


# Effects of Food and Pharmaceutical Formulation on Desmopressin Pharmacokinetics in Children

Robin Michelet<sup>1</sup>  · Lien Dossche<sup>2</sup> · Pauline De Bruyne<sup>2</sup> · Pieter Colin<sup>1,4</sup> · Koen Boussery<sup>1</sup> · Johan Vande Walle<sup>3</sup> · Jan Van Bocxlaer<sup>1</sup> · An Vermeulen<sup>1</sup>

Published online: 22 April 2016  
© Springer International Publishing Switzerland 2016

## Abstract

**Introduction** Desmopressin is used for treatment of nocturnal enuresis in children. In this study, we investigated the pharmacokinetics of two formulations—a tablet and a lyophilisate—in both fasted and fed children.

**Methods** Previously published data from two studies (one in 22 children aged 6–16 years, and the other in 25 children aged 6–13 years) were analyzed using population pharmacokinetic modeling. A one-compartment model with first-order absorption was fitted to the data. Covariates were selected using a forward selection procedure. The final model was evaluated, and sensitivity analysis was performed to improve future sampling designs. Simulations were subsequently performed to further explore the relative bioavailability of both formulations and the food effect.

**Results** The final model described the plasma desmopressin concentrations adequately. The formulation and the fed state were included as covariates on the relative bioavailability. The

lyophilisate was, on average, 32.1 % more available than the tablet, and fasted children exhibited an average increase in the relative bioavailability of 101 % in comparison with fed children. Body weight was included as a covariate on distribution volume, using a power function with an exponent of 0.402. Simulations suggested that both the formulation and the food effect were clinically relevant.

**Conclusion** Bioequivalence data on two formulations of the same drug in adults cannot be readily extrapolated to children. This was the first study in children suggesting that the two desmopressin formulations are not bioequivalent in children at the currently approved dose levels. Furthermore, the effect of food intake was found to be clinically relevant. Sampling times for a future study were suggested. This sampling design should result in more informative data and consequently generate a more robust model.

R. Michelet, L. Dossche, P. De Bruyne, J.V. Walle, J. Van Bocxlaer and A. Vermeulen: On behalf of the SAFE-PEDRUG Consortium; <http://safepedrug.eu>.

✉ Robin Michelet  
robin.michelet@ugent.be

<sup>1</sup> Laboratory of Medical Biochemistry and Clinical Analysis, Department of Bioanalysis, Faculty of Pharmaceutical Sciences, Ghent University, Ghent, Belgium

<sup>2</sup> Department of Pediatrics and Medical Genetics, Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium

<sup>3</sup> Department of Pediatric Nephrology, Ghent University Hospital, Ghent, Belgium

<sup>4</sup> Department of Anesthesiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

## Key Points

Population pharmacokinetic modeling was applied to pediatric desmopressin pharmacokinetic data and used to extract more information from existing pediatric drug data, generate new information, and improve the collection of future information.

In this study, it was found that the established bioequivalence of desmopressin in adults might differ in the pediatric population. A profound food effect was also quantified.

In order to draw solid conclusions regarding the efficacy of desmopressin in children, pharmacokinetic and pharmacodynamic data should be gathered simultaneously in a well-designed study, for which some design suggestions are presented in this paper.

## 1 Introduction

Off-label use of drugs in the pediatric population is widespread: 50–90 % of prescriptions in pediatrics are off-label and/or unlicensed [1]. The SAFE-PEDRUG Project (<http://safepedrug.eu>) aims to reinvent the strategy for pediatric drug research, using a rational combination of bottom-up and top-down approaches, starting from pediatric specificities and opportunities. Desmopressin (1-deamino-8-D-arginine vasopressin; DDAVP), one of the drugs under study, is a synthetic vasopressin analog acting on V2 receptors located in the collecting ducts of the kidney. It has been applied clinically for more than 30 years through use of a range of different formulations: an intranasal solution (since 1972), an injectable solution (since 1981), tablets (since 1987), and, most recently, an oral lyophilisate (since 2005) [2].

Initially, DDAVP was developed to treat adult patients with central diabetes insipidus. Following the observation by Rittig et al. that children with enuresis showed a significantly smaller nocturnal increase in arginine vasopressin (AVP) [3], it was subsequently used for an indication primarily seen in children: enuresis nocturna. Until now, DDAVP has been the only drug therapy with an evidence level 1 grade A recommendation for the indication of monosymptomatic nocturnal enuresis (MNE) [4]. Reported adverse events are generally described as mild and include headache, abdominal pain, nausea, and—typically with the nasal spray [5]—nasal epistaxis and congestion/rhinitis. Hyponatremia remains an infrequent but very serious adverse event associated with the antidiuretic effect of DDAVP treatment [6] and has been reported after intake of DDAVP with simultaneous excess intake of fluids [7, 8]. In 2007, the US Food and Drug Administration (FDA) requested an update of the prescribing information for DDAVP nasal spray following increasing reports of hyponatremia [7, 9]. Since then, DDAVP spray has no longer been indicated for the treatment of MNE or in patients at risk of hyponatremia in the USA and most European countries [9].

Currently, two oral formulations of DDAVP are labeled for the indication of MNE: a tablet (TAB) and a lyophilisate (MELT). Their bioequivalence at dose strengths of 200 and 120 µg, respectively, has been established in adults [10, 11] but not in children. In a previous study, the lyophilisate was shown to have a superior effect on diuresis in children, which was hypothesized to arise from a less pronounced food interaction [12]. DDAVP should be taken in a fasted state before bedtime, which is challenging in young children because of the short time between the last meal in the evening and bedtime. This suggests that the food effect on DDAVP pharmacokinetics and

pharmacodynamics should be investigated more thoroughly, as this effect has been established before in adults [13] but not in children. A published pilot study from our group investigated the pharmacokinetics of both the tablet and lyophilisate formulations in children who were fed a standard meal [14]. However, only an influence of the formulation on the variability in pharmacokinetics was detected, and no fasted control group was included in the analysis. Additionally, suggestions of a body-size effect were found. Given these results, it was decided to set up a new study using a more elaborate sampling scheme to investigate these effects more thoroughly. This paper describes a model-based analysis we set up to increase the efficiency of this future trial.

The purpose of this analysis was twofold:

1. By pooling previously published pediatric data on DDAVP pharmacokinetics and using a population pharmacokinetic approach, a more in-depth understanding of the effects of the formulation, concomitant food intake, and patient size on DDAVP pharmacokinetics could be obtained.
2. The developed model was subsequently used to formulate experimental design strategies for the follow-up clinical trial, so that the analysis objectives could be reached as efficiently as possible.

## 2 Materials and Methods

### 2.1 Study Data

Only two studies on the pharmacokinetics of orally formulated DDAVP in children have been published [14, 15], both of which are included in the current analysis. Österberg et al. [15] assessed the pharmacokinetics of an oral lyophilisate in 72 children with MNE in comparison with the pharmacokinetics in 28 healthy, adult volunteers, using a double-blind, randomized, parallel-group, multicenter study design. Data from 25 of these children were available for the current analysis. In a second study, De Bruyne et al. used a two-period crossover design to compare the oral lyophilisate and tablet formulations in children with MNE. Of the 23 children who were included, 22 successfully completed the study, and their data were available for the current analysis [14]. The two datasets are compared in Table 1.

