ABSTRACT

Aim: Dapagliflozin improves glycaemic control in patients with type 2 diabetes mellitus (T2DM) and is approved in European and Japanese patients with type 1 diabetes mellitus (T1DM) with inadequate glycaemic control. The objectives of this work were to characterise the dapagliflozin pharmacokinetics (PK) in patients with T1DM, assess the influence of covariates on dapagliflozin PK, and compare dapagliflozin systemic exposure between patients with T1DM and T2DM.

Methods: Population PK analysis was performed using a non-linear mixed-effect modelling approach. The analysis included 5,793 dapagliflozin plasma concentrations from 1,150 adult patients with T1DM, collected from one phase 2 (NCT01498185) and two phase 3 studies (DEPICT-1, NCT02268214; DEPICT-2, NCT02460978). Covariate effects were investigated using stepwise covariate modelling. Model-derived area under the concentration-time curve (AUC) was compared with AUC in patients with T2DM.

Results: The final two-compartmental model adequately described the dapagliflozin concentrations in patients with T1DM. The estimated apparent clearance was 20.5 L/h. Model-predicted systemic exposure for 5 mg and 10 mg of dapagliflozin indicated dose-proportionality and was comparable between patients with T1DM and T2DM.

The identified covariate relationships showed that patients with better renal function (measured as estimated glomerular filtration rate), males, and heavier patients had lower dapagliflozin systemic exposure. Among the covariates studied, no covariates affected dapagliflozin systemic exposure to a clinically relevant extent.

Conclusions: Dapagliflozin PK in patients with T1DM was adequately described by the population PK model and no clinically relevant covariates were identified. Dapagliflozin systemic exposure was comparable between patients with T1DM and T2DM.

NCT01498185, NCT02268214, NCT02460978

1 INTRODUCTION

Dapagliflozin improves glycaemic control in patients with type 2 diabetes mellitus (T2DM) and is currently licensed in many countries worldwide. Dapagliflozin inhibits the sodium-glucose cotransporter 2 (SGLT2), leading to urinary excretion of glucose [1]. Since the mode of action of dapagliflozin is independent of insulin, investigations using dapagliflozin for the treatment of patients with type 1 diabetes mellitus (T1DM) and inadequate glycaemic control was undertaken in two phase 3 studies (DEPICT-1, NCT02268214 [2]; DEPICT-2, NCT02460978 [3]). Both studies showed a positive benefit of dapagliflozin (5 mg and 10 mg) on haemoglobin A1C (HbA1C) as an adjunct therapy to insulin treatment after 26 and 52 weeks of treatment [2]. Consequently, dapagliflozin has been approved for use in T1DM in Europe (5 mg, once daily) and Japan (5 mg and 10 mg, once daily). No dose adjustments based on different patient characteristics (e.g. age or renal function) are required [4].

The pharmacokinetics (PK) of dapagliflozin has been studied in a wide dose range (0.1–500 mg) in different populations, such as healthy subjects, adults with T2DM and adolescents with T2DM [5, 6]. Doses of dapagliflozin up to 500 mg were, in general, safe and well tolerated in healthy subjects, and had a dose-proportional exposure. The peak concentrations of dapagliflozin are usually reached within 2 hours, and the terminal half-life was approximately 12.5 hours. Dapagliflozin is mainly metabolised in the kidneys and liver by UDP glucuronosyltransferase family 1 member A9 (UGT1A9) to the inactive metabolite, dapagliflozin 3-O-glucuronide (D3OG) [7]. A previously established semi-mechanistic population pharmacokinetic (popPK) model of dapagliflozin included the PK of D3OG and was, therefore, able to assess the contribution of renal (normal renal function: 40%–55%) and hepatic elimination to the metabolite formation [8]. The analysis also identified creatinine clearance as a covariate on both renal and non-renal clearance, as well as hepatic impairment status on clearance and volume of distribution. In addition, sex was identified as a covariate on dapagliflozin apparent clearance, whereas, no impact of race was found [8]. However, none of these covariates were deemed clinically relevant. The effect of dapagliflozin on HbA1c correlates with the area under the concentration-time curve (AUC) [9] and AUC has, therefore, been selected as the pharmacokinetic parameter of interest for the current analysis.

