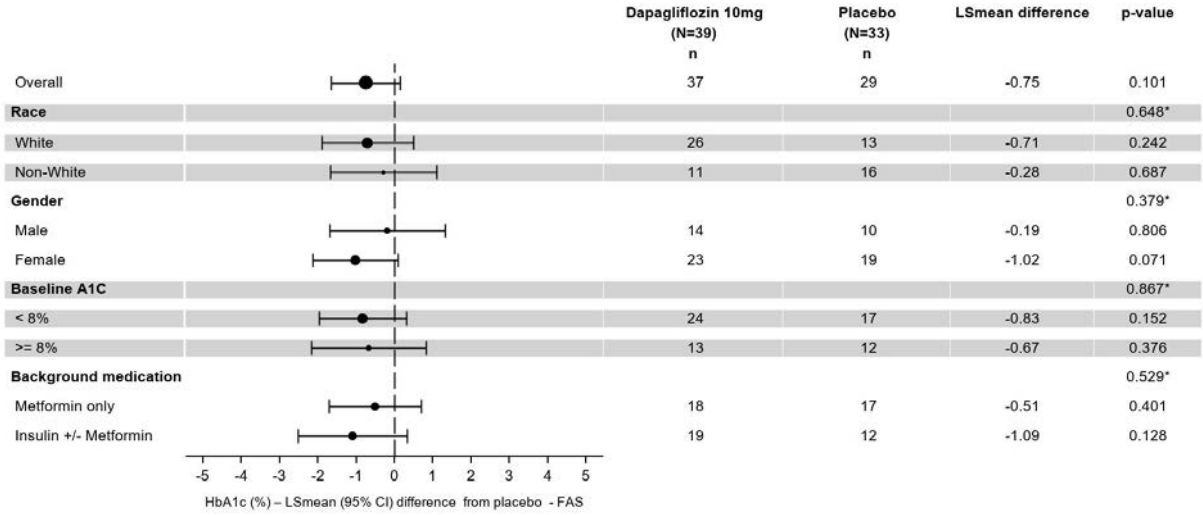


Table 18: Change from Baseline in HbA1c (%) by Screening Age Category (year) at Week 24 – Longitudinal Repeated Measures Analysis Excluding Values After Rescue Medication Initiation or Discontinuation From Study Drug (Full Analysis Subjects Set)

Week		Dapagliflozin 10 mg (N = 39)	Placebo (N = 33)
Screening age < 18 years			
Baseline	N#	27	21
	Mean (SD)	7.77 (1.70)	8.05 (1.08)
Week 24	N##	22	17
	Mean (SD)	7.31 (1.91)	8.53 (2.32)
	Mean change from baseline (SD)	-0.05 (1.35)	0.55 (2.09)
	Adjusted Mean chg from Baseline-LSmean (SE)	-0.03 (0.35)	0.56 (0.40)
	Adjusted Mean chg from Baseline-95% CI	(-0.73, 0.67)	(-0.24, 1.36)
	Diff from Placebo- LSmean (SE)	-0.59 (0.53)	
	Diff from Placebo- 95% CI	(-1.66, 0.48)	
	p-value	0.272	
Screening age ≥ 18 years			
Baseline	N#	10	8
	Mean (SD)	8.40 (1.38)	7.11 (1.20)
Week 24	N##	9	6
	Mean (SD)	6.73 (1.05)	7.25 (1.66)
	Mean change from baseline (SD)	-1.52 (1.84)	0.17 (0.73)

N Number of subjects in the treatment group.

N# Number of subjects with baseline value and at least one post-baseline value prior to rescue therapy initiation or discontinuation from study drug and no missing screening age assessment.

N## Number of subjects with baseline and Week 24 values and no missing screening age assessment.

Stratified age as recorded by IXRS.

The subgroup analysis includes all values at scheduled time points following randomisation up to and including Week 24 excluding values after rescue therapy initiation or discontinuation from study drug.

Where there are less than 10 subjects in each subgroup/treatment group, only summary statistics will be provided.

From the MMRM model Change = Randomisation Strata, Age Category, Week, Treatment, Baseline HbA1c, Treatment*Week, Baseline HbA1c*Week, Age Category*Week, Treatment*Age Category, Treatment*Week*Age Category.

Chg, change; HbA1c, glycated haemoglobin; LS, least squares; MMRM, mixed model for repeated measures SD, standard deviation; SE, standard error of the mean; CI, confidence interval.

Summary of main study

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 19 Summary of Efficacy for trial D1690C00017

Title: A 24-Week, Multicentre, Randomised, Double-Blind, Parallel Group, Phase 3 Trial with a 28-Week Long-Term Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin 10 mg in T2DM Patients Aged 10-24 Years			
Study identifier	D1690C00017		
Design	Prospective, multicentre, 24-week, placebo-controlled, double-blind, randomised study (ST period) with a 28-week open-label active treatment extension (LT period)		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks 4 weeks 28 weeks
Hypothesis	Superiority		
Treatments groups	Blinded dapagliflozin		10 mg dapagliflozin, 24 weeks, 39 patients
	Blinded placebo		10 mg placebo, 24 weeks, 33 patients
Endpoints and definitions	Primary endpoint	Mean HbA1c (%)	Change from baseline in HbA1c at Week 24
	Secondary endpoint	FPG (mmol/L)	Change from baseline in FPG at Week 24
	Secondary endpoint	Rescue/ discontinued	Percentage of patients who required glycaemic rescue medication or who permanently discontinued treatment due to lack of glycaemic control over the 24-week double-blind treatment period
	Secondary endpoint	Responders	Percentage of patients with baseline HbA1c ≥ 7% who achieved HbA1c level < 7% at Week 24
Database lock	primary analysis 02 April 2020 - final database lock 18 May 2020		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	The Full analysis subjects data set (FAS) consisted of all patients who were randomised and assigned to a treatment group through the IXRS. This data set was used for efficacy analysis.		
Descriptive statistics and estimate variability	Treatment group	Dapa 10 mg	Placebo 10mg
	Number of subjects	39	33
	Mean HbA1c (%) Mean	7.15	8.20

	SD	1.71	2.21
	FPG (mmol/L) Mean	8.26	9.06
	SD	3.41	3.32
	Rescue/discontinued n/N (%)	2/39 (5.1%)	7/33 (9.1%)
	Responders n/N (%)	7/28 (25.0%)	1/24 (4.2%)
Effect estimate per comparison	Primary endpoint HbA1c (%) at week 24	Comparison groups	Dapa 10 mg vs Placebo 10 mg
		LS mean (SE)	-0.75 (0.45)
		95% CI	-1.65, 0.15
		P-value	0.101
	Secondary endpoint FPG (mmol/L) at Week 24	Comparison groups	Dapa 10 mg (n=31) vs Placebo 10 mg (n=23)
		LS mean (SE)	-0.78 (0.81)
		95% CI	-2.42, 0.85
		P-value	0.340
	Secondary endpoint Rescue/discontinued	Comparison groups	Dapa 10 mg (n=39) vs Placebo 10 mg (n=33)
		Difference in proportion (%)	-3.96
		95% CI	-20.11, 9.62
		P-value	0.655
	Secondary endpoint Responders	Comparison groups	Dapa 10 mg (n=28) vs Placebo 10 mg (n=24)
		Difference in proportion (%)	20.83
		95% CI	0.50, 41.11
		P-value	0.056
Notes			

3.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Study D1690C00017 was a prospective, multicentre, 24-week, placebo-controlled, double-blind, randomised study (ST period) with a 28-week open-label active treatment extension (LT period). This pivotal Phase 3 study was designed to evaluate the efficacy and safety of dapagliflozin in children with T2DM and to test the hypothesis that treatment with dapagliflozin results in a greater mean reduction from baseline in HbA1c compared with placebo.

A single dose of 10 mg (the approved dose for adults in the EU) was selected on the basis of the PK/PD study D1690C00016 (MB102091) results.

The study patients were children and young adults aged 10 to 24 years and with a confirmed diagnosis of T2DM. According to the applicant, young adults aged 18 to 24 years were included due to recruitment challenges in the target population (although the number of patients was limited to less than 40% of patients, to ensure that the study population would adequately represent the target population).

Background treatment included diet and exercise as well as a stable dose of metformin, insulin or a combination of both for a minimum of 8 weeks prior to screening.

The overall design of the study as well as the study duration were adequate. The selection of patients was adequate, in order to recruit a representative study population. The exclusion criteria included concomitant medications and conditions that might have rendered the interpretation of data difficult. Other exclusion criteria were in place to for the safety of the patients. Of note, previous or concomitant use of SGLT-2 inhibitors was prohibited, whereas previous use of thiazolidinediones and GLP-1 RA was allowed, after a washout period.

Dapagliflozin was given in accordance with the recommendations in the SmPC for Forxiga/ Edistride. Rescue medication (addition or up-titration of insulin regime) was allowed, according to prespecified rescue criteria.

The primary objective was to compare the mean change from baseline in HbA1c achieved with dapagliflozin against the mean achieved with placebo after 24 weeks of double-blind add-on treatment in patients aged 10 to less than 25 years with T2DM who have inadequate glycaemic control on diet and exercise with metformin or insulin ± metformin.

