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Pharmacokinetics of Sapropterin in Patients with Phenylketonuria

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Abstract

Background and objective: Untreated phenylketonuria is characterized by neurocognitive and neuromotor impairment, which result from elevated blood phenylalanine concentrations. To date, the recommended management of phenylketonuria has been the use of a protein-restricted diet and the inclusion of phenylalanine-free protein supplements; however, this approach is often associated with poor compliance and a suboptimal clinical outcome. Sapropterin dihydrochloride, herein referred to as sapropterin, a synthetic formulation of 6R-tetrahydrobiopterin (6R-BH4), has been shown to be effective in reducing blood phenylalanine concentrations in patients with phenylketonuria. The objective of the current study was to characterize the pharmacokinetics and pharmacokinetic variability of sapropterin and to identify the characteristics that influence this variability.

Patients and methods: This was a 12-week, fixed-dose phase of an open-label extension study. The study was conducted at 26 centres in North America and Europe.

Patients with phenylketonuria were eligible to participate if they were ≥8 years of age and had received ≥80% of the scheduled doses in a previous 6-week, randomized, placebo-controlled study or had been withdrawn from that study after exceeding a plasma phenylalanine concentration of ≥1500 μmol/L to ≥1800 μmol/L, depending on the subject's age and baseline plasma phenylalanine concentration. A total of 78 patients participated. Patients received oral once-daily doses of sapropterin (Kuvan®) 5, 10 or 20 mg/kg/day.

Blood samples for the pharmacokinetic analysis were obtained during weeks 6, 10 and 12. A D-optimal sparse sampling strategy was used, and data were analysed by population-based, nonlinear, mixed-effects modelling methods.

Main outcome measure: In a prospectively planned analysis, the apparent clearance, apparent volume of distribution, absorption rate constant and associated interindividual variabilities of each parameter were estimated by modelling observed BH4 plasma concentration-time data.

Results: The best structural model to describe the pharmacokinetics of sapropterin was a two-compartment model with first-order input, first-order elimination and a baseline endogenous BH4 concentration term. Total bodyweight was the only significant covariate identified, the inclusion of which on both the apparent clearance

(mean = 2100 L/h/70 kg) and central volume of distribution (mean = 8350 L/70 kg) substantially improved the model's ability to describe the data. The mean (SD) terminal half-life of sapropterin was 6.69 (2.29) hours and there was little evidence of accumulation, even at the highest dose.

Conclusion: These findings, taken together with the observed therapeutic effect, support bodyweight-based, once-daily dosing of sapropterin 5–20 mg/kg/day.

Background

Phenylketonuria is caused by phenylalanine hydroxylase deficiency. Untreated phenylketonuria is characterized by elevated blood phenylalanine concentrations, which result in neurocognitive and neuromotor impairment.[1] Current management of patients with phenylketonuria focuses on reducing plasma phenylalanine concentrations by dietary restriction of natural proteins and replacement with phenylalanine-free protein supplements.[2] Although the most significant benefits of dietary management occur within infancy and early childhood, lifelong phenylalanine control is recommended to prevent neurological and behavioural manifestations in adulthood. An alternative approach to therapy is to increase the residual phenylalanine hydroxylase activity by treatment with the cofactor 6R-tetrahydrobiopterin (6R-BH4) or its synthetic, US FDA-approved formulation sapropterin dihydrochloride (herein referred to as sapropterin). Studies have shown that this approach can reduce or, in some cases, eliminate the need for dietary protein restriction and phenylalanine-free protein supplements.[3-5]

A recent phase III study[6] has investigated the efficacy and safety of prolonged (22 weeks) sapropterin treatment in patients with phenylketonuria who had previously responded to an 8-day course of treatment with sapropterin 10 mg/kg/day. This study included a population pharmacokinetic analysis in a subgroup of patients, designed to evaluate BH4 pharmacokinetics and pharmacokinetic variability after administration of sapropterin in individuals with phenylketonuria. The results of this analysis are presented here.

Methods

The parent trial was a phase III, open-label, extension study conducted at 26 centres in North America (Canada and the US) and Europe (France, Germany, Ireland, Italy, Poland and the UK). The study was approved by institutional review boards or ethics committees at all centres and was performed according to the principles of the International Conference on Harmonization Guideline for Good Clinical Practice, and the Declaration of Helsinki. The population pharmacokinetic substudy was performed in patients from the parent study.