A previous PK analysis by Tang et al, indicated that the PK properties of dapagliflozin were similar in patients with T1DM and T2DM based on a non-compartmental analysis using only phase 2 data [1]. The objective of the present analysis was to characterise the PK of dapagliflozin in patients with T1DM by employing a popPK approach using phase 2a and

phase 3 clinical trial data and to compare the exposure of dapagliflozin between patients with T1DM and T2DM.

2 METHODS

2.1 Study design

For the current analysis, studies in patients with T1DM including PK sampling of dapagliflozin plasma concentrations were identified and have been summarised in Table 1. All studies were conducted according to the Declaration of Helsinki, Good Clinical Practice and local ethics standards. All patients signed the informed consent before study initiation.

A single phase 2 study (NCT01498185 [10]) and two phase 3 studies (NCT02268214 [2], NCT02460978 [3]) were available for patients with T1DM. In the phase 3 studies, all patients were on ordinary insulin therapy. Overall, 5,793 dapagliflozin plasma concentrations (91%) of the available samples from 1,150 patients with T1DM meet inclusion criteria and were used for the current analysis. Complete list of exclusions is available in the supporting information.

2.2 Population pharmacokinetic model

2.2.1 Model development

The structural model (two-compartmental model with first-order absorption and lag time) from a previous popPK model established in patients with T2DM and healthy subjects was used as the basis for the current model {, #174}{, #174}{, #174}(See Supporting information) [11]. The model was initially estimated using only data from the phase 2a study (NCT01498185), before the phase 3 data were added (NCT02268214 and NCT02460978). The absorption model was re-assessed, whereas no further disposition models were evaluated.

2.2.2 Covariate assessment

Pre-specified covariates were selected based on physiological plausibility, prior knowledge and correlation between covariates. Covariates assessed for apparent clearance (CL/F) included age, sex, race, body weight, and estimated glomerular filtration rate (eGFR). Covariates assessed for central volume of distribution (Vc/F) included age, sex, race, and body weight. Modification of Diet in Renal Disease (MDRD) equation was used for calculating eGFR [12]. Covariates were identified using a stepwise covariate modelling

procedure implemented in Perl-speaks-NONMEM (PsN [13]) to derive statistically significant covariate effects. Stepwise testing of linear and power relationships was performed in a forward inclusion (difference in objective function value [ΔOFV] of 6.63, $p < 0.01$ for 1 degree of freedom [DF]) and backward exclusion (ΔOFV of 10.8, $p < 0.001$ for 1 DF) procedure.

In addition, the full covariate approach was applied to allow for assessing the impact on CL/F for all statistically significant and non-significant covariates in a forest plot. In this approach, all covariates with correlation coefficient ≤ 0.4 were added as covariates on CL/F. As body mass index (BMI) was highly correlated with body weight (r^2: 0.84), and age was correlated with estimated glomerular filtration rate (eGFR; r^2: -0.5), these covariates (BMI and age) were not included. Hence, sex, race, body weight, and eGFR were added as covariates on CL/F.

The impact of these covariates on dapagliflozin systemic exposure (i.e. AUC) was illustrated in Forest plots. For this purpose, predicted dapagliflozin AUC for the reference subject (Caucasian male with median covariates) was compared with predicted AUC for patients with different sets of covariates (5th or 95th percentile of baseline body weight, 5th or 95th percentile of baseline eGFR, 5th or 95th percentile of baseline age, female, different race, etc.). Dapagliflozin CL/F was sampled 1,000 times from the variance-covariance matrix and was used to derive AUC according to equation 1. The 90% confidence interval for dapagliflozin AUC was generated from the 5th and 95th percentiles.

$$AUC = \frac{Dose}{CL/F} \qquad \text{(eq 1)}$$

2.2.3 Model selection and evaluation

Model selection was based on the inspection of goodness of fit (GOF) plots and changes in the OFV. The difference in OFV (ΔOFV) between nested models is approximately χ^2 distributed and a difference of -6.635 corresponds to a p-value of < 0.01 for 1 DF. Models were also judged by plausibility of parameter estimates and parameter precision (fixed-effects > 30% relative standard error [RSE], random-effects > 50% RSE [14]).