Secondary endpoints included FPG, the percentage of patients requiring rescue treatment and the percentage of patients with baseline HbA1c > 7% who achieve a HbA1c level < 7%.

The primary and secondary efficacy objectives were assessed at Week 24, but also exploratively at Week 52, to assess the long-term trend of glycaemic control with dapagliflozin.

Primary and secondary endpoints were adequate.

Efficacy data and additional analyses

A total of 168 patients (with 13 re-screened patients) were enrolled in 7 countries and 72 were randomised: 39 patients in the dapagliflozin group and 33 patients in the placebo group (24 (33.3%) patients in Europe). Demographics and patient characteristics were generally balanced between study groups. Most patients (62.5%) were obese, with an average baseline BMI of 32.38 kg/m^2. There was a high spread of the body weight data but the MAH has provided additional analyses that indicate that the outcome is not affected by body weight.

The disease-related characteristics at screening were representative of the paediatric and young adult population of patients with T2DM in clinical practice. Mean HbA1c at baseline was 7.90%, with 13% of patients in the dapagliflozin group and 6% in the placebo group having an HbA1c of < 6.5%. The mean FPG was 8.94 mmol/L at baseline. Baseline eGFR was similar between groups.

Overall, the number of patients with concomitant insulin treatment was higher in the dapagliflozin group (56.4% [22/39] of patients) compared with the placebo group (42.4% [14/33] of patients). The combination of metformin and insulin at baseline was more frequent in the dapagliflozin group (38.5%) vs placebo (24.2) whereas metformin alone was more frequent in the placebo group (60% vs 44% dapagliflozin). Mean doses of metformin and/or insulin were similar between study groups.

Compliance was high (>90%) and similar between study groups during both the randomized and the safety follow-up phase.

The study did not meet the primary efficacy endpoint, although there was a numerical difference favouring dapagliflozin. At Week 24, the adjusted mean change from baseline (LS mean) in HbA1c was -0.25% and 0.50% in the dapagliflozin and placebo groups, respectively, resulting in a difference of -0.75% (SE 0.45; 95% CI -1.65 to 0.15).

Five pre-specified sensitivity analyses were performed. Among those, the multiple imputation based on "copy to reference" method and the tipping point analysis do not rely on the MAR assumption. Those are considered most relevant.

The post-hoc analysis performed with one single patient excluded cannot be accepted since this was performed after unblinding and with full knowledge of results on both individual and group level.

None of the secondary endpoints at week 24 were statistically significant. A numerical reduction from baseline in mean FPG was observed in the dapagliflozin group compared with a numerical increase in the placebo group. The difference was more pronounce after 4 weeks as compared to week 24, where the FPG in the dapagliflozin group had returned to baseline values. The proportion of patients who required glycaemic rescue or permanent treatment discontinuation due to lack of glycaemic control over the 24 weeks of double-blind add-on treatment was numerically smaller in the dapagliflozin group (5.1% [2/39] of patients) compared with placebo (9.1% [3/33] of patients). The proportion of patients with baseline HbA1c ≥ 7% achieving HbA1c < 7% at Week 24 was higher with dapagliflozin than placebo (25.0% [7/28] dapagliflozin vs 4.2% [1/24] placebo).

The mean difference in HbA1c between study groups (dapagliflozin/dapagliflozin and placebo/dapagliflozin) decreased at week 52, as compared to Week 24. A decrease from baseline in HbA1c and FPG after 52 weeks of treatment was observed in both dapagliflozin/dapagliflozin and placebo/dapagliflozin groups. The proportion of patients who required glycaemic rescue or permanent treatment discontinuation due to lack of glycaemic control over the ST + LT periods were similar for the dapagliflozin/dapagliflozin and placebo/dapagliflozin groups. Along the course of the whole study (ST+LT period) fewer patients achieved an HbA1c < 7% among those switched from placebo to dapagliflozin as compared to patients who were treated with dapagliflozin throughout the whole study.

A numerical improvement in dapagliflozin-treated patients over placebo in HbA1c was consistent across race, sex, baseline HbA1c, and background medication subgroups. A subgroup analysis by the age groups 10-18 years and >18 years for the primary endpoint was provided. The analysis show that the outcome was in favour in both age groups, however interpretation has to be made with caution due to the small size of the study.

3.4.3. Conclusions on the clinical efficacy

The effect of dapagliflozin on the primary endpoint (mean change from baseline in HbA1c vs placebo) was not statistically significant, although there was a numerical difference favouring dapagliflozin. The study also failed to meet the secondary objectives. Thus, the findings are uncertain and cannot fully confirm or support the PK/PD data available. However, the study does not contradict the extrapolation model and the totality of data points in favour of effect of dapagliflozin.

3.5. Clinical safety

Introduction

The safety profile of dapagliflozin has been well established in adults with T2DM as well as patient with HFrEF and CKD.

In paediatric T2DM patients, safety and tolerability data from 2 clinical studies support this submission: the pivotal paediatric study (MB102138 /D1690C00017) in children aged 10 to 17 years (and young

adults aged 18 to 24 years) with T2DM, with a 24-week randomised, placebo-controlled part and a 28-week open-label safety extension during which all patients received dapagliflozin.

The applicant has also presented supportive safety data from the Phase 1 PK/PD single-dose study in children aged 10 to 17 years and with T2DM (D1690C00016 (MB102091)). As no relevant safety finding arouse from this single dose study, the clinical safety assessment is mainly based on the pivotal paediatric study D1690C00017 (MB102138).

Patient exposure

Overall, 90 paediatric T2DM patients were exposed to at least 1 dose of dapagliflozin, of whom 24 patients were exposed to 1 dose of 2.5 mg, 5 mg, or 10 mg in the pharmacokinetic/pharmacodynamic study D1690C00016 (MB102091), and 66 patients were exposed to at least 1 dose of 10 mg in study D1690C00017 (MB102138) (including 39 patients in the dapagliflozin group during the ST period and 27 patients in the placebo/dapagliflozin group in the LT period).

Of the 72 randomised patients, 34 (87.2%) and 27 (81.8%) patients completed the ST period in the dapagliflozin and placebo groups, respectively, and 60 (83.3%) patients entered the LT period, including 33 (84.6%) patients who had previously received dapagliflozin and 27 (81.8%) patients who had previously received placebo.

Exposure During the 24-week Double-blind Period

All 72 randomised patients received at least 1 dose of study drug during the 24-week double-blind ST treatment period and were included in the treated subjects set. The mean (SD) duration of exposure was longer in the dapagliflozin group compared with the placebo group (156.0 days [37.7] and 141.3 days [55.3], respectively); median exposure was 168 days in both treatment groups (Table 20). The duration of exposure was 16.7 and 12.8 patient-years in the dapagliflozin and placebo groups, respectively.

Table 20: Duration of Exposure During the 24-week Double-blind Short-term Period Regardless Rescue Medication Initiation in Study D1690C00017 (Treated subjects set)

		Dapagliflozin 10 mg (N=39)	Placebo (N=33)
Duration of exposure (days)	Mean (SD)	156.0 (37.7)	141.3 (55.3)
	Median	168.0	168.0
	Min, Max	9, 179	7, 202
	1st quartile, 3rd quartile	167.0, 171.0	141.0, 174.0
	Total treatment days	6084	4664
Duration of exposure (patient-year)	Total patient-years	16.7	12.8
Duration of exposure category (days) n (%)	1-7	0	1 (3.0)
	8-14	2 (5.1)	0
	15-28	0	3 (9.1)
	29-42	0	1 (3.0)
	43-56	0	0
	57-70	0	0
	71-84	0	0

		Dapagliflozin 10 mg (N=39)	Placebo (N=33)
	85-98	0	1 (3.0)
	99-140	4 (10.3)	2 (6.1)
	141-182	33 (84.6)	24 (72.7)
	>182	0	1 (3.0)

Exposure During the 52-week Short-term Plus Long-term Period

The mean (SD) duration of exposure in the dapagliflozin/dapagliflozin group was 308.4 (107.8) days, with a total duration of exposure of 32.9 patient-years.

In the placebo/dapagliflozin group, in which patients switched from double-blind placebo to open-label dapagliflozin during the open-label (LT) period, the mean (SD) duration of exposure to dapagliflozin was 188.1 (40.6) days, with a total duration of exposure of 12.9 patient-years. Overall, the duration of exposure to dapagliflozin 10 mg was 45.8 patient-years, which is considered as adequate for the evaluation of safety during the ST + LT treatment period in this study.

Of the 30 patients treated with dapagliflozin for the entire 52-week duration of the study (ie, 24-week randomised treatment + 28 week-open-label, uncontrolled treatment period), 29 patients were exposed for > 350 days. Of the 27 patients randomised to placebo and (subsequently) treated with dapagliflozin for the 28 week-open-label, uncontrolled treatment period, 24 patients were exposed for at least 351 days.

