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

Jardiance

empagliflozin

Procedure no: EMEA/H/C/002677/P46/007

Note

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

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1. Introduction

On 22 July 2016, the MAH submitted a completed paediatric study and a population PK-PD study for Jardiance (Empagliflozin), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure PIP (P/2011/2015).

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that studies 1245.87 and er-uge-t2dm-pediatrics are part of a paediatric clinical development program.

2.2. Information on the pharmaceutical formulation used in the study

For the paediatric study 1245.87, 5 mg, 10 mg and 25 mg empagliflozin tablets originally developed for adult patients were used.

2.3. Clinical aspects

2.3.1. Introduction

A pharmacokinetic/pharmacodynamic and a population pharmacokinetic/pharmacodynamic analysis (exposure-response) was performed to characterise and compare the relationship between empagliflozin plasma exposure and 24 h urinary glucose excretion following a single dose of empagliflozin in adult and paediatric patients.

The MAH submitted study reports for:

- Study 1245.87: An open-label, randomised, multicentre, single-dose, parallel group trial to evaluate pharmacokinetics and pharmacodynamics of empagliflozin in children and adolescents from 10 to less than 18 years of age with type 2 diabetes mellitus.
- er-uge-t2dm-pediatrics: Population pharmacokinetic/pharmacodynamic analysis to characterise the exposure-response relationship for the effect of empagliflozin on 24 h urinary glucose excretion in adults, children and adolescent type 2 diabetes mellitus patients.

For adult patients two dose strengths of Empgliflozin are approved, Jardiance 10 mg and 25 mg film-coated tablets. During clinical development a dose rage of 0.5 mg to 800 mg empagliflozin has been evaluated in clinical studies.

Empagliflozin is a reversible, highly potent and selective competitive inhibitor of sodium-glucose co-transporter 2 (SGLT2) which is highly expressed in the kidney. SGLT2 is responsible for the reabsorption of glucose from the glomerular filtrate back into the circulation. In patients with type 2 diabetes and hyperglycaemia a higher amount of glucose is filtered and reabsorbed. Empagliflozin improves glycaemic control in patients with type 2 diabetes by reducing renal glucose reabsorption. The amount of glucose removed by the kidney through this glucuretic mechanism is dependent on blood glucose concentration and GFR. A dose-dependent increase in urinary glucose excretion (UGE) was observed with a near maximal effect for the 10mg and 25mg dose.

The pharmacokinetics of empagliflozin have been extensively characterised in healthy volunteers and patients with type 2 diabetes. After oral administration, empagliflozin was rapidly absorbed with peak plasma concentrations occurring at a median t_{max} of 1.5 hours post-dose. Thereafter, plasma concentrations declined in a biphasic manner with a rapid distribution phase and a relatively slow terminal phase with a apparent terminal elimination half-life of 12.4 hours. The steady state mean plasma AUC and Cmax were 1870 nmol.h/l and 259 nmol/l with empagliflozin 10 mg and 4740 nmol.h/l and 687 nmol/l with empagliflozin 25 mg once daily. Empagliflozin displays approximately linear pharmacokinetics up to a dose of 400mg.

2.3.2. Clinical studies

Study 1245.87

Description

PK/PD study

Methods

Objective(s)

The primary objective of trial 1245.87 was to assess the pharmacokinetics of a single dose of 5 mg, 10 mg, or 25 mg empagliflozin in paediatric patients with T2DM. The secondary objective of this study was to investigate the pharmacodynamics of a single dose of empagliflozin in the same population. Safety of empagliflozin in paediatric patients was also assessed in this trial.

Study design

This was a randomised, single-dose, parallel group trial with 3 treatment arms with 1 dose of empagliflozin each (5 mg, 10 mg, and 25 mg). Randomisation was stratified so that 1 third to 2 thirds of the patients were female and at least 6 participants were younger than 15 years of age.

Study population /Sample size

Patients with T2DM who were in the age range of 10 to less than 18 years and who had insufficient glycaemic control (HbA1c of ≤10.5%) despite treatment with diet and exercise and/or stable metformin and/or stable basal or multiple dose injection (MDI) insulin therapy were included in this trial. A total of 27 patients were randomised to 1 of the 3 treatment groups (9 patients to the 5 mg dose group, 8 patients to the 10 mg dose group, and 10 patients to the 25 mg dose group) and completed the trial as planned. No important protocol violations were identified, and no patient was excluded from any of the patient analysis sets.

Table 1 Demographic data and baseline characteristics- TS

	5 mg empagliflozin	10 mg empagliflozin	25 mg empagliflozin	Total
Number of patients, N (%)	9 (100)	8 (100)	10 (100)	27 (100)
<15 years, N (%)	4 (44.4)	4 (50.0)	5 (50.0)	13 (48.1)
≥15 years, N (%)	4 (44.6)	4 (50.0)	5 (50.0)	14 (51.9)
Gender, N (%)				
Male	3 (33.3)	3 (37.5)	3 (30.0)	9 (33.3)
Female	6 (66.7)	5 (62.5)	7 (70.0)	18 (66.7)
Race, N (%)				
American Indian/Alaska Native	0	3 (37.5)	0	3 (11.1)
Asian	1 (11.1)	0	0	1 (3.7)
Black/African American	3 (33.3)	4 (50.0)	4 (40.0)	11 (40.7)
Hawaiian/Pacific Isle	0	0	0	0
White	5 (55.6)	1 (12.5)	6 (60.0)	12 (44.4)
Age, mean (SD) [years]	13.7 (2.0)	14.5 (1.9)	14.2 (2.1)	14.1 (2.0)
Weight, mean (SD) [kg]	90.0 (19.0)	111.0 (21.3)	91.1 (25.7)	96.7 (23.5)
BMI, mean (SD) [kg/m^2]	33.9 (5.8)	39.6 (6.2)	33.7 (7.0)	35.5 (6.7)
BMI SDS, mean (SD)	2.9 (0.7)	3.4 (0.5)	2.8 (0.9)	3.0 (0.8)
Smoking status, N (%)				
Never smoked	9 (100)	8 (100)	9 (90.0)	26 (96.3)
Ex-smoker	0	0	0	0
Currently smokes	0	0	1 (10.0)	1 (3.7)
Follow diet/exercise recommendation, N (%)				
No	2 (22.2)	1 (12.5)	1 (10.0)	4 (14.8)
Yes	7 (77.8)	7 (87.5)	9 (90.0)	23 (85.2)
Tanner scale score[1], N (%)				
1	0	0	0	0
2	0	1 (12.5)	0	1 (3.7)
3	1 (11.1)	1 (12.5)	1 (10.0)	3 (11.1)
4	2 (22.2)	4 (50.0)	1 (10.0)	7 (25.9)
5	6 (66.7)	2 (25.0)	8 (80.0)	16 (59.3)
HbA_{1c}, mean (SD) [%]	7.4 (1.4)	7.4 (1.1)	6.3 (1.0)	7.0 (1.2)
eGFR[2], mean (SD) [ml/min/1.73m^2]	178.3 (17.4)	162.3 (38.8)	157.3 (15.2)	165.8 (25.8)
UGE, mean (SD) [g/24 h]	16.2 (30.3)[3]	12.3 (25.4)	0.08 (0.05)	8.8 (22.1)
FPG, mean (SD) [mg/dL]	153.8 (75.1)	154.5 (55.2)	114.4 (25.9)	139.4 (56.3)

[1] The physical development of the paediatric patients was judged based on a modified version of the Tanner staging (see Section 9.5.4.3 of this report and Appendix 10.3 of the clinical trial protocol).
[2] The eGFR values, presented here, were calculated based on the Schwartz formula (see Section 9.5.3.3).
[3] Mean UGE baseline in the 5 mg dose group was based on the data of only 8 patients, as the predose urine collection of 1 patients (Patient No. 701) was incomplete.

Treatments

For the paediatric study 1245.87, 5 mg, 10 mg and 25 mg empagliflozin tablets originally developed for adult patients were used.

Outcomes/endpoints

The following pharmacokinetic parameters of empagliflozin were analysed as primary endpoints:

- AUC0-∞ (area under the plasma concentration-time curve from time 0 to infinity)
- AUC0-tz (area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration)
- Cmax (maximum observed plasma concentration)
- tmax (time from dosing until maximum observed concentration is reached in plasma)
- t1/2 (terminal half-life in plasma)

The following pharmacodynamic parameters were analysed as secondary endpoints:

- Change from baseline in urinary glucose excretion (UGE) over 24 h after study drug intake
- Change from baseline in fasting plasma glucose (FPG) 24 h after study drug intake
- Change from baseline in 8-point plasma glucose profile over 24 h after study drug intake (as defined by change from baseline in mean daily glucose (MDG))

Safety was determined based on monitoring of adverse events (including adverse events of special interest (AESIs) as well as clinically relevant findings from the physical examination and the 12-lead electrocardiogram (ECG)), recording vital signs, and conducting safety laboratory measurements (haematology, clinical chemistry, lipids, and urinalysis including electrolytes and acido-base equilibrium).

Sample collection

For quantification of empagliflozin plasma concentrations, EDTA-anticoagulated blood samples were collected at -0.5 (predose) and 0.5, 1.0, 1.5, 2.0, 4.0, 8.0, 12, 24, 34 and 48 hours post dose.