The simulation-based visual predictive check (VPC) method was used to assess the adequacy of the model. The model was used to simulate 1,000 replicates of the analysis dataset stratified on study. The 5th, 50th and 95th percentiles of the simulated, and observed data

were derived and used for graphical comparison. Prediction-corrected VPCs were used to assess performance of all doses simultaneously [15].

2.2.4 Dapagliflozin systemic exposure in different subpopulations

To assess individual model-predicted systemic exposure in different subpopulations, box plots of different subpopulations based on age, sex, race, body weight, and eGFR, were explored. In addition, dapagliflozin systemic exposure from the previous T2DM submission was extracted and used for comparison. Information regarding the T2DM submission, including studies used and the popPK model, can be found in the Supporting information.

2.2.5 Software

The popPK model was established in NONMEM 7.3 (Icon Development Solutions, Ellicott City, MD, USA, 2009 [16]) using PsN 4.4.8 (psn.sourceforge.net).

3 RESULTS

3.1 Patient population and exploratory data analysis

In total, data from 1,150 patients with T1DM were used for model development. As seen in Table 2, the median age and body weight were slightly higher in the phase 3 studies compared with the phase 2a study. Renal function (measured as eGFR calculated by Modification of Diet in Renal Disease [MDRD] equation) was comparable in all three studies. Most of the patients in the studies were Caucasians (87.7%), followed by Asians (8.96%), whereas the distribution of females and males was similar (females, 53.7%; males, 46.3%).

As expected, the dapagliflozin plasma concentration-time profiles normalised to 10 mg indicated dose-proportionality and showed a biphasic decline (Figure 1). In addition, no major differences were observed between studies.

3.2 Population pharmacokinetic model

The final model was a two-compartmental model with first-order absorption and first-order elimination. The dapagliflozin first-order absorption rate constant (K_a) was fixed to the estimate from the previous popPK model (2.97/h, Table S1) due to limited data in the absorption phase. Estimated dapagliflozin CL/F was 20.9 L/h and Vc/F was 87 L. The estimated between-subject variability was low for dapagliflozin Vc/F (16.6%) and

intermediate for CL/F (34.1%) and apparent inter-compartmental clearance (Q/F, 35.4%). Shrinkage was rather large for dapagliflozin Vc/F and Q/F (~60%). For residual variability, separate proportional errors were included for the phase 2a (32.3%) and phase 3 studies (37.3%). As seen in Table 3, all dapagliflozin PK parameters were estimated with accurate precision (RSE < 30%).

After the step-wise covariate analysis, eGFR (higher dapagliflozin CL/F with higher eGFR), body weight (higher CL/F with higher body weight) and sex (higher CL/F for males) were added as covariates on dapagliflozin CL/F. In addition, body weight (higher dapagliflozin Vc/F with higher body weight), sex (higher Vc/F for males) and age (lower Vc/F for higher age) were added for Vc/F. The equations, including respective covariate relationships for dapagliflozin CL/F and Vc/F, are shown in equations 2 and 3, respectively.

