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Procedure Management and Committees Support Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Forxiga

dapagliflozin

Procedure no: EMEA/H/C/002322/P46/016

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. Introduction

Forxiga (dapagliflozin) is approved in the EU since 12 November 2012 for treatment of adults with type 2 diabetes mellitus (T2DM). A clinical programme to support treatment of paediatric patients is currently ongoing, as described in the Paediatric Investigation Plan (PIP) agreed with the Paediatric Committee of the European Medicines Agency (EMA/PDCO).

On 2015-09-07, the MAH submitted a completed paediatric study for Forxiga, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

No changes to the labelling are proposed based on the results from the current study.

2. Scientific discussion

2.1. Information on the development program

AstraZeneca hereby submits an Article 46 “stand-alone” PAM which is a completed study referenced in the Paediatric Investigational Plan (EMEA-00694-PIP-01-09).

2.2. Information on the pharmaceutical formulation used in the study

Standard Forxiga 5 mg & 10 mg Tablets were used.

2.3. Clinical aspects

2.3.1. Introduction

Study MB102-091 is a randomised single-dose pharmacokinetics and pharmacodynamics study of dapagliflozin in children and adolescents aged 10-17 years with type 2 diabetes mellitus and its purpose is to support dosing in studies of efficacy in children and adolescents with diabetes mellitus.

2.3.2. Clinical study MB102-091

Description

The primary objective was to assess the pharmacokinetics of a single dose of dapagliflozin in the range of 2.5 to 10 mg in paediatric subjects aged 10 to 17 years with T2DM. Secondary objectives were to assess the pharmacodynamics, safety and tolerability and to characterise the pharmacokinetics of dapagliflozin 3-O-glucuronide (BMS-801576) following a single dose of dapagliflozin in the range of 2.5 to 10 mg in paediatric subjects aged 10 to 17 years with T2DM.

Methods

Objectives

The primary objective was to assess the PK of a single dose of dapagliflozin in the range of 2.5 to 10 mg in pediatric subjects aged 10 to 17 years with T2DM.

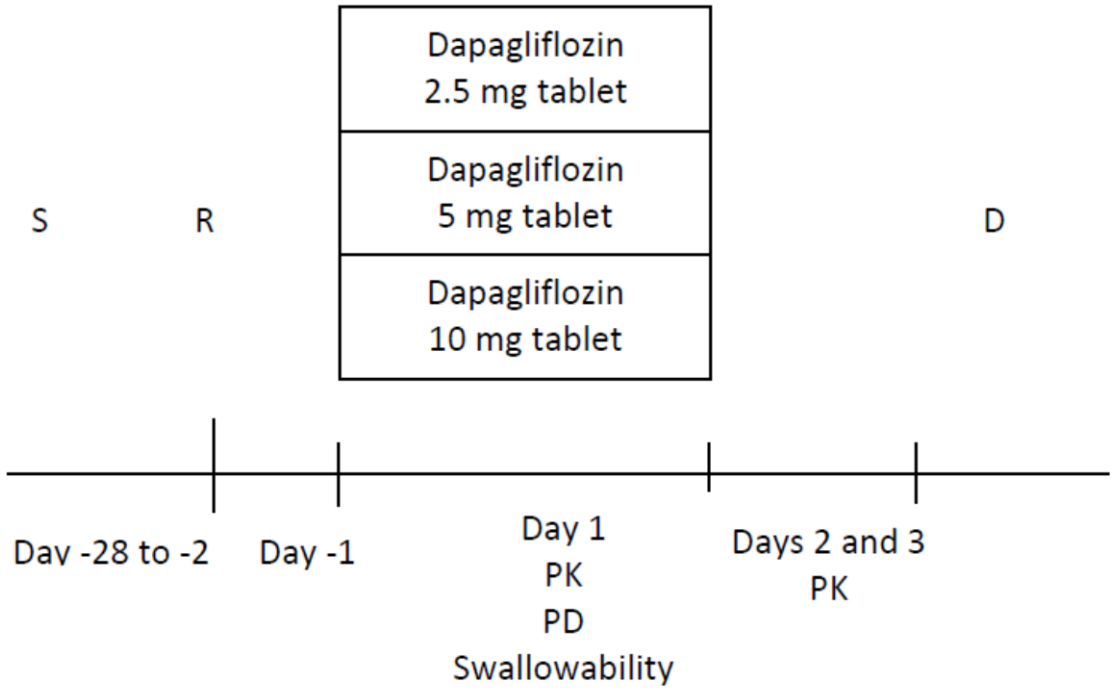
Secondary objectives were to assess the pharmacodynamics, safety and tolerability and to characterise the pharmacokinetics of dapagliflozin 3-O-glucuronide (BMS-801576).