Adverse events

Overall adverse events during the 24-week double-blind period

Overall AEs during the 24-week double-blind treatment period regardless rescue medication are summarised in Table 21. Non serious events of hypoglycaemia and DKA were not collected as AEs and are not included in the general AE presentations (see section on adverse event of special interest).

A total of 27 (69.2%) patients in the dapagliflozin group and 19 (57.6%) in the placebo group reported at least 1 AE, and 7 (17.9%) and 2 (6.1%) patients, respectively, reported related AEs.

Table 21: Overall Adverse Events During the 24-week Double-blind Short-term Period Regardless Rescue Medication Initiation in Study D1690C00017 (Treated subjects set)

AE category	Number (%) of patients[a]	
	Dapagliflozin 10mg (N=39)	Placebo (N=33)
At least 1 AE	27 (69.2)	19 (57.6)
At least 1 serious hypoglycaemia event	0	0
At least 1 AE or serious hypoglycaemia event	27 (69.2)	19 (57.6)
At least 1 related AE	7 (17.9)	2 (6.1)
At least 1 adjudicated and confirmed DKA event reported as an SAE	0	0

AE category	Number (%) of patients[a]	
	Dapagliflozin 10mg (N=39)	Placebo (N=33)
Deaths	0	0
At least 1 SAE	1 (2.6)	2 (6.1)
At least 1 related SAE	0	0
SAE leading to discontinuation of study medication	0	0
AE leading to discontinuation of study medication	1 (2.6)	0
Serious hypoglycaemia event leading to discontinuation of study medication	0	0
DKA event leading to discontinuation of study medication reported as an SAE	0	0

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories. Note that the maximum action taken for an AE is presented in the table.

Overall adverse events during the 52-week short-term plus long-term period

Overall AEs during the 52-week ST + LT period regardless of rescue medication are summarised in Table 22.

Among the 39 patients receiving dapagliflozin over the total 52-week treatment period, 29 (74.4%) patients reported at least 1 AE, whereas only 1 (2.6%) patient had an AE leading to discontinuation of study drug (occurring during the 24-week double-blind treatment period). Two [5.1%]) patients reported an SAE (1 during the 24-week double-blind period, and 1 during the 28-week open-label period), and none of these were considered related to study drug by the investigator.

Among the 33 patients randomised to placebo during the 24-week double-blind period and were switched to dapagliflozin treatment for the 28-week open-label period, 23 patients (69.7%) reported at least 1 AE and 3 patients (9.1%) reported an SAE over the entire course of the study. None of the reported SAEs was considered related to the study drug by the investigator.

No SAEs of hypoglycaemia or DKA and no deaths were reported during the study.

Table 22: Overall Adverse Events During the 52-week Short-term Plus Long-term Period Regardless Rescue Medication Initiation in Study D1690C00017 (Treated subjects set)

AE category	Number (%) of subjects[a]	
	Dapagliflozin 10 mg / Dapagliflozin 10 mg (N=39)	Placebo / Dapagliflozin 10 mg (N=33)
At least one AE	29 (74.4)	23 (69.7)
At least one serious hypoglycaemia event	0	0
At least one AE or serious hypoglycaemia event	29 (74.4)	23 (69.7)

	Number (%) of subjects[a]	
AE category	**Dapagliflozin 10 mg / Dapagliflozin 10 mg (N=39)**	**Placebo / Dapagliflozin 10 mg (N=33)**
At least one AE	29 (74.4)	23 (69.7)
At least one related adverse event	7 (17.9)	5 (15.2)
At least one adjudicated and confirmed DKA event reported as an SAE	0	0
Deaths	0	0
At least one SAE	2 (5.1)	3 (9.1)
At least one related SAE	0	0
SAE leading to discontinuation of study drug	0	0
AE leading to discontinuation of study drug	1 (2.6)	0
Serious hypoglycaemia event leading to discontinuation of study drug	0	0
DKA event leading to discontinuation of study drug reported as an SAE	0	0

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories. Note that the maximum action taken for an AE is presented in the table.

Common Adverse Events

Adverse events during the 24-week double-blind period

The most common AEs (reported by > 5% of patients) during the 24-week double-blind period are presented in Table 23.

In the dapagliflozin group, the most common AEs were headache, nasopharyngitis, and vitamin D deficiency (10.3%); nausea and oropharyngeal pain (7.7%); and cough, diarrhoea, viral gastroenteritis, hypertension, streptococcal pharyngitis, sinus congestion, urinary tract infection, vomiting, and increased weight (5.1%). The most common AEs in the placebo group were headache and hyperglycaemia (9.1%); and diarrhoea, hypertriglyceridaemia, and toothache (6.1%).

During the 24-week double-blind treatment period, the majority of the reported AEs occurred prior to rescue medication initiation: 66.7% (26/39) of patients reported 65 AEs in the dapagliflozin group and 54.5% (18/33) of patients reported 60 AEs in the placebo group.

Among the most common AEs according to the known safety profile of dapagliflozin in adults, only urinary tract infections were reported as a common AE (> 5% of patients) in this study, with a similar incidence in both treatment groups (5.1% and 3.0% in the dapagliflozin and placebo groups, respectively).

Table 23: Adverse Events, Most Common (Frequency of >5%), During the 24 week Double-blind Short-term Period Regardless Rescue Medication Initiation in Study D1690C00017 (Treated subjects set)

Preferred term	Number (%) of patients[a]	
	Dapagliflozin 10mg (N=39)	Placebo (N=33)
Patients with any AE[a]	27 (69.2)	19 (57.6)
Headache	4 (10.3)	3 (9.1)
Nasopharyngitis	4 (10.3)	0
Vitamin D deficiency	4 (10.3)	1 (3.0)
Nausea	3 (7.7)	0
Oropharyngeal pain	3 (7.7)	1 (3.0)
Cough	2 (5.1)	1 (3.0)
Diarrhoea	2 (5.1)	2 (6.1)
Gastroenteritis viral	2 (5.1)	0
Hypertension	2 (5.1)	1 (3.0)
Pharyngitis streptococcal	2 (5.1)	0
Sinus congestion	2 (5.1)	0
Urinary tract infection	2 (5.1)	1 (3.0)
Vomiting	2 (5.1)	0
Weight increased	2 (5.1)	0
Hypertriglyceridaemia	1 (2.6)	2 (6.1)
Toothache	1 (2.6)	2 (6.1)
Hyperglycaemia	0	3 (9.1)

[a] Number (%) of subjects with AEs, sorted by decreasing frequency for preferred term according to Dapagliflozin 10mg group. Subjects with multiple events in the same preferred term are counted only once in that preferred term. Subjects with events in more than 1 preferred term are counted once in each of those preferred terms. Percentage is using number of subjects from the treated subjects set in the treatment group as denominator.

Adverse events during the 52-week short-term plus long-term period

The most common AEs (> 5% of patients) during the 52-week ST + LT treatment period are presented in Table 24. In the dapagliflozin/dapagliflozin group, the most common AEs were headache, nasopharyngitis, and vitamin D deficiency (12.8% [5/39] of patients); oropharyngeal pain (10.3% [4/39] of patients); nausea and urinary tract infection (7.7% [3/39] of patients); and back pain, cough, diarrhoea, dyslipidaemia, fatigue, fungal infection, viral gastroenteritis, hypertension, pain in extremity, streptococcal pharyngitis, rash, sinus congestion, upper respiratory tract infection, vomiting, and weight increased (5.1% [2/39] of patients).

The most common AEs in the placebo/dapagliflozin group were headache and hyperglycaemia (12.1% [4/33] of patients); hypertriglyceridaemia (9.1% [3/33] of patients); and cough, diarrhoea, microalbuminuria, toothache, and pharyngotonsillitis (6.1% [2/33] of patients).

All AEs of vitamin D deficiency were mild and considered not related to the study drug by the Investigator. It is noted that vitamin D deficiency was reported as a medical history condition in 15 patients (20.5% [8/39] of patients in the dapagliflozin group and 21.2% [7/33] of patients in the placebo group; most of whom had concomitant treatment with vitamin D/analogues during the study, and none of them had an AE of vitamin D deficiency or decrease during the study.

During the 52-week ST + LT treatment period prior to rescue medication, the majority of the reported AEs occurred prior to rescue medication initiation: 71.8% (28/39) of patients reported 92 AEs in the dapagliflozin/dapagliflozin group and 66.7% (22/33) of patients had 87 AEs in the placebo/dapagliflozin group.