$$\frac{CL}{F}=\frac{CL_{REF}}{F}\cdot\left(\frac{BWT}{BWT_{REF}}\right)^{BWT\ \frac{CL}{F}}\cdot\left(\frac{eGFR}{eGFR_{REF}}\right)^{eGFR\ \frac{CL}{F}}\cdot\left(1+SEX\quad CL/F\right) \text{ (eq 2)}$$

$$\frac{Vc}{F}=\frac{Vc_{REF}}{F}\cdot\left(1+BWT\quad\frac{Vc}{F}\right)\cdot\left(BWT-BWT_{REF}\right)\cdot\left(\frac{AGE}{AGE_{REF}}\right)^{AGE\ \frac{Vc}{F}}\cdot\left(1+SEX\quad Vc/F\right) \text{ (eq 3)}$$

As seen in the prediction-corrected VPCs stratified by study (Figure 2), no unacceptable trends in diagnostic plots were observed, indicating that the final popPK model accurately describes the data.

3.3 Inference from population pharmacokinetic model

The estimates for the full covariate model (Table S2) were very similar to the estimates of the final popPK model. The Forest plot (Figure 3) indicated that no individual covariate at extreme values resulted in changes in systemic exposure of more than 25% relative to a reference individual (Caucasian male with median covariates). None of the covariates were, therefore, considered to be clinically relevant.

3.4 Comparing exposure in different subpopulations

Model-predicted dapagliflozin AUC normalised to 10 mg stratified by sex, race, age group, renal function, and body weight is presented in Figure 4. Overall, slightly higher model-predicted dapagliflozin median AUC normalised to 10 mg was observed in females compared with males (1.24-fold higher), in patients older than 60 years compared with patients 40–60 years old (1.15-fold), in patients with eGFR less than 60 mL/min/1.73 m^2 compared with eGFR > 90 mL/min/1.73 m^2 (1.4-fold), and in patients with body weight below 70 kg

compared with 70–100 kg (1.21-fold). However, these differences were not deemed clinically relevant since some drug-drug interactions result in larger dapagliflozin AUC changes, yet no clinical action is recommended [7]. In addition, the distributions (as shown by the box plots in Figure 4) were largely overlapping, indicating no difference between the groups. No difference in dapagliflozin systemic exposure was observed between racial groups.

3.5 Comparison of systemic exposure between patients with T1DM and T2DM

As seen in Figure 5, the distributions of the model-predicted dapagliflozin AUC normalised to 10 mg for T1DM and T2DM were largely overlapping. Model-predicted median dapagliflozin AUC normalised to 10 mg was similar in adult patients with T1DM (526 ng*h/mL) compared with adult patients with T2DM (464 ng*h/mL), corresponding to a 1.13-fold higher dapagliflozin systemic exposure in T1DM compared with T2DM.

4 DISCUSSION

The aim of the current analysis was to characterise the PK of dapagliflozin in adults with T1DM using data from one phase 2a study (NCT01498185) and two phase 3 studies (NCT02268214 and NCT02460978). In addition, the analysis sought to identify covariates with significant impact on PK parameters, and to compare dapagliflozin systemic exposure between patients with T1DM and T2DM (extracted from a previous analysis).

The established two-compartmental disposition model with first-order absorption and elimination adequately described the dapagliflozin plasma concentrations in patients with T1DM. Model diagnostics indicated a good description of the data, and PK parameters were estimated with high precision.

The current analysis showed that body weight, sex and eGFR had an impact on dapagliflozin systemic exposure. Higher body weight and eGFR were associated with higher clearance and, therefore, lower dapagliflozin systemic exposure. In addition, males had lower dapagliflozin systemic exposure compared with females. Renal function (creatinine clearance) and sex were previously identified as covariates for dapagliflozin apparent clearance in patients with T2DM (Supporting information). The current analysis is, therefore, consistent with the previous observations and supports the impact of renal function and sex on dapagliflozin systemic exposure, regardless of the underlying disease. Although eGFR and sex were identified as statistically significant covariates, no clinically relevant changes were identified between males and females and for the observed eGFR range in the current studies.

Therefore, adjustment of the dapagliflozin dose based on sex and eGFR (in the studied eGFR range) was considered unnecessary.