Urine samples were collected for the following intervals: -24 h to 0 h (predose), 0h to 5h, 5 h to 12h, 12 h to 24 h, 24 h to 48 h post dose. Urine collection from before trial drug administration served as the baseline measurement. Patients should preferably empty their bladder at the end of each sampling interval. The urine was to be pooled with all the urine collected during the respective sampling interval. As urine of all sampling intervals was needed for both pharmacokinetic and pharmacodynamic (UGE) purposes, the urine was collected in the same containers for both.

MDG at baseline and on Day 1 were calculated based on the 8-point plasma profiles of Day -1 and Day 1, respectively. Plasma glucose was measured at the following times:

	Day -1	Day 1
Within 10 min before breakfast and following an overnight fast of at least 8 h	(Baseline)	(After study drug administration)
Approximately 120 min after start of breakfast	+	+
Within 10 min before lunch	+	+
Approximately 120 min after start of lunch	+	+
Within 10 min before dinner	+	+
Approximately 120 min after start of dinner	+	+
Within 10 min before bedtime (if more than 60 min after previous time point)	+	+
Within 10 min before breakfast (after an overnight fast of at least 8 h)	(before study drug administration on Day 1)	+ (on Day 2)

Analytical and Statistical Methods

Plasma and urine concentrations of empagliflozin were determined using a validated high performance liquid chromatography, tandem mass spectrometry (HPLC-MS/MS) assay. The analyses were performed at BASi (Bioanalytical Systems Inc.), West Lafayette, USA. Empagliflozin in human plasma and urine have previously been validated at BASi (Respectively SAP.1217 and SAP.1216).

All endpoints (pharmacokinetic, pharmacodynamic, and safety) were analysed using descriptive statistics. Dose proportionality of empagliflozin was explored using a regression model on the double-log scale. A 95% confidence interval (CI) for the slope was computed. For the changes from baseline in UGE, adjusted means per treatment group were calculated based on an analysis of covariance (ANCOVA) including 'treatment' as a fixed effect and 'UGE at baseline' and 'FPG at baseline' as continuous covariates. For the changes from baseline in MDG and FPG, adjusted means per treatment group were calculated based on an ANCOVA including 'treatment' as fixed effect and 'MDG at baseline' or 'FPG at baseline', respectively, as continuous covariate.

SAS® version 9.4 was used for all statistical analyses. Non-compartmental pharmacokinetic analyses were performed using WinNonlinTM software (professional Network version6.3, Pharsight Corporation, Mountain View, USA).

Population pharmacokinetic/pharmacodynamic analysis (er-uge-t2dm-pediatrics)

The following modelling steps were performed:

• Development of a exposure-response model in adult patients with T2DM to characterize the effect of a single dose of empagliflozin on 24 h UGE

• Comparison of the UGE exposure-response in adult and paediatric patients with T2DM by clinical trial simulations

• Development of an exposure-response model to characterize the effect of a single dose of empagliflozin on 24 h UGE in paediatric patients with T2DM.

Study population

Adult Dataset	226	from previously submitted studies 1245.2[c01801234], 1245.4 [c01796495], 1245.15 [c01793570]
Paediatric Dataset	26	from study 1245.87 (one subject has been excluded due to the absence of baseline UGE 24h measurements)
Joint dataset (adult and paediatric patients)	252	

Treatments

Empagliflozin:

Adult patients	Placebo, 1, 2.5, 5, 10, 25 and 100 mg q.d.
Paediatric patients	5, 10 and 25 mg

The adult dataset comprised data from 3 clinical studies with a total number of 226 adult patients with T2DM. Each patient contributed two 24 h UGE measurements: one at baseline and one on the first day of drug administration. The patients received either placebo (49 patients), 1 mg (19 patients), 2.5 mg (9 patients), 5 mg (21 patient), 10 mg (45 patients), 25 mg (44 patients) or 100 mg (39 patients) of empagliflozin, with exposures ranging from 163.4 nmol·h/L in the 1 mg dose group to 27660 nmol·h/L in the 100 mg dose group. Of the 226 total patients, 190 were male and 36 were female, 123 were White, 101 were Asian , and two were Black patients. The median eGFR was 96.2 ml/min/1.73 m^2, median baseline MDG was 186 mg/dL, median age was 58.0 years (37.6 to 69.0 years) and median body weight was 82.3 kg (50.0 to 120 kg). The median baseline UGE was slightly lower in study 1245.4 (0.67 g/d) compared to the median baseline UGE in study 1245.2 (4.08 g/d) and study 1245.15 (6.81 g/d).

The main differences between the adult studies were that study 1245.15 was a study in Japanese subjects while the other two studies were conducted in Caucasian populations. Further the PK sampling schemes were not identical and oral glucose tolerance tests (OGTT) and meal tolerance tests (MTT) were conducted at different moments during the studies. Also the study duration varied between studies, but this is considered irrelevant for model development as only predose data and data of the first day have been used in the model.

The demographics of the paediatric population is described in **Table 1**. Paediatric subjects had a higher eGFR (165.8 ml/min/1.73 m^2), a higher median bodyweight (96.7 kg) and in the paediatric study no OGTT was conducted.

Methods

The population analysis was performed using non-linear mixed-effects modelling techniques implemented in the software NONMEM, combined with graphical visualization methods.

Investigation of pre-selected covariate effects on maximal effect, Emax, estimated baseline UGE, and AUC50 (area under the curve resulting in 50% of Emax) was undertaken following a stepwise covariate model-building (SCM) procedure. During SCM for the joint (adult and paediatric) population a special focus was laid on potential differences between the two populations.

The predictive performance of best current models for the adult and joint population was evaluated by basic goodness of fit plots and visual predictive checks. Simulations based on the best current model for adult patients with T2DM and the joint population were performed to examine the impact of covariates identified as statistically significant during the analysis on the pharmacodynamics of empagliflozin.

The best current model based on adult data was used to simulate the exposure-response profile of a typical adult patient which was compared to observed change from baseline in 24 h UGE in the respective dose groups of the paediatric trial. Moreover, simulations were performed to assess the absolute change from baseline (and % from maximal effect) in 24 h UGE for a typical adult and typical paediatric patient with T2DM.

Criteria for Model Evaluation:

The key and final models were evaluated with regard to the minimization process, the covariance matrix of the parameter estimates and basic goodness of fit plots.

Goodness of fit plots have been presented for:

- Conditional and individually weighted residuals versus time, observation, and population or individual predicted value: Data should be evenly distributed around the zero reference line
- Observed versus population predicted and individual predicted values: Data should be evenly distributed around the line of identity
- Histograms of the random effects (post hoc estimates of individual realizations and residuals)
- Assessment of shrinkage in the random effects.

Additionally, visual predictive checks (VPC) for each randomization group in each study have been performed to assess the predictive performance of the model.

Covariate analysis:

The following covariates have been evaluated:

- FPG or HbA1c or MDG as a measure of glycaemic control
- eGFR as the measure of renal function
- Demographics (age, weight, sex, Caucasian/Asian/Black race)
- Metformin background medication

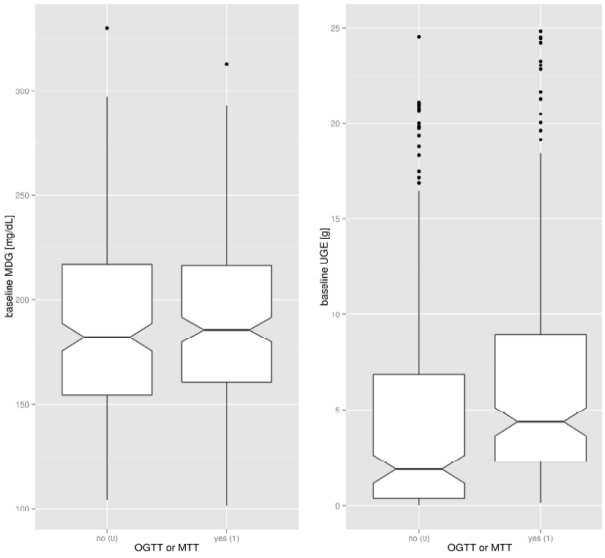
Assumptions:

The company made several assumptions during model development.

It was assumed that the performance of oral glucose tolerance test and deviating plasma glucose measurements do not impact MDG and UGE. To test this assumption a sensitivity analysis has been performed to compare MDG and UGE on days with OGTT and without OGTT in raw data.

This sensitivity analysis shows that oral glucose tolerance tests do not have a major impact on baseline MDG or UGE (figure 5).

Figure 1 Comparison of baseline MDG and baseline UGE for patients with oral glucose tolerance test (OGTT) and meal tolerance test (MTT)



In study 1245.2 only a baseline day with OGTT was available, for 1245.4 and 1245.15 a baseline day with and without tolerance test were available.

It was assumed that the exposure-response between adult and paediatric patients is comparable and/or can be scaled based on available covariates as maturation processes in kidney are completed by age of 2. This was tested by pooling the adult and paediatric data. The differences in model parameters between paediatric and adult patients have been evaluated by investigating patient population as covariate.

It was assumed that dose-normalized AUCs can be used to scale exposure for different doses during simulations as dose-linear PK after single/multiple dose between 0.5 to 800/100 mg of empagliflozin has been established. The dose proportionality was previously tested in adult program and has been tested during statistical analysis of 1245.87 data.

It is assumed that the same empagliflozin exposure results in the same 24 h UGE in adults and children as it is assumed that there are no differences in SGLT-2 expression and activity and renal function. The differences in model parameters between paediatric and adult patients were evaluated by investigating patient population as covariate or by comparing parameter estimates from separate (adult and paediatric) models.