Table 24: Adverse Events, Most Common (Frequency of >5%), During the 52-Week Short-term plus Long-term Period Regardless Rescue Medication Initiation in Study D1690C00017 (Treated subjects set)

	Number (%) of patients[a]	
	Dapagliflozin 10 mg / Dapagliflozin 10 mg (N=39)	Placebo / Dapagliflozin 10 mg (N=33)
Patients with any AE[a]	29 (74.4)	23 (69.7)
Headache	5 (12.8)	4 (12.1)
Nasopharyngitis	5 (12.8)	2 (6.1)
Vitamin D deficiency	5 (12.8)	2 (6.1)
Oropharyngeal pain	4 (10.3)	1 (3.0)
Nausea	3 (7.7)	0
Urinary tract infection	3 (7.7)	1 (3.0)
Back pain	2 (5.1)	1 (3.0)
Cough	2 (5.1)	2 (6.1)
Diarrhoea	2 (5.1)	2 (6.1)
Dyslipidaemia	2 (5.1)	1 (3.0)
Fatigue	2 (5.1)	1 (3.0)
Fungal infection	2 (5.1)	1 (3.0)
Gastroenteritis viral	2 (5.1)	0
Hypertension	2 (5.1)	1 (3.0)
Pain in extremity	2 (5.1)	0
Pharyngitis streptococcal	2 (5.1)	1 (3.0)
Rash	2 (5.1)	1 (3.0)
Sinus congestion	2 (5.1)	0
Upper respiratory tract infection	2 (5.1)	0
Vomiting	2 (5.1)	0
Weight increased	2 (5.1)	0
Hypertriglyceridaemia	1 (2.6)	3 (9.1)
Microalbuminuria	1 (2.6)	2 (6.1)
Toothache	1 (2.6)	2 (6.1)
Dizziness	0	2 (6.1)

	Number (%) of patients[a]	
Hyperglycaemia	0	4 (12.1)
Pharyngotonsillitis	0	2 (6.1)

[a] Number (%) of subjects with AEs, sorted by decreasing frequency for preferred term according to Dapagliflozin 10mg group. Subjects with multiple events in the same preferred term are counted only once in that preferred term. Subjects with events in more than 1 preferred term are counted once in each of those preferred terms. Percentage is using number of subjects from the treated subjects set in the treatment group as denominator.Source: study D1690C00017 CSR, Table 36.

Analysis of Adverse Events by Organ System or Syndrome

Hepatic Adverse Events

Hepatic AEs were reported in 2 patients during study D1690C00017: 1 patient in the dapagliflozin group had an AE of increased AST during the double-blind ST period (although no AST values were reported as marked laboratory abnormality during the study), and 1 patient in the placebo/dapagliflozin group had an AE of increased ALT during the LT period. None of these events was identified as a potential liver-injury case

Diabetic Ketoacidosis Events

No events of DKA were reported in study D1690C00017.

Overall, 35 and 27 patients in the dapagliflozin and placebo groups, respectively, had at least one self-monitored blood ketone measurement during the study. Ketone values > 0.6 mmol/L were observed in 4 (10.3%) and 2 (6.1%) patients in the dapagliflozin and placebo groups, respectively, from Week 1 to Week 4; 5 (12.8%) and 1 (3.0%) patient after Week 4 to Week 24; 4 (10.3%) patients in the dapagliflozin/dapagliflozin group after Week 24 to Week 28; and by 2 (5.1%) and 3 (9.1%) patients in the dapagliflozin/dapagliflozin and placebo/dapagliflozin groups, respectively, after Week 28 to Week 52. Elevations in ketone measurements > 3.8 mmol/L were rare (1 [2.6%] patient in the dapagliflozin group in the period after Week 4 to Week 24). None of the elevated values resulted in a confirmed adjudicated DKA event.

Hypoglycaemic Events

- *Hypoglycaemic events during the 24-week double-blind period*

Hypoglycaemic events according to ADA/ISPAD classifications during the 24-week double-blind treatment period regardless of rescue medication initiation are summarised in Table 25. The ISPAD classification assesses events in patients with age < 18 years.

A higher percentage of patients in the dapagliflozin group experienced hypoglycaemic events compared with placebo by ADA classification (11 [28.2%] patients in the dapagliflozin group and 6 [18.2%] patients in the placebo group) and by ISPAD classification (8 [27.6%] patients and 2 [8.3%] patients, respectively) during the 24-week double-blind period.

Most patients had asymptomatic hypoglycaemia by ADA classification (20.5% and 12.1%, respectively), and mild/moderate hypoglycaemia by ISPAD classification (27.6% and 4.2%). Severe hypoglycaemia was reported in 2 patients in the dapagliflozin group during the 24-week double-blind treatment period. These patients were receiving insulin and metformin as background diabetic medication and had dietary indiscretion as contributing factors. None of the hypoglycaemic events was reported as SAE (Table 25) or led to discontinuation of study drug.

During the 24-week double-blind treatment period, the majority of hypoglycaemic events occurred in patients on insulin medication and/or following insulin as the study medication used for glycaemic rescue, including the 2 patients with severe hypoglycaemia. Overall hypoglycaemic events in patients on insulin medication and/or following glycaemic rescue medication were reported in 20.5% (8/39) and 15.2% (5/33) of patients in the dapagliflozin and placebo groups, respectively, by ADA classification, and in 17.2% (5/29) and 8.3% (2/24), respectively, by ISPAD classification.

During the 24-week double-blind treatment period, the majority of hypoglycaemic events occurred prior to rescue medication initiation, including the 2 patients with severe hypoglycaemia. Overall hypoglycaemic events prior to rescue medication initiation were reported in 25.6% (10/39) and 18.2% (6/33) of patients in the dapagliflozin and placebo groups, respectively, by ADA classification, and by ISPAD classification in 24.1% (7/29) and 8.3% (2/24), respectively, during the 24-week double-blind period.

Table 25: Hypoglycaemic Events During the 24-week Double-blind Short-term Period Regardless of Rescue Medication Initiation in Study D1690C00017 (Treated Subjects Set)

Classification system	Number (%) of patients			
	Dapagliflozin 10 mg (N=39)		Placebo (N=33)	
	Number[%] of patients [a]	Number of Events	Number[%] of patients [a]	Number of Events
ADA classification				
Overall	11 (28.2)	21	6 (18.2)	27
Severe hypoglycaemia	2 (5.1)	2	0	0
Documented symptomatic hypoglycaemia	3 (7.7)	4	1 (3.0)	7
Asymptomatic hypoglycaemia	8 (20.5)	14	4 (12.1)	19
Probable symptomatic hypoglycaemia	0	0	0	0
Relative hypoglycaemia	1 (2.6)	1	1 (3.0)	1
ISPAD classification				
N#	29		24	
Overall	8 (27.6)	18	2 (8.3)	16
Severe hypoglycaemia	2 (6.9)	2	0	0
Mild/moderate hypoglycaemia	8 (27.6)	16	1 (4.2)	15
Unclassified[b]	0	0	1 (4.2)	1

[a] Subjects with multiple hypoglycemia events in the same category are counted only once in that category. Subjects with hypoglycemia events in more than 1 category are counted once in each of those categories.
[b] Unclassified hypoglycemia events refer to Probable symptomatic or Relative hypoglycemia event using ADA classification.

- *Hypoglycaemic events during the 52-week short-term plus long-term period*

Hypoglycaemic events according to ADA/ISPAD classifications during the 52-week ST + LT treatment period regardless of rescue medication initiation are summarised in Table 26.

The percentage of patients with hypoglycaemic events during the 52-week ST + LT treatment period was 33.3% (13/39) and 27.6% (9/33) by ADA classification in the dapagliflozin/dapagliflozin and placebo/dapagliflozin groups, respectively, and 34.5% (10/29) and 20.8% (5/24) by ISPAD classification.

Most patients had asymptomatic hypoglycaemia by ADA classification (25.6% [10/39] and 21.2% [7/33], respectively), and mild/moderate hypoglycaemia (34.5% [10/29] and 16.7% [4/24] by ISPAD classification). During the LT treatment period, severe hypoglycaemia was reported in 1 additional patient by ADA and ISPAD in the dapagliflozin/dapagliflozin group and 1 additional patient in the placebo/dapagliflozin group by ADA. The patient in the dapagliflozin/dapagliflozin group was on background metformin and insulin as antidiabetic medication and no contributing factors were reported. The patient in the dapagliflozin/placebo group had metformin as background diabetic medication and no reported contributing factors.

None of the hypoglycaemic events was reported as SAE or led to discontinuation of study drug.

During the 52-week ST + LT treatment period for patients on insulin medication and/or following glycaemic rescue medication, the majority of hypoglycaemic events occurred in patients on insulin medication and/or following glycaemic rescue medication, including the 3 patients with severe hypoglycaemia. Overall hypoglycaemic events, excluding events of hypoglycaemia after rescue medication initiation, were reported in 25.6% (10/39) and 15.2% (5/33) of patients in the dapagliflozin/dapagliflozin and placebo/dapagliflozin groups, respectively, by ADA classification, and by ISPAD classification in 24.1% (7/29) and 8.3% (2/24), respectively, during the 52-week ST + LT period.

During the 52-week ST + LT treatment period, patients on insulin medication and/or following administration of insulin for glycaemic rescue experienced the majority of hypoglycaemic events occurring during the 52-week ST + LT treatment period. Events in patients on background insulin as an antidiabetic medication or rescued with insulin included the 3 patients with severe hypoglycaemia. Overall, hypoglycaemia, excluding events after rescue medication initiation, was reported in 28.2% (11/39) and 27.3% (9/33) of patients in the dapagliflozin/dapagliflozin and placebo/dapagliflozin groups, respectively, by ADA classification, and by ISPAD classification in 27.6% (8/29) and 20.8% (5/24), respectively, during the 52-week ST + LT period.

Table 26: Hypoglycaemic Events During the 52-week Short-term plus Long-term Period Regardless of Rescue Medication Initiation in Study D1690C00017 (Treated Subjects Set)

Classification system	Number (%) of patients			
	Dapagliflozin 10 mg / Dapagliflozin 10 mg (N=39)		Placebo / Dapagliflozin 10 mg (N=33)	
	Number[%] of patients [a]	Number of events	Number[%] of patients [a]	Number of events
ADA classification				
Overall	13 (33.3)	37	9 (27.3)	71
Severe hypoglycaemia	3 (7.7)	3	1 (3.0)	1
Documented symptomatic hypoglycaemia	4 (10.3)	6	3 (9.1)	13
Asymptomatic hypoglycaemia	10 (25.6)	26	7 (21.2)	56
Probable symptomatic hypoglycaemia	0	0	0	0
Relative hypoglycaemia	2 (5.1)	2	1 (3.0)	1
ISPAD classification				
N#	29		24	
Overall	10 (34.5)	34	5 (20.8)	52
Severe hypoglycaemia	3 (10.3)	3	0	0
Mild/moderate hypoglycaemia	10 (34.5)	30	4 (16.7)	51
Unclassified [b]	1 (3.4)	1	1 (4.2)	1

[a] Subjects with multiple hypoglycemia events in the same category are counted only once in that category. Subjects with hypoglycemia events in more than 1 category are counted once in each of those categories.
[b] Unclassified hypoglycemia events refer to Probable symptomatic or Relative hypoglycemia event using ADA classification.

Serious adverse event/deaths/other significant events

Serious adverse events during the 24-week double-blind period

Three SAEs were reported during the 24-week double-blind ST treatment period: 1 in the dapagliflozin group (depression: 1 [2.6%] patient) and 2 in the placebo group (hyperglycaemia and spontaneous abortion, each 1 [3.0%] patient) (Table 27). None of the reported SAEs was assessed as related to the study drug by the Investigator.

Table 27: Serious Adverse Events with Onset During the 24-week Double-blind Short-term Period Regardless Rescue Medication Initiation, by System Organ Class and Preferred Term in Study D1690C00017 (Treated subjects set)

System organ class / Preferred term	Dapagliflozin 10mg (N=39)		Placebo (N=33)	
	Number[%] of patients[a]	Number of events	Number[%] of patients[a]	Number of events
Any SAE[b]	1 (2.6)	1	2 (6.1)	2

System organ class / Preferred term	Dapagliflozin 10mg (N=39)		Placebo (N=33)	
	Number[%] of patients[a]	Number of events	Number[%] of patients[a]	Number of events
Psychiatric disorders	1 (2.6)	1	0	0
Depression	1 (2.6)	1	0	0
Metabolism and nutrition disorders	0	0	1 (3.0)	1
Hyperglycaemia	0	0	1 (3.0)	1
Pregnancy, puerperium and perinatal conditions	0	0	1 (3.0)	1
Abortion spontaneous	0	0	1 (3.0)	1

[a] Number (%) of subjects with SAE, sorted by decreasing frequency within each system organ class and preferred term according to the Dapagliflozin 10 mg treatment group. Subjects with multiple serious events in the same preferred term are counted only once in that preferred term. Subjects with events in more than 1 preferred term are counted once in each of those preferred terms.
Percentage is using number of subjects from the treated subjects set in the treatment group as denominator.
[b] include All SAEs (including hypoglycemic events and DKA events), regardless of rescue therapy initiation, that occurred during the 24-week double-blind short-term period thus SAEs with an onset from Day 1 of the 24-week short-term period up to and including 30 days after the last dose date in the period or the start date of the long-term treatment period, whichever comes first.

Serious adverse events during the 52-week short-term plus long-term period

During the 52-week ST + LT treatment period, SAEs were reported in 2 (5.1%) patients in the dapagliflozin/dapagliflozin group and 3 (9.1%) patients in the placebo/dapagliflozin group (Table 28). The additional SAEs reported during the LT period were one SAE of lower abdominal pain (dapagliflozin/dapagliflozin group) and one SAE of hyperglycaemia (placebo/dapagliflozin group).

None of the reported SAEs was assessed as related to the study drug by the Investigator.

Table 28: Serious Adverse Events with Onset During the 52-week Short-term Plus Long-term Period Regardless Rescue Medication Initiation, by System Organ Class and Preferred Term in Study D1690C00017 (Treated subjects set)

System organ class / Preferred term	Dapagliflozin 10 mg / Dapagliflozin 10 mg (N=39)		Placebo / Dapagliflozin 10 mg (N=33)	
	Number [%] of patients[a]	Number of events	Number [%] of patients[a]	Number of events
Any SAE[b]	2 (5.1)	2	3 (9.1)	3
Gastrointestinal disorders	1 (2.6)	1	0	0
Abdominal pain lower	1 (2.6)	1	0	0
Psychiatric disorders	1 (2.6)	1	0	0
Depression	1 (2.6)	1	0	0
Metabolism and nutrition disorders	0	0	2 (6.1)	2
Hyperglycaemia	0	0	2 (6.1)	2
Pregnancy, puerperium and perinatal conditions	0	0	1 (3.0)	1

System organ class / Preferred term	Dapagliflozin 10 mg / Dapagliflozin 10 mg (N=39)		Placebo / Dapagliflozin 10 mg (N=33)	
	Number [%] of patients[a]	Number of events	Number [%] of patients[a]	Number of events
Abortion spontaneous	0	0	1 (3.0)	1

[a] Number (%) of subjects with SAE, sorted by decreasing frequency within each system organ class and preferred term according to the Dapagliflozin 10 mg treatment group.
Subjects with multiple serious events in the same preferred term are counted only once in that preferred term. Subjects with events in more than 1 preferred term are counted once in each of those preferred terms. Percentage is using number of subjects from the treated subjects set in the treatment group as denominator.
[b] include All SAEs (including hypoglycemic events and DKA events), regardless of rescue therapy initiation, that occurred during the 52-week short-term plus long-term period thus SAEs with an onset from Day 1 of the 24-week short-term period up to and including 30 days after the last dose date.
Note: Summary based on actual treatment group. During long-term open-label period all subjects were treated with dapagliflozin 10 mg.

Deaths

No deaths were reported in studies D1690C00016 (MB102091) or D1690C00017 (MB102138)

Laboratory findings

Haematology

No clinically meaningful mean changes over the course of the study were observed in the haematology parameters, except for slight mean increases in haematocrit and haemoglobin with dapagliflozin.

The majority of patients had baseline haematocrit and haemoglobin values within normal paediatric reference ranges and remained within those ranges over time. There were no individual clinically important abnormalities in the haematology parameters.

Clinical Chemistry

No clinically meaningful mean changes over the course of the study were observed in any of the clinical chemistry parameters. The majority of patients had baseline values within normal paediatric reference ranges for the clinical chemistry parameters and remained within those ranges over time.

Elevations in ALT or AST accompanied by elevations in total bilirubin

No patients had ALT ≥ 3 × ULN or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN.

Marked laboratory abnormalities

During the 24-week double-blind period, the following marked laboratory abnormalities were observed in liver function tests:

- ALT ≥ 3 × ULN: 3/37 (8.1%) patients in the dapagliflozin group and 1/30 (3.3%) patients in the placebo group. For 1 of these patients in the dapagliflozin group, ALT values returned to within the normal range, and for the other 3 patients, values were high at baseline and remained high through Week 52.

- Total bilirubin ≥ 1.5 × ULN: 2/30 (6.9%) patients in the placebo group. For 1 of these patients, values returned to normal and for the other, values remained high through the end of study.

During the LT period, an additional patient in the dapagliflozin/dapagliflozin group reported ALT ≥ 3 × ULN.

The following marked laboratory abnormalities occurred prior to rescue medication initiation:

- ALT ≥ 3 × ULN: 3/39 (7.7%) patients in the dapagliflozin group
- Total bilirubin ≥ 1.5 × ULN: 2/33 (6.7%) patients in the placebo group

Urine analysis

The majority of patients had an albumin/creatinine ratio < 3.4 mg/mmol at baseline (82.1% [32/39] in the dapagliflozin group and 83.9% [26/31] in the placebo group), and few shifts were observed during the study, with no differences between the treatment groups.

Pregnancy

One pregnancy was reported during study D1690C00017 in the placebo group, with a positive test result at Week 16 that led to discontinuation of study drug. The pregnancy outcome was spontaneous abortion, reported as an SAE.

Growth and Maturation Markers

In study D1690C00017, no clinically meaningful mean changes over the course of the study were observed in any of the growth and maturation markers, and no impact of treatment was observed in the growth and maturation markers.

Particularly, no clinically meaningful mean changes over the course of the study were observed in 25-hydroxyvitamin D: mean baseline value for the treated population were 48.20 nmol/L in the dapagliflozin group and 47.90 nmol/L in the placebo group; at Week 24, mean change from baseline was -0.15 and 2.25 nmol/L, respectively; and at Week 52, 2.28 and -0.02 nmol/L in the dapagliflozin/dapagliflozin and placebo/dapagliflozin groups, respectively.