Patients

Patients aged ≥8 years of age with phenylketonuria responsive to BH4 treatment were eligible for inclusion in the study if they had previously shown ≥30% reduction in plasma phenylalanine concentration in an 8-day trial with sapropterin treatment (the PKU-001 study);[7] had subsequently participated in a 6-week, randomized, placebo-controlled study (the PKU-003 study);[8] and had received at least 80% of the scheduled doses in the PKU-003 study or had been withdrawn from the study after exceeding a plasma phenylalanine concentration of ≥1500 μmol/L (25 mg/dL) or ≥1800 μmol/L (30 mg/dL), or ≥1800 μmol/L and ≥30% of the baseline value, depending on the subject's age and baseline plasma phenylalanine concentration. Patients were required to be willing to continue with their current diet during the study. In addition, women of child-bearing potential were required to have a negative urine pregnancy test within 24 hours prior to enrolment and to be using acceptable measures of contraception. The exclusion criteria were: failure to complete the PKU-003 study for any reason other than withdrawal because of high phenylalanine concentrations (as indicated above); an expected need for any investigational product or vaccine prior to completion of the study; pregnancy (or intended pregnancy) or lactation; concurrent medical conditions or diseases that would interfere with the conduct of the study; indications for drug treatments known to inhibit folate synthesis (e.g. methotrexate); or concurrent use of levodopa.

Informed written consent was obtained from all patients before inclusion in the study. In the case of children, written informed consent was obtained from parents or guardians, and the child provided his or her assent.

Study Design

The parent study comprised a 6-week forced dose-titration phase, followed by a 4-week dose-analysis phase and a 12-week fixed-dose phase. During the forced dose-titration phase, all pa-

Table I. D-Optimal sampling design

Group	Dose (mg/kg/day)[a]	Time post-dose (h)
1	5	0–0.1[b]
1	5	0–0.1[b]
1	5	1.2–3.7
1	5	5.6–8.0
2	20	0–0.1
2	20	0.3–1.0
2	20	5–5.9
2	20	7.0–8.0

a Patients receiving sapropterin 10 mg/kg/day in the fixed-dose phase were assigned to either group and followed the dosing schedule for that group.

b It was recommended that one sample be taken before dosing and one within the first 10 min after dosing.

tients received sapropterin (Kuvan®,[1] BioMarin Pharmaceutical Inc., Novato, CA, USA) at doses of 5, 10 and 20 mg/kg/day for 2 weeks each consecutively. During the dose-analysis phase, all patients received 10 mg/kg/day. Patients received sapropterin at doses of 5, 10 or 20 mg/kg/day during the 12-week fixed-dose phase, as determined by the patient's plasma phenylalanine concentrations at weeks 2 and 6 during the dose-titration phase. All doses were given once daily prior to the first meal in the morning and were provided as tablets containing sapropterin dihydrochloride 100 mg, which were dissolved in 120–240 mL of water, orange juice or apple juice. Doses were calculated by multiplying the patient's bodyweight in kilograms by the assigned dose (5, 10 or 20 mg/kg/day) and rounding up to the next 100 mg unit dose.

Pharmacokinetic Sampling

A D-optimal sparse sampling strategy[9] was used in this study, and data were analysed by population-based nonlinear mixed-effects modelling methods. Blood samples for the pharmacokinetic analysis were obtained during weeks 16, 20 and 22. It was anticipated that four samples would be obtained from each patient at specified sample windows up to 8 hours after dosing, according to the schedule shown in table I.

Tetrahydrobiopterin Assay

As BH4 and its metabolites are unstable in plasma, BH4 concentrations were measured indirectly by measuring the concentration of L-biopterin, which has been shown to be stable,[10,11] and correcting for the oxidative conversion of BH4 to L-biopterin.

The quantitative analysis of the plasma concentrations of 6R-BH4 was performed on 0.1% dithioerythritol pretreated plasma. The test sample was spiked with an internal standard, basified with sodium hydroxide solution and oxidized with iodine solution. Upon incubation in the dark at room temperature, ascorbic acid was added to reduce excess iodine. Oxidized samples were extracted by protein precipitation. L-biopterin concentration of the reconstituted extracts was analysed using reversed-phase, high-performance liquid chromatography with Turbo Ion Spray® tandem mass spectrometry detection; negative ions for L-biopterin were monitored in the multiple reaction-monitoring mode. A linear calibration curve of the drug to internal standard peak-area ratios for the standards was created, using a $1/x^2$ weighted least-squares regression analysis. The assay was independently validated for the quantification of L-biopterin (5–1000 ng/mL) in human plasma by Quest Pharmaceutical Services (Newark, DE, USA) and the nominal conversion ratio of BH4 to L-biopterin was determined to be 47.3% up to week 8. The conversion ratio was stable within at least 8 weeks of storage at −70°C.

The results of the analyses are expressed according to the calculated BH4 concentrations.

Pharmacokinetic Modelling

A series of pharmacokinetic structural models were evaluated, including one-, two- and three-compartment models with zero-order, first-order, or a combination of zero- and first-order input. Zero- and first-order elimination models were also evaluated. The necessity of including a baseline or endogenous concentration was also established. The data were best described by a linear two-compartment model with first-order absorption and elimination. The following pharmacokinetic parameters and their associated interindividual variabilities were modelled: apparent oral clearance (CL/F), apparent volume of distribution of the central compartment after oral administration (V_1/F), absorption rate constant (k_a) and baseline (endogenous) BH4 concentration. Interindividual variability was described using the following model (equation 1):

$$P_j = TVP \bullet e^{\eta j} \quad \text{(Eq. 1)}$$

where P_j is the value for the pharmacokinetic parameter in the jth individual and ηj is an independent random variable with a mean of zero and variance of ω_P^2. Further adjustments were made for interoccasion variability and residual variability.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

The categorical variables assessed as covariates were sex (male = 0; female = 1) and race (White = 0; non-White = 1). The continuous variables evaluated in the models were age, height, bodyweight, body surface area, serum creatinine, albumin, ALT, AST, total bilirubin and phenylalanine. All covariates were examined as potential predictors of BH4 disposition: there were no missing covariate data. Covariate models that included sex were parameterized such that different estimates of pharmacokinetic parameters were obtained for men and women, according to equation 2:

$$TVP = \theta_1 \bullet Sex + \theta_2 \bullet (1 - Sex) \quad \text{(Eq. 2)}$$

where TVP represents the model-predicted pharmacokinetic parameter (e.g. the CL/F or the volume of distribution of the peripheral compartment after oral administration [V_2/F]) for the 'typical' individual, and θ_1 and θ_2 are scale factors. Covariate models that evaluated continuous variables were parameterized to represent the covariate as a shift in the parameter of interest from the value observed in a hypothetical reference patient with demographic factors (e.g. height and bodyweight) equivalent to the mean value for the dataset (equation 3):

$$TVP = P_{Pop} \bullet \prod_{i=1}^{n} COV_i^{\theta_i} \quad \text{(Eq. 3)}$$

where P_{Pop} represents the population central tendency for the pharmacokinetic parameter and COV_i represents the individual value for the parameter normalized to the population mean. In such models, if $\theta_i = 0$, the covariate is dropped from the model, while $\theta_i = 1$ indicates a direct proportional relationship; θ_i values of <1 or >1 indicate a nonlinear relationship. The appropriateness of covariate models was assessed during model development by the use of diagnostic plots.

Covariates were first examined for their potential effects on the CL/F and V_1/F by graphical assessment, followed by a model-based analysis if any trends were observed. The relative impact of these covariates on the pharmacokinetics of BH4 was ultimately assessed by the associated decrease in objective function, together with the size of the covariate effects and any associated decrease in interindividual variability. Standard model-building approaches for identification of covariates were used.[12] Initial covariate selection was conducted using the base model with all covariates initially modelled individually for effects on each parameter. Covariates were then combined based on the results of the likelihood ratio test (forward addition). The first-order conditional estimation method with interaction was used because the change in objective function has been shown to follow a χ^2 distribution.[13,14] For nested models, improvements to the model were tested at each step by means of the likelihood ratio test. Only covariates that individually influenced the pharmacokinetic parameters were to be added, in decreasing order of magnitude (the forward addition method). Such covariates were included in the final model if they resulted in a reduction in the objective function value of at least 10 points compared with the previous model. Covariates were included at a p value of <0.001 to minimize the number of covariates that were included falsely. Other improvements included reduction in interindividual variability[15] and improvements in diagnostic plots.

Table II. Demographic characteristics of study patients

Characteristic	Patients (n = 78)[a]
Sex [n (%)]	
males	45 (58)
females	33 (42)
Race [n (%)]	
White	76 (97)
non-White	2 (3)
Age (y)	21.1 (9.64) [9–50]
Bodyweight (kg)	67.2 (21.8) [28.2–144]
Height (cm)	165 (13.3) [126–191]
Body surface area (m^2)	1.72 (0.31) [1.05–2.65]
ALT (U/L)	28.4 (18.3) [11–127]
AST (U/L)	25.7 (5.8) [14–43]
Bilirubin (mg/dL)	0.55 (0.33) [0.1–1.9]
Serum creatinine (mg/dL)	0.89 (0.15) [0.6–1.3]
CL_{CR} (mL/min)[b]	114 (26) [48–231]
Baseline phenylalanine (μmol/L)	811 (393) [53–2190]
Baseline phenylalanine (mg/dL)	13.5 (6.6) [0.9–36.5]

a Values are presented as mean (SD) [range] unless specified otherwise.

b Calculated from plasma creatinine.

CL_{CR} = creatinine clearance.

The model was tested and qualified by determining the symmetrical 95% confidence intervals from the asymptotic standard errors of the parameter estimates and nonparametric bootstrapped 95% confidence intervals. Model stability was tested by evaluating the condition number. In addition, a visual predictive check[16] was conducted on 5000 simulated patients to compare the distribution of simulated concentrations from the final model with those obtained from the original data in the model building set.

Pharmacokinetic modelling and analysis were performed using NONMEM® version V concentration 1.1 software (Icon Develop-

ment Solutions, Hanover, MD, USA). The compiler was Compaq Digital Visual Fortran version 6.6.3C (Hewlett-Packard Inc., Palo Alto, CA, USA). S-Plus 6.2 Professional Edition (Insightful Inc., Seattle, WA, USA) was used for graphical outputs and data manipulation.

Results

A total of 78 patients (45 males, 33 females) took part in this study. Of these, six (7.7%) received sapropterin 5 mg/kg/day, 37 (47.4%) received 10 mg/kg/day and 34 (43.6%) received 20 mg/kg/day; the dose was not recorded in one patient (data for this patient were not included in the reported analyses). The demographic characteristics of the patients are summarized in table II.

Pharmacokinetic Modelling

The final dataset consisted of 315 observations from 78 patients. Of these, 38 were below the limit of quantification of the assay and four concentration values were not reported; a further eight observations were considered unreliable and were therefore excluded from the evaluation. Hence the final database used for model building consisted of 265 observations (84.1% of the originals) from 76 patients (97.4%).

The best structural base model to describe the pharmacokinetics of sapropterin was a two-compartment model with first-order input, first-order elimination and a baseline endogenous BH4 concentration (figure 1). This model was parameterized in terms of the CL/F, V_1/F, V_2/F and apparent intercompartmental oral clearance (Q/F). A term accounting for the endogenous BH4 concentration (BASE) was also included.

In general, this model showed good agreement between observed and typical predicted BH4 concentrations, although there was considerable interpatient variability. The typical model parameters showed that sapropterin is rapidly absorbed (k_a = 0.552 h^{-1}), with peak concentrations occurring approximately 2 hours after dosing. Clearance is also rapid (CL/F = 2030 L/h) and the drug has a large volume of distribution (V_1/F = 7730 L).

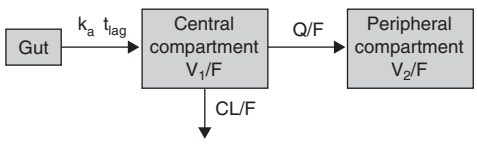

Fig. 1. Schematic representation of the pharmacokinetic model. **CL/F** = apparent oral clearance; **k_a** = absorption rate constant; **Q/F** = apparent intercompartmental oral clearance; **t_{lag}** = lag time; **V_1/F** = apparent volume of distribution of the central compartment after oral administration; **V_2/F** = apparent volume of distribution of the peripheral compartment after oral administration.

Table III. Parameter estimates and associated standard errors (SEs) for the final covariate model

Parameter	Population mean (SE)[a]	SD of interindividual variance (SE)[a]
t_{lag} (h)	0.275 (13.7)	NA
k_a (h)	0.518 (24.1)	NA
CL/F (L/h/70 kg)	2100 (9.9)	0.539 (25.3)
Power function on CL/F	0.586 (34.0)	NA
V_1/F (L/70 kg)	8350 (16.9)	0.557 (41.3)
Power function on V_1/F	1.13 (24.7)	NA
V_2/F (L)	4240 (42.5)	NA
Q/F (L/h)	862 (43.5)	NA
BASE (ng/mL)	13.5 (8.2)	NA
R	0.336	NA
Constant CV residual error (as %CV)	21.7 (13.3)	

a SE presented as % CV.