For dapagliflozin Vc/F, covariates included body weight (higher Vc/F with increasing body weight), sex (higher Vc/F for males) and age (lower Vc/F with increasing age). Body weight was identified for dapagliflozin Vc/F in the previous analysis, whereas sex and age were not identified. Vc/F does not affect AUC but will have an impact on C_{max} of dapagliflozin. As the therapeutic effect of dapagliflozin is mainly driven by AUC, our assessment focused on AUC rather than on C_{max}.

The model-predicted systemic AUC was compared between different subgroups to support the lack of clinically relevant covariates in the current analysis. The comparison indicated no clinically relevant impact of sex, age group, race or renal function on dapagliflozin AUC (Figure 4). For these reasons, the results from the popPK analysis suggests that no dose adjustments are needed in these subpopulations.

As the aim of the current analysis was to compare the dapagliflozin systemic exposure between patients with T1DM and T2DM, dapagliflozin plasma concentrations judged to be post-dose rather than pre-dose (concentrations > $C_{max}/2$) were excluded from the analysis. This was not thought to bias the analysis, as, in most cases, individual dapagliflozin C_{max} values were available to compare the suspected post-dose plasma concentrations. Tang et al, which included data from the same Phase 2 study as in the current manuscript, showed similar exposure in patients with T1DM and T2DM. This was confirmed by the similar model-predicted AUC in the current analysis, which in addition considered Phase 3 data from 1,096 patients with T1DM [1].

In addition, the dapagliflozin CL/F in T1DM patients (20.5 L/h) was similar to a previous estimate in patients with T2DM and healthy subjects (22.9 L/h), further confirming the previous findings. Dapagliflozin CL/F is also in the same range as the previous estimate of 19.5 L/h in adults and adolescents with T1DM [17].

In conclusion, the PK of dapagliflozin in patients with T1DM was adequately described by the popPK model, and no clinically relevant covariates were identified. Moreover, the identified covariates in patients with T1DM were similar to the covariates identified in patients with T2DM. Systemic dapagliflozin exposure in patients with T1DM following administration of 5 mg and 10 mg dapagliflozin was found to be dose-proportional and comparable to the exposure in patients with T2DM receiving the same doses. This confirms

that PK properties of dapagliflozin are similar for both patient populations and suggests that there is no PK-attributed reason to adjust dapagliflozin doses in patients with T1DM.

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Conflict of interest

JM, WT, DR, BH, RCP, DWB and JP are employees of AstraZeneca and own AstraZeneca stock.

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Data availability

Research data are not shared

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TABLES

TABLE 1. Summary of studies included in the analysis for patients with type 1 diabetes mellitus

Study number	Study description	Doses (mg)	Number of subjects	PK sampling times	Samples/ subject median (range)
NCT01498185 (MB102072)	Randomised, double-blind, placebo-controlled, parallel-group, exploratory Phase 2a	1, 2.5, 5, and 10	54	Day 7 (pre-dose, and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose)	10 (9–10)
NCT02268214, DEPICT-1 (MB102229)	Randomised, double-blind, placebo-controlled, parallel-group, multicentre, Phase 3	5 and 10	566	Day 1 (60, 90, and 180 minutes post-dose) and weeks 12, 18 and 24	6 (1–6)
NCT02460978, DEPICT-2 (MB102230)	Randomised, double-blind, placebo-controlled, parallel-group, multicentre, Phase 3	5 and 10	530	Day 1 (60, 90, and 180 minutes post-dose) and weeks 12, 18 and, 24	6 (1–7)

PK = pharmacokinetics

TABLE 2. Patient demographics for all patients in the analysis and stratified by study