Bone Biomarkers in Study

In study D1690C00017, no clinically meaningful mean changes over the course of the study were observed in the bone biomarkers, and no impact of treatment was observed in the bone biomarkers.

In the treated population, mean baseline bone specific alkaline phosphatase values were 28.41 and 33.98 µg/L in the dapagliflozin and placebo groups, respectively. At Week 24, mean change from baseline in bone specific alkaline phosphatase were -2.78 and -3.29 µg/L, respectively; and at Week 52 were -4.16 and -6.07 µg/L in the dapagliflozin/dapagliflozin and placebo/dapagliflozin groups, respectively. Mean baseline osteocalcin values were 34.79 and 33.48 µg/L in the dapagliflozin and placebo groups, respectively. At Week 24, mean change from baseline in osteocalcin were -1.75 and 0.52 µg/L, respectively; and at Week 52 were -8.37 and -1.11 µg/L in the dapagliflozin/dapagliflozin and placebo/dapagliflozin groups, respectively.

Tanner Staging

In study D1690C00017, a normal progression of sexual maturation was observed over time, as assessed by the change from baseline in the percentages of patients at each Tanner stage.

Vital Signs

No clinically meaningful mean changes over the course of the study were observed in heart rate or blood pressure. In particular, mean baseline systolic blood pressure was 119.4 and 118.2 mmHg in the dapagliflozin and placebo groups, respectively. At Week 24, mean change from baseline in systolic blood pressure were -0.3 and 1.6 mmHg, respectively; and at Week 52 were 1.4 and -1.8 mmHg in the dapagliflozin/dapagliflozin and placebo/dapagliflozin groups, respectively.

A mild increase in measured height was observed over the course of the study, which was similar in both treatment groups. When adjusted for age and sex, no changes from baseline in standardised height (z-score) were observed at Week 24 (mean change from baseline of 0.014 and -0.029 in the dapagliflozin and placebo groups, respectively) or Week 52 (mean change from baseline of 0.013 and -0.012 in the dapagliflozin/dapagliflozin and placebo/dapagliflozin groups, respectively). Similarly, no notable impact of treatment was observed over the course of the study in weight or BMI. The change from baseline in standardised weight (z-score) at Week 24 were -0.074 and -0.121 in the dapagliflozin and placebo groups, respectively, and at Week 52 were -0.215 and -0.192 in the dapagliflozin/dapagliflozin and placebo/dapagliflozin groups, respectively. The change from baseline in standardised BMI (z-score) at Week 24 were -0.077 and -0.113 in the dapagliflozin and placebo groups, respectively, and at Week 52 were -0.239 and -0.191 in the dapagliflozin/dapagliflozin and placebo/dapagliflozin groups, respectively.

Electrocardiograms

The majority of patients had a normal ECG at baseline (90.6% [29/32] in the dapagliflozin group and 76.0% [19/25] in the placebo group), and at Week 24 (90.6% [29/32] and 88.0% [22/25], respectively). Similar results were observed at Week 52

Safety in special populations

Intrinsic Factors

In study D1690C00017, no remarkable differences by subgroup were observed in the incidence of AEs during the ST period or during the 52-week ST + LT treatment period regardless rescue medication. An overview of AEs during the 24-week double-blind treatment period and 52-week ST + LT safety follow-up period is presented by age, sex, and race regardless of rescue medication initiation in the study report. No remarkable differences by subgroup were observed in the incidence of AEs.

Extrinsic Factors

In study D1690C00017, no remarkable differences by subgroup were observed in the incidence of AEs by diabetic background medication during the 24-week double-blind treatment period or during the 52-week ST + LT treatment period regardless of rescue medication. The use of insulin in conjunction with dapagliflozin increase the frequency of hypoglycaemia.

Discontinuation due to adverse events

In study D1690C00017, one AE that led to discontinuation of study drug was reported during the 24-week double-blind treatment ST period: 1 event of fungal infection (reported as vaginal yeast infection) in 1 (2.6%) patient in the dapagliflozin group. The AE was considered related to the study drug by the investigator. An additional patient was reported as having discontinued study drug due to AE during the ST period, but this AE (hyperglycaemia) had a start date during the lead-in period before the first dose of study drug. There were no additional reports of AEs leading to discontinuation of study drug during the (open-label) LT period.

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. Dapagliflozin is indicated as an adjunct to diet and exercise for the treatment of diabetes in adults with T2DM and in the EU and Japan also as an oral adjunct treatment to insulin in adults with T1DM.

The annual dapagliflozin PBRER with data lock 04 October 2019, included approximately 7926295 patient-years of post-marketing exposure (cumulative until 30 September 2019). At the data lock of the dapagliflozin PBRER (04 October 2019), there was no new information to alter the overall positive benefit-risk profile for dapagliflozin in the approved indications.

3.5.1. Discussion on clinical safety

The safety profile of dapagliflozin has been well established in adults with T2DM as well as patient with HFrEF and CKD. In paediatric T2DM patients, safety and tolerability data from the pivotal paediatric study D1690C00017 (MB102138) in children aged 10 to 24 years support this submission. The Phase 1 PK/PD single-dose study D1690C00016 (MB102091) in children aged 10 to 17 years provides supportive safety data but no relevant safety findings.

The mean (SD) duration of exposure in the dapagliflozin/dapagliflozin group was 308.4 (107.8) days, with a total duration of exposure of 32.9 patient-years. Few patients have been exposed > 350 days (29 patients). Thus, there is a lack of long-term safety data in the paediatric population.

There were no SAEs of hypoglycaemia or DKA and no deaths in either treatment group during the ST treatment period. Few patients reported SAEs (1 dapagliflozin vs 2 placebo) or had AEs leading to discontinuation of study drug (1 dapagliflozin vs 0 placebo). None of the reported SAEs was considered related to the study drug by the investigator.

The number and intensity of AE did not differ significantly between treatment groups during the placebo controlled 24 weeks and up to 52 weeks (placebo-controlled and safety follow-up).

The most common AEs in the dapagliflozin group were headache, nasopharyngitis and vitamin D deficiency (10,3%). The most common AEs in the placebo group were headache (9.1%) and hyperglycaemia, diarrhoea, hypertriglyceridemia and toothache (6.1%). Among the most common AEs according to the known safety profile of dapagliflozin in adults, only urinary tract infections were reported as a common AE (> 5% of patients) in this study, with a similar incidence in both treatment groups (5.1% and 3.0% in placebo).

No clinically significant differences between study groups in terms of AE were seen up to 52 weeks. All AEs of vitamin D deficiency were mild and considered not related to the study drug. Urinary tract infections were more common in the dapagliflozin group (3 (7.7%) vs 1 (3.0%) in placebo).

Elevated ketone measurements were reported during the study in the dapagliflozin group, although without clinical relevance. This is in line the known mechanism of action of dapagliflozin and the safety profile in adults. None of the elevated values resulted in a confirmed adjudicated DKA event (including a case of >3.8 mmol/L (1 patient [2.6%]).

A higher percentage of patients in the dapagliflozin group experienced hypoglycaemic events compared with placebo during the placebo-controlled phase, both according to the ADA criteria (11 [28.2%] dapagliflozin group vs 6 [18.2%] in placebo) and by ISPAD classification (up to 18 yo) (8 [27.6%] dapagliflozin vs [8.3%] placebo). As expected, these differences fade away during the 52-week ST + LT treatment period.

Severe hypoglycaemia was reported in 2 patients in the dapagliflozin group during the 24-week double-blind treatment period. These patients were receiving insulin and metformin and had dietary indiscretion as contributing factors. During the LT treatment period, severe hypoglycaemia was reported in 1 additional patient in the dapagliflozin / dapagliflozin group and 1 additional patient in the placebo/ dapagliflozin. The patient in the dapagliflozin/dapagliflozin group was on background metformin and insulin as antidiabetic medication and no contributing factors were reported. The patient in the dapagliflozin/placebo group had metformin as background diabetic medication and no reported contributing factors.

Thus, the reporting of hypoglycaemias was rather high, but it should be noted that a large proportion of the patients were on concomitant insulin treatment. The reporting rates are in line with the rates reported in adults concomitantly treated with dapagliflozin and insulin. The risk of hypoglycaemia with concomitant use of insulin is already reflected in the SmPC of dapagliflozin.

No imbalance between study groups was seen concerning SAE. No deaths were reported during the study.

No clinically meaningful mean changes over the course of the study were observed in the haematology and clinical chemistry tests. Few cases of increased liver enzymes were reported and none of them were considered as clinically significant and were not deemed to require further follow up.

No clinically meaningful mean changes over the course of the study were neither observed in any of the growth and maturation markers (in particular 25-hydroxyvitamin D), nor in bone biomarkers (bone specific ALP, osteocalcin). Likewise, a normal progression of sexual maturation was observed over the course of the study.

No clinically meaningful mean changes over the course of the study were observed in heart rate or blood pressure. In both treatment groups, a mild increase in measured height was observed over the course of the study, as expected.

In contrast to what has been observed in adults, no notable impact of treatment was observed over the course of the study in weight or BMI, neither at 25 nor 52 weeks.