### 2.2 Model Development

A one-compartment model with first-order absorption was chosen as a starting point. The log-transform-both-sides

**Table 1** Characteristics of the Österberg dataset and the De Bruyne dataset [14, 15]

Characteristic	Österberg et al.	De Bruyne et al.
Patients ( <i>n</i> )	25	22
Age (years; median [range])	9.7 [6.7–13]	12.5 [7–16]
Body weight [kg; median (range)]	32 [25–63]	51 [24–82]
Sex (female/male)	5/20	4/18
Height [cm; median (range)]	138 [121–165]	162 [115–186]
Formulation	Lyophilisate	Lyophilisate and tablet (2 weeks between treatments)
Dose (µg)	0–480	200 (tablet) 120 (lyophilisate)
Fed state	Fasted	Fed (standardized 510 kcal meal)
Average no. of samples	1.9 per patient	3 per formulation
Sampling times (h)	0–24	1, 2, and 6
Analytical method	Radioimmunoassay	LC-MS/MS
Linear range (pg·mL <sup>-1</sup> )	0.8–100	2.00–100

LC-MS/MS liquid chromatography–tandem mass spectrometry

(LTBS) approach was used, meaning that the logarithms of the plasma concentrations were modeled. The development of the population model proceeded iteratively, and the interindividual variability (IIV) was assumed to follow a log-normal distribution. A proportional residual error model (=additive error model in the log domain) was used throughout the entire process. Once an appropriate mixed-effects model was obtained, covariate relationships were investigated using forward selection by adding them to the model one at a time and selecting the models with the best performance metrics to proceed with. The covariates that were tested were the formulation (MELT), the fed state (FED), age (AGE), body weight (WT), sex (SEX), and the Tanner Index (TAN).

The decision to include or exclude certain model components was guided by several performance metrics: the objective function value (OFV), Akaike information criterion (AIC), condition number (CN), the relative standard error (RSE) of the parameter estimates, obtained through the covariance step in NONMEM. A drop in the OFV of 3.84 was assumed to indicate a significantly better fit. Both the OFV and the AIC are based on likelihood ratio tests, which cannot be reliably used to guide inclusion/exclusion of IIV parameters, especially for sparse data [16]. Thus, for those parameters, decisions were made on the basis of the RSE and CN values (both should be as low as possible) and standard goodness-of-fit plots (plots of the observed concentrations versus population-predicted and individual-predicted concentrations, and plots of the residuals).

### 2.3 Model Evaluation

In order to establish confidence in the final model, different evaluation techniques were applied. A visual predictive

check (VPC) and numerical predictive check (NPC) were performed, without binning or calculation of confidence intervals (CIs) on the (sparse) data. Plots of individual and population predictions versus observations were also used, and bootstrap analysis was performed. For the latter analysis, 1000 datasets of 47 subjects were resampled with replacement from the original dataset. The bias-corrected bootstrap with an acceleration constant (BCa) method was used in order to obtain second-order correct 90 % CIs around the parameter estimates [17]. This method corrects for bias and skewness in the standard bootstrap CIs and thus provides a more reliable estimate of the parameter CIs.

The last evaluation technique consisted of normalized prediction distribution error (NPDE) analysis. For this method, the final model was simulated 1000 times, using the same design as that of the original dataset, after which the NPDEs were obtained using the table step in NONMEM [18, 19]. Under the null hypothesis that the model describes the data, the distribution of NPDEs should be equal to the standard normal distribution  $N(0, 1)$ .

This hypothesis was formally tested using the Wilcoxon signed-rank test ( $H_0: \mu = 0$ ), the Fisher variance ratio test ( $H_0: \sigma^2 = 1$ ), and the Shapiro–Wilks normality test ( $H_0: Z \sim N(\mu, \sigma^2)$ ).

### 2.4 Sensitivity Analysis and Sampling Design

Sensitivity analysis was performed on the final model. This means, in the broadest sense, that the influence of the different model inputs on the output was studied in a quantitative way. The results can point to parameters that can be excluded (model reduction) or errors in the model structure. Furthermore, these results show at which point in time the model output is most sensitive to an input and thus

when the most information can be gained from an experiment. Therefore, this technique can be used to perform optimal experimental design (OED). In general, two kinds of sensitivity analysis exist: local sensitivity analysis (LSA) and global sensitivity analysis (GSA) [20–22], of which the former was performed in this study.

In this LSA, the influence of the model parameters was examined in a small window around the nominal (estimated) value. Because of this small perturbation, the change in response can be described by a first-order approximation, and the sensitivity of the output to each input can be calculated using the partial derivative of that output to each specific parameter.

In order to be able to compare these sensitivities, they were normalized to elasticity indices (EIs), which have the same units ( $\text{pg}\cdot\text{mL}^{-1}$ ) as the output (see Eq. 1). These EIs can be compared between different parameters, independently of the parameter values.

$$\text{EI}_{y\text{ to } \theta_i} = \frac{\partial y(\boldsymbol{\theta})}{\partial \theta_i} \times \theta_i \quad (1)$$

The results of the LSA were compared with an OED performed using PopED for R software [18]. In this design, optimal sampling times were calculated on the basis of optimization of the population Fisher information matrix (FIM) [21], which should result in more efficient designs than use of an LSA on its own. Five iterations of a sequence of random search (300 iterations), stochastic gradient (150 iterations), and linear search (step size = 40) algorithms were used to identify the optimal design.

## 2.5 Simulation-Based Analysis

Once confidence in the model had been achieved during the evaluation step, it was used for simulation. On the one hand, the established average bioequivalence of the 120  $\mu\text{g}$  lyophilisate and 200  $\mu\text{g}$  tablet [10, 11], and the food effect [13] previously reported in adults, were further analyzed for their clinical relevance in this pediatric dataset. On the other hand, the previously identified optimal sampling times were applied in a sample size calculation for a bioequivalence trial.

To investigate the effects of the two DDAVP formulations and food intake, clinical trial simulations (CTSs) were performed. For this, 20 patients were sampled randomly (by body weight, as no other covariates were present in the final model) from a log-normal body weight distribution for children aged 7–16 years [23]. These 20 patients were then simulated to undergo four scenarios: administration of a 120  $\mu\text{g}$  lyophilisate while fed (MELT + FED), administration of a 200  $\mu\text{g}$  tablet while fed (TAB + FED), administration of a 120  $\mu\text{g}$  lyophilisate while fasted (MELT + FAST), and administration of a 200  $\mu\text{g}$  tablet

while fasted (TAB + FAST). For each scenario and patient, the area under the plasma concentration–time curve (AUC) from time zero extrapolated to infinity ( $\text{AUC}_\infty$ ) and the maximum drug concentration ( $C_{\text{max}}$ ), and their logarithms, were calculated from eight simulated samples, taken at the optimal times determined by the LSA. As is recommended by the FDA [20], an additional sample at 24 h as included in this design, to minimize extrapolation in the AUC calculation.

For each trial of each individual, the following ratios were calculated to separate the formulation and the food effect.

Formulation effect:

$$\Delta \log(\text{AUC}_A) = \log\left(\frac{\text{AUC}_{\text{TAB},A}}{\text{AUC}_{\text{MELT},A}}\right)$$

$$\Delta \log(C_{\text{max},A}) = \log\left(\frac{C_{\text{max},\text{TAB},A}}{C_{\text{max},\text{MELT},A}}\right)$$

Food effect:

$$\Delta \log(\text{AUC}_B) = \log\left(\frac{\text{AUC}_{\text{B},\text{FAST}}}{\text{AUC}_{\text{B},\text{FED}}}\right)$$

$$\Delta \log(C_{\text{max},B}) = \log\left(\frac{C_{\text{max},\text{B},\text{FAST}}}{C_{\text{max},\text{B},\text{FED}}}\right)$$

where A = FED or FAST and B = TAB or MELT. Two formulations are considered bioequivalent when the 90 % CIs of the geometric means of their AUC and  $C_{\text{max}}$  ratios fall between 80 and 125 % [24, 25]. As these means are equal to the log average, the CIs of the log ratios were calculated using the modified Cox method (Eq. 2) [26] and subsequently exponentiated to obtain the normal CIs.

$$\text{CI} = \exp\left(\hat{Y} + \frac{\sigma^2}{2} \pm t \times \sqrt{\frac{\sigma^2}{n} + \frac{\sigma^4}{2(n-1)}}\right) \quad (2)$$

where  $\hat{Y}$  is the mean of the log ratios,  $\sigma$  is the standard deviation,  $n$  is the sample size (20), and  $t$  is the 90 % value of the two-sided t-distribution with  $n - 1$  degree of freedom ( $\approx 1.33$  for  $n = 20$ ). The CI for the food effect was calculated and interpreted in the same way, as is recommended by the FDA [27], resulting in the acceptance or rejection of bioequivalence and the food effect for that particular trial. These trials were repeated 1000 times, and the resulting CIs were then summarized by taking the medians of the lower, upper, and mean values. Furthermore, the percentage of trials that resulted in acceptance of bioequivalence was calculated. Eventually, a sample size calculation for a two-period crossover bioequivalence study, with doses suggested by the estimated model parameters, was performed in both fed and fasted patients. This sample size calculation took parameter uncertainty into account by sampling each parameter from a

Multivariate normal distribution based on the variance-covariance matrix, resulting in 1000 parameter sets for each number of individuals.

## 2.6 Software

The model development and parameter estimation were performed using NONMEM version 7.3 [28], with first-order conditional estimation (FOCE) as the estimation algorithm, accessed with Perl-Speaks-NONMEM (PSN) [29], embedded in the Piraña workbench [30]. RStudio (version 0.98; <http://www.rstudio.com/>) was used to prepare the datasets, perform the simulations, and post-process all results, which included the statistical calculations and plot generation. The LSA was performed using the biointense model environment in Python. This package is “an object oriented Python implementation for model building and analysis, focusing on sensitivity and identifiability analysis” [31]. It was accessed using Spyder version 2.3.3 [32].

## 3 Results

### 3.1 Model Development

The model development path is depicted in Table 2. The available data were used to their limits, as not all random effects could be estimated without inflating the CN. This was caused by the sparseness of the data. After model 29 was run (the final model), other covariates (age, the Tanner Index, body mass index, and sex) were tested on all of the fixed effects. Different relations [the maximum effect ( $E_{\max}$ ) and sigmoidal, exponential, and allometric scaling]

were also tested for these covariates. None of them improved the model significantly, and often a significant increase in the OFV was found instead (data not shown). Therefore, model 29 was chosen as the final model. The final model structure and parameters are shown in Table 3.

### 3.2 Model Evaluation

In Fig. 1, VPCs for the three different scenarios present in the data (MELT + FAST, MELT + FED, and TAB + FED) are shown. The model seems to perform best for patients who receive the lyophilisate formulation. The NPC was performed on the full VPC (Fig. 2). Of the observations, 2.80 % lay above the 90 % prediction interval (PI) and 3.50 % lay below the 90 % PI, indicating good model performance. Figure 3 shows the population and individual predictions plotted against the observations; no significant deviations from the line of unity are seen.

The 90 % CIs of the BCa analysis (818/1000 runs completed minimization) are included in Table 3. The bootstrap estimates deviated between  $-7.53$  and  $+4.50$  % from the model estimates, with an average deviation of 0.21 %. Bootstrap-estimated RSE values (between 18.2 and 84.9 %) were consistently higher than the standard error values estimated in NONMEM (between 10 and 46 %).

The NPDE results are shown in Fig. 4. No significant deviations from the standard normal distribution could be detected, as Table 4 shows.

### 3.3 Sensitivity Analysis and Sampling Design

The calculated EIs versus time are presented in Fig. 5. Sensitivity function optima are marked with green stars. These

**Table 2** Model development path to the final model

Run #	Ref #	OFV	$\Delta$ OFV	AIC	CN	Max (RSE %)	Description
1		-4.482		5.518			One-compartment model with first-order absorption; estimation of fixed effects
7	1	-32.237	-27.755	-20.237	34	35	Estimation of IIV on $F_1$ + fixed effects
11	1	-4.482	0	3.518			FIX $F_1$ (no IV data) to 1
15	11	-32.237	-27.755	-22.237	17	35	Estimation of IIV on $F_1$ + fixed effects
17	15	-35.976	-3.739	-23.976	34	77	Estimation of IIV on $F_1$ and $V_d$ + fixed effects
21	11	-49.413	-44.931	-37.413			Addition of formulation effect covariate to model before estimation of IIVs; estimation of fixed effects and IIV on formulation effect
23	21	-70.275	-20.862	-56.275	32	36	Estimation of IIV on formulation effect and $V_d$ + fixed effects
27	23	-85.594	-15.319	-69.594	84	56	Addition of food effect covariate to model before estimation of IIV on formulation effect and $V_d$ + fixed effects
28	27	-83.954	1.64	-67.954	84	47	IIV put on $F_1$ (lumped) instead of on formulation effect
<b>29</b>	<b>28</b>	<b>-87.758</b>	<b>-3.804</b>	<b>-69.758</b>	<b>40</b>	<b>46</b>	<b>Addition of body weight as a covariate for <math>V_d</math>, using a power function (final model)</b>

Final model step values are in bold

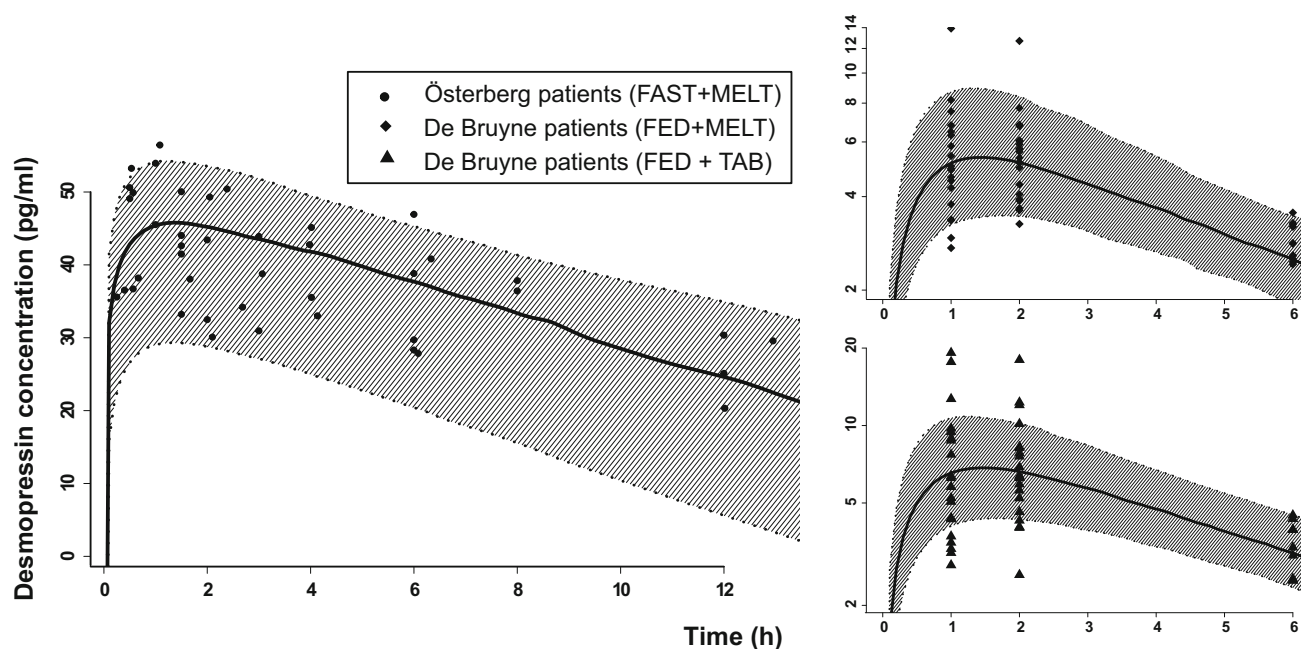
AIC Akaike information criterion, CN condition number,  $F$  bioavailability, IV intravenous administration, IIV interindividual variability, Max maximum, OFV objective function value, RSE relative standard error,  $V_d$  apparent volume of distribution

**Table 3** Population pharmacokinetic model parameter estimates and bootstrap values

Parameter	Estimate [RSE]	Bootstrap [90 % CI]
$CL/F = \theta_1 \times e^{\eta_1}$	4982 L/h [12 %]	4964 [4002–5820]
$V_d/F = \theta_2 \times (WT/45.5)^{\theta_7} \times e^{\eta_7}$	23,346 L [13 %]	23,345 [17,817–28,366]
$K_a = \theta_3 \times e^{\eta_3}$	1.65 h <sup>-1</sup> [25 %]	1.72 [1.01–2.58]
$F = (\theta_4 + \theta_5 * MELT + \theta_6 * FASTED) \times e^{\eta_4}$	1 FIX	1 FIX
Influence of MELT ( $\theta_5$ )	0.321 [46 %]	0.333 [0.0486–0.548]
Influence of FASTED ( $\theta_6$ )	1.01 [25 %]	1.05 [0.579–1.45]
Influence of WT ( $\theta_7$ )	0.402 [44 %]	0.397 [0.118–0.731]
IIV on CL	0 FIX	0 FIX
IIV on $V_d$	27.3 % <sup>a</sup> [15 %] (39 % shrinkage)	25.2 % [16.5–46.0 %]
IIV on $K_a$	0 FIX	0 FIX
IIV on $F$	21.1 % [10 %] (39 % shrinkage)	21.1 % [11.6–31.2 %]
Proportional residual error	38.5 CV % [14 %]	37.8 CV % [34.4–44.1 %]

CI confidence interval, CL apparent total clearance, CL/F apparent total clearance after oral administration, CV coefficient of variation, F bioavailability, FASTED fasted state, IIV interindividual variability,  $K_a$  first-order absorption rate constant, MELT formulation, RSE relative standard error,  $V_d$  volume of distribution,  $V_d/F$  apparent volume of distribution after oral administration, WT body weight

<sup>a</sup> Coefficient of variation, calculated as  $CV \% = 100 \% \times \sqrt{e^{\omega} - 1}$

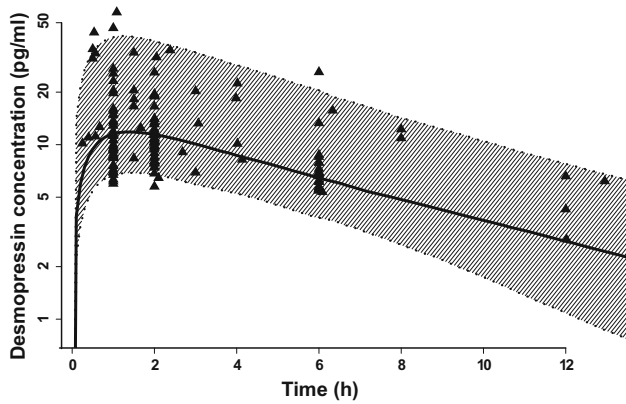


**Fig. 1** Visual predictive check of the different scenarios present in the Österberg dataset [15] (left panel) and the De Bruyne dataset (right upper and lower panels) [14]. The solid line represents the

median model prediction for each scenario, and the hatched area represents the 90 % prediction interval. FAST fasted state, FED fed state, MELT lyophilisate, TAB tablet

optima are considered good sampling time points, as the output is the most sensitive to a certain parameter at those points, enabling optimal estimation of this parameter [33, 34]. The most important parameters (i.e., the ones with the largest areas under the sensitivity function) were the relative bioavailability and dose, the effect of food intake, the apparent volume of distribution ( $V_d$ ), and the apparent total clearance (CL).

On the basis of this analysis, sampling times for a subsequent clinical study with rich sampling were suggested. Intensive sampling of the absorption phase (<3 h) is needed to capture all information present during this phase of the pharmacokinetic profile. The elimination phase is much less informative and should not be sampled as intensively. The proposed sampling scheme for a study



**Fig. 2** Visual predictive check of all data pooled together. The *solid line* represents the total median model prediction, and the *hatched area* represents the 90 % prediction interval

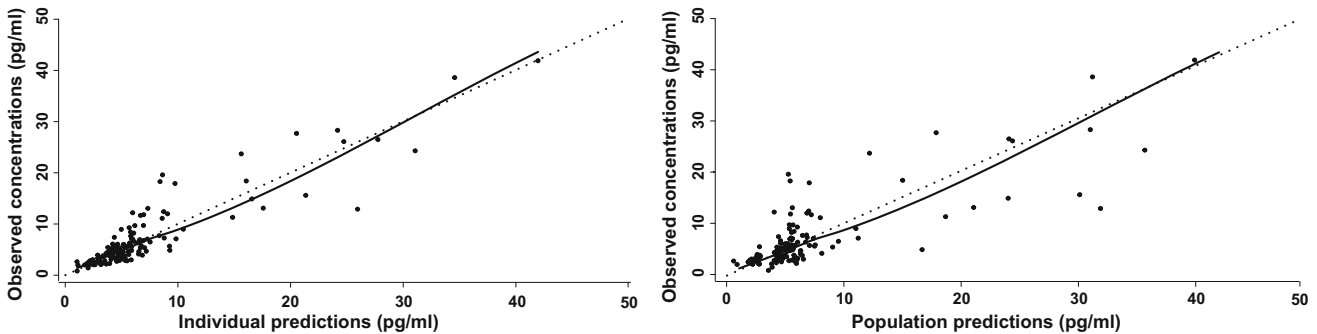
with eight time points involves sampling at 0.25, 0.5, 1, 1.5, 2, 3, 5, and 6 h.

The results of the FIM-based OED are shown in Fig. 6. The resulting sampling scheme for eight time points is presented in Table 5. The optimal design was 1.34 times more efficient than the initial (LSA-derived) design. Merging of optimal times close to each other resulted in minimal loss of efficiency. This reduced design was 1.22 times more efficient than the initial LSA-derived design.

### 3.4 Simulation-Based Exploration

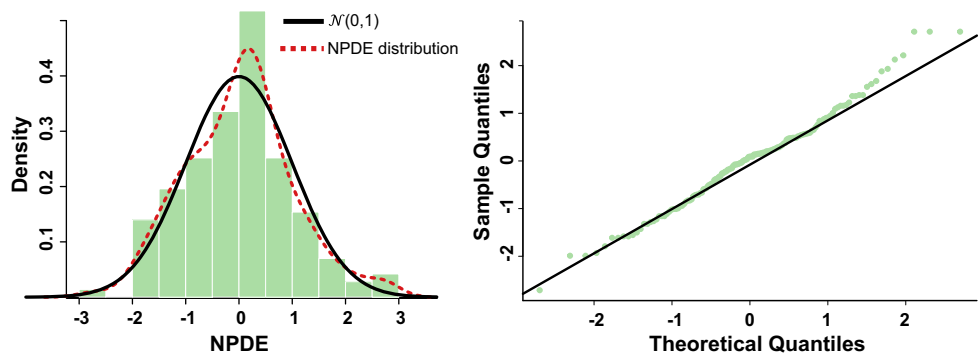
#### 3.4.1 Bioequivalence and the Food Effect

The CTSs are summarized in Fig. 7. In none of the simulated trials were the different formulations/fed states found



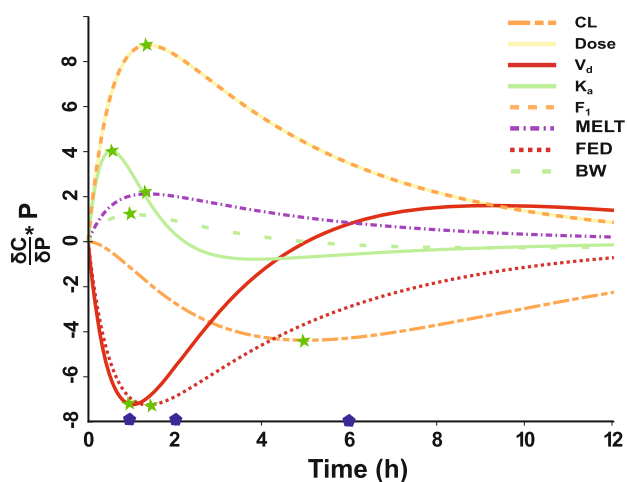
**Fig. 3** Population predictions versus observed concentrations (*left panel*) and individual predictions versus observed concentrations (*right panel*). The *dotted line* represents the line of unity, and the *solid line* represents a Loess smoother through the data points

**Fig. 4** Normalized prediction distribution error (NPDE) distribution (*left panel*) and quantile–quantile plot (*right panel*).  $\mu = 0.00569$ ,  $\sigma = 1.01$



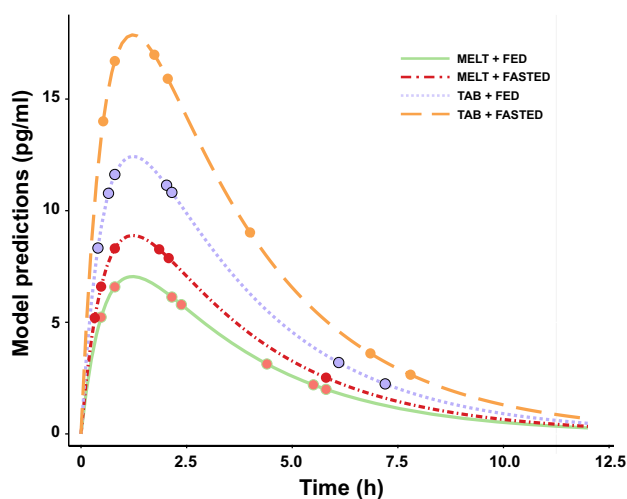
**Table 4** Formal tests for  $H_0$ : normalized prediction distribution error (NPDE) distribution =  $N(0, 1)$

Test	$H_0$	Value	$P$ value	Conclusion
Wilcoxon signed-rank	$\mu = 0$	$V = 5153$	0.994	$H_0$ cannot be rejected
Fisher variance ratio	$\sigma^2 = 0$	$F = 1.03$	0.770	$H_0$ cannot be rejected
Shapiro–Wilks	$Z \sim N(\mu, \sigma^2)$	$W = 0.989$	0.315	$H_0$ cannot be rejected



**Fig. 5** Relative sensitivity of the predicted plasma desmopressin concentrations to the model parameters. The *blue pentagons* represent the original sampling times [8], and the *green stars* represent the proposed optimal sampling times. *BW* body weight, *CL* apparent total clearance, *F* bioavailability, *FED* fed/fasted state, *K<sub>a</sub>* first-order absorption rate constant, *MELT* formulation, *V<sub>d</sub>* apparent volume of distribution

to be bioequivalent. The simulations in Fig. 7 show how the food effect was more apparent than the formulation effect. Simulated subjects experienced greater exposure to DDAVP when they were fasted than when they had received a standard meal. In addition, a 200 µg tablet resulted in greater exposure than a 120 µg lyophilisate, whereas in adults, these dose levels resulted in equivalent exposure. In order to quantify the relevance of these effects, the median 90 % CIs for the ratios of the geometric means of the  $AUC_{\infty}$  and  $C_{max}$  were calculated and are presented below. Formulation effect:



**Fig. 6** Fisher information matrix-based optimal sampling design. The *lines* represent the expected population averages for the different scenarios, and the *circles* represent the suggested sampling times. *FASTED* fasted state, *FED* fed state, *MELT* lyophilisate, *TAB* tablet

$AUC$  ratio = 138 % [133–144 %]

$C_{max}$  ratio = 144 % [135–153 %]

Food effect:

$AUC$  ratio = 194 % [187–201 %]

$C_{max}$  ratio = 202 % [190–215 %]

When European Medicines Agency (EMA) and FDA guidelines are applied to the results of this simulation study, a significant food effect is concluded to be present for DDAVP in children [24, 25]. The established bioequivalence of a 200 µg tablet and a 120 µg lyophilisate is also rejected on the basis of these simulations. It can thus be expected that in a real trial, bioequivalence between the 200 µg tablet and the 120 µg lyophilisate cannot be claimed. Indeed, a point estimate of 138 % suggests that the ratio of dose strengths (the 120 µg lyophilisate versus the 200 µg tablet) is suboptimal, and a higher lyophilisate dose is needed to achieve exposure similar to that achieved with the 200 µg tablet. Using the parameter estimate of the formulation effect (0.3208), we calculated that the lyophilisate dose equivalent to a 200 µg tablet is 151.4 µg. At this point, a new CTS was performed, using these newly suggested dose strengths. The results are shown in Fig. 8 and show an almost complete overlap of the concentration–time profiles for both formulations.

In order to further support this new dose, a proper two-period crossover bioequivalence trial should be performed with a 150 µg lyophilisate and a 200 µg tablet. A power curve was approximated for this design, by simulating this trial 1000 (parameter uncertainty)  $\times$  1000 (IIV) times for 1 up to 50 patients and calculating the power as the number of times that bioequivalence was proven divided by the total number of trials (1000). The results for fed patients are shown in Fig. 9; approximately 20 patients would be needed for a median power of 80 %. Using fasted patients, approximately 250 patients would be needed (results not shown).

## 4 Discussion

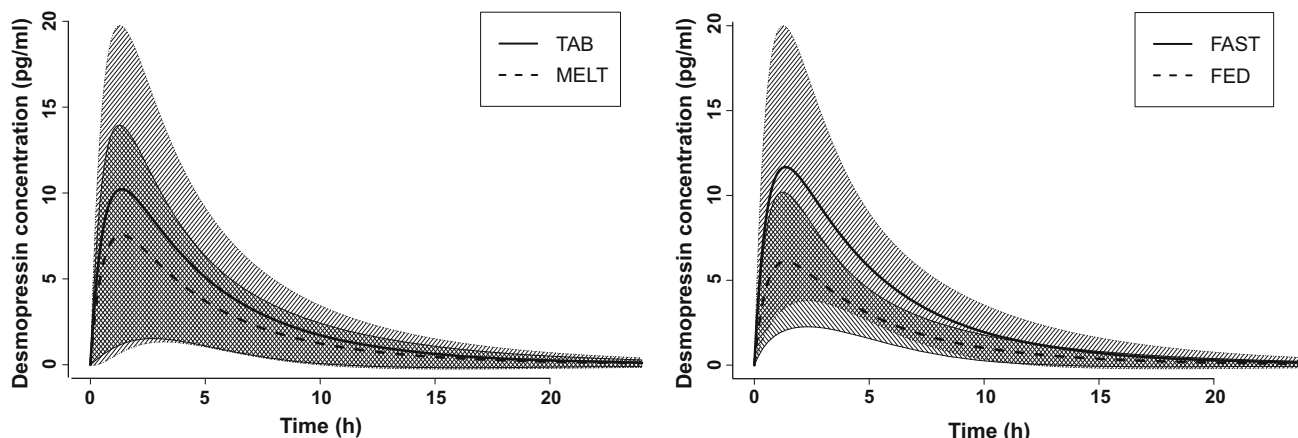
In this study, we investigated the pharmacokinetics of desmopressin in a pediatric population. In order to do this, two datasets from previously published clinical trials were combined, enabling use of the specifics (e.g., food intake or not, sampling schemes) of both datasets and thus extraction of more information from the data. Nonlinear mixed-effects modeling was used, and a one-compartment model with first-order absorption was able to describe the data well. In previous studies, more complex models—such as a two-compartment model [35], a three-compartment model



**Table 5** Optimal experimental design

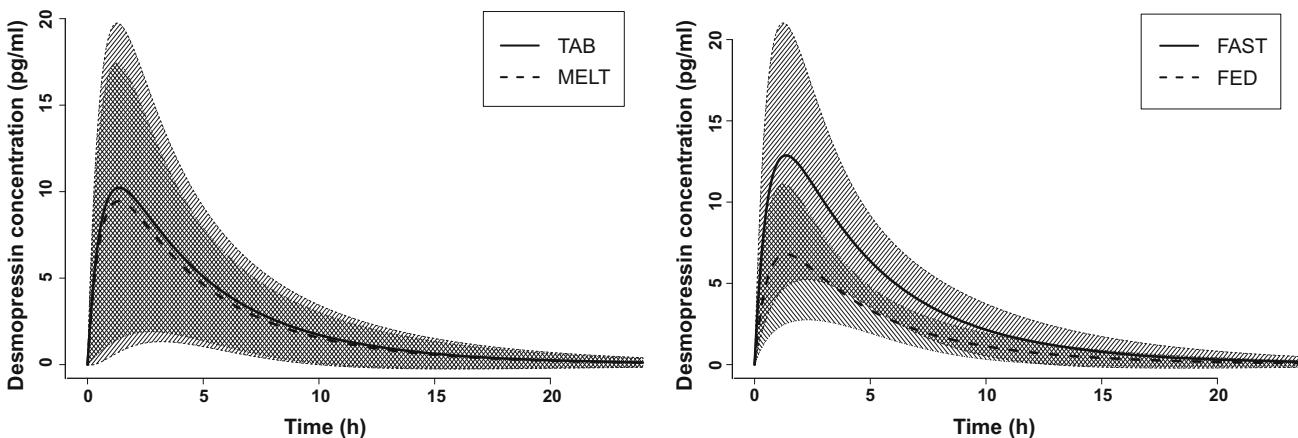
Scenario	Sampling times (h)								
MELT + FED	0.475	0.8	0.8	2.15	2.375	4.4	5.5	5.8	
MELT + FASTED	0.3259	0.475	0.8	1.85	2.075	5.8	5.8	5.8	
TAB + FED	0.4	0.65	0.8	2.025	2.15	6.1	7.2	7.2	
TAB + FASTED	0.525	0.525	0.8	1.735	2.053	4	6.85	7.8	

*FASTED* fasted state, *FED* fed state, *MELT* lyophilisate, *TAB* tablet



**Fig. 7** Simulated plasma desmopressin concentrations in the four different scenarios (120 µg lyophilisate, 200 µg tablet). The *solid and dashed lines* represent the average responses, and the *hatched areas* represent the 95 % prediction intervals. In the *left panel*, the effect of

the different formulations is shown; in the *right panel*, the food effect is shown. *FAST* fasted state, *FED* fed state, *MELT* lyophilisate, *TAB* tablet

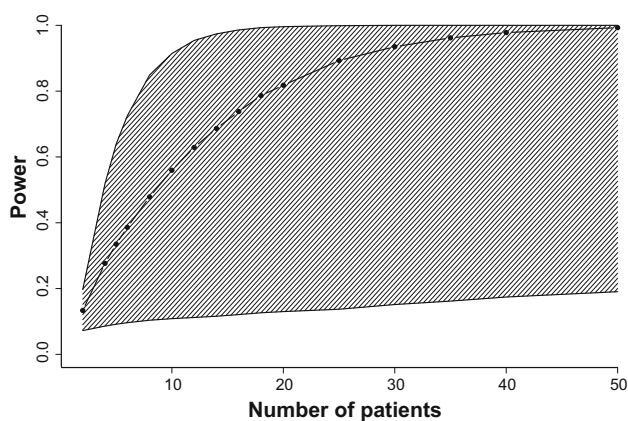


**Fig. 8** Simulated plasma desmopressin concentrations in the four different scenarios (150 µg lyophilisate, 200 µg tablet). The *solid and dashed lines* represent the average responses, and the *hatched areas* represent the 95 % prediction intervals. In the *left panel*, the effect of

the different formulations is shown; in the *right panel*, the food effect is shown. *FAST* fasted state, *FED* fed state, *MELT* lyophilisate, *TAB* tablet

[36], and a one-compartment model with transit compartments [15]—were used to describe DDAVP pharmacokinetics. The first two, however, described DDAVP pharmacokinetics after intravenous dosing, which indeed follow biphasic kinetics [37]. Possibly, this biphasic behavior is masked by the absorption process after oral

dosing. A two-compartment model was tried but resulted in a significantly worse fit than the one-compartment model ( $\Delta\text{OFV} = +81.3$ ). The use of a transit model could be debated, as the absorption kinetics of DDAVP do seem to be delayed; the mean residence time and number of compartments in children have been estimated as 0.237 and



**Fig. 9** Approximated power curve for a two-period crossover bioequivalence trial with fed patients. The *hatched area* represents the 90 % prediction interval

1.19 h, respectively [15]. The simple first-order absorption model was compared with the transit compartment model, but this showed no significant improvement ( $\Delta\text{OFV}_{\text{transit}} = +8.502$ ). For reasons of parsimony, the first-order absorption model was thus retained.

In our study, a population apparent total clearance after oral administration (CL/F) value of 4892 L/h was found. This is almost twice the value found in the pediatric dataset by Österberg et al. [15]. However, in our study, we allowed the relative bioavailability to change, depending on the formulation and the fed state. If we calculate the population CL/F for a fasted population receiving the lyophilisate formulation, CL/F becomes  $4892/(1 + 0.3208 + 1.011) = 2098$  L/h, which corresponds to the reported value of 2330 L/h by Österberg et al. [15]. The same reasoning can be followed for the apparent volume of distribution after oral administration ( $V_d/F$ ). However, to compare both values correctly,  $V_d/F$  should be calculated for the average body weight from the full Österberg dataset (28 kg) [15].  $V_d/F$  then becomes  $23.346 \times (28/45.5)^{0.4020} = 8237$  L, which corresponds to the reported value of 8510 L [15].

The bioequivalence between the 200 µg tablet and the 120 µg lyophilisate found in adults [10, 11, 37] could not be supported by the current analysis. The statistical significance of the formulation effect is apparent from our model, suggesting that the 120 µg lyophilisate is 32.1 % more bioavailable than the 200 µg tablet. In adults, this value was found to be  $(200/120 - 1) = 66.7$  % for a similar-strength lyophilisate and tablet. Indeed, when a lyophilisate dose of 150 µg (33.3 % lower than 200 µg) is simulated (Fig. 7), the desmopressin exposure of the two formulations in children shows a much better overlap. A possible explanation for this phenomenon could be reduced sublingual absorption in children, caused by either the smaller surface area in comparison with adults or the fact that the lyophilisate is swallowed sooner by children. This

could be formally tested in a two-period crossover clinical bioequivalence trial.

The effect of food intake was also found to be clinically significant. Attributing this effect exclusively to food intake might be considered too simplistic, as all fasted patients originated from the study by Österberg et al. and all fed patients originated from the study by De Bruyne et al., which means that other factors might have confounded our analysis. There were two major differences between the studies: the bioanalytical method and the level of hydration. Since the two analytical methods were both validated and had a similar linear range, it seems unlikely that this confounded our estimate of the food effect to any significant degree. In the study by De Bruyne et al., hydration was maintained by oral water administration 5 h after the dose. Patients in the study by Österberg et al., however, drank 1.5 % of their body weight as water over a 30-minute period, after which urinary output loss was replaced with an equivalent amount of tap water [14, 15]. Notwithstanding this difference in hydration methods, it was previously shown that hydration does not significantly influence the pharmacokinetics of DDAVP [35], and it is thus highly improbable that the difference between the two study groups could be attributed to this. However, between-study variability might still be present in this effect parameter, as is—for example—indicated by the large difference in the power curve for a two-period crossover bioequivalence study in the fed population (20 patients for 80 % power) and the fasted population (250 patients).

As children are not always fasted when they take DDAVP (right before bedtime), this food effect may have consequences for the optimal dosing. Even though the effect on the maximal response might be negligible, as it is in adults, there might be an influence on the duration of action [13].

An effect of WT on  $V_d/F$  was also found, indicating that dose adjustment could be necessary to maximize efficacy in this pediatric population. However, the extent of the body weight influence is quite unclear from these data, as the exponent of the power relation exhibits quite a large uncertainty. More informative trials may result in smaller CIs for this (and other) parameters. Indeed, although the model evaluation was positive, the amount of information in the data seemed to be exhausted in this (relatively simple) model. This was, for example, clear from the failure to additionally estimate IIV on CL and the first-order absorption rate constant ( $K_a$ ). However, the variability in CL in the population was still somewhat captured by the model, as CL and  $V_d$  are correlated via bioavailability,  $F$ . This way, the IIV on CL is partially captured by the IIV on  $F$  and  $V_d$ .  $K_a$ , and especially its IIV, should be estimated though, which is why a new trial with more intensive sampling of the absorption phase is needed.

Therefore, a sensitivity analysis was conducted in order to suggest sampling times for a new trial. More intensive sampling in the absorption phase is advisable, as is proposed by both the LSA and the OED. We suggest designing the trial according to the LSA results, as these time points are more practical in a clinical setting, and the OED was only 1.34 times more efficient than the LSA design. This design was based on eight samples, while—*theoretically speaking*—three sampling points (the number of parameters in the model) should be sufficient [34]. However, because the follow-up study will also investigate pharmacodynamics, and because of logistical risks, more samples are preferable.

As the difference between the two formulations is not only a matter of pharmacokinetics, pharmacodynamics will also be monitored in this new trial. It was, for example, demonstrated in adults that there is a significant effect of sex on DDAVP pharmacodynamics [38]. This effect is thought to be caused by a difference in V2 receptor expression [39] and should also be investigated in children. As our study was based exclusively on pharmacokinetic data, no inferences about the optimal sampling scheme for pharmacodynamic analysis could be made. In the newly designed trial, pharmacodynamic characteristics, such as urine volume and plasma osmolality, will be measured, after which a population approach will be used to gain knowledge about the complete pharmacokinetic/pharmacodynamic behavior of DDAVP in the pediatric population.

## 5 Conclusion

In this analysis, we presented evidence on the effects of body weight and the fed state on the pharmacokinetics of desmopressin in children. Furthermore, the relative bioavailability between the lyophilisate and tablet formulations is probably not the same in children as it is in adults. We should be reluctant to accept that bioequivalence exists in children on the basis of adult data alone. Our study also offered suggestions for optimizing the sampling design of a new trial, and a sample size calculation for a bioequivalence trial was also provided.

### Compliance with Ethical Standards

**Funding** This study was supported by the Agency for Innovation by Science and Technology in Flanders (IWT) through the SAFE-PEDRUG Project (IWT/SBO 130033).

**Conflict of interest** An Vermeulen is an employee of Johnson & Johnson and holds stock/stock options in Johnson & Johnson. Pauline De Bruyne has received a travel reimbursement from Ferring Pharmaceuticals for a presentation at the Ghent-Aarhus Springschool. Johan Vande Walle has received consulting fees and travel

reimbursements from Ferring Pharmaceuticals, and has received payment for lectures from Ferring Pharmaceuticals and Astellas Pharma. Robin Michelet, Lien Dossche, Pieter Colin, Koen Boussery, and Jan Van Bocxlaer have no potential conflicts of interest that might be relevant to the content of this manuscript.