BASE = endogenous baseline concentration of tetrahydrobiopterin; **CL/F** = apparent oral clearance; **CV** = coefficient of variation; **k_a** = absorption rate constant; **NA** = not applicable; **Q/F** = apparent intercompartmental oral clearance; **R** = correlation between parameters CL/F and V_1/F; **t_{lag}** = lag time; **V_1/F** = volume of distribution of the central compartment after oral administration; **V_2/F** = volume of distribution of the peripheral compartment after oral administration.

The principal covariate found to affect pharmacokinetic variability was bodyweight; no other covariates were found to improve the model at the $p < 0.001$ level of significance. The addition of bodyweight as a covariate reduced the interindividual variability in clearance from 58% in the base model to 54% in the final model, and it also reduced the interindividual variability in the volume of distribution from 70% in the base model to 56% in the final model. The parameter estimates and associated standard errors for this model are summarized in table III. After inclusion of bodyweight, the mean clearance was 2100 L/h/70 kg and the mean V_1/F was 8350 L/70 kg. The mean (SD) initial and terminal half-lives were 1.45 (0.47) hours and 6.69 (2.29) hours, respectively.

This model showed good agreement between observed and predicted BH4 concentrations (figure 2), although substantial interindividual variability remained. The 95% confidence intervals obtained by nonparametric bootstrapping were generally narrow (table IV), with the exception of Q/F, and the visual predictive check showed that the model was capable of reproducing the observed data (figure 3).

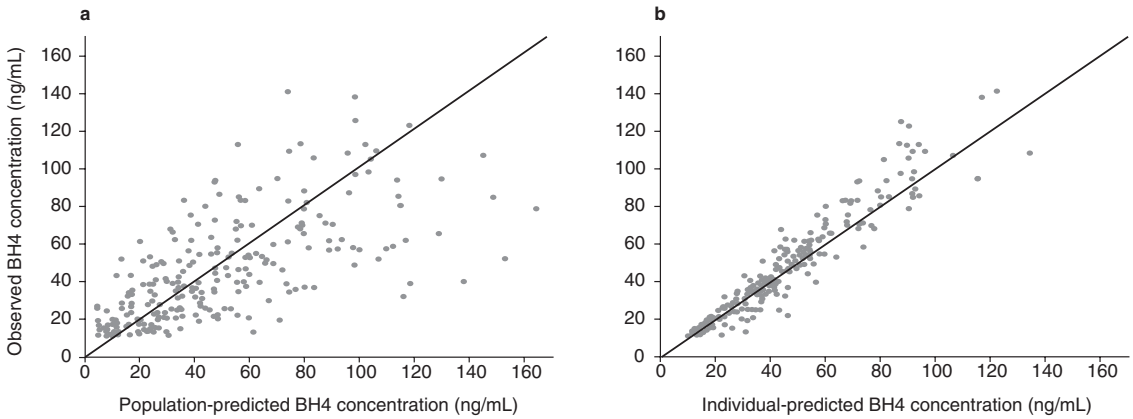

Fig. 2. Agreement between observed and (**a**) population-predicted and (**b**) individual-predicted tetrahydrobiopterin (BH4) concentrations. Fixed or structural parameters reflect the central tendency of the parameter distribution. Individual parameters deviate from the central tendency based on that individual's data and the fit of the structural model to that data. Predictions of the BH4 concentration are based only on the structural parameters of a model and are referred to as population-predicted BH4 concentrations. Predictions of BH4 concentrations using individual parameter estimates are referred to as individual-predicted BH4 concentrations.

Stochastic simulations were performed, based on five daily doses of 5, 10 or 20 mg/kg (sapropterin dihydrochloride), in order to investigate potential accumulation of BH4. The results showed little evidence of accumulation, even at the highest dose (figure 4).