One patient in the dapagliflozin group discontinued study drug due to fungal infection during the placebo-controlled period (deemed as drug-related by investigator).

As the current application concerns the extension of the indication to include patients aged 10-18 years whereas the pivotal study included patients aged 10-24 years of age, the MAH has provided the available safety data for the age group 10-18 years separately. No differences in the safety profile compared to adults is observed but the data is limited.

Pre-clinical data has previously pointed towards a concern on kidney related AEs due to the observation of dilated kidney pelvis in juvenile animal models due to increased urine volume output secondary to glucosuria. As discussed by the MAH, the pre-clinical findings are not relevant for the proposed target population (patients aged 10-18 years), since in humans the kidney is fully matured by the age of 2 years. The safety data provided in this application did not observe any imbalances in kidney related AEs, nor any signs of decreased kidney function or other urologic AEs.

3.5.2. Conclusions on clinical safety

The safety profile of dapagliflozin has been well established in adults with T2DM as well as patient with HFrEF and CKD. Although exposure data is very limited in the paediatric population, add-on treatment with dapagliflozin 10 mg to metformin or insulin ± metformin for up to 52 weeks seems to be well

tolerated in patients aged 10 to 24 years with T2DM. No cases of DKA were reported during the study, even though several cases of ketosis without further clinical consequences were reported.

No new safety concerns were identified in children and young adults from 10 up to 24 years-of-age as compared with the established safety profile in adults with T2DM. However, long-term safety data beyond 52 weeks is lacking. In order to address the long-term safety in the paediatric population (aged 10 years and above) receiving dapagliflozin, the week 104 safety follow-up for ongoing study D1680C00019 has been included in the RMP as a Category 3 PASS study.

3.5.3. PSUR cycle

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

4. Risk management plan

The WSA submitted an updated RMP (version 26.3) with this application. The updated RMP consolidates versions 21 and 26.

4.1. Summary of the safety concerns

Table SVIII.1: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Diabetic Ketoacidosis including events with atypical presentation
Important potential risks	Bladder cancer Breast cancer Prostate cancer Lower limb amputation
Missing information	Use in patients with NYHA class IV ***Long-term safety in the paediatric population*** ***(aged 10 years and above)***

4.2. Pharmacovigilance plan

Table Part III.3.1: On-going 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 3* - Required additional pharmacovigilance activities (by the competent authority)				
MB102118 (D1690R00007) - Observational study: Cancer in Patients on	To assess the incidence of breast and bladder cancer among new users of dapagliflozin compared to those	Risk of cancer	Submission of Interim data	2016, 2019, 2021, 2023

Study (study short name, and title) Status (planned/ongoing)	Summary of objectives	Safety concerns addressed	Milestones (required by regulators)	Due dates
Dapagliflozin and Other Antidiabetic Treatment Ongoing	who are new users of certain other antidiabetic drugs.		Submission of final data	2025
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
D169CC00001 Deliver An International, Double-blind, Randomised, Placebo-Controlled Phase III Study to Evaluate the Effect of Dapagliflozin on Reducing CV Death or Worsening Heart Failure in Patients with Heart Failure with Preserved Ejection Fraction (HFpEF)	To determine whether dapagliflozin is superior to placebo, when added to standard of care, in reducing the composite of CV death and HF events (hospitalisation for HF or urgent HF visit) in patients with HF and preserved systolic function	Lower limb amputation	Submission of final data	Q3 2022
D1680C00019 (CV181375) T2NOW A 26-Week, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Parallel Group, Phase 3 Trial with a 26-Week Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin and Saxagliptin in Paediatric Patients with T2DM Who Are Between 10 and < 18 Years of Age	***To assess the safety and tolerability of dapagliflozin and saxagliptin in paediatric T2DM subjects aged from 10 to < 18 years, when administered for up to 52 weeks of total treatment. Long term safety data including measures of growth and maturity and Tanner staging and markers of bone health will be collected for up to 104 weeks.***	***Long-term safety in the paediatric population (aged 10 years and above) receiving dapagliflozin.***	***Submission of final data***	***2024***

*Category 3 studies are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

4.3. Risk minimisation measures

Routine risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risks	
Diabetic Ketoacidosis including events with atypical presentation	Routine risk communication: SmPC sections 4.4, 4.8.

Safety concern	Routine risk minimisation activities
	PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: Symptoms of DKA included, and direction to assess patients immediately, regardless of blood glucose level, if these symptoms occur. Information included 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). Information that FORXIGA should not be used for patients with T1DM (SmPC section 4.4). Information on how to detect symptoms of DKA and instructions to seek medical attention (PL section 2, 4).
Important potential risks	
Bladder cancer	None
Breast cancer	None
Prostate cancer	None
Lower limb amputation	Routine risk minimisation activities recommending specific clinical measures to address the risk: Guidance provided on potential class effect (SmPC section 4.4) and counsel on routine preventative foot care (SmPC section 4.4 and PL section 2).
Missing information	
Use in patients with NYHA class IV	Routine risk communication: SmPC section 4.4
Long-term safety in the paediatric population (aged 10 years and above)	***None***

The changes to the RMP are acceptable.

5. Changes to the Product Information

As a result of this variation, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are being updated to include information on the use of dapagliflozin in paediatric patients. The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

5.1.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the WSA and has been found acceptable for the following reasons:

The package leaflet recently underwent readability testing in new indication application (WS-1737) to add an indication for the treatment of symptomatic chronic heart failure with reduced ejection fraction. The package leaflet passed the readability test. With this variation, only minor updates are proposed to the package leaflet.

This is considered acceptable.

6. Benefit-Risk Balance

6.1. Therapeutic Context

6.1.1. Disease or condition

The proposed extension of the indication in T2DM is:

"Forxiga/ Edistride is indicated in adults ***and children aged 10 years and above*** 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."

The incidence of T2DM in children is increasing worldwide, and the main driver is the increased prevalence and degree of childhood obesity. Childhood T2DM is still relatively rare in Europe, with a prevalence of approximately 2.5 per 100 thousand.

Developing T2DM at a younger age is associated with a considerably higher risk of long-term cardiovascular disease compared with those who develop T2DM in the middle age. The rapid deterioration in glucose regulation in children as compared with adults may contribute to the greater risk for micro- and macrovascular complications in children with T2DM as they develop into adults.

6.1.2. Available therapies and unmet medical need

Management of T2DM in children involves lifestyle modifications. Pharmacologic glucose-lowering treatment is often necessary and includes metformin or insulin or a combination of both. Recently, a GPL1-RA (liraglutide) has been approved for the use in children aged 10 or older.

There is a need for additional effective, well tolerated and easily administered treatments to achieve and maintain target HbA1c levels as early as possible in children with T2DM.

6.1.3. Main clinical studies

Study D1690C00017 was a prospective, multicentre, 24-week, placebo-controlled, double-blind, randomised study (ST period) with a 28-week open-label active treatment extension (LT period), which included patients ≥10 years and < 25 years of age, with confirmed diagnosis of T2DM, who were being treated with diet and exercise and a stable dose of metformin, insulin or a combination of both.

The study patients were children and young adults aged 10 to 24 years and with a confirmed diagnosis of T2DM. Young adults aged 18 to 24 years were included due to recruitment challenges in the target population (although the number of patients was limited to less than 40% of patients, to ensure that the study population would adequately represent the target population). Background treatment included diet

and exercise as well as a stable dose of metformin, insulin or a combination of both for a minimum of 8 weeks prior to screening.

The primary objective was to compare the mean change from baseline in HbA1c achieved with dapagliflozin against the mean achieved with placebo after 24 weeks of double-blind add-on treatment in patients aged 10 to less than 25 years with T2DM who have inadequate glycaemic control on diet and exercise with metformin or insulin ± metformin.

Secondary endpoints included FPG, the percentage of patients requiring rescue treatment and the percentage of patients with baseline HbA1c > 7% who achieve a HbA1c level < 7%.

The primary and secondary efficacy objectives were assessed at Week 24, but also exploratively at Week 52, to assess the long-term trend of glycaemic control with dapagliflozin.

A total of 168 patients (with 13 re-screened patients) were enrolled in 7 countries and 72 were randomised: 39 patients in the dapagliflozin group and 33 patients in the placebo group (24 (33.3%) patients in Europe).

Demographics and patient characteristics were generally balanced between study groups. Most patients (62.5%) were obese, with an average baseline BMI of 32.38 kg/m^2. The disease-related characteristics at screening were representative of the paediatric and young adult population of patients with T2DM in clinical practice.

6.2. Favourable effects

Favourable effects

Treatment with dapagliflozin led to point estimate of adjusted mean change from baseline (LS mean) in HbA1c of -0.25% and +0.50% in the dapagliflozin and placebo groups, respectively at week 24, resulting in a treatment difference of -0.75% (95% CI -1.65, 0.15). Thus, dapagliflozin was not superior to placebo and therefore, the study did not meet the primary efficacy endpoint. However, the numerical difference favoured dapagliflozin.

A numerical reduction from baseline mean FPG was observed in the dapagliflozin group compared with a numerical increase in the placebo group.