Discussion on the methodology

The design of paediatric study 1245.87 and its analytical and statistical methods used for the evaluation of the pharmacokinetics and pharmacodynamics of Empagliflozin are acceptable.

The methodology used in the Population PK-PD study er-uge-t2dm-pediatrics is considered appropriate, standard statistical an model building techniques were used. The company appropriately explained al model building steps, has verified the relevant covariates and justified and tested the assumptions of the model.

The three studies in the adult model differed with regard to assessing mean daily glucose (1245.2 had a different glucose sampling scheme and an OGTT was performed) and the study population (1245.15 was a trial in Asian patients including 101 patients). Both differences were explicitly tested for either

during the covariate analysis (Asian race) or during a sensitivity analysis (OGTT) based on the best current model for adult patients and did not show a significant influence on parameter estimation.

The data from the paediatric trial (1245.87) differed from the adult dataset mostly in terms of baseline glycaemic control (e.g. median MDG), median body weight, renal function in terms of eGFR and distribution of race. Also, the glucose measurements, which were used to calculate the mean daily glucose, were conducted at different time points when compared to the adult trials. Despite difference in sampling frequency and number of samples as well as the performance on an OGTT, mean daily glucose was still the best descriptor for baseline UGE and Emax when comparing OFV, basic goodness of fit plots and VPCs of models with different measures of glycaemic control. With regard to explaining interindividual variability in baseline UGE, mean daily glucose performed better than the rest of the measures for glucose control in both, the adult and the joint population. Therefore baseline MDG has been included as a marker for glycaemic control in the final models (adult and joint population).

Results

Pharmacokinetics

Following single dose administration, empagliflozin was rapidly absorbed in paediatric patients with T2DM, with a median t_{max} of approximately 1.5 h. After reaching peak concentrations, plasma levels declined biphasically. Empagliflozin exposure (both with respect to AUC and Cmax) increased with increasing dose. Mean $t_{1/2}$ was 7 to 8 h for all dose groups. The primary pharmacokinetic parameters of empagliflozin in plasma are shown in Table 2 below for all three dose groups.

Table 2 Arithmetic mean values for primary pharmacokinetic parameters of empagliflozin in plasma following single dose administration to paediatric patients with T2DM

	empagliflozin		
	5 mg	**10 mg**	**25 mg**
	(N = 9)	(N = 8)	(N = 10)
	Mean (%CV)	Mean (%CV)	Mean (%CV)
AUC0-∞ [nmol·h/L]	1270 (51.9)	1450 (17.2)	5250 (27.6)
AUC0-tz [nmol·h/L]	1240 (54.2)	1420 (16.9)	5150 (27.6)
Cmax [nmol/L]	175 (54.2)	211 (59.1)	692 (57.3)
tmax [1] [h]	1.50 (0.95 - 7.92)	1.25 (0.97 - 4.17)	1.78 (0.50 - 4.00)
t1/2 [h]	7.03 (18.9)	7.61 (27.0)	8.09 (26.8)

[1] For tmax, the median and range are given (instead of mean and %CV).

The pharmacokinetic exposure was generally comparable between paediatric and adult patients with T2DM (see table 3)

Table 3 Comparison of pharmacokinetic parameters1 of empagliflozin in paediatric and adult patients with T2DM following single dose empagliflozin administration

Population/ trial	Empagliflozin dose [mg]	$AUC_{0-\infty}$ [nmol·h/L]	AUC_{0-24} [nmol·h/L]	C_{max} [nmol/L]	t_{max} [h]	$t_{1/2}$ [h]	Weight [kg]
Paediatrics/ 1245.87 (n=8)	10	1450 (17.2)	1310 (18.9)	211 (59.1)	1.25 (0.97-4.17)	7.61 (27.0)	111 (21.3)
Adults/ 1245.4 (n=16)	10	1740 (16.4)	1550 (16.2)	309 (45.2)	1.50 (1.00-2.50)	8.76 (13.0)	91.7 (12.3)
Adults/ Pop PK analysis[2]		2300 (955-13600)					
Paediatrics/ 1245.87 (n=10)	25	5250 (27.6)	4720 (27.4)	692 (57.3)	1.78 (0.50-4.00)	8.09 (26.8)	91.1 (25.7)
Adults/ 1245.4 (n=16)	25	4340 (23.1)	3930 (22.9)	722 (20.0)	1.50 (0.75-2.00)	8.24 (14.9)	93.6 (16.0)
Adults/ Pop PK analysis[2]		5750 (2390-34 000)					

[1] For $AUC_{0-\infty}$, AUC_{0-24}, C_{max}, and $t_{1/2}$, the mean and %CV are given. For t_{max} and AUC of the PopPK analysis, the median and range are given. For the weight, mean and SD are listed.
[2] AUC at steady state as determined by population pharmacokinetic modelling of empagliflozin in adult patients with T2DM [c02090424-03].

Pharmacodynamics

A dose-dependent increase from baseline in urinary glucose excretion (UGE) in the 24 h following empagliflozin administration was observed, with mean changes from baseline (adjusted for baseline UGE) of 53.1 g/24 h in the 5 mg dose group, 73.0 g/24 h in the 10 mg dose group, and 87.4 g/24 h in the 25 mg dose group (table 4).

In all three dose groups, this increase in UGE was accompanied by a decrease from baseline in FPG at 24 h postdose. The mean change in FPG from baseline (adjusted for baseline FPG) was -15.5 mg/dL in the 5 mg dose group, -16.6 mg/dL in the 10 mg dose group, and -20.4 mg/dL in the 25 mg dose group at 24 h postdose (table 5).

The mean baseline UGE and FPG were comparable between the 5mg and 10mg group but considerably lower in the 25mg group.

Further the Mean daily glucose (MDG) levels were evaluated. The MDG analysis was based on the data of all patients with at least 7 out of 8 measurements evaluable per 8-point plasma glucose profile, taken within the required time windows. In addition two different sensitivity analysis were performed, one was including all patients with at least 6 out of 8 measurements and one excluded all patients on insulin background therapy.

Mean baseline MDG differed between the 3 dose groups, with lowest values in the 25 mg group. For all 3 dose groups, MDG was lower following single-dose empagliflozin administration compared with the baseline value The mean MDG change from baseline as well as the adjusted mean change from baseline in MDG are shown per treatment group in Table 6.

Table 4 Mean and adjusted mean change from baseline in urinary glucose excretion on Day 1 and Day 2

	empagliflozin		
	5 mg (N = 8)	**10 mg** (N = 8)	**25 mg** (N = 10)
Baseline, mean (SD) [g/24 h]	16.2 (30.3)	12.3 (25.4)	0.1 (0.05)
Change from baseline on Day 1			
Mean (SD) [g/24 h]	58.2 (21.1)	77.5 (45.8)	79.8 (25.6)
Adjusted mean[1] (SE) [g/24 h]	53.1 (10.2)	73.0 (10.1)	87.4 (9.4)
95% CI	(31.8, 74.4)	(51.9,94.1)	(67.9, 107.0)
Change from baseline on Day 2			
Mean (SD) [g/24 h]	17.6 (16.0)	13.6 (10.1)	35.9 (19.7)
Adjusted mean[1] (SE) [g/24 h]	15.5 (5.7)	12.2 (5.6)	38.7 (5.2)
95% CI	(3.7, 27.3)	(0.5, 23.9)	(27.9, 49.6)

[1] The mean change from baseline of UGE was adjusted for baseline UGE.

Table 5 Mean and adjusted mean change from baseline in fasting plasma glucose in the morning of Day 2

	empagliflozin		
	5 mg (N = 7)	**10 mg** (N = 8)	**25 mg** (N = 10)
Baseline, mean (SD) [mg/dL]	141.1 (58.3)	154.5 (55.2)	114.4 (25.9)
Change from baseline on Day 2			
Mean (SD) [mg/dL]	-18.3 (19.0)	-25.2 (41.9)	-11.5 (9.6)
Adjusted mean[1] (SE) [mg/dL]	-15.5 (6.5)	-16.6 (6.3)	-20.4 (5.7)
95% CI	(-29.1, -1.9)	(-29.7, -3.5)	(-32.2, -8.6)

[1] The mean change from baseline of FPG was adjusted for baseline FPG

Table 6 Mean and adjusted mean change from baseline in mean daily glucose on Day 1 (primary analysis)

	empagliflozin		
	5 mg (N = 5)	**10 mg** (N = 4)	**25 mg** (N = 7)
Baseline, mean (SD) [mg/dL]	137.4 (56.7)	151.5 (43.2)	113.1 (20.4)
Change from baseline on Day 1			
Mean (SD) [mg/dL]	-15.9 (11.0)	-15.5 (46.3)	-5.9 (10.0)
Adjusted mean[1] (SE) [mg/dL]	-12.9 (8.0)	-6.5 (9.2)	-13.2 (7.0)
95% CI	(-30.3, 4.4)	(-26.5, 13.6)	(-28.4, 2.1)

[1] The mean change from baseline of MPG was adjusted for baseline MPG

Safety

Safety was monitored descriptively. For 7 out of 27 patients (25.9%), at least 1 adverse event was reported during the on treatment phase of the trial. This comprised 4 out of 9 patients (44.4%) in the 5 mg dose group, 1 out of 8 patients (12.5%) in the 10 mg dose group, and 2 out of 10 patients (20.0%) in the 25 mg dose group. All adverse events were of mild or moderate intensity. No serious adverse events, no deaths, and no other 'significant adverse event' according to ICH E3 were reported for any of the patients. No patient discontinued the trial due to an adverse event. All 3 single doses of empagliflozin were well tolerated in this trial. The safety results of this trial were consistent with those observed in previous empagliflozin trials conducted in adults.