Table IV. Base model parameters

Parameter	Final model estimate[a]	Bootstrap model estimate[b]
t_{lag} (h)	0.306 (0.245, 0.367)	0.313 (0.157, 0.385)
k_a (h)	0.552 (0.309, 0.795)	0.564 (0.334, 1.13)
CL/F (L/h)	2030 (1630, 2430)	2040 (1620, 2490)
V_1/F (L)	7730 (4900, 10 600)	7420 (3567, 11 500)
V_2/F (L)	4000 (1158, 6842)	4390 (1600, 25 900)
Q/F (L)	937 (171, 1700)	922 (198, 183 000)
BASE (ng/mL)	13.9 (11.8, 16.0)	13.8 (11.1, 15.8)
R	0.436	0.443 (0.155, 0.735)
IIV CL/F	0.580[c]	0.570 (0.444, 0.690)
IIV V_1/F	0.700[c]	0.704 (0.405, 1.31)
Constant CV (%CV)	21.4	21.1 (18.2, 23.9)
RUV (%CV)	21.4	21.1 (18.2, 23.9)

a Population mean (95% CI).

b Median (95% CI).

c Standard deviation.

BASE = endogenous baseline concentration of tetrahydrobiopterin; **CL/F** = apparent oral clearance; **CV** = coefficient of variation; **IIV** = interindividual variability; **k_a** = absorption rate constant; **Q/F** = apparent intercompartmental oral clearance; **R** = correlation between parameters CL/F and V_1/F; **RUV** = random unexplained variability; **t_{lag}** = lag time; **V_1/F** = volume of distribution of the central compartment after oral administration; **V_2/F** = volume of distribution of the peripheral compartment after oral administration.

Discussion

A D-optimal, sparsely sampled population pharmacokinetic approach was used in this study, for several reasons. First, D-optimal sampling was selected as the method for sample schedule design because this approach suggests windows of time where sampling will be most informative relative to a proposed model, without undue penalty against the identification of alternative models. This approach allows for patients to have fewer blood samples drawn than with traditional pharmacokinetic sample designs, which often require eight or more pharmacokinetic samples per patient. D-optimal sampling weighs various sample schemes based on the efficiency of a proposed design, the expected bias and precision of estimated parameters, and practical considerations. The fact that patients in this study received different dosing regimens of sapropterin further improved the information content of the data obtained in the present study.

The use of population pharmacokinetic methods for evaluation of data is not a new concept. Population methods allow pharmacokinetic parameters to be determined when data are sparse, and can be used to investigate the influence of covariates on pharmacokinetic variability. Population pharmacokinetic approaches are highly dependent on the quality and sufficiency of the data available for analysis. For example, poor compliance with taking medications can result in poor parameter estimation. In a related situation, loss of information can occur when a large fraction of samples are lost because of assay limitations. In the present evaluation, the loss of samples due to results below the limit of quantification may have resulted in an upwardly biased estimation of BASE, which is primarily informed via the lowest concentration data, although it

should not have had a substantial impact on other parameters such as the CL/F.

The results of this study show that, following oral administration of sapropterin, BH4 concentrations increase in the peripheral circulation after a short lag period, with peak concentrations being attained after approximately 2 hours. The concentrations subsequently declined in a bi-exponential manner, which suggests that the pharmacokinetics of sapropterin can best be described by a two-compartment, first-order input model with first-order elimination. As biopterin is an endogenous substance, a term was included in the model to account for endogenous baseline concentrations. The validity of this model is supported by the narrow 95% confidence intervals obtained from nonparametric bootstrapping and the results of the visual predictive check.

The plots showing observed versus population-predicted and population concentration (figures 2 and 3) suggest that the model may slightly underpredict the data. However, the deviation in the plot of observed versus population-predicted concentrations is very small and not significant. Fitting a simple regression line to the data with the intercept fixed to zero gives an estimate of the slope of 1.068, which suggests that the data are generally evenly distributed around the line of identity. For the population concentration, individual predictions for data below the limit of quantification were not overlaid on this plot. There were several observations below the limit of quantification at approximately 25 hours post-dose. However, as the model only included a population estimate of the baseline concentration, all predictions would asymptotically approach this prediction of the baseline value, with no predictions falling below the 10th prediction interval, hence the values below the limit of quantification were not included in this figure. These values, taken together with the endogenous (baseline) component of the model, explain why the observations are only within or above the prediction interval. The overall model performance is acceptable over most of the dose interval. The only region where there appears to be some valid underestimation of concentrations is at, or near, the peak concentrations. However, the model did not include any variability in k_a or lag time (t_{lag}) which might explain the slight underprediction at approximately 2.5 hours post-dose.