The proportion of patients who required glycaemic rescue or permanent treatment discontinuation due to lack of glycaemic control was numerically smaller in the dapagliflozin group (5.1% [2/39] of patients) compared with placebo (9.1% [3/33] of patients).

The proportion of patients with baseline HbA1c ≥ 7% achieving HbA1c < 7% at Week 24 was higher with dapagliflozin than placebo (25.0% [7/28] dapagliflozin vs 4.2% [1/24] placebo).

A numerical improvement in dapagliflozin-treated patients over placebo in HbA1c was consistent across race, sex, baseline HbA1c, and background medication subgroups.

The popPK analysis is considered adequate to describe the PK in paediatric patients. The dapagliflozin exposure in children 10-17 years is similar to the exposure in adults. This supports that the same dose as adults (10 mg) is adequate also for paediatric patients aged of 10-17 years old.

6.3. Uncertainties and limitations about favourable effects

The study did not meet the primary nor any of the secondary endpoints, as the difference was not statistically significant. The limited size of the study, conditioned by the difficulties in recruiting patients,

and the wide variability of the baseline characteristics, may have influence the results of the statistical analysis. However, the study does not contradict the extrapolation model and the totality of data points in favour of an effect of dapagliflozin.

6.4. Unfavourable effects

The safety profile of dapagliflozin has been well established in adults with T2DM as well as patient with HFrEF and CKD. In paediatric T2DM patients, safety and tolerability data comes mainly from the pivotal paediatric study D1690C00017 in children aged 10 to 17 years.

A higher percentage of patients in the dapagliflozin group experienced hypoglycaemic events compared with placebo during the placebo-controlled phase, both according to the ADA criteria (11 [28.2%] dapagliflozin group vs 6 [18.2%] in placebo) and by ISPAD classification (up to 18 yo) (8 [27.6%] dapagliflozin vs [8.3%] placebo). No SAE of hypoglycaemia were reported. The majority of hypoglycaemias were reported in patients on concomitant treatment with insulin.

Elevated ketone values > 0.6 mmol/L were observed in 4 (10.3%) and 2 (6.1%) patients in the dapagliflozin and placebo groups, respectively, from Week 1 to Week 4; 5 (12.8%) and 1 (3.0%) patients after Week 4 to Week 24, but no cases of adjudicated DKA were reported.

AEs of vitamin D deficiency were observed in 5 (12.8%) and 2 (6.1%) patients in the dapagliflozin and placebo groups, respectively. All AEs of vitamin D deficiency were mild and considered not related to the study drug.

Urinary tract infections were more common in the dapagliflozin group (3 (7.7%) vs 1 (3.0%) in placebo)

No clinically meaningful mean changes over the course of the study were observed in any of the growth and maturation markers (in particular 25-hydroxyvitamin D), as well as bone biomarkers (bone specific ALP, osteocalcin). Likewise, a normal progression of sexual maturation was observed over the course of the study.

The change from baseline in standardised weight (z-score) at Week 24 were -0.074 and -0.121 in the dapagliflozin and placebo groups, respectively, and at Week 52 were -0.215 and -0.192 in the dapagliflozin/dapagliflozin and placebo/dapagliflozin groups, respectively.

The change from baseline in standardised BMI (z-score) at Week 24 were -0.077 and -0.113 in the dapagliflozin and placebo groups, respectively, and at Week 52 were -0.239 and -0.191 in the dapagliflozin/dapagliflozin and placebo/dapagliflozin groups, respectively.

6.5. Uncertainties and limitations about unfavourable effects

The current safety database in the target population includes 90 paediatric T2DM patients exposed to at least 1 dose of dapagliflozin, of whom 24 patients were exposed to single doses in the pharmacokinetic/pharmacodynamic study D1690C00016 (MB102091), and 66 patients who were exposed to at least 1 dose of 10 mg in study D1690C00017 (MB102138) (including 39 patients in the dapagliflozin group during the ST period and 27 patients in the placebo/dapagliflozin group in the LT period). Thus, the safety data set is very limited. Further follow-up of long-term safety in the paediatric population is deemed necessary and the RMP has been updated accordingly to include the ongoing study D1680C00019 as a Category 3 study.

6.6. Effects Table

Table 29 Effects Table for Forxiga/Edistride in the treatment of T2DM patients aged 10 to 24 years (data cut-off: 18 May 2020)

Effect	Short description	Unit	Treatment	Control	Uncertainties /Strength of evidence	References
Favourable Effects						
Prim endpoint	change from baseline in HbA1c (%) at Week 24	LS mean (SE) (95% CI)	-0.25 (0.30) (-0.85, 0.34)	0.50 (0.34) (-0.18, 1.17)	-0.75 (0.45) (-1.65, 0.15) p=0.101	Study D1690 C00017
Sec endpoint	Change from baseline in FPG (mmol/L) at Week 24	LS mean (SE) (95% CI)	-0.07 (0.53) (-1.13, 1.00)	0.72 (0.61) (-0.51, 1.95)	-0.78 (0.81) (-2.42, 0.85) p=0.340	
	Proportion of patients discontinued due to lack of glycaemic control or rescued at or prior to Week 24	N (%)	2/39 (5.1%)	3/33 (9.1%)	-3.96% (-20.11, 9.62) P=0.655	
	Proportion of patients with baseline HbA1c ≥ 7% who achieve HbA1c < 7% at Week 24	N (%)	7/28 (25.0%)	1/24 (4.2%)	20.83% (0.50, 41.11) P=0.056	
Unfavourable Effects (randomized period – 24 weeks)						
At least 1 AE		n (%)	27 (69.2)	19 (57.6)		
At least 1 serious hypoglycaemia event		n (%)	0	0		
At least 1 AE or serious hypoglycaemia event		n (%)	27 (69.2)	19 (57.6)		
At least 1 related AE		n (%)	7 (17.9)	2 (6.1)		
At least 1 adjudicated and confirmed DKA event reported as an SAE		n (%)	0	0		
Deaths		n (%)	0	0		
At least 1 SAE		n (%)	1 (2.6)	2 (6.1)		
At least 1 related SAE		n (%)	0	0		
SAE leading to discontinuation of study medication		n (%)	0	0		

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

T2DM in children is still relatively rare in Europe but is increasing due to increasing childhood obesity. The progression of the disease is more rapid in children than in adults and developing T2DM at a younger age is associated with a considerably higher risk of long-term cardiovascular disease compared with those who develop T2DM in the middle age.

Treatment options are limited in children as currently only metformin insulin and one GLP-1RA product are approved for the use in paediatric patients.

In study D1690C00017 the treatment difference between dapagliflozin and placebo in reduction of HbA1c was 0.75%, but since neither the primary nor the secondary endpoints reached statistical significance, the data are not robust enough to support on its own the proposed paediatric indication. The lack of statistical significance may partly be due to the variability observed in baseline characteristics in the study population. It may also be due to an underpowered study due to higher-than-expected variability. The SA given by the CHMP in 2014 states that limited clinical data in combination with PK/PD data could support an extension of the indication. The popPK analysis is considered adequate to describe the PK in paediatric patients. The dapagliflozin exposure in children 10-17 years is similar to the exposure in adults. This supports that the same dose as adults (10 mg) is adequate also for paediatric patients aged of 10-17 years old.

The MAH has justified that there are no significant differences between the paediatric and adult T2DM patients with regards to disease characteristics and pathophysiology, which supports an approval in the paediatric population granted based on extrapolation of efficacy from adults to the paediatric patients in view of similar systemic exposure and PK/PD relationship of dapagliflozin.

Thus, the approval of the paediatric indication in this application relies on extrapolation of efficacy data from adults to children as well as supportive data from the clinical study since the totality of data points is in favour of dapagliflozin and does not contradict the extrapolation model.

In contrast to what has been observed in adults, no notable impact of treatment was observed over the course of the study in weight or BMI, neither at 24 nor 52 weeks.

The safety database in the paediatric patients is limited both in terms of number of patients exposed as well as the exposure time. The data provided generally support a similar safety profile for dapagliflozin in paediatric patients as the one known from extensive use of dapagliflozin in adult patients even though there was an imbalance in hypoglycaemias. However, long-term safety in the paediatric population needs to be followed and an ongoing paediatric study is included in the RMP to address this concern.

6.7.2. Balance of benefits and risks

A clinically relevant glucose lowering effect of dapagliflozin in children aged 10 years and above is expected based on extrapolation of results from adults and supportive data from a clinical trial. The popPK analysis is considered adequate to describe the PK in paediatric patients and indicates a similar exposure in paediatric patients to the exposure in adults. This supports that the same dose as adults (10 mg) is adequate also for paediatric patients aged of 10-17 years old. This effect is considered to outweigh the risks related to dapagliflozin. Therefore, the benefit/risk balance of dapagliflozin in the treatment of paediatric patients aged 10 years and above is considered positive.

6.7.3. Additional considerations on the benefit-risk balance

None

6.8. Conclusions

The overall benefit-risk of dapagliflozin in the treatment of paediatric patients aged 10 years and above is positive.