	All patients *n* = 1150	**T1DM, Phase 2a study NCT01498185 *n* = 54**	**T1DM, Phase 3 study NCT02268214 *n* = 566**	**T1DM, Phase 3 study NCT02460978 *n* = 530**
Variables	median (min–max)	median (min–max)	median (min–max)	median (min–max)
Age, years	43 (18–75)	30 (18–65)	43 (18–75)	44 (18–75)
BMI, kg/m^2	27.2 (18.2–65.8)	24 (19–33.4)	27.9 (18.2–65.8)	26.9 (18.6–56.6)
Body weight, kg	78.6 (45.9–185)	74.5 (54.7–118)	80.9 (46.9–185)	76.8 (45.9–160)
eGFR, mL/min/1.73 m^2	88.5 (33.1–179)	89.3 (49.4–144)	88 (33.1–173)	89.1 (41.5–179)
	N (%)	*N* (%)	*N* (%)	*N* (%)
Females	618 (53.7)	24 (44.4)	299 (52.8)	295 (55.7)
Males	532 (46.3)	30 (55.6)	267 (47.2)	235 (44.3)
Caucasians	1008 (87.7)	48 (88.9)	540 (95.4)	420 (79.2)
Black/African American	26 (2.26)	4 (7.41)	12 (2.12)	10 (1.89)
Asian	103 (8.96)	1 (1.85)	2 (0.353)	100 (18.9)
Other	13 (1.13)	1 (1.85)	12 (2.12)	-

Data source: S229_S230_S072.csv; r-script: s02_EGA.R; 2017-12-22 12:04:02

BMI = body mass index; eGFR = estimated glomerular filtration rate

TABLE 3. Final parameter estimates for population pharmacokinetic model

Condition number		**42.3**		
Parameters	**Units**	**Population mean**	**RSE (%)**	**Shrinkage (%)**
K_a	/h	2.97 (fix)	NA	-
CL/F	L/h	20.5	1.95	-
Vc/F	L	87	2.53	-
Vp/F	L	141	7.45	-
Q/F	L/h	12.3	5.89	-
BWT~CL/F[a]		0.41	14.8	-
eGFR~CL/F[a]		0.33	15.9	-
SEX~CL/F[b]		-0.14	14.7	-
AGE~Vc/F[b]		-0.00338	27.9	-
SEX~Vc/F[b]		-0.175	12.9	-
BWT~Vc/F[b]		0.00811	8.5	-
Between-subject variability				
CL/F	% CV	34.1	3.86	8.23
Vc/F	% CV	16.6	13.3	60.1
Q/F	% CV	35.4	11.3	59.5
Residual variability				
Proportional error NCT02268214 & NCT02460978	% CV	37.3	1.91	9.54
Proportional error NCT01498185	% CV	32.3	8.52	7.06

% CV = percent coefficient of variation, BWT = body weight; CL/F = apparent clearance; eGFR = estimated glomerular filtration rate; K_a = first-order absorption rate constant; OFV = objective function value; Q/F =apparent inter-compartmental clearance; RSE = relative standard error; Vc/F = apparent central volume of distribution; Vp/F = apparent peripheral volume of distribution.

[a]power model.

[b]linear model.

FIGURE LEGENDS

FIGURE 1. Dapagliflozin plasma concentration profiles *vs.* time stratified by dose in patients with type 1 diabetes mellitus from one phase 2 study (NCT01498185) and two phase 3 studies (NCT02268214, NCT02460978).

FIGURE 2. Prediction-corrected visual predictive check stratified by study. Lines: 10th, 50th and 90th percentiles of observed data. Shaded areas: 95% confidence interval around 10th, 50th and 90th percentiles of simulated data (n = 1000). Circles: Observations.

FIGURE 3. Forest plot showing covariate effect of the full dapagliflozin covariate model for model-predicted AUC. AUC = area under the concentration-time curve; eGFR = estimated glomerular filtration rate

FIGURE 4. Dose-normalised dapagliflozin AUC in T1DM stratified on different covariates. AUC = area under the concentration-time curve; eGFR = estimated glomerular filtration rate; T1DM = type 1 diabetes mellitus

FIGURE 5. Dose-normalised dapagliflozin AUC in patients with T1DM vs patients with T2DM. AUC = area under the concentration-time curve; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus