ORIGINAL ARTICLE

Exposure–response relationships of dapagliflozin on cardiorenal risk markers and adverse events: A pooled analysis of 13 phase II/III trials

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Aims: Dapagliflozin is a sodium–glucose co-transporter 2 inhibitor that has been developed as oral glucose lowering drug. The original dosefinding studies focused on optimal glycaemic effects. However, dapagliflozin also affects various cardiorenal risk markers and provides cardiorenal protection. To evaluate whether the currently registered doses of 5 and 10 mg are optimal for cardiorenal efficacy and safety, we characterized the relationship between dapagliflozin exposure and nonglycaemic cardiorenal risk markers as well as adverse events.

Methods: Data were obtained from a pooled database of 13 24-week randomized controlled clinical trials of the clinical development programme of dapagliflozin. The exposure–response relationship was quantified using population pharmacodynamic and repeated time-to-event models.

Results: A dose of 10 mg dapagliflozin resulted in an average individual exposure of 638 ng h/mL (95% prediction interval [PI]: 354–1061 ng h/mL), which translated to 71.2% (95% PI: 57.9–80.5%), 61.1% (95% PI: 58.0–64.8%), 91.3% (95% PI: 85.4–94.6%) and 25.7% (95% PI: 23.5–28.3%) of its estimated maximum effect for fasting plasma glucose, haematocrit, serum creatinine and urinary albumin–creatinine ratio, respectively.

Conclusion: We demonstrate that doses higher than 10 mg could provide additional beneficial effects in haematocrit, systolic blood pressure, urinary albumin–creatinine ratio and uric acid, without obvious increases in the rate of adverse events. These results raise the question whether future outcome studies assessing the benefits of higher than currently registered dapagliflozin doses are merited.

KEYWORDS
albuminuria, cardiovascular risk markers, dapagliflozin, exposure–response, pharmacodynamics, SGLT-2 inhibition, type 2 diabetes

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Jeroen V. Koomen and Jasper Stevens contributed equally

No principal investigators were involved in this analysis.

1 | INTRODUCTION

The sodium–glucose co-transporter-2 (SGLT-2), located in the S1 segment of the proximal tubule of the kidney, regulates glucose reabsorption and plays an important role in glucose homeostasis.[1] Inhibition of SGLT-2 by dapagliflozin causes glucosuria[2] and, in patients with type 2 diabetes, improvements in glycated haemoglobin (HbA1c) and fasting plasma glucose (FPG).[3–7]

Favourable effects of dapagliflozin have been demonstrated on other cardiorenal risk markers including systolic blood pressure (SBP), haematocrit (HCT), albuminuria and uric acid (UA).[8,9] The Dapagliflozin Effect on Cardiovascular Events—Thrombolysis in Myocardial Infarction (DECLARE-TIMI) 58 trial observed long-term improvements in heart failure and kidney outcomes with dapagliflozin once daily *vs* placebo.[10–13] The modest reduction in HbA1c and the observed early time course of a reduction in events in the DECLARE-TIMI 58 trial as well as findings from other clinical trials indicate that these beneficial effects of dapagliflozin are unlikely to be explained by improvements in glycaemic control.[9,14–16] Other mechanisms, such as the reduction of plasma volume as a consequence of the natriuretic effects of dapagliflozin, have been proposed to explain the beneficial effects of SGLT2 inhibitors on heart and kidney failure.[17]

At present, dapagliflozin is registered for clinical use at therapeutic doses of 5 and 10 mg once daily based on dose finding studies that targeted urinary glucose excretion as the primary glycaemic efficacy parameter.[1,2,18,19] As the efficacy of SGLT2 on clinical outcomes appears to be largely independent of glycaemic control, this raises the question of whether glycaemic parameters are the most appropriate parameters to determine the optimal dose for dapagliflozin. We therefore aimed to characterize the exposure–response relationship between dapagliflozin and a range of cardiorenal risk markers as well as adverse events, in order to evaluate the currently registered dosing regimen.

2 | MATERIALS AND METHODS

The 13 phase II/III trials of the dapagliflozin clinical development programme that formed the basis for the dose registration of dapagliflozin were included in this analysis, an overview of the included studies is depicted in Table 1. All studies received approval of the final protocol by an independent ethics committee or institutional review board. Studies were performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonization/Good Clinical Practice and applicable regulatory requirements and the AstraZeneca policy on bioethics.

2.1 | Estimation of exposure to dapagliflozin

Pharmacokinetic data were not available for all patients in our analysis. However, the pharmacokinetics of dapagliflozin have been

What is already known about this subject

- Dapagliflozin is registered for clinical use at therapeutic doses of 5 and 10 mg once daily based on dose finding studies that targeted urinary glucose excretion as the primary glycaemic efficacy parameter.

What this study adds

- This study indicates that the exposure–response relationship for glycaemic markers differs from the exposure–response relationships of cardiorenal risk markers. As a consequence, the optimal glycaemic dose of dapagliflozin might be different than the optimal cardiorenal dose. Dose finding for cardiorenal indications should ideally be based on a panel of markers.

quantified in a previous study by Van der Walt *et al.* using a semimechanistic population pharmacokinetic model.[20] Child–Pugh score, ideal bodyweight, baseline creatinine clearance and age were identified in this model as covariates that explained variability in the pharmacokinetic profile between patients. These individual patient characteristics were available for all patients in our analysis; therefore, we used this pharmacokinetic model to predict the individual exposure to dapagliflozin. For each patient in our analysis, 1000 simulations including interindividual variability were performed. The median predicted area under the curve for 24 hour at steady state (AUC_{0-24}) for each individual was estimated.

2.2 | Modelling of cardiorenal risk markers

Population pharmacodynamic analyses explored the exposure–response relationship between dapagliflozin and various (cardiorenal) risk markers. Favourable effects have been demonstrated for serum creatinine (SCr), HCT, SBP, urinary albumin–creatinine ratio (UACR) and UA, and were therefore selected for the current analysis. In addition, FPG was used in the dose–response studies and therefore selected as glycaemic parameter in this study.

For each trial, observations during the randomized period were included in the analysis. Observations after rescue medication were excluded from the analysis and, for the UACR dataset, only patients with microalbuminuria (UACR >30 mg/g, $n = 1859$) at baseline were included. UACR observations were log-transformed. For each of the analyses datasets, AUC_{0-24} was assumed to be zero at baseline and, after baseline, the individual model predicted AUC_{0-24} was incorporated in the datasets.

A nonlinear mixed effects modelling approach was used to develop a population pharmacodynamic model for each (cardiorenal)

TABLE 1 Study description of studies included in the exposure–response analysis

Study number	Study description	Patient population	Treatment groups	Background medication	Number of patients randomized	Study duration
MB102008	Phase II, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the safety and efficacy of dapagliflozin as monotherapy	Treatment naive T2D	Placebo, metformin, dapagliflozin 2.5, 5.0, 10.0, 20.0 or 50.0 mg	None	389	12 wk
MB102013	Phase III, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the safety and efficacy of dapagliflozin as monotherapy	Treatment naive T2D	Placebo, dapagliflozin 2.5, 5.0, 10.0 mg	None	210	24 wk
MB102014	Phase III, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the safety and efficacy of dapagliflozin in combination with metformin	T2D inadequately controlled with metformin alone	Placebo, dapagliflozin 2.5, 5.0, 10.0 mg	Stable dose of metformin ≥1500 mg	546	24 wk
MB102028	Phase III, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy and safety of dapagliflozin in combination with glimepiride	T2D inadequately controlled with glimepiride alone	Placebo, dapagliflozin 2.5, 5.0, 10.0 mg	Stable dose of glimepiride 4 mg	589	24 wk
MB102029	Phase II/III, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy, renal safety, pharmacokinetics and pharmacodynamics of dapagliflozin as monotherapy	Treatment naive T2D with moderate renal impairment	Placebo, dapagliflozin 5.0, 10 mg	None	169	24 wk
MB102030	Phase III, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the safety and efficacy of dapagliflozin in combination with thiazolidinedione therapy	T2D inadequately controlled with thiazolidinedione therapy alone	Placebo, dapagliflozin 5.0, 10 mg	Stable dose of pioglitazone 30 or 45 mg	420	24 wk
MB102032	Phase III, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the safety and efficacy of dapagliflozin as monotherapy	Treatment naive T2D	Placebo, dapagliflozin 1.0, 2.5, 5.0 mg	None	282	24 wk
MB102033	Phase III, randomized, double-blind, placebo-controlled, parallel group	T2D inadequately controlled with insulin therapy alone	Placebo, dapagliflozin 2.5, 5.0, 10.0	Stable insulin regimen with a mean dose of at least 30 IU	800	24 wk

TABLE 1 (Continued)

Study number	Study description	Patient population	Treatment groups	Background medication	Number of patients randomized	Study duration
	trial to evaluate the safety and efficacy of dapagliflozin added to insulin					
MB102034	Phase III, randomized, double-blind, active-controlled, parallel group trial to evaluate the safety and efficacy of the combination of metformin and dapagliflozin, vs dapagliflozin monotherapy and metformin monotherapy	Treatment naïve T2D	Placebo, dapagliflozin 10 mg, metformin XR 500 mg	None	638	24 wk
MB102047	Phase III, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the effect of dapagliflozin in combination with metformin on bodyweight	T2D inadequately controlled with metformin therapy alone	Placebo, dapagliflozin 10 mg	Stable metformin monotherapy ≥1500 mg/d	182	24 wk
MB102061	Phase III, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the safety and efficacy of dapagliflozin added to sitagliptin or combination of sitagliptin with metformin	T2D inadequately controlled with sitagliptin alone or on sitagliptin in combination with metformin.	Placebo, dapagliflozin 10 mg	Open-label sitagliptin 100 mg ± metformin ≥1500 mg/d	447	24 wk
MB102067	Phase III, randomized, double-blind, age-stratified, placebo-controlled trial to evaluate the safety and efficacy of dapagliflozin 10 mg	T2D, cardiovascular disease and hypertension, inadequately controlled on usual care	Placebo, dapagliflozin 10 mg	Stable monotherapy or combination therapy with metformin, pioglitazone, SU, or a DPP-4 inhibitor or insulin	914	24 wk
MB102080	Phase III, randomized, double-blind, age-stratified, placebo-controlled trial to evaluate the safety and efficacy of dapagliflozin	T2D, cardiovascular disease and inadequately controlled on usual care	Placebo, dapagliflozin 10 mg	Stable monotherapy or combination therapy with metformin, pioglitazone, SU, or a DPP-4 inhibitor or insulin	962	24 wk

T2D = type 2 diabetes; DPP-4 = dipeptidyl peptidase-4; SU = Sulfonylurea Derivative.

risk marker. First-order conditional estimation with interaction was used to obtain parameter estimates. An individual baseline parameter was estimated for each patient in the placebo-group as a first step in the model development. Subsequently, several empirical structural models were evaluated in the placebo group to evaluate the effect of placebo administration and disease progression;Linear, power, exponential, Emax, Gompertz, Weibull, Bateman and cosine functions were evaluated both additive and proportional to the estimated baseline parameter.[21] Interindividual variability was formally tested on model parameters using a normal or log-normal distribution. Also, covariance between model parameters was explored. After evaluating the placebo response, patients were stratified by treatment; dapagliflozin or placebo. The effect of treatment was then tested on the structural model parameters by estimating a drug effect per model parameter. The relationship between individual dapagliflozin exposure (AUC_{0-24}) and response was explored using linear, log-linear or Emax functions. Additive, proportional and combined error models were evaluated to describe the residual variability. Finally, a covariate step was performed by plotting interindividual variability parameters *vs* covariates. When $R^2 > .15$ and $P < .05$, covariate relationships were formally tested in the model. Covariates evaluated were: age, bodyweight, body mass index, compliance, duration of diabetes, ethnicity, FPG, haemoglobin, HbA1c, height, ideal bodyweight, liver function markers, SBP, SCr, race, region, sex, study identifier, UA. Model selection and evaluation was based on numerical and graphical evaluation as described by Byon *et al.*[22]

2.3 | Modelling of adverse events

Repeated time-to-event models were developed to investigate the exposure–response relationship between dapagliflozin and the probability of developing a genital tract infection (GTI) and urinary tract infection (UTI) in the 24 week study period. Studies MB102014, MB102067 and MB102080 were included in the repeated time-to-event analysis, since these datasets contained information about adverse events. Model parameters were obtained using the Laplacian estimation method. It was anticipated that the probability of developing an event was relatively low for both GTIs and UTIs. Therefore, at first, several structural models were evaluated to describe the hazard for each event of interest using the full datasets. Constant, Gompertz and Weibull functions were evaluated to describe the hazard. Second, the effect of dapagliflozin was explored using a similar approach as described above for the population pharmacodynamic models. The exposure–response relationship was evaluated using linear, log-linear or Emax functions proportional to the hazard function. Model selection and evaluation was based on numerical diagnostics (i.e. the change in MOFV and reduction in relative standard error [RSE] of the population parameter estimates) and graphically using survival based visual predictive checks. Third, covariates were evaluated graphically by stratification of the survival based visual predictive checks. The covariate was formally tested if a discrepancy was discovered between observed *vs* predicted survival.

2.4 | Exploring the exposure–response relationships

Simulations with the final population pharmacodynamic models were performed to compare the exposure–response relationships between the cardiorenal risk markers. We evaluated the exposure–response relationship on week 24, as most of the clinical trials included in our analysis had a follow-up of 24 weeks. For each model, 1000 patients were simulated per dapagliflozin dose group. Each simulation included interindividual random effects and assumed similar exposure and covariate distributions as observed in the population per dose group. For each cardiorenal risk marker, we estimated the maximum effect of dapagliflozin assuming an infinite high exposure (exposure of 1 000 000 ng h/mL). For both UTI and GTI, we estimated the probability of developing an event during 24 weeks. This probability was estimated by predicting the number of events in 24 weeks and dividing this number by the total number of subjects.

2.5 | Software

All data preparation and presentation was performed using R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria). NONMEM version 7.3.0 (ICON Development Solutions, Ellicott City, MD, USA) was used for the pharmacokinetic simulations, development of population pharmacodynamic models and repeated time-to-event models and all simulations of the final models.

3 | RESULTS

3.1 | Demographics and estimation of exposure to dapagliflozin

In total, 7005 patients with type 2 diabetes mellitus randomized in 13 phase II/III randomized controlled trials of 12–24 week duration were included in the analysis. Baseline characteristics by treatment assignment are displayed in Table 2. A dose range of 1.0–50.0 mg was evaluated, although a majority of patients received 5.0 mg (14.4%) or 10.0 mg (37.4%) dapagliflozin once daily. No apparent differences are visible between treatment groups in the patient characteristics, except for a difference in the duration of type 2 diabetes mellitus (Table 2). The individual median predicted dapagliflozin systemic exposure, stratified by treatment group, demonstrated that the exposure to dapagliflozin is dose proportional and the variability is such that dapagliflozin systemic exposure overlaps between the different treatment groups (Figure 1).

3.2 | Modelling of cardiorenal risk markers

Most patients were included for all risk markers (Table 3), except for UACR. Patient numbers per study have been provided in supplement 5. Several empirical population pharmacodynamic models were

TABLE 2 Summary of demographic characteristics at baseline for the randomized population

Dose (mg)	Placebo	1.0	2.5	5.0	10.0	20.0	50.0	Total
Number of subjects	2426	72	758	1010	2624	59	56	7005
Age (y)	58.9 (10.1)	53.7 (9.0)	56.9 (10.1)	56.5 (10.7)	58.0 (10.5)	54.9 (10.3)	52.9 (10.2)	57.9 (10.4)
Sex (male)	1401 (57.7)	38 (52.8)	375 (49.5)	518 (51.3)	1487 (56.7)	32 (54.2)	25 (44.6)	3876 (55.3)
Asian	166 (6.8)	11 (15.3)	71 (9.4)	96 (9.5)	187 (7.1)	2 (3.4)	1 (1.8)	534 (7.6)
African American	79 (3.3)	4 (5.6)	15 (2.0)	33 (3.3)	97 (3.7)	5 (8.5)	5 (8.9)	238 (3.4)
Caucasian	2084 (85.9)	56 (77.8)	653 (86.1)	850 (84.2)	2242 (85.4)	51 (86.4)	48 (85.7)	5984 (85.4)
Other	97 (4.0)	1 (1.4)	19 (2.5)	31 (3.1)	98 (3.7)	1 (1.7)	2 (3.6)	249 (3.6)
Bodyweight (kg)	90.4 (19.1)	88.1 (18.5)	87.6 (19.1)	88.2 (19.0)	90.7 (19.5)	88.2 (18.2)	91.5 (18.9)	89.8 (19.3)
Duration of diabetes (y)	8.7 (8.1)	1.6 (2.6)	6.9 (7.1)	7.3 (7.7)	8.6 (8.3)	2.5 (3.9)	2.4 (3.3)	8.1 (8.0)
Fasting plasma glucose (mg/dL)	165.3 (45.9)	157.4 (49.6)	168.8 (48.5)	172.6 (52.8)	169.3 (51.3)	N/A	N/A	168.2 (49.4)
Glycated haemoglobin (%)	8.2 (1.0)	7.8 (1.0)	8.2 (0.9)	8.3 (1.1)	8.3 (1.1)	N/A	N/A	8.2 (1.0)
Serum creatinine (mg/dL)	0.9 (0.3)	0.9 (0.2)	0.9 (0.2)	0.9 (0.3)	0.9 (0.2)	0.9 (0.2)	0.8 (0.2)	0.9 (0.2)
Haematocrit (%)	42.4 (4.0)	43.2 (3.3)	42.2 (4.0)	42.0 (3.9)	42.3 (4.1)	43.3 (3.9)	43.7 (3.8)	42.3 (4.0)
Systolic blood pressure (mmHg)	130.9 (15.5)	127.5 (13.6)	131.9 (17.5)	130.5 (17.2)	130.7 (15.9)	127.3 (17.1)	126.9 (14.7)	130.8 (16.1)
Uric acid (mg/dL)	5.6 (1.6)	5.4 (1.4)	5.4 (1.4)	5.4 (1.6)	5.6 (1.5)	N/A	N/A	5.5 (1.6)

The data are displayed as number of subjects (percentage of the population) or as mean (standard deviation) for continuous variables. N/A: Not available.

developed to describe the trend over time for each cardiorenal marker for each subject included in the analysis. A brief description of the model development, model structure, model parameters and visual predictive checks stratified by treatment are displayed in
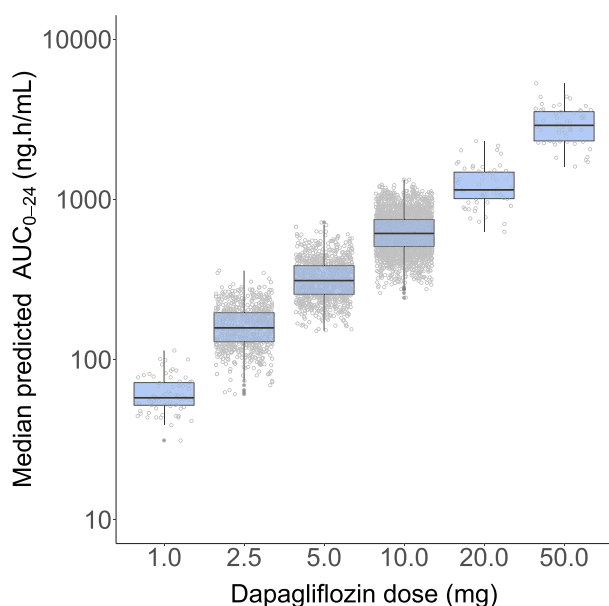

FIGURE 1 Relationship between dose and individual exposure (AUC_{0-24} at steady state) per treatment group. The points represent the predicted median AUC_{0-24} at steady state for each individual patient. The boxplot demonstrates the distribution of individual predicted exposures per dose group

Figures S1–6 and Tables S1–6 for all population pharmacodynamic models.

Table 3 provides an overview of the structures used in the population pharmacodynamic models. An individual baseline parameter was estimated for each patient. For all models, the individual baseline parameters were best described using a log-normal distribution, except for HCT, which was best described using a normal distribution. A placebo response was identified for FPG and UACR, characterized by a proportional Weibull and power function, respectively. Drug effects could be identified for each pharmacodynamic parameter of interest, which could also be related to individual exposure. In general, Emax or log-linear relationships were able to describe the exposure–response relationships. However, for HCT and SCr, drug effects were best described using a power- and a Bateman function, respectively. All goodness-of-fit plots demonstrate that the model predictions follow the central trend of the data, indicating appropriate structural models. No bias over time was observed in the conditional weighted residuals *vs* time plots. In general, model parameters were estimated with high precision (average RSE 11.6%, highest RSE was 60.9%, see Tables S1–6).

Interindividual variability was identified on the baseline parameters of all models. In addition, interindividual variability could be identified on other model parameters for SCr, FPG, HCT and UACR, but not for SBP and UA. Significant covariates that explained variability between patients in the different models were: age, bodyweight, duration of diabetes, serum creatinine, sex and UA (Table 3). Goodness-of-fit plots demonstrated that the individual model predictions followed the individual trend of the data. The residual error was

TABLE 3 Overview of model structure and number of patients per cardiorenal risk marker or adverse event. Serum creatinine (SCr), fasting plasma glucose (FPG), serum haematocrit (HCT), systolic blood pressure (SBP), urinary albumin–creatinine ratio (UACR), uric acid (UA), genital tract infections (GTI) and urinary tract infections (UTI)

Model structure	Population pharmacodynamic models						Repeated time-to-event models	
	SCr (n = 7004)	FPG (n = 6613)	HCT (n = 7005)	SBP (n = 6814)	UACR (n = 1859)	UA (n = 6616)	GTI (n = 2430)	UTI (n = 2430)
Baseline	Ln-distributed estimated baseline	Ln-distributed estimated baseline	Normally-distributed estimated baseline	Ln-distributed estimated baseline	Ln-distributed estimated baseline	Ln-distributed estimated baseline	Weibull function	Weibull function
Placebo		Proportional Weibull function			Proportional power function			
Drug effect	Proportional Bateman function with Emax function on DREC	Emax function on ALPHA, log-linear function on K, Emax function on baseline	Power function with log-linear function on ALPHA	Log-linear function on baseline	Log-linear function on ALPHA	Log-linear function on baseline	Emax function on SHP	Log-linear function on Weibull function
Covariates	Age, sex, uric acid	Duration of diabetes,	Duration of diabetes, serum creatinine, sex	Age, bodyweight	Serum creatinine, sex	Bodyweight, serum creatinine	Region, sex,	ACE inhibitor use, region, sex,
Interindividual variability	Normally distributed Emax parameter	Normally distributed ALPHA parameter	Normally distributed ALPHA parameter	Normally distributed ALPHA parameter	Normally distributed ALPHA, log-normally distributed power parameter		N/A	N/A
Error	Proportional	Proportional	Combined	Proportional	Additive	Combined	N/A	N/A

N/A = not applicable; DREC = amplitude parameter of bateman function; ALPHA = amplitude parameter of power function; SHP = shape parameter of Weibull function; ACE = angiotensin converting enzyme.

estimated using either an additive, proportional or combined error model (Table 3).