No new safety signals were detected in paediatric patients who received empagliflozin.

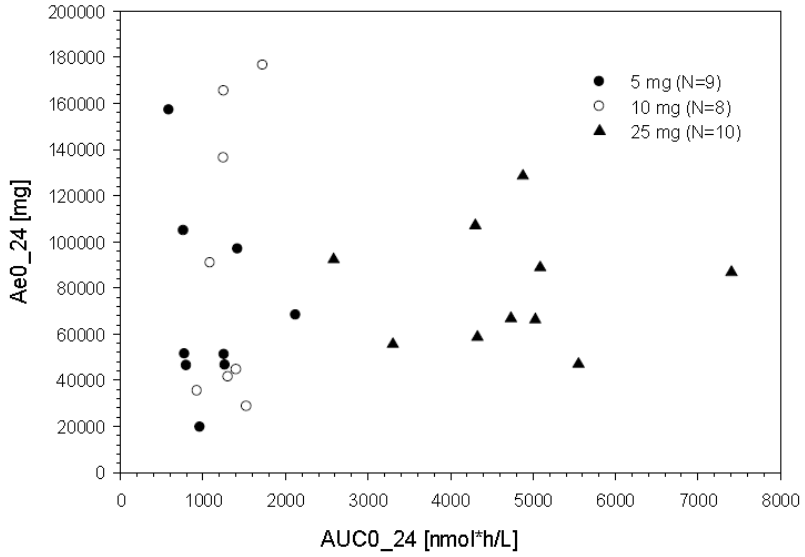
Pharmacokinetic - pharmacodynamic evaluation

The relationship between empagliflozin exposure and UGE was graphically explored.

The individual UGE_{0-24} and UGE_{0-48} values versus the respective empagliflozin AUC_{0-24}, and C_{max} values for empagliflozin following single oral administration of 5 mg, 10 mg, and 25 mg empagliflozin have been presented by the company. A large variability of the data was observed, especially the UGE values in the 5 mg and 10 mg dose groups. No clear correlation between exposure and UGE was observed.

In this report only the UGE ($Ae_{0-24)}$ versus AUC_{0-24} of empagliflozin is presented (figure 1).

Figure 2 Comparison of individual amount of UGE (Ae_{0-24}) versus AUC_{0-24} of empagliflozin following single oral administration of 5 mg, 10 mg, or 25 mg empagliflozin to paediatric patients with T2DM



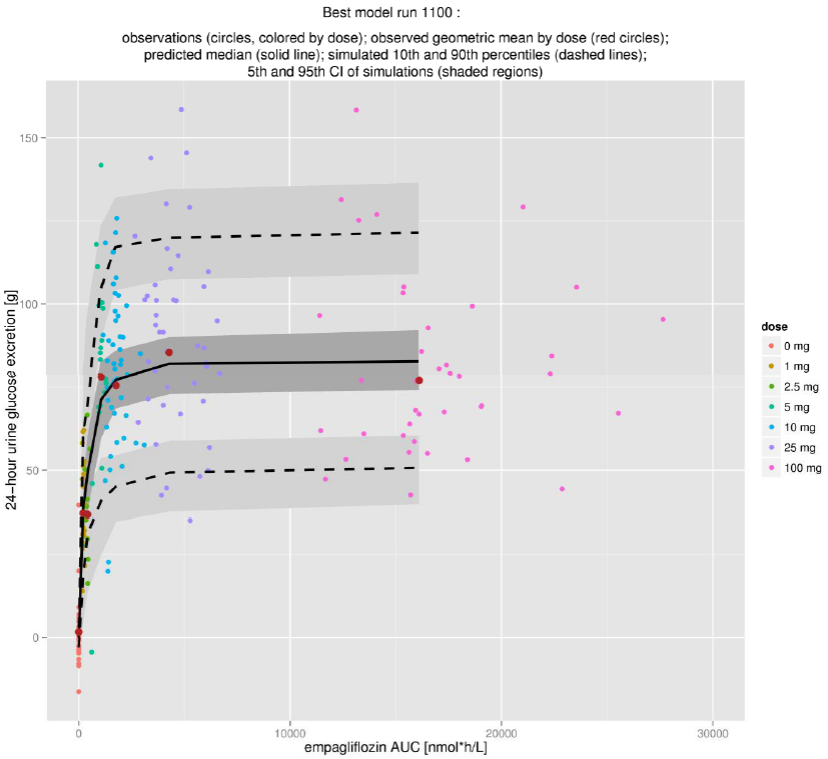
Population pharmacokinetic/pharmacodynamic analysis.

The base models characterizing the exposure-response for the adult and the joint (adult and paediatric) population were Emax models estimating baseline urinary glucose excretion (UGE), the maximal drug effect (Emax) and the AUC50 parameter (area under the curve which results in 50% of Emax). Interindividual variability was estimate for baseline UGE in both models and the residual variability was described by a combined (additive and proportional error model). Based on the base models covariate effects were investigated and simulations to characterize the exposure-response were carried out.

<u>Adult model</u>

Figure 2 shows the best current model based on the adult population, which comprised sex and baseline mean daily glucose (MDG) as covariates for baseline UGE and age and baseline MDG as covariates for Emax. For the dose range 5-25 mg empagliflozin, the relationship between empagliflozin exposure and glucose excretion is rather flat.

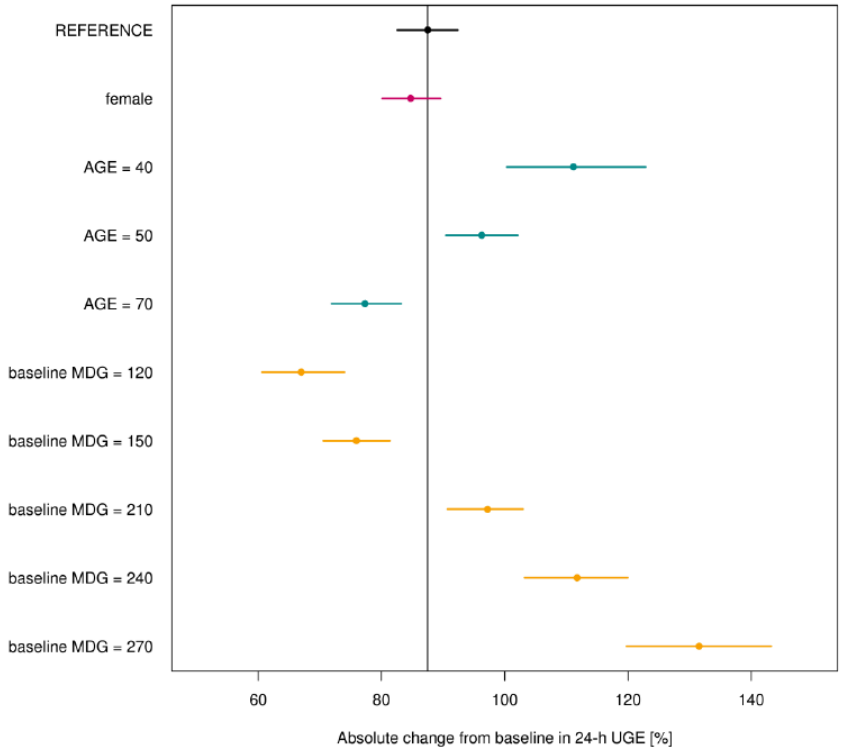
Figure 3 Visual predictive check for the best current adult model (1100).



Note: for geometric mean calculation UGE values which were 0 were excluded (7 baseline observations).
Solid (dashed) line: median (5.0th and 95th percentile) of 1000 simulations. Shaded areas: 95% CI of simulations. Colored small points: Observed data at respective area under the curve (AUC) for each patient. Red point: geometric mean of observations in each dose group

The influence of covariates on absolute change from baseline in 24 h UGE for a 25 mg dose of empagliflozin (q.d.) is shown in figure 3. The plot shows that change from baseline in UGE increases the younger the patient and increases with increasing baseline MDG compared to a reference patient (male, age: 58 years, baseline MDG: 185 mg/dL). Although having a statistically significant effect on baseline UGE, female sex showed only a minor influence on the overall drug effect compared to a male reference patient, with a slightly lower change from baseline in 24 h UGE (95% CI included the reference value).