## References

- Rocchi F, Tomasi P. The development of medicines for children. *Pharmacol Res.* 2011;64(3):169–75.
- Vande Walle J, Stockner M, Raes A, Nørgaard JP. Desmopressin 30 years in clinical use: a safety review. *Curr Drug Saf.* 2007;2(3):232–8.
- Rittig S, Knudsen UB, Nørgaard JP, Pedersen EB, Djurhuus JC. Abnormal diurnal rhythm of plasma vasopressin and urinary output in patients with enuresis. *Am J Physiol.* 1989;256(4 Pt 2):664–71.
- Glazener CM, Evans JH. Desmopressin for nocturnal enuresis in children. *Cochrane Database Syst Rev.* 2002;(3):CD002112.
- Robson WLM, Leung AKC, Nørgaard JP. The comparative safety of oral versus intranasal desmopressin for the treatment of children with nocturnal enuresis. *J Urol.* 2007;178(1):24–30.
- Van Herzeele C, De Bruyne P, Evans J, Eggert P, Lottmann H, Nørgaard JP, Vande Walle J. Safety profile of desmopressin tablet for enuresis in a prospective study. *Adv Ther.* 2014;31(12):1306–16.
- Lucchini B, Simonetti GD, Ceschi A, Lava SAG, Faré PB, Bianchetti MG. Severe signs of hyponatremia secondary to desmopressin treatment for enuresis: a systematic review. *J Pediatr Urol.* 2013;9(6 Pt B):1049–53.
- Dehoorne JL, Raes AM, van Laecke E, Hoebeke P, Vande Walle JG. Desmopressin toxicity due to prolonged half-life in 18 patients with nocturnal enuresis. *J Urol.* 2006;176(2):754–8.
- Vande Walle J, Van Herzeele C, Raes A. Is there still a role for desmopressin in children with primary monosymptomatic nocturnal enuresis? A focus on safety issues. *Drug Saf.* 2010;33(4):261–71.
- Ferring Pharmaceuticals. Minirin® Melt: desmopressin. 2007. [Online]. <http://secure.healthlinks.net.au/content/ferring/pi.cfm?product=fppminiw10611>. Accessed 29 May 2015.
- Medicines and Healthcare Products Regulatory Agency (MHRA). License file DDAVP MELT oral lyophilisate (desmopressin acetate). 2006. [Online]. <http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con2023731.pdf>. Accessed 28 May 2015.
- De Guchteneere A, Van Herzeele C, Raes A, Dehoorne J, Hoebeke P, Van Laecke E, Vande Walle J. Oral lyophilisate formulation of desmopressin: superior pharmacodynamics compared to tablet due to low food interaction. *J Urol.* 2011;185(6):2308–13.
- Rittig S, Jensen AR, Jensen KT, Pedersen EB. Effect of food intake on the pharmacokinetics and antidiuretic activity of oral desmopressin (DDAVP) in hydrated normal subjects. *Clin Endocrinol (Oxf).* 1998;48:235–41.
- De Bruyne P, De Guchteneere A, Van Herzeele C, Raes A, Dehoorne J, Hoebeke P, Van Laecke E, Vande Walle J. Pharmacokinetics of desmopressin administered as tablet and oral lyophilisate formulation in children with monosymptomatic nocturnal enuresis. *Eur J Pediatr.* 2014;173(2):223–8.
- Østerberg O, Savic RM, Karlsson MO, Simonsson USH, Nørgaard JP, Vande Walle J, Agersø H. Pharmacokinetics of desmopressin administered as an oral lyophilisate dosage form in children with primary nocturnal enuresis and healthy adults. *J Clin Pharmacol.* 2006;46(10):1204–11.

16. Wählby U, Bouw MR, Jonsson EN, Karlsson MO. Assessment of type I error rates for the statistical sub-model in NONMEM. *J Pharmacokinet Pharmacodyn*. 2002;29(3):251–69.
17. Efron B. Better bootstrap confidence intervals. *J Am Stat Assoc*. 1987;82(397):171–85.
18. Brendel K, Comets E, Laffont C, Laveille C, Mentré F. Metrics for external model evaluation with an application to the population pharmacokinetics of gliclazide. *Pharm Res*. 2006;23(9):2036–49.
19. Comets E, Brendel K, Mentré F. Computing normalised prediction distribution errors to evaluate nonlinear mixed-effect models: the NPDE add-on package for R. *Comput Methods Programs Biomed*. 2008;90(2):154–66.
20. Food and Drug Administration (FDA). Guidance for industry bioequivalence studies with pharmacokinetic endpoints for drugs submitted under an ANDA. Silver Spring: CDER; 2013.
21. European Agency for the Evaluation of Medicinal Products (EMA). Note for guidance on the investigation of bioavailability and bioequivalence. London: EMA; 2001.
22. Food and Drug Administration (FDA). Guidance for industry - statistical approaches to establishing bioequivalence. Rockville: CDER; 2001.
23. Portier K, Keith Tolson J, Roberts SM. Body weight distributions for risk assessment. *Risk Anal*. 2007;27(1):11–26.
24. Donckels BMR. Optimal experimental design to discriminate among rival dynamic mathematical models. PhD thesis. Ghent: Ghent University; 2009.
25. Saltelli A, Ratto M, Andres T, Campolongo F, Cariboni J, Gatelli D, Saisana M, Tarantola S. *Global sensitivity analysis: the primer*. Chichester: Wiley; 2008.
26. Olsson U. Confidence intervals for the mean of a log-normal distribution. *J Stat Educ*; 2005:13(1).
27. Food and Drug Administration (FDA). Guidance for industry food-effect bioavailability and fed bioequivalence studies. Rockville: CDER; 2002.
28. Boeckmann AJ, Sheiner LB, Beal SL. *NONMEM users guide—part VIII: help guide*. Ellicott City: Icon Development Solutions; 2006.
29. Lindbom L, Pihlgren P, Jonsson N. PsN-Toolkit—a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. *Comput Methods Programs Biomed*. 2005;79(3):241–57.
30. Piraña: installation guide and manual. 2015. <http://www.pirana-software.com>. Accessed 2 Sept 2015.
31. Van Daele T, Van Hoey S, Van Hauwermeiren D, and Van den Bossche J. Biointense package. 2015. <https://github.ugent.be/pages/biomath/biointense/>. Accessed 2 Sept 2015.
32. Raybaut P. Documentation Spyder. 2013. <https://pythonhosted.org/spyder>. Accessed 2 Sept 2015.
33. Banks HT, Dediu S, Ernstberger SL, Kappel F. Generalized sensitivities and optimal experimental design. *J Invers Ill-Posed Probl*. 2010;18:1–44.
34. Tod M, Mentré F, Merlé Y, Mallet A. Robust optimal design for the estimation of hyperparameters in population pharmacokinetics. *J Pharmacokinet Biopharm*. 1998;26(6):689–716.
35. Callreus T, Odeberg J, Lundin S. Indirect-response modeling of desmopressin at different levels of hydration. *J Pharmacokinet Biopharm*. 2000;27(5):513–29.
36. Agersø H, Larsen LS, Riis A, Lövgren U, Karlsson MO, Senderovitz T. Pharmacokinetics and renal excretion of desmopressin after intravenous administration to healthy subjects and renally impaired patients. *Br J Clin Pharmacol*. 2004;58:352–8.
37. van Kerrebroeck P, Nørgaard JP. Desmopressin for the treatment of primary nocturnal enuresis. *Public Health*. 2009;3(4):317–27.
38. Juul KV, Klein BM, Sandström R, Erichsen L, Nørgaard JP. Gender difference in antidiuretic response to desmopressin. *Am J Physiol Renal Physiol*. 2011;300(5):F1116–22.
39. Liu J, Sharma N, Zheng W, Ji H, Tam H, Wu X, Manigrasso MB, Sandberg K, Verbalis JG. Sex differences in vasopressin f3V2 receptor expression and vasopressin-induced antidiuresis. *Am J Physiol Renal Physiol*. 2011;300(2):F433–40.