The primary safety outcome measures included adverse events (AEs) monitored from administration of investigational product. Safety assessments were based on medical review of adverse event (AE) reports and the results of vital sign measurements, ECGs, physical examinations, and clinical laboratory tests collected at specified time points. The incidence of AEs was tabulated and reviewed for potential significance and clinical importance.

Study design

This was an open-label, randomized, parallel-group designed study.

The study design schematic is presented below:



S = Screening; R = Randomization; PK = Pharmacokinetics; PD = Pharmacodynamics; D = Study Discharge

Twenty-four children or adolescents with T2DM were randomly assigned to receive a single oral dose of 2.5, 5, or 10 mg dapagliflozin (8 per dose group). There must have been at least 3 males and 3 females in each dose group. For each dose group, at least 3 subjects must have been between the ages of 10 and 15 years and at least 3 subjects must have been >15 and 17 years.

Subjects were admitted to the clinical facility the evening prior to dosing (Day 1). Alternatively, subjects could report to the clinical facility early in the morning on the day of dosing having confirmed (orally) that the subject had fasted since 2400 hours (midnight) the preceding evening. Subjects were confined to the clinical facility for at least 24 hours after study drug administration. Subjects returned to the clinical facility on the morning of Day 3 for the 48 hour PK sample collection and complete study discharge procedures.

Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECGs), and clinical laboratory evaluations were performed at selected times during the study. Blood samples were collected for up to 48 hours after study drug administration for PK analysis.

The approximate duration of the study was 31 days including the 28-day screening period.

The clinical portion of the study was conducted at 18 clinical sites located in the United States and Mexico. The first subject was enrolled on 19-Jul-2012 and the last subject completed the study on 13-Sep-2014.

Study population /Sample size

Male and female pediatric subjects, previously diagnosed as having T2DM by World Health Organization (WHO) or American Diabetes Association (ADA) diagnostic criteria, 10 years of age, up to but not including 18 years of age at Day 1, as determined by medical history, physical examination, 12-lead ECG, and clinical laboratory evaluations, with body weight ≥30 kg, were eligible to participate in the study. Subjects had HbA1c >6.0% to <10.0% obtained at screening visit. Subjects who received metformin must have been on a stable dose for at least 2 weeks prior to Day 1. Subjects who received insulin must have been on a clinically stable dose for at least 2 weeks prior to Day 1.

The number of subjects was not based on statistical power considerations since no formal hypothesis was planned to be statistically tested.

Treatments

Subjects who met the inclusion and exclusion criteria were randomly assigned to one of the following treatment panels:

Panel 1: dapagliflozin 2.5 mg single dose orally on Day 1

Panel 2: dapagliflozin 5 mg single dose orally on Day 1

Panel 3: dapagliflozin 10 mg single dose orally on Day 1

Subjects were required to fast for at least 8 hours prior to study drug administration until 2 hours after study drug administration. All subjects consumed 240 mL of water 1 hour post-dose. Subjects were prohibited from drinking water one hour before and after study drug administration except with dosing. A breakfast or snack was served approximately 2 hours postdose. A standard lunch was served approximately 4 hours postdose. A standard dinner was served approximately 10 hours postdose and a standard light snack was served approximately 12 hours postdose.