Figure 4 Covariate forest plot depicting influence (and precision) of covariates on absolute change from baseline in 24 h UGE for a 25 mg dose of empagliflozin (q.d.) (best adult model)



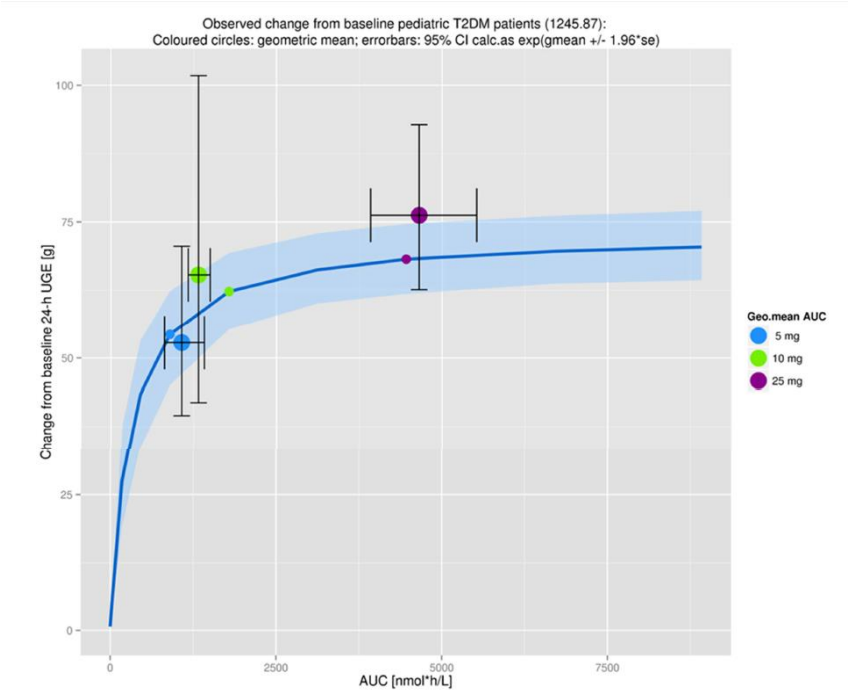
Dots represent the median effect based on simulations and horizontal lines the 95% CI of simulations. Black represents the reference patient: male, T2DM patient with Age: 58 years, baseline MDG: 185 mg/dL.

Comparison of the exposure response profile of a typical adult patient (58 year old, male patient with T2DM, with a baseline MDG: 185 mg/dL) with observed change from baseline in 24 h UGE in the paediatric population has been presented in table 6 and figure 4. From the presented data it appears that the exposure response is comparable between paediatric and adult patients.

Table 7 Summary of simulated change from baseline in 24 h UGE for a typical adult patient with T2DM (male, 58 years) with a baseline MDG of 124 mg/dL and observed change from baseline in 24 h UGE for the paediatric patients with T2DM in 1245.87

Dose [mg]	Change from baseline in 24 h UGE [g/d]	
	Adult patient (Simulations) Median (95% CI)	Paediatric patient (observations) gMean (95% CI)
5	54.0 (45.8 to 61.8)	53.7 (38.8 to 74.4)
10	61.9 (55.1 to 68.9)	65.3 (41.9 to 102)
25	68.0 (61.3 to 74.6)	76.2 (62.6 to 92.8)

Figure 5 Exposure-response profile for a typical adult patient with T2DM (58 year old, male T2DM patient with a baseline MDG: 124 mg/dL) compared to observed change from baseline in 24 h UGE for the paediatric patients with T2DM in 1245.87.



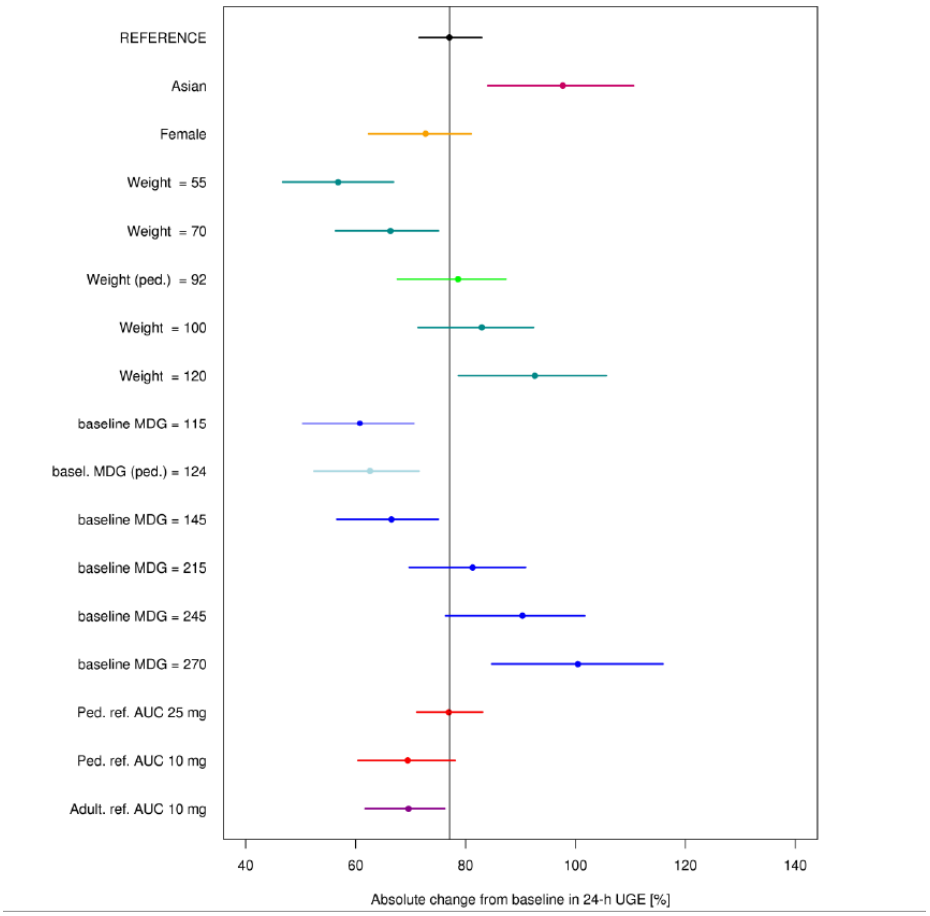
Blue line: Median of simulations, blue shaded area: 95% CI of simulated median. Small points: change from baseline in 24 h UGE at the median 24 h AUC in the respective dose group of the simulations (adult patient). Large points: gMean change from baseline in 24 h UGE for paediatric patients at the gMean AUC of the respective dose group. Error bars: 95% CI of the gMeans in each dose group in paediatric patients

Joint model

The best current model based on the joint population comprised sex and baseline MDG as covariates for baseline UGE and baseline MDG, weight and Asian race as covariates for Emax. During covariate analysis no statistically significant influence of the study population (adult versus paediatric patients) was identified on the model parameters, i.e. the exposure-response between the two populations was comparable after accounting for the identified significant covariates.

The influence of covariates on absolute change from baseline in 24 h UGE for a 25 mg dose of empagliflozin (q.d.) is shown in figure 6. The plot shows that change from baseline in 24 h UGE increases with increasing body weight and increasing baseline MDG compared to a reference patient (male, non-Asian, weight: 83 kg, baseline MDG: 182 mg/dL). Female sex only had a minor influence resulting in a slightly lower change from baseline in 24 h UGE with the 95% CI including the reference value. Asian patients showed a slightly higher change from baseline in 24 h UGE. It should be noted that the influence of this covariate is driven by the adult dataset as only one paediatric Asian patient was included in 1245.87.

Figure 6 Covariate forest plot depicting influence (and precision) of covariates on absolute change from baseline in 24 h UGE for a 25 mg dose of empagliflozin (q.d.) Joint model



Dots represent the median effect based on simulations and horizontal lines the 95% CI of simulations. Black represents the reference patient: male, non-Asian T2DM patient with a baseline MDG: 186 mg/dL and a body weight of 82 kg. For comparison the median weight, baseline MDG and AUC for the paediatric population is depicted (marked as "ped.")

Simulations based on the best current model for the joint population were carried out to characterize the effect of different doses of empagliflozin on change from baseline in 24 h UGE in the two populations (typical adult patient: male, non-Asian, body weight: 82 kg, baseline MDG: 186 mg/dL; typical paediatric patient: female, non-Asian, body weight: 92 kg, baseline MDG: 124 mg/dL) (table 7). Overall the simulated change from baseline in 24 h UGE was in line with the observed change from baseline. The absolute change from baseline for a typical paediatric patient was predicted to be slightly lower compared to a typical adult patient. The exposure-response was comparable between the two populations (Table 8).

Table 8 Summary of simulated change from baseline in 24 h UGE for a typical adult and paediatric patient with T2DM and gMean of observed change from baseline in the two populations

Dose	Change from baseline in 24 h UGE [g/d] Median (95% CI)			
[mg]	Typical adult patient		Typical paediatric patient	
	Simulations Median (95% CI)	Observations gMean (95% CI)	Simulations Median (95% CI)	Observations gMean (95% CI)
5	62.6 (52.7 to71.3)	63.4 (41.1 to 97.9)	54.0 (43.6 to 66.3)	53.7 (38.8 to 74.4)
10	72.4 (65.1 to 78.4)	75.4 (67.7 to 84.0),	62.9 (54.1 to 72.6)	65.3 (41.9 to 102)
25	79.7 (73.5 to 85.6)	85.4 (77.2 to 94.4)	70.1 (62.6 to 78.5)	76.2 (62.6 to 92.8

Table 9 Summary of simulated change from baseline in 24 h UGE for a typical adult and paediatric patients with T2DM expressed as % change from maximal effect

Dose	Change from baseline in 24 h UGE [g/d] Median (95% CI)	
[mg]	Typical adult patient	Typical paediatric patient
5	74.4 (62.6 to 84.7)	72.7 (58.7 to 89.2)
10	86.0 (77.3 to 93.1)	84.7 (72.7 to 97.7)
25	94.6 (87.3 to 102)	94.3 (84.2 to 106)

The analysis of data from the joint (adult and paediatric) population showed that the exposure-response profile of adult and paediatric patients is comparable after accounting for significant covariates.