3.3 | Modelling of adverse events

For modelling of adverse events, data were available for 2430 out of the 7005 patients included in our analysis from studies MB102014, MB102067 and MB102080. A total of 77 and 92 patients reported a GTI and UTI, respectively, during the study period of 24 weeks. Instead of time-to-event models that only include 1 observation per patient, we developed repeated time-to-event models that included all available observations. For GTI and UTI, a total of 87 and 108 events were observed during the clinical trials during the study period of 24 weeks. A brief description of the model development, model structure, model parameters and visual predictive checks stratified by treatment are displayed in Figures S7 and 8, and Tables S7 and S8.

Table 3 provides an overview of the repeated time-to-event models for UTI and GTI. A Weibull model was used to describe the survival distribution over time for both GTI and UTI. Drug effects were identified for both GTI and UTI, which could also be related to individual exposure. For GTI, an Emax function was used to relate individual exposure to the probability of developing an event. For UTI, the individual dapagliflozin systemic exposure was log-linearly related to the probability of developing an event. Significant covariates that explained differences in the probability of developing an event were sex and region for both GTI and UTI. In addition, for UTI, the use of an angiotensin converting enzyme inhibitor was also a significant covariate. Both models were estimated with good precision (average RSE 32.7%, highest RSE was 72.42%, see Tables S7 and S8). Furthermore, the goodness-of-fit plots indicate that the central trend of the data is adequately described by the model.

3.4 | Exploration of the exposure–response relationships

Figure 2 demonstrates the exposure–response relationship between dapagliflozin and each of the pharmacodynamic markers of interest at week 24. The individual exposure for 5 mg dapagliflozin was on average 327 ng h/mL (95% prediction interval [PI]: 187–547 ng h/mL), which translated in 55.9% (95% PI: 42.0–68.0%), 57.6% (95% PI: 54.6–60.3%) and 84.3% (95% PI: 75.5–90.0%) of its estimated maximum effect for FPG, HCT and SCr, respectively. Furthermore, 10 mg dapagliflozin resulted in an average individual exposure of 638 ng h/mL (95% PI: 354–1061 ng h/mL), which translated in 71.2% (95% PI: 57.9–80.5%), 61.1% (95% PI: 58.0–64.8%) and 91.3% (95% PI: 85.4–94.6%) of its estimated maximum effect for FPG, HCT and SCr, respectively.

The effects of dapagliflozin on SBP, UA and UACR did not approach the maximum effect of dapagliflozin. For UACR, 10 mg dapagliflozin achieved 25.7% (95% PI: 23.5–28.3%) of the maximum

effect. Moreover, for both SBP and UA, 10 mg dapagliflozin induced <10% of the estimated maximum effect.

The relationship between individual exposure to dapagliflozin and the probability of developing a GTI and UTI in 24 weeks is shown in Figure 3. For GTI, the probability of developing an infection appeared to reach a maximum around an exposure of 500 ng h/mL, which is covered by the individual exposures following a dose of 5.0–10.0 mg dapagliflozin. For UTI, the maximum probability seems not to have been reached as the trend of developing an UTI is still increasing at a maximum exposure of 1000 ng h/mL.

4 | DISCUSSION

In this pooled analysis, we quantified the exposure–response relationship between dapagliflozin and several (cardiorenal risk) markers and adverse events. Dapagliflozin given at 10 mg/d was close to its maximum effect for serum creatinine. For both FPG and HCT, 10 mg dapagliflozin resulted in effects that appeared to approach the maximum effect, although there was room for higher efficacy. For SBP, UA and UACR, the effects of dapagliflozin 10 mg/d reached <25.7% of their maximum effects, suggesting that a higher dose of dapagliflozin could confer additional effect. From a safety perspective, the probability of developing a GTI reached a plateau around a dose of 5–10 mg. Since HCT, SBP and UACR are strong risk markers for renal and heart failure outcomes, our results suggest that a higher dose of dapagliflozin may confer additional clinical benefit in the long-term.

This exposure–response analysis contains 13 phase II and III trials of the clinical development programme of dapagliflozin that investigated efficacy and safety in patients with type 2 diabetes mellitus. The included patient population of all studies demonstrated a broad range of patient characteristics, which were comparable amongst studies. Using a previously developed population pharmacokinetic model by van der Walt et al.,[20] we were able to predict the individual exposure for each patient included in our analysis. Model simulation techniques resulted in an average individual exposure of 638 ng h/mL and a 95% prediction interval ranging from 354 to 1061 ng h/mL following a 10 mg dapagliflozin dose at steady state. The prediction interval is comparable to previously reported interindividual variability at steady state for a 10 mg dose,[18] indicating the appropriateness of the model to predict individual exposures. In addition, a similar structural model was used in patients with type 1 diabetes mellitus confirming the generalizability of the population pharmacokinetic model.[23]

Favourable effects of dapagliflozin have been demonstrated on a range of cardiorenal risk markers including long-term improvements in heart failure and kidney outcomes that are unlikely to be explained by improvements in glycaemic control.[13] In our analysis, and as expected, the dose–response relationship between dapagliflozin and FPG was in line with previous studies.[4] Interestingly, the exposure–response relationship for several other cardiorenal risk markers differed from FPG. As a consequence, for most cardiorenal risk markers, the maximal effects were not yet achieved at the registered antihyperglycaemic
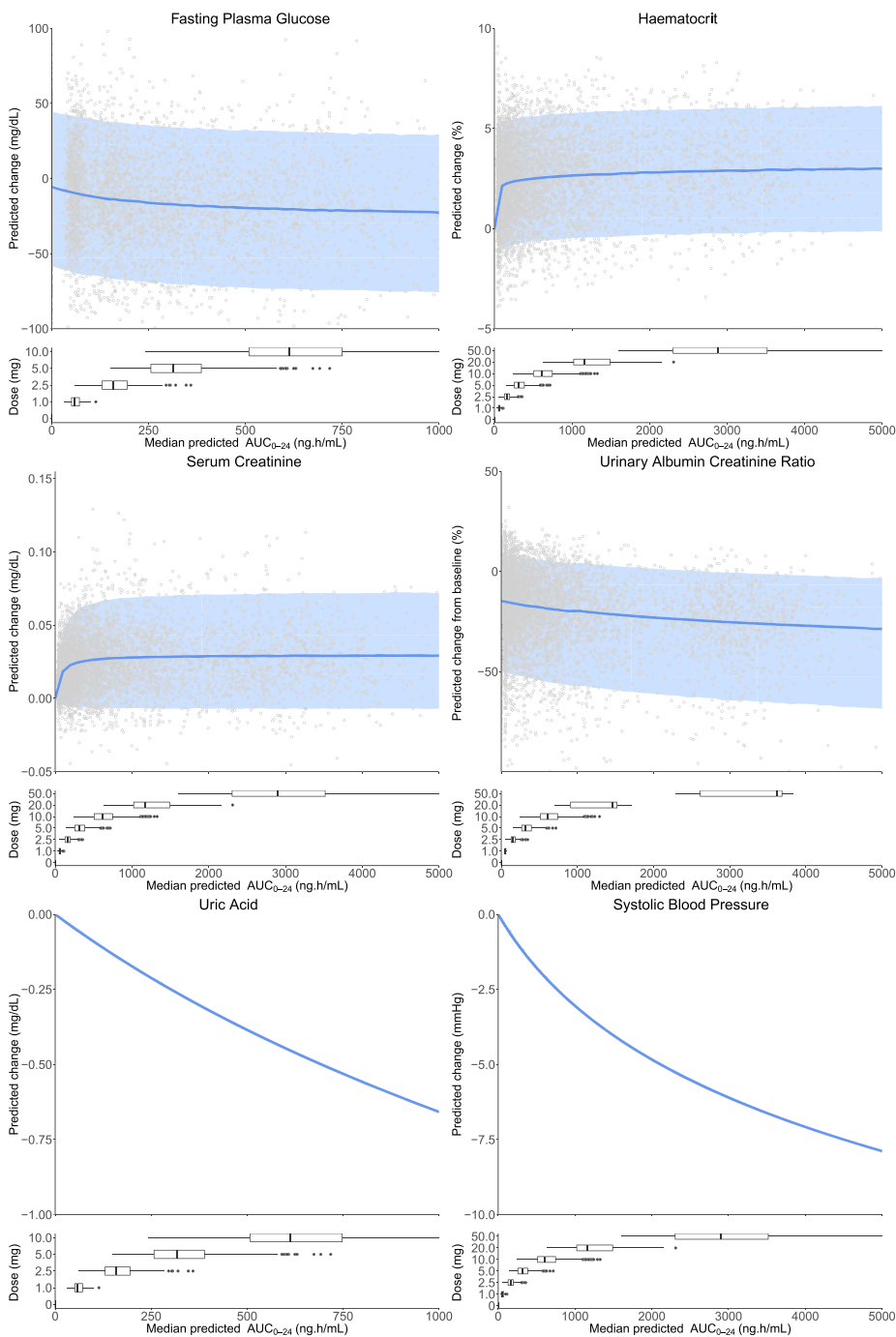
FIGURE 2 Exposure–response relationships at week 24 for fasting plasma glucose (top left), haematocrit (top right), serum creatinine (middle left), urinary albumin–creatinine ratio (middle right), uric acid (bottom left) and systolic blood pressure (bottom right). The line demonstrates the exposure–response relationship for the typical individual, individual points demonstrate the individual predictions. The 90% prediction interval has been included, if applicable, as interindividual random effects could only be identified on baseline and could not be identified in drug response for systolic blood pressure and uric acid. In each plot, the relationship between dose and median predicted AUC_{0-24} is displayed for patients included in the pharmacodynamic datasets. Data were not available for dapagliflozin dose levels higher than 10 mg for both fasting plasma glucose and uric acid

dose. This effect is reminiscent of angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers. Although these agents are registered as antihypertensive drugs, their benefits are likely mediated by their albuminuria lowering effect.[24] Dose-finding studies have demonstrated that higher than maximum antihypertensive doses of these drugs result in additional albuminuria reduction and long-term clinical benefits on kidney function.[25–27] Collectively, these data complicate the optimal dose finding for a new drug, as the exposure–response relationship may be different among cardiorenal risk markers. Consequently, to determine the optimal dose of a new drug, the exposure–response relationships on a composite score including

multiple pharmacodynamic efficacy and safety markers may be considered.[28]

Establishing efficacy at higher doses should be weighed against the risk of developing more adverse events. We therefore characterized the relationship between exposure and adverse events with dapagliflozin.[13] For GTIs, the probability of developing an infection plateaued around a dose of 5–10 mg dapagliflozin. The probability of developing a UTI still increased at a dose of 10 mg dapagliflozin suggesting that based on our studies, higher efficacy may occur at the expense of more UTIs. We note, however, that the overall probability of developing an event was low for both GTIs and UTIs limiting the
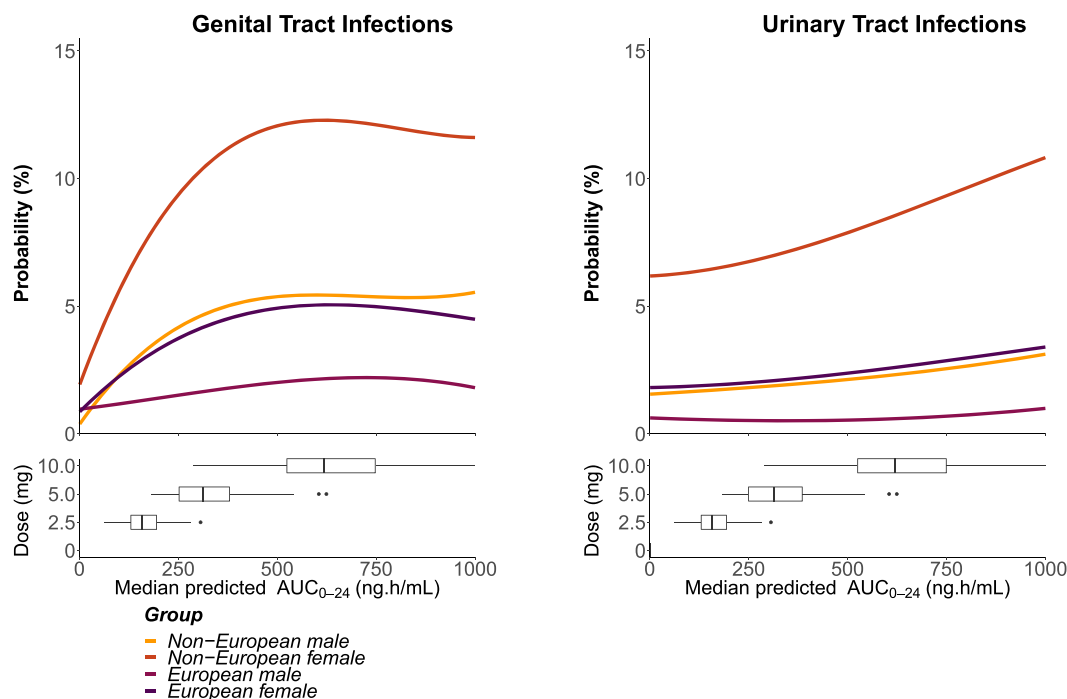
FIGURE 3 Exposure–response relationship for genital (left) and urinary tract infections (right). The figures demonstrate the exposure–response relationship for the typical individual and are stratified by sex and region of inclusion. Non-European females (orange), non-European males (yellow), European female (purple) and European male (red)

precision of the estimated probabilities. In addition, although earlier clinical trials, including those used for our study, reported differences in incidence of UTIs, the overall rate of these infections did not differ between SGLT2 and placebo treated patients in more recent cardiovascular outcome trials.[10,12,13]

The efficacy and safety of dapagliflozin as a treatment for chronic kidney disease is currently being investigated in patients with and without diabetes in the Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (Dapa-CKD, NCT03036150). In addition, the Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure (Dapa-HF, NCT03036124) demonstrated that dapagliflozin reduced the risk of heart failure or cardiovascular death compared to placebo regardless of the presence of diabetes mellitus type 2.[16] In these studies, patients without diabetes receive the highest approved antihyperglycaemic dapagliflozin dose of 10 mg/d. In patients without diabetes it is unlikely that dapagliflozin lowers Hba1c because of both decreased renal glucose filtration, reducing the drug's efficacy to inhibit tubular glucose reabsorption, and increasing hepatic glucose production that compensates for the increased urinary glucose loss.[29,30] The optimal dose for nondiabetic patients should therefore be based on other cardiorenal risk markers. Our study offers a first assessment on the exposure–response relationship for dapagliflozin for other cardiorenal risk markers but future dedicated dose finding studies would be required to identify the optimal dose that reduces the risk for heart failure and kidney outcomes in the nondiabetic populations.

This study has limitations including that in our analysis we were not able to identify interindividual variability in SBP and UA response. A possible explanation for this phenomenon, is that both markers already reached a maximum effect when the first observation after baseline had been collected. In that case, more densely sampled data in the first week after administration of dapagliflozin would be required to fully characterize the effects in these markers over time. Also, we acknowledge that only a limited number of patients were included in the analysis who received a dapagliflozin dose >10 mg possibly limiting the precision of the estimated maximum effect. From the simulated exposures, it is, however, clear that there is large overlap in individual exposure between the different dose levels. In addition, we only included 6 cardiorenal markers and 2 types of adverse events. Therefore, we might have missed important cardiorenal risk markers or adverse events. Nonetheless, there was a clear difference between the exposure–response relationships, which could also be the case for other cardiorenal risk markers and adverse events. In the DECLARE-TIMI 58 trial, an increased risk of diabetic ketoacidosis and GTIs was observed in patients using dapagliflozin.[13] In the studies included in our analysis, there was only 1 event of diabetic ketoacidosis and therefore no model could be developed for this adverse event. Future research will be necessary to quantify the influence of dose on diabetic ketoacidosis. Furthermore, a lot of covariates were screened during the analysis; however, we cannot exclude that we missed important factors, such as smoking status, that could have affected the relationship between exposure and cardiorenal risk markers. Finally, in the exposure–response relationships for GTIs and UTIs, Europeans

vs non-Europeans appeared to be a significant covariate. There is no clear explanation for this finding and may be a chance finding due to the limited number of events.

In conclusion, the exposure–response analysis demonstrates that the exposure–response relationship of dapagliflozin differs between various cardiorenal risk markers. A dapagliflozin dose >10 mg could provide additional beneficial effects in FPG, HCT, SBP, albuminuria and UA. The exposure–response relationship between dapagliflozin and adverse events demonstrated that a higher dose could be safe, as the overall incidence of developing an event was low. Given that the investigated cardiorenal risk markers are strong risk markers for cardiovascular and renal outcomes raises the question whether clinical outcome trials specifically assessing the benefits of higher than currently registered doses of dapagliflozin are needed.

COMPETING INTERESTS

J.V.K. and J.S. have no competing interests. H.J.L.H. is consultant to Abbvie, AstraZeneca, Boehringer Ingelheim, Fresenius, Gilead, Janssen, Merck, Mundipharma, Mitsubishi Tanabe. He received research support from AstraZeneca, Abbvie, Boehringer Ingelheim and Janssen.

CONTRIBUTORS

J.V. Koomen and J. Stevens analysed and interpreted the data. J.V. Koomen, J. Stevens and H.J.L. Heerspink wrote the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from AstraZeneca but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

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REFERENCES

1. Komoroski B, Vachharajani N, Feng Y, Li L, Kornhauser D, Pfister M. Dapagliflozin, a novel, selective SGLT2 inhibitor, improved glycemic control over 2 weeks in patients with type 2 diabetes mellitus. *Clin Pharmacol Ther*. 2009;85(5):513-519.
2. Komoroski B, Vachharajani N, Boulton D, et al. Dapagliflozin, a novel SGLT2 inhibitor, induces dose-dependent glucosuria in healthy subjects. *Clin Pharmacol Ther*. 2009;85(5):520-526.
3. List JF, Woo V, Morales E, Tang W, Fiedorek FT. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. *Diabetes Care*. 2009;32(4):650-657.
4. Bailey CJ, Gross JL, Hennicken D, Iqbal N, Mansfield TA, List JF. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. *BMC Med*. 2013;11:43–7015-11-43.
5. Zhang L, Feng Y, List J, Kasichayanula S, Pfister M. Dapagliflozin treatment in patients with different stages of type 2 diabetes mellitus: effects on glycaemic control and body weight. *Diabetes Obes Metab*. 2010;12:510-516.
6. Strojek K, Yoon KH, Hruba V, Elze M, Langkilde AM, Parikh S. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. *Diabetes Obes Metab*. 2011;13(10):928-938.
7. Wilding JP, Norwood P, T'joen C, Bastien A, List JF, Fiedorek FT. A study of dapagliflozin in patients with type 2 diabetes receiving high doses of insulin plus insulin sensitizers: applicability of a novel insulin-independent treatment. *Diabetes Care*. 2009;32(9):1656-1662.
8. Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. *Circulation*. 2016;134(10):752-772.
9. Inzucchi SE, Zinman B, Fitchett D, et al. How does Empagliflozin reduce cardiovascular mortality? Insights from a mediation analysis of the EMPA-REG OUTCOME trial. *Diabetes Care*. 2018;41(2):356-363.
10. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644-657.
11. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375(4):323-334.
12. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128.
13. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2018.
14. Heerspink HJ, Johnsson E, Gause-Nilsson I, Cain VA, Sjostrom CD. Dapagliflozin reduces albuminuria in patients with diabetes and hypertension receiving renin-angiotensin blockers. *Diabetes Obes Metab*. 2016;18(6):590-597.
15. Heerspink HJ, Desai M, Jardine M, Balis D, Meininger G, Perkovic V. Canagliflozin slows progression of renal function decline independently of glycemic effects. *J am Soc Nephrol*. 2017;28(1):368-375.
16. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381(21):1995-2008.
17. Heerspink HJL, Kosiborod M, Inzucchi SE, Cherney DZI. Renoprotective effects of sodium-glucose cotransporter-2 inhibitors. *Kidney Int*. 2018;94:26-39.
18. Kasichayanula S, Liu X, Lacreta F, Griffen SC, Boulton DW. Clinical pharmacokinetics and pharmacodynamics of dapagliflozin, a selective inhibitor of sodium-glucose co-transporter type 2. *Clin Pharmacokinet*. 2014;53:17-27.
19. Kasichayanula S, Chang M, Hasegawa M, et al. Pharmacokinetics and pharmacodynamics of dapagliflozin, a novel selective inhibitor of sodium-glucose co-transporter type 2, in Japanese subjects without and with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2011;13(4):357-365.
20. van der Walt JS, Hong Y, Zhang L, Pfister M, Boulton DW, Karlsson MO. A nonlinear mixed effects pharmacokinetic model

for Dapagliflozin and Dapagliflozin 3-O-glucuronide in renal or hepatic impairment. *CPT Pharmacometrics Syst Pharmacol*. 2013; 2:e42.

21. Pilla Reddy V, Kozielska M, Johnson M, et al. Structural models describing placebo treatment effects in schizophrenia and other neuropsychiatric disorders. *Clin Pharmacokinet*. 2011;50(7):429-450.

22. Byon W, Smith MK, Chan P, et al. Establishing best practices and guidance in population modeling: an experience with an internal population pharmacokinetic analysis guidance. *CPT Pharmacometrics Syst Pharmacol*. 2013;2:e51.

23. Busse D, Tang W, Scheerer M, et al. Comparison of pharmacokinetics and the exposure-response relationship of dapagliflozin between adolescent/young adult and adult patients with type 1 diabetes mellitus. *Br J Clin Pharmacol*. 2019;85(8):1820-1828.

24. de Zeeuw D, Remuzzi G, Parving HH, et al. Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. *Kidney Int*. 2004;65(6):2309-2320.

25. Burgess E, Muirhead N, de Cotret PR, Chiu A, Pichette V, Tobe S. Supramaximal dose of candesartan in Proteinuric renal disease. *J am Soc Nephrol*. 2009;20(4):893-900.

26. Rossing K, Schjoedt KJ, Jensen BR, Boomsma F, Parving HH. Enhanced renoprotective effects of ultrahigh doses of irbesartan in patients with type 2 diabetes and microalbuminuria. *Kidney Int*. 2005; 68(3):1190-1198.

27. Hou FF, Xie D, Zhang X, et al. Renoprotection of optimal Anti-proteinuric doses (ROAD) study: a randomized controlled study of benazepril and losartan in chronic renal insufficiency. *J am Soc Nephrol*. 2007;18(6):1889-1898.

28. Heerspink HJ, Grobbee DE, de Zeeuw D. A novel approach for establishing cardiovascular drug efficacy. *Nat Rev Drug Discov*. 2014;13: 942-c2. Epub 2014 Nov 14

29. Merovci A, Solis-Herrera C, Daniele G, et al. Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. *J Clin Invest*. 2014;124(2):509-514.

30. Al Jobori H, Daniele G, Adams J, et al. Determinants of the increase in ketone concentration during SGLT2 inhibition in NGT, IFG and T2DM patients. *Diabetes Obes Metab*. 2017;19(6):809-813.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.