Outcomes/endpoints

Pharmacokinetic endpoints were derived from plasma concentration versus time data collected on Days 1, 2 and 3:

Study Day	Time Event	Time (Relative To Dosing) Hour: Min	PK Blood Sample (for plasma)	PK Blood Sample (for Dried Blood Spot)	Urine Collection for PD Analysis
1	0 (predose)	00:00	x		x[a]
	0.5	00:30	x		
	0.75	00:45	x		
	1.0	1:00	x	x	
	1.5	1:30	x		
	4.0	4:00	x	x	
	8.0	8:00	x	x	
	12.0	12:00	x		
	14.0	14:00	x		
2	24.0	24:00	x	x	
3	48.0[b]	48:00	x		
Number of Samples			11	4	

[a] Urine samples will be collected for 24 hr to measure the total amount of glucose excreted in the urine. Urine samples will be collected at the start of the interval; natural voids during the collection interval and a void at the end of the collection

[b] Return for blood draw for 48 h post-dose time point can be within ±3 h window (i.e. between 45-51 h post-dose)

The single dose PK parameters of dapagliflozin (BMS-512148) and its 3-O-glucuronide metabolite (BMS-801576) that were assessed include:

- Cmax Maximum observed plasma concentration
- Tmax Time of maximum observed plasma concentration
- AUC(INF) Area under the plasma concentration-time curve from time zero extrapolated to infinite time
- AUC(0-T) Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration
- T-HALF Plasma half-life
- MR_Cmax Ratio of metabolite Cmax to parent Cmax, corrected for molecular weight
- MR_AUC(INF) Ratio of metabolite AUC(INF) to parent AUC(INF), corrected for molecular weight

Pharmacodynamic endpoints were measured on Days 1 and 2:

- The 24-h urinary glucose excretion following the administration of a single dose of dapagliflozin on Day 1.
- The fasting plasma glucose concentration on at pre-dose on Day 1 and Day 2.
- The change from baseline in fasting plasma glucose concentration on Day 2 with baseline value at pre-dose on Day 1.

Formulation Swallowability:

Subjects responded to a questionnaire on Day 1 regarding their experience swallowing the dapagliflozin tablet. The question regarding ease of swallowability consisted of the following categories for a response: easy, acceptable, difficult, and unable to swallow. If a subject was regularly taking metformin, they were also asked to complete the questionnaire to assess their experience swallowing the metformin tablet.

Statistical Methods

Standard summary statistics were used.

Results

Recruitment / Number analysed

A summary of subject disposition is presented below:

	2.5 mg Dapagliflozin	5 mg Dapagliflozin	10 mg Dapagliflozin	Total
No. of Subjects Enrolled	-	-	-	53
No. of Subjects Not Randomized	-	-	-	29
Withdrew Consent	-	-	-	2 (3.8%)
No Longer Meets Study Criteria	-	-	-	25 (47.2%)
Other	-	-	-	2 (3.8%)
No. of Subjects Treated	8	8	8	24
No. of Subjects Completed	7 (87.5%)	8 (100.0%)	8 (100.0%)	23 (95.8%)
No. of Subjects Not Completing the Study	1 (12.5%)	0	0	1 (4.2%)
Reason for Not Completing the Study				
Other (early termination)	1 (12.5%)	0	0	1 (4.2%)

Baseline data

Table 5.3.1-1: Demographic Characteristics and Baseline Physical Measurements Summary

	2.5 mg Dapagliflozin (N=8)	5 mg Dapagliflozin (N=8)	10 mg Dapagliflozin (N=8)	Total (N=24)
Age (Years)				
Mean	15.0	14.0	14.6	14.5
Median	15.0	13.5	15.5	15.0
Min, Max	12, 17	11, 17	11, 17	11, 17
SD	1.69	2.39	2.13	2.04
Age Categorization (%)				
10 to <= 15	5 (62.5)	5 (62.5)	4 (50.0)	14 (58.3)
16 to <= 17	3 (37.5)	3 (37.5)	4 (50.0)	10 (41.7)
Gender				
Male	3 (37.5)	3 (37.5)	3 (37.5)	9 (37.5%)
Female	5 (62.5)	5 (62.5)	5 (62.5)	15 (62.5)
Race				
White	2 (25.0)	5 (62.5)	4 (50.0)	11 (45.8)
Black/African American	6 (75.0)	2 (25.0)	3 (37.5)	11 (45.8)
Other	0	1 (12.5)	1 (12.5)	2 (8.3)
Weight, kg				
Mean	100.96	92.03	106.21	99.73
Min, Max	72.8, 169.5	61.5, 123.8	64.0, 159.6	61.5, 169.5
SD	30.30	21.87	27.74	26.36
BMI, kg/m^2				
Mean	36.08	31.79	39.18	35.68
Min, Max	27.3, 52.5	26.3, 39.7	23.8, 51.9	23.8, 52.5
SD	8.52	4.61	8.27	7.68
HbA1C				
Mean	7.20	7.46	7.23	-
Min, Max (%)	6.1, 8.4	6.3, 9.7	6.2, 9.7	-
SD	0.907	1.284	1.152	-