2.3.3. Discussion on clinical aspects

Paediatric study 1245.87

Demographic characteristic showed some differences between the treatment groups and were not unexpected due to the small sample size. The mean weight was higher in the 10 mg dose group with 111.0 kg than in the 5 mg and 25 mg dose groups with 90.0 kg and 91.1 kg, respectively. This was reflected in differences in the BMI; BMI was not an independent covariate. Mean MDG and FPG at baseline was lowest in the 25 mg dose group. Baseline MDG was 113.1 mg/dL in the 125mg group, 137.4 mg/dL in the 5mg group and 151.5 mg/dL in the 10 mg dose group. Likewise, mean UGE at baseline was lowest in the 25 mg dose group with 0.08 g/24h compared with 16.2 g/24h in the 5 mg dose group and 12.3 g/24h in the 10 mg dose group. The low baseline FPG and MDG in the 25 mg may affect the effect of empagliflozin, as the sodium-glucose linked transporter is less active when glucose levels are (almost) normal. Furthermore, the race distribution was uneven, with the 3 treated American Indian/Alaska Native being all in the 10 mg dose group.

In paediatric trial (1245.87) the pharmacokinetics of empagliflozin has been appropriately characterised. Empagliflozin plasma exposure increased with increasing dose in the studied population, there was no obvious deviation from dose proportional pharmacokinetics. The median tmax was approximately 1.5 h for all dose groups and the mean terminal half-life was 7 to 8 h. These results are in line with the PK characteristics and exposure in adults, according to current SPC (based on adult data only) empagliflozin displays linear pharmacokinetics, has a t_{max} of 1.5 h and a terminal half-life of

12.4 h. The steady state mean plasma AUC and Cmax were 1870 nmol.h/l and 259 nmol/l with empagliflozin 10 mg and 4740 nmol.h/l and 687 nmol/l with empagliflozin 25 mg once daily.

The median body weight differed considerable between the dosing groups weight (5 mg: 86.6 kg, 10mg: 120 kg, 25 mg: 82.4 kg) which might explain the slightly lower exposure in the 10 mg dose group compared to the 5 and 25 mg dose group.

A dose-dependent increase from baseline in UGE in the 24 h following empagliflozin administration was observed in the paediatric patients. In all 3 dose groups, this increase in UGE was accompanied by a decrease from baseline in FPG at 24 h post-dose and by a decrease from baseline in MDG in the 24 h following empagliflozin administration.

The relationship between empagliflozin exposure and UGE was graphically explored. Due to the large variability of the data (especially the UGE values in the 5 mg and 10 mg dose groups), probably caused by differences in body weight and effect of body weight on UGE. However, the exposure-response profile seemed comparable in the paediatric subjects as in adults (Figure 4).

All 3 single doses of empagliflozin were well tolerated in this trial. The safety results of this trial were consistent with those observed in previous empagliflozin trials with adults. No new safety signals were observed.

Population PK-PD study er-uge-t2dm-pediatrics

The exposure-response characterizing the change from baseline in 24 h UGE was best described by an Emax model with inter-individual variability on baseline UGE during both analyses, the analysis of the adult population and the joint population.

The results from the covariate analysis are in line with results from previous analysis (c02089743 and c02090424).Only the influence of body weight with a higher drug effect in heavier patients was not previously identified as such. Therefore, weight based dosing may be more appropriate than fixed dosing.

The effect of the covariate Asian race is entirely driven by the adult population, only one Asian paediatric subject was included in the analysis, therefore the model cannot be used to predict appropriate dose for Asian paediatric subjects.

Based on the population PK/PD model age is apparently not a relevant covariate.

The covariate analysis based on the base model for the joint (adult and paediatric) population did not reveal any statistically significant difference between the two populations after accounting for significant covariates (baseline MDG, weight, Asian race, female Sex). The included covariates were able to explain the slightly lower absolute increase in UGE in the paediatric population at comparable doses. However the paediatric baseline 24 h UGE observations (table 6 and 7) mentioned in the population report are not identical to the values mentioned in the study report 1245.87 (table 1). The company should explain the difference and provide the correct calculations if needed.

3. Rapporteur's overall conclusion and recommendation

Based on the results of paediatric study 1245.87 and the Population PK-PD study er-uge-t2dm-pediatrics it can be concluded that Empagliflozin displays comparable pharmacokinetics between adult and paediatric patients with T2DM and it can be concluded that the exposure-response of adult and paediatric patients with T2DM is comparable after accounting for significant covariates which explain differences in the studied patient populations. Some of the data present in study 1245.87 and the pop

PK-PD study seemed to be inconsistent. However, the Applicant has explained the figures and no inconsistency was present.

Given the uncertainties, the use of empagliflozin 10 and 25 mg in the planned Phase III study in in children and adolescent patients with T2DM which corresponds to the same doses that are approved in adult patients with T2DM, is considered acceptable.

☒ **Fulfilled:**

☐ **Not fulfilled:**

4. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. MAH should explain the difference between the paediatric baseline 24 h UGE observations mentioned in the population report and the baseline 24 h UGE observations mentioned in the study report 1245.87 , as the values are not identical. If needed the company should provide correct recalculations.
2. Body weight was identified as a relevant covariate for urine glucose excretion. The company is asked to evaluate the effect of weight in adolescents and children in the other planned studies in the paediatric population and to assess if weight based dosing may be more appropriate
3. Based on the PK results provided in the paediatric study 1245.87, it can be concluded that empagliflozin increases in AUC and Cmax were less than dose proportional from 5 to 10 mg empagliflozin and more than dose proportional from 10 to 25 mg empagliflozin. The lower exposure in the 10 mg dose group could be related to a body weight factor. In comparison to the original results obtained in adult patients with T2DM and in healthy volunteers in which a linear PK is shown, dose-proportionality/linearity in the paediatric population within the therapeutic range should be further discussed taking into account the body weight factor and the potential impact on efficacy/safety should be investigated.
4. NCA was used to characterise patient exposure. However, AUC0 to 24h on day 1 was used as exposure marker, with relatively sparse sampling in the paediatric population. The MAH should comment the possibility to use a model based approach for PK description and to test the influence of covariates such as bodyweight on drug PK.

5. MAH responses to Request for supplementary information

Question 1

MAH should explain the difference between the paediatric baseline 24h UGE observations mentioned in the population report and the baseline 24 h UGE observations mentioned in the study report 1245.87, as the values are not identical. If needed the company should provide correct recalculations.

Applicant's response

The distribution of baseline UGE for the paediatric study population of 1245.87 is summarised in Table 15.3: 2 of the population report [c09146085] and in Table 15.1.4: 8 of the clinical trial report [c09062077]. As given in Table 15.3: 2 of the population report, the mean baseline UGE is reported to

be 8.79 g/d with a standard deviation of 22.1 g/d. This is identical to the values given in Table 15.1.4: 8 of the clinical trial report, where the mean baseline UGE is reported to be 8.79 g/24 h with a standard deviation of 22.13 g/24 h. In addition to the mean, the median baseline UGE is provided. In Table 15.3: 2 of the population report, the median (2.5th, 95th percentile) is reported to be 0.08 (0.00, 77.1) g/d; the minimum value is 0.0 g/d and the maximum value is 88.0 g/d. This corresponds to the values as given in Table 15.1.4: 8 of the clinical trial report where the median is reported to be 0.08 g/d with a minimum value of 0.0 g/d and a maximum value of 88.0 g/d.

Assessor's response

The Applicant has explained the figures of baseline UGE in the paediatric study and the population report. There are no differences between the paediatric baseline 24 h UGE observations mentioned in both reports.

Conclusion

Issue resolved.

Question 2

Body weight was identified as a relevant covariate for urine glucose excretion. The company is asked to evaluate the effect of weight in adolescents and children in the other planned studies in the paediatric population and to assess if weight based dosing may be more appropriate.

Applicant's response

The MAH did so far not consider weight-based dosing in adolescent and paediatric patients with type 2 diabetes mellitus due to the following reasons (details are presented below):

- in adult patients with type 2 diabetes mellitus body size in terms of body mass index (BMI) did only show a minor impact on empagliflozin exposure and efficacy in terms of HbA1c lowering which was not considered to be clinically relevant, and
- the distribution of BMI in the paediatric and adult population was comparable in the present study and is expected to be comparable in future studies.

Nevertheless, the impact of covariates such as a measure of body size on pharmacokinetic (PK) and pharmacodynamic (PD) endpoints will be characterized when further data from the paediatric development program will become available.

During the exposure-response analysis for the effect of a single dose of empagliflozin on 24 h urinary glucose excretion in the joint (adult and paediatric) population, body weight was identified as a covariate with a statistically significant influence. In the current best model, a higher body weight results in a higher drug effect. Previous population analyses also showed an influence of body size on the PK of empagliflozin and its effect on fasting plasma glucose (FPG)/HbA1c lowering. In these previous analyses body mass index (BMI) was identified to have an effect on PK (with a higher BMI resulting in lower exposure) and on PD (with a higher BMI resulting in less HbA1c reduction). The different findings, i.e. higher body weight leading to higher UGE and higher BMI leading to less HbA1c reduction have been discussed in the population PK/PD report. The influence of BMI on PK and PD identified in the previously conducted population PK and PK/PD analyses was considered to be not clinically relevant in the adult population as the influence was only minor. When compared to a

reference patient (BMI 25 kg/m^2), a BMI of 20 kg/m^2 resulted in a median increase in AUC of only 7.5% and a BMI of 45 kg/m^2 in a median decrease in AUC of only -17.3%.

To further assess the impact of BMI on HbA1c, simulations were carried out based on the current best model for FPG/HbA1c lowering. The simulations were performed using the fixed-effects parameters and their uncertainty obtained from the covariance matrix of the estimates; the results are summarized below (Figure 2: 1). The simulations show that compared to a reference patient (BMI 25 kg/m^2; duration of diabetes 1.5 years with no concomitant antidiabetic therapy), the change from baseline in HbA1c was increased by a factor of only 1.0 for a patient with a BMI of 20 kg/m^2 and decreased by a factor of 0.88 for a patient with a BMI of 45 kg/m^2. Based on these findings there is no weight-based dosing recommendation for adult patients with type 2 diabetes mellitus.

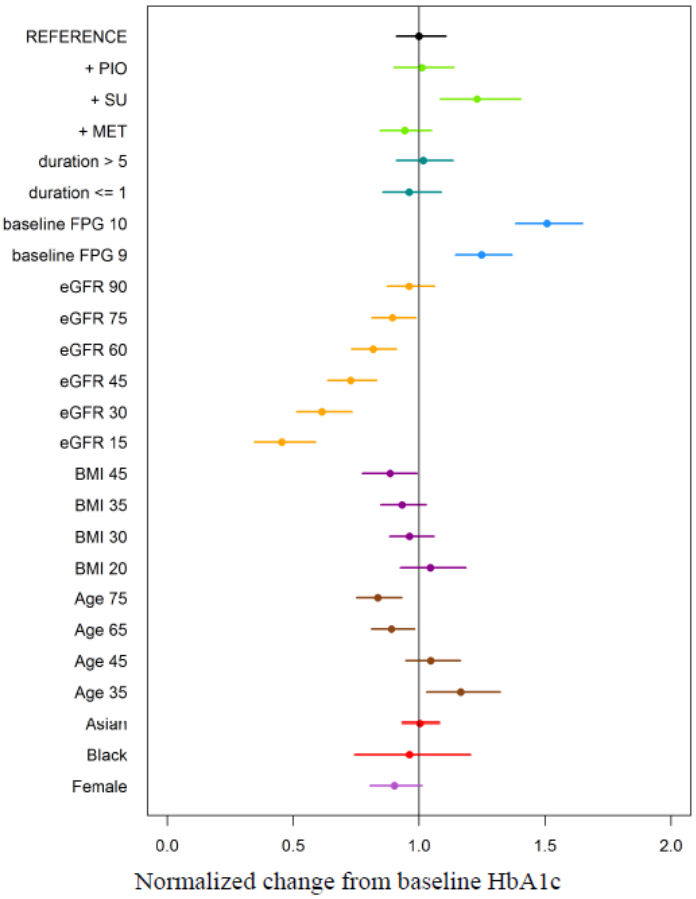


Figure 2: 1 Covariate effects on the change from baseline in HbA1c after 24 weeks of treatment with empagliflozin 25 mg normalized to a reference patient.

Reference: male; non-black, non-Asian; age 50 years; eGFR 100 mL/min/1.73 m2; BMI 25 kg/m2; BFPG 8 mM; duration of diabetes 1.5 years with no concomitant antidiabetic therapy. Points represent the median, horizontal lines the 95% CI of the covariate effect. CIs were determined from 1000 simulations taking parameter uncertainty into account. BFPG baseline fasting plasma glucose, BMI body mass index, CI confidence interval, eGFR estimated glomerular filtration rate, FPG fasting plasma glucose, HbA1c glycated hemoglobin, MET metformin, PIO pioglitazone, SU sulfonylurea

Table 2: 1 summarizes the BMI distribution based on a population PK analysis (pool of 10 studies in adult patients with type 2 diabetes mellitus, PK dataset which is comparable to the one in the

paediatric study population of 1245.87 and the paediatric study population of 1218.56, a Phase IIb dose-finding trial for linagliptin in children and adolescent patients with type 2 diabetes mellitus. It shows that in terms of body size the paediatric patient populations are comparable to the adult population and hence, no influence of body size beyond the influence that was seen in adult patients is expected. Nevertheless, the MAH will investigate the influence of body size (e.g. weight or BMI) on PK and the primary PD endpoint (change from baseline HbA1c after 24 weeks) in the upcoming Phase 3 trial investigating the efficacy and safety of empagliflozin and linagliptin over 24 weeks in children and adolescents with T2DM. This study is part of the approved PIPs for empagliflozin and linagliptin.

Table 2: 1 Distribution of BMI in adult (population PK analysis) and paediatric patients (1245.87, 1218.56)

Study	Population	BMI [kg/m²]	
		Median	Range
Population PK analysis	Adult	28.9	16.8 to 50.3
1245.87	Paediatric (10-17 years)	35.8	23.4 to 48.3
1218.56	Paediatric (10-17 years)	29.6	18.0 to 44.0

Assessor's response

The Applicant provided information on the effect of the BMI on the PK of empagliflozin, but not on the effect of body weight on the PK. The MAH stated that they will investigate the influence of body size (e.g. weight or BMI) on PK and the primary PD endpoint (change from baseline HbA1c after 24 weeks) in the upcoming Phase 3 trial investigating the efficacy and safety of empagliflozin and linagliptin over 24 weeks in children and adolescents with T2DM. The MAH is requested to investigate the influence of weight and BMI on PK and the primary PD endpoint in the upcoming Phase 3 trial in order to answer this question.

Conclusion

Issue **not** resolved. The company is asked to commit to investigate the influence of weight and BMI on PK and the primary PD endpoint in the upcoming Phase 3 trial.

Question 3

Based on the PK results provided in the paediatric study 1245.87, it can be concluded that empagliflozin increases in AUC and C_{max} were less than dose proportional from 5 to 10 mg empagliflozin and more than dose proportional from 10 to 25 mg empagliflozin. The lower exposure in the 10 mg dose group could be related to a body weight factor. In comparison to the original results obtained in adult patients with type 2 diabetes mellitus and in healthy volunteers in which a linear PK is shown, dose-proportionality/linearity in the paediatric population within the therapeutic range should be further discussed taking into account the body weight factor and the potential impact on efficacy/safety should be investigated.

Applicant's response

The MAH believes that there was no significant deviation from dose proportionality in the paediatric population over the range of empagliflozin 5 to 25 mg; body weight affected the pharmacokinetics of empagliflozin, but not to a clinically important degree.

In the adult population, empagliflozin exposure increased in a roughly dose proportional manner following single oral administration over the dose range 0.5 mg to 800 mg in healthy volunteers, as well as following multiple once daily doses over the studied dose range 2.5 mg to 100 mg. In the paediatric study 1245.87, the dose-normalized AUC and C_{max} values were similar between empagliflozin 5 mg and 25 mg doses, but were ~ 32% and 26% lower, respectively, with empagliflozin 10 mg. The lower exposure at empagliflozin 10 mg may be partially explained by the larger body size in this dose group (mean BMI 39.6 kg/m^2 at 10 mg vs ~ 33.8 kg/m^2 at the other doses).

Based on the population PK model developed in adult patients with type 2 diabetes mellitus where BMI was identified as a covariate, an increase in BMI from 33.8 to 39.6 kg/m^2 would lead to a 4.91% decrease in AUC. The remaining unexplained deviation from linearity at the 10 mg dose may be due to the variability inherent with the small sample size of the study, particularly in the context of dose linearity observed in adults and overall comparable exposure between the adult and paediatric population.

In order to further understand the effect of body size on dose-proportionality, an additional analysis of dose proportionality was performed for trial 1245.87, first including weight as an additional covariate in the power model, and second including BMI as an additional covariate. This was done for the three PK parameters $AUC_{0-\infty}$, AUC_{0-tz}, and C_{max}. A summary of the results is displayed in Table 3: 1 below. The slope parameter for log(dose) is denoted by β, and the slope parameter for the additional covariate is denoted by α. For comparison reasons, the initial model with α=0 is included in the table.

Table 3: 1 Dose proportionality analysis of $AUC_{0-\infty}$, AUC_{0-tz}, and C_{max} after single dose administration of empagliflozin to paediatric patients, without and with an additional covariate

PK parameter / model	N	Point of estimate of slope β	Standard error of slope β	95% CI for slope β		Point of estimate of slope α	Standard error of slope α	95% CI for slope α	
				Lower limit	Upper limit			Lower limit	Upper limit
$AUC_{0-\infty}$ [nmol·h/L]									
• α=0	27	0.949	0.108	0.728	1.17				
• x=weight		0.943	0.092	0.753	1.13	-0.009	0.003	-0.014	-0.003
• x=BMI		0.933	0.092	0.743	1.12	-0.030	0.010	-0.050	-0.011
AUC_{0-tz} [nmol·h/L]									
• α=0	27	0.960	0.109	0.736	1.18				
• x=weight		0.953	0.094	0.759	1.15	-0.009	0.003	-0.014	-0.003
• x=BMI		0.943	0.019	0.750	1.14	-0.030	0.010	-0.050	-0.010
C_{max} [nmol/L]									
• α=0	27	0.855	0.148	0.550	1.16				
• x=weight		0.845	0.115	0.607	1.08	-0.014	0.003	-0.021	-0.007
• x=BMI		0.829	0.118	0.586	1.07	-0.048	0.012	-0.073	-0.023

Source data: c09062077, Table 11.2.2.5: 1; Q3_stats_outputs, Table S.1.1: 1, Table S.1.1: 2, Table S.1.2: 1, Table S.1.2: 2, Table S.1.3: 1, Table S.1.3: 2

The results show that adjusting the dose proportionality model for weight or BMI does not relevantly change the initial slope estimates β for log(dose). The standard errors for the slope estimates are reduced, resulting in narrower confidence intervals, which still include 1 in each case. The slope estimates α for weight and BMI, respectively, are negative (as expected), and their confidence intervals do not include 0. However, due to the small magnitudes of these slopes, varying the weight

or the BMI over the observed ranges in the trial would not result in relevant changes in log(AUC) or log(C_{max}), respectively.

The results of this linearity analysis are consistent with the population PK model in adult patients with type 2 diabetes mellitus which assessed the influence of body size on empagliflozin exposure (see Question 2). The impact of BMI is small and is not considered clinically meaningful. Taken all together, the MAH is of the opinion that body size does statistically influence the pharmacokinetics of empagliflozin, but the effect is not clinically meaningful. The PK is roughly dose-proportional in the paediatric patients despite the variability observed at the 10 mg dose.

Assessor's response

Empagliflozin exposure increased in a roughly dose proportional manner following single oral administration over the dose range 0.5 mg to 800 mg in healthy adult volunteers and over a dose range of 5 mg to 25 mg in the paediatric population. The Applicant stated that the less than dose-proportional increase at a dose of 5 to 10 mg is most likely due to an increase in BMI compared to the 5 mg and 25 mg dose group and to variability due to the small sample size. A 4.9% decrease in AUC would be expected based on Population PK modelling. However, the decrease in exposure of 26-32% is more than expected based on the Population PK modelling.

The Applicant provided information on the effect of the BMI on the PK of empagliflozin. However, as in Question 2 the MAH was also requested to provide information on the effect of weight on the PK. Since Question 2 is not resolved, this issue will not be pursued and the answer to Question 2 is awaited.

Conclusion

Issue no longer pursued.

Question 4

Non-compartmental analysis was used to characterise patient exposure. However, AUC 0 to 24h on day 1 was used as exposure marker, with relatively sparse sampling in the paediatric population. The MAH should comment the possibility to use a model based approach for PK description and to test the influence of covariates such as bodyweight on drug PK.

Applicant's response

The MAH is of the opinion, that it is valid to use AUC_{0-24} calculated via non-compartmental analysis as input for the exposure-response analysis for the following reasons:

- using the AUC_{0-24} from a non-compartmental analysis the influence of covariates, including body weight, is implicitly considered.
- due to the number of patients included in 1245.87, using a model-based approach might lead to imprecise PK parameter estimates, which, in turn might influence the characterization of the exposure-response relationship.
- The reduced sampling scheme in 1245.87 (compared to adult studies) leads to less than 5% difference in parameter estimates for the C_{max} and the AUC_{0-24} based on non-compartmental analysis.
- In 1245.78 AUC_{0-24} covers approximately 90% of $AUC_{0-\infty}$ consistently across all dose groups (5, 10 and 25 mg).

Nevertheless, the impact of covariates on pharmacokinetic (PK) and pharmacodynamic (PD) endpoints will be characterized when further data from the paediatric development program will become available (see also response to Question 2).

The objective of the analysis was to compare the exposure-response in paediatric patients with type 2 diabetes mellitus with the one in adult patients. In the single dose setting of study 1245.87, the parameter which was considered most suitable was urinary glucose excretion during the first 24 h after drug administration (UGE_{0-24}) and the corresponding exposure measure AUC_{0-24} (only UGE_{0-24} (not e.g. UGE_{0-48}) was available in adults). The sample size calculation was based on a precision calculation for C_{max} and $AUC_{0-\infty}$, in order to ensure that PK parameters in the paediatric patient population can be determined with the required precision for the within-group geometric means (90% probability for a factor of two between upper and lower limit of the 95% confidence interval). The calculations considered inter-individual variability of the PK parameters from two studies conducted in adult patients with type 2 diabetes mellitus which had a rather rich PK sampling schedule. As the frequency of blood sampling is often of concern in paediatric studies, study 1245.87 was designed to obtain meaningful results with a reduced sampling scheme compared to the adult studies. To evaluate the reduced sampling scheme of 1245.87 on parameter estimation, the PK parameters in adult patients with type 2 diabetes mellitus of study 1245.4 were re-estimated based on the reduced sampling scheme as implemented in 1245.87. The differences in C_{max} and AUC_{0-24} were less than 0.4% and 5.0%, respectively (see Table 4: 1), further supporting the adequacy of the sampling scheme for a non-compartmental analysis in the paediatric study.

Table 4: 1 comparison of day 1 pharmacokinetic parameters in adult patients with T2DM (1245.4) using the original (extensive) and a reduced sampling scheme [c09062077].

Dose [mg]	Sampling	Median	Arithmetic Mean	
		T_{max} [h]	C_{max} [nmol/L]	AUC $_{0-24}$ [h*nmol/L]
10	Extensive[1]	1.5	309	1550
	Reduced[#]	1.5	308	1626
	% difference	0.0	0.324	-4.90
25	Extensive[1]	1.5	722	3930
	Reduced[#]	1.5	721	4116
	% difference	0.0	0.139	-4.73

[1] extensive sampling from 1245.4 [c01796495]
[#] recalculated PK parameters with reduced sampling scheme same as in 1245.87 [c09062077]
* % diff = (from 1245.4 - recalculated with reduced samples)/(from 1245.4)*100

The small differences in PK parameter estimates are most likely due the fact, that although PK blood sampling was less frequent in study 1245.87 compared to that in adults, the sampling scheme in paediatrics (11 samples per patient) was not sparse and describes the plasma concentration profiles of empagliflozin reasonably well. The C_{max} was adequately captured with two samples before t_{max} (~1.5 h) and seven samples up to 48 h post t_{max} which covered $\geqslant$5 times terminal half-lives and sufficiently described the distribution/elimination phase. Furthermore, the contribution of AUC_{0-24} to $AUC_{0-\infty}$ was calculated based on the non-compartmental analysis results and was 89.5%, 90.2% and 90.1% for the empagliflozin 5, 10 and 25 mg dose groups, respectively.

Based on the fact that the sample size of the study was calculated to enable the characterization of PK via non-compartmental analysis, the fact that there is less than 5.0% difference in parameter estimates when comparing the extensive with the reduced sampling scheme, and the fact that for all dose groups AUC_{0-24} covers approximately 90% of $AUC_{0-\infty}$ in study 1245.87 the MAH is of the opinion that it is valid to use AUC_{0-24} calculated via non-compartmental analysis as input for the exposure response analysis. Moreover by using the observed AUC the influence of covariates, including body weight, is implicitly considered. Due to the relatively small sample size in study 1245.87 using a model-based approach might lead to imprecise PK parameter estimates which in turn might influence parameter estimation for the characterization of the exposure-response.

The influence of body size on empagliflozin exposure was previously assessed in a population PK analysis in adult patients with type 2 diabetes mellitus and only showed a minor impact (see Question 2). When compared to a reference patient (body mass index, BMI: 25 kg/m^2) a BMI of 20 kg/m^2 resulted in a median change in AUC of only 7.5% and a BMI of 45 kg/m^2 in a change of AUC of -17.3%). The distribution of BMI in the study population of 1245.87 was comparable to the one in the population PK analysis with a median (range) in adult patients of 28.9 (16.8-50.3) kg/m^2 and a median (range) in paediatric patients of 35.8 (23.4-48.3) kg/m^2. With further data from the paediatric development program becoming available, the impact of covariates on PK and PD endpoints will be characterized (see response to Question 2).

Assessor's response

Non-compartmental analysis was used to calculate the PK parameters in paediatric study 1245.87. The reduced sampling schedule was based on the inter-individual variability of the PK parameters from two studies conducted in adult patients with type 2 diabetes mellitus which had a rather rich PK sampling schedule. The sampling schedule in study 1245.87 consisted of 11 blood samples with two samples before t_{max} (~1.5 h), 2 samples around C_{max} and seven samples up to 48 h post t_{max} (covering $\geqslant$5 times terminal half-lives and sufficiently described the distribution/elimination phase). The contribution of AUC_{0-24} to $AUC_{0-\infty}$ was 89.5%, 90.2% and 90.1% for the 5, 10 and 25 mg empagliflozin dose groups, respectively, calculated using non-compartmental analysis. Overall, the sampling schedule in the paediatric population is sufficient to accurately calculate the PK parameters using non-compartmental analysis. AUC_{0-24} can be used for PK-PD correlation determination with UGE_{0-24} in the paediatric population. The use of a model based approach to calculate the PK parameters in the paediatric study is not needed.

The influence of body weight on the PK is further discussed in the response to Question 2.

Conclusion

Issue resolved. The influence of bodyweight on the PK is further pursued in Question 2.

6. Additional clarification requested

Question 1

The company is asked to commit to investigate the influence of weight and BMI on PK and the primary PD endpoint in the upcoming Phase 3 trial.

7. MAH responses to Request for supplementary information

Question 1

Non-compartmental analysis was used to characterise patient exposure. However, AUC 0 to 24h on day 1 was used as exposure marker, with relatively sparse sampling in the paediatric population. The MAH should comment the possibility to use a model based approach for PK description and to test the influence of covariates such as bodyweight on drug PK.

Applicant's response

The MAH commits investigating the influence of weight and BMI on PK and the primary PD endpoint in the upcoming paediatric Phase 3 trial 1218.91**.**

Conclusion

Issue resolved.