Abbreviations: SD = Standard Deviation; BMI = Body Mass Index

CHMP's comment:

The age of the patients included ranged from 11 to 17 years. Notably the majority of patients were overweight as could be expected. The metabolic control, as reflected by HbA1c, ranged from 6.1 to 9.7.

Pharmacokinetics

A summary of dapagliflozin PK parameters is provided below:

Table 9.2.1-1: Dapagliflozin Pharmacokinetic Parameters

PARAMETER STATISTIC	Dapagliflozin Dose 2.5 mg	5 mg	10 mg
Cmax (ng/mL)			
Geo.Mean [N]	24.8 [7]	48.4 [8]	118 [8]
(%CV)	(34)	(41)	(35)
Tmax (h)			
Median [N]	1.50 [7]	0.960 [8]	0.875 [8]
(Min - Max)	(0.75 - 2.00)	(0.58 - 1.53)	(0.75 -4.00)
AUC(INF) (ng*h/mL)			
Geo.Mean [N]	101 [7]	199 [8]	427 [8]
(%CV)	(23)	(29)	(31)
AUC(0-T) (ng*h/mL)			
Geo.Mean [N]	92.3 [7]	189 [8]	418 [8]
(%CV)	(27)	(31)	(31)
T-HALF (h)			
Mean [N]	14.1 [7]	10.3 [8]	10.7 [8]
(SD)	(5.59)	(3.72)	(2.16)
CL/F (mL/min)			
Geo.Mean [N]	413 [7]	418 [8]	391 [8]
(%CV)	(26)	(27)	(25)
Vz/F (L)			
Geo.Mean [N]	468 [7]	343 [8]	355 [8]
(%CV)	(34)	(45)	(34)

Source: Table S.8.2.4.A

N represents the evaluable PK data for each dose. One subject was excluded from the summary statistics for the 2.5 mg dose group due to anomalous PK profile. Additional details are presented in Section 5.2.3 of the clinical study report.

Abbreviations: N=number. CV=coefficient of variation. SD=standard deviation

A statistical analysis (power model described by Gough et al (1995)) for dose proportionality is summarized below:

Table 9.2.3-1: Dose Proportionality Assessment for Dapagliflozin PK Parameters

Parameter	Unit	Estimated Slope	90% CI of the Slope
Cmax	ng/mL	1.13	(0.870,1.389)
AUC(0-T)	ng*h/mL	1.09	(0.910,1.272)
AUC(INF)	ng*h/mL	1.04	(0.872,1.211)

Source: Source: Table S.8.2.6

Abbreviations: CI = confidence interval

CHMP's comment:

Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Given that the 3-O-glucuronide is inactive, such data from the performed study is therefore not presented in this AR by the CHMP.

In adults, the recommended dose is 10 mg dapagliflozin once daily.

According to the MAH, similar PK is seen in the adolescent population and adults:

"In pediatric subjects aged 10 to 17 years, dapagliflozin was rapidly absorbed following oral administration, with maximum concentrations achieved within 1.5 h after administration. Mean terminal elimination half life of dapagliflozin appeared independent of dose and ranged between 10 to 14 h across the studied dose range and is similar to the reported half life of dapagliflozin of 12.9 h in adults. The increase in peak and total systemic exposure of dapagliflozin was dose proportional, as has been demonstrated for adults."

The comparison with other adult PK data (AUC, Cmax) is not presented in the documentation, however, data indicate similar PK.

When deciding on dose for the efficacy study, it is anticipated that any underlying trends in dapagliflozin PK due to age or weight is considered.

Pharmacodynamics

Urinary Glucose Excretion

Table 10.1-1 shows the amount of glucose excreted in urine over 24 hours by dose of dapagliflozin. Following administration of a single oral dapagliflozin dose of 2.5 to 10 mg to pediatric subjects with T2DM, the amount of glucose in the urine over the 0 to 24 h interval increased in a dose-related manner.

Table 10.1-1: Total Amount of Glucose Excreted in Urine over24 hours by Dose of Dapagliflozin (All Subjects)

Dose of Dapagliflozin	24h Urinary Glucose Excretion (g/24h)
	Mean (N[a], SD)
2.5 mg	52.84 (5, 27.18)
5 mg	62.39 (8, 26.55)
10 mg	89.04 (7, 41.25)

[a] N represents the available PD data for each dose. One subject was excluded from the summary statistics for the 2.5 mg group due to anomalous PK and PD profile. Additional details are presented in Section 5.2.4 of the clinical study report.

Abbreviations: N=number, SD=standard deviation

Table 10.1-2 provides a comparison of the amount of glucose in urine over 24 hours in subjects that were receiving insulin treatment versus those that were not receiving any insulin. Overall, only a small number of subjects were receiving insulin in any dose group and the 24-h urinary glucose excretion for these subjects were variable, but generally similar in patients with and without concomitant insulin treatment.

Table 10.1-2: Total Amount of Glucose Excreted in Urine over 24 hours by Dose of Dapagliflozin (Subjects with vs. Subjects without Insulin)

Dose of Dapagliflozin	With Insulin 24h Urinary Glucose Excretion (g/24h) Mean (N[a], SD)	Without Insulin 24h Urinary Glucose Excretion (g/24h) Mean (N[a], SD)
2.5 mg	53.3 (2, 53.03)	52.53 (3, 8.41)
5 mg	60.7 (2, 46.39)	62.95 (6, 23.56)
10 mg	116.8 (3, 51.24)	68.22 (4, 17.45)

[a] N represents the available PD data for each dose. One subject was excluded from the summary statistics for the 2.5 mg group due to anomalous PK and PD profile. Additional details are presented in Section 5.2.4 of the clinical study report.

Abbreviations: N=number, SD=standard deviation

In both groups, the mean amount of glucose in urine increased with dose. Mean amounts of glucose excreted in urine were generally similar for the 2.5-mg and 5-mg dose of dapagliflozin in subjects with and without insulin. There appeared to be a greater urinary glucose excretion in subjects being treated with insulin that received the highest dose of dapagliflozin (10 mg); however, the small number of subjects suggests that this result should be interpreted with caution.

CHMP's comment:

A dose dependent increase in urinary glucose excretion was observed. No direct comparison to data in adults with T2DM can be made since no single dose study was included in the MAA for dapagliflozin. The 24h glucose excretion is in the same range as observed in the short-term study in adults with T2DM. It should, however, be taken into account that the glucose excretion is partly affected by the blood glucose levels as reflected by the differences observed between adult healthy subjects and adult patients with T2DM (see EPAR for Forxiga). In this context it should be noted that there was a rather large variation in metabolic control among the patients included.

Fasting Plasma Glucose

The fasting plasma glucose concentration was lower for all dapagliflozin dose panels on Day 2 versus pre-dose on Day 1. Summary statistics for fasting plasma glucose and changes from baseline are displayed in Table 10.2-1.

Table 10.2-1: Summary Statistics for the Fasting Plasma Glucose (mg/dL) and Changes from Baseline (US Standard Units)

								----------Change from Baseline----------					
Dapagliflozin Dose	Evaluation Day	N[a]	Mean	Median	SD	Min	Max	N[a]	Mean	Median	SD	Min	Max
2.5 mg	Day 1 Pre-Dose	6	146.2	115.0	72.56	104	292						
	Day 2	3	124.0	102.0	45.21	94	176	3	-46.7	-14.0	60.08	-116	-10
5 mg	Day 1 Pre-Dose	8	152.1	151.0	49.06	95	208						
	Day 2	8	119.4	119.5	17.18	94	143	8	-32.8	-10.0	42.41	-90	5
10 mg	Day 1 Pre-Dose	8	139.8	133.5	39.63	83	201						
	Day 2	7	119.0	116.0	29.15	80	160	7	-22.0	-11.0	27.32	-70	4

[a] N represents the evaluable PK data for each dose. One subject was excluded from the summary statistics for the

2.5 mg dose group due to anomalous PK profile. Additional details are presented in Section 5.2.3 of the clinical study report.

Abbreviations: N=number, SD=standard deviation

CHMP's comment:

In this single dose study, no dose dependent effect was observed with regards to FPG although all doses resulted in a lowering of FPG. This may be due to the small number of patients included and the rather large variation in baseline FPG. Thus this finding does not raise any concerns regarding the PD effect of dapagliflozin in children and adolescents.

Formulation Swallowability

The results from this study indicate that dapagliflozin 2.5-mg, 5-mg, and 10-mg tablets were easy to swallow. Twenty-three subjects reported easy swallowability, and 1 subject reported acceptable swallowability. None of the subjects reported the dapagliflozin tablets as difficult or unable to swallow.

CHMP's comment:

Considering the age of the patients included, i.e. > 11 years, this information is of somewhat limited value but still reassuring.

Safety results

Administration of a single dose of dapagliflozin in the range of 2.5 to 10 mg in pediatric subjects aged 10 to 17 years with T2DM was generally well tolerated and was not associated with clinically significant safety findings.

There were no deaths, SAEs or discontinuation due to AEs in this study. There were no occurrences of adverse events of special interest in this study.

Overall, 6 subjects (25%) had an AE in the study. Three subjects (37.5%) from the dapagliflozin 10 mg panel (N = 8) had AEs of upper abdominal pain (12.5%), nausea (12.5%), vomiting (12.5%), decreased neutrophil count (12.5%), back pain (12.5%), rash (12.5%), and skin irritation (12.5%). One subject (12.5%) from the dapagliflozin 5 mg panel (N = 8) had an AE of pyrexia (12.5%). Two subjects (25.0%) from the dapagliflozin 2.5 mg panel (N = 8) had AEs of peripheral swelling (12.5%), influenza (12.5%), pollakiuria (12.5%), and cough (12.5%).

Table 8.6-1: Adverse Event Summary

System Organ Class (%) Preferred Term (%)	Dapa 2.5 mg N = 8	Dapa 5 mg N = 8	Dapa 10 mg N = 8	All Subjects N = 24
Total Subjects with an Event	2 (25.0)	1 (12.5)	3 (37.5)	6 (25.0)
Gastrointestinal Disorders	0	0	2 (25.0)	2 (8.3)
Abdominal Pain Upper[a]	0	0	1 (12.5)	1 (4.2)
Nausea[a]	0	0	1 (12.5)	1 (4.2)
Vomiting	0	0	1 (12.5)	1 (4.2)
General Disorders and Administration Site Conditions	1 (12.5)	1 (12.5)	0	2 (8.3)
Peripheral Swelling	1 (12.5)	0	0	1 (4.2)
Pyrexia	0	1 (12.5)	0	1 (4.2)
Infections and Infestations	1 (12.5)	0	0	1 (4.2)
Influenza	1 (12.5)	0	0	1 (4.2)
Investigations	0	0	1 (12.5)	1 (4.2)
Neutrophil Count Decreased	0	0	1 (12.5)	1 (4.2)
Musculoskeletal and Connective Tissue Disorders	0	0	1 (12.5)	1 (4.2)
Back Pain[a]	0	0	1 (12.5)	1 (4.2)
Renal and Urinary Disorders	1 (12.5)	0	0	1 (4.2)
Pollakiuria[a]	1 (12.5)	0	0	1 (4.2)
Respiratory, thoracic and Mediastinal Disorders	1 (12.5)	0	0	1 (4.2)
Cough	1 (12.5)	0	0	1 (4.2)
Skin and Subcutaneous tissue Disorders	0	0	1 (12.5)	1 (4.2)
Rash	0	0	1 (12.5)	1 (4.2)
Skin Irritation	0	0	1 (12.5)	1 (4.2)

[a] Considered by investigator to be related to study drug.

Two subjects (8.3%) had mild AEs considered by the investigator to be related to study treatments. One subject (N = 8) had AEs of nausea (12.5%), upper abdominal pain (12.5%), and back pain (12.5%) on Day 1 following administration of dapagliflozin 10 mg. One subject (N = 8) had an AE of pollakiuria (12.5%) on Day 1 following administration of dapagliflozin 2.5 mg.

Nine subjects had a total of 17 clinical laboratory test results that met marked abnormality (MA) criteria (decreased leukocytes [N=2], decreased neutrophils [N=1], elevated AST [N=1], elevated ALT [N=1], elevated serum glucose [N=2], protein in urine [N=3], blood in urine [N=2], RBC in urine [N=3] and WBC in urine [N=2]; none of the MAs were considered to be clinically significant. Nine subjects are listed as having MAs of glucose in urine. However glucose in urine is entirely expected via the mode of action (MOA) of dapagliflozin and therefore may not accurately represent a safety signal.

There were no clinically significant ECG findings, vital sign abnormalities, or physical examination findings after dosing.

CHMP's comment:

One subject reported gastrointestinal AEs not listed for dapagliflozin which were considered related to treatment. All other AEs were either in line with the safety profile or mechanism of action for dapagliflozin or considered unrelated to treatment. Overall the safety data does not raise any new safety concerns in relation to the use of dapagliflozin in children or adolescents.

2.3.3. Discussion on clinical aspects

The primary objective of study MB102-091 was to assess the pharmacokinetics of a single dose of dapagliflozin in the range of 2.5 to 10 mg in paediatric subjects aged 10 to 17 years with T2DM. Secondary objectives were to assess the pharmacodynamics, safety and tolerability and to characterise the pharmacokinetics of dapagliflozin 3-O-glucuronide (BMS-801576) following a single dose of dapagliflozin in the range of 2.5 to 10 mg in paediatric subjects aged 10 to 17 years with T2DM.

The age of the patients included ranged from 11 to 17 years. Notably the majority of patients were overweight as could be expected. The metabolic control, as reflected by HbA1c, ranged from 6.1 to 9.7.

Regarding PK, data indicate that exposure to dapagliflozin is likely similar when comparing the adult population and the current population administered the same doses. The increase in peak and total systemic exposure of dapagliflozin was also demonstrated dose proportional in paediatric subjects aged 10 to 17 years with T2DM.

A dose dependent increase in urinary glucose excretion was observed. No direct comparison to data in adults with T2DM can be made since no single dose study was included in the MAA for dapagliflozin. The 24h glucose excretion is in the same range as observed in the short-term study in adults with T2DM. It should, however, be taken into account that the glucose excretion is partly affected by the blood glucose levels as reflected by the differences observed between adult healthy subjects and adult patients with T2DM (see EPAR for Forxiga). In this context it should be noted that there was a rather large variation in metabolic control among the patients included.

In this single dose study, no dose dependent effect was observed with regards to FPG although all doses resulted in a lowering of FPG. This may be due to the small number of patients included and the rather large variation in baseline FPG. Thus this finding does not raise any concerns regarding the PD effect of dapagliflozin in children and adolescents.

Swallowability of the tablets was also assessed and the majority of patients reported that the tablets were easy to swallow. Considering the age of the patients included, i.e. > 11 years, this information is of somewhat limited value but still reassuring.

With regards to safety, one subject reported gastrointestinal AEs not listed for dapagliflozin which were considered related to treatment. All other AEs were either in line with the safety profile or mechanism of action for dapagliflozin or considered unrelated to treatment. Overall the safety data does not raise any new safety concerns in relation to the use of dapagliflozin in children or adolescents.

3. CHMP's overall conclusion and recommendation

Overall conclusion

Study MB102-091 was a phase II study investigating the PK and PD for dapagliflozin in children and adolescents aged 10-17 years. The study is part of the PIP for dapagliflozin and precedes a planned phase III study in this population.

The data presented indicate that there are no relevant differences in the PK and PD in this population compared to adults. No new safety concerns arise.

Recommendation

☒ Fulfilled:

No regulatory action required.

Additional clarifications requested

Not applicable.