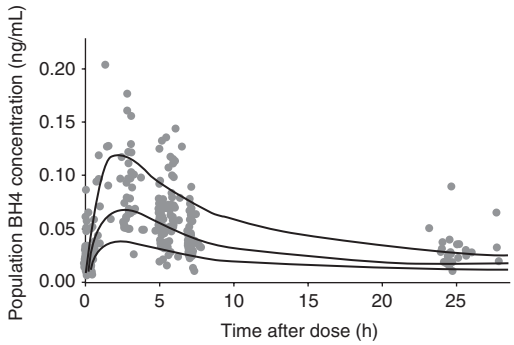

Fig. 3. Visual predictive check of the final covariate model. The points represent data observed. The upper, middle and lower lines indicate the 90th, 50th and 10th simulated percentiles, respectively. **BH_4** = tetrahydrobiopterin.

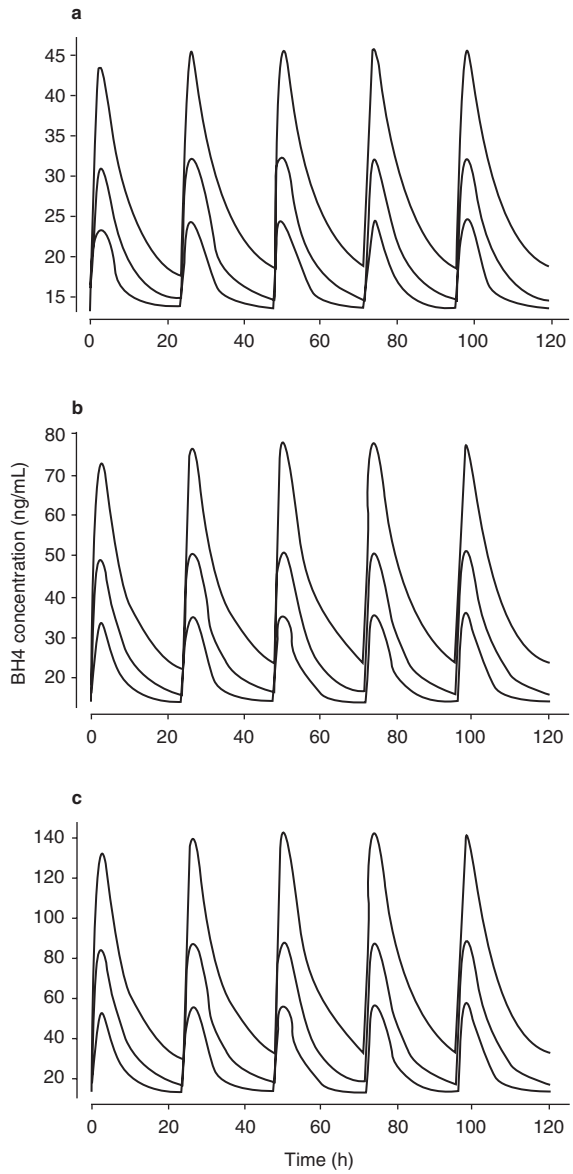

Fig. 4. Stochastic simulations of tetrahydrobiopterin (BH4) concentration-time profiles for five daily doses of sapropterin (**a**) 5 mg/kg; (**b**) 10 mg/kg; and (**c**) 20 mg/kg. The upper, middle and lower lines indicate the 90th, 50th and 10th simulated percentiles, respectively.

The estimated elimination phase half-life of BH4 was approximately 6–7 hours, which is consistent with that reported in previous studies of single oral doses of BH4.[10] Given that it takes

approximately 4–5 half-lives to clear >95% of a drug from the system, these findings support the once-daily dosing regimen for sapropterin in this population.[17] Furthermore, studies have indicated that the effect of a single dose of BH4 to suppress plasma phenylalanine concentrations in responsive patients with phenylketonuria is estimated to persist for at least 24 hours.[18,19] Importantly, stochastic simulations showed no evidence of accumulation with daily dosing, even at the highest dose evaluated (20 mg/kg/day).

Bodyweight was the only covariate found to significantly influence pharmacokinetic variability. When doses were adjusted for bodyweight, exposure was similar across a wide range of bodyweights. Serum creatinine had a small effect on BH4 pharmacokinetics, but this was not sufficiently large to warrant inclusion of serum creatinine as a covariate in the model. It should be noted, however, that only patients with normal renal function or mild renal impairment were included in this study.

Baseline phenylalanine concentrations were not found to be predictive of pharmacokinetic variability. However, caution is needed in interpreting this finding, as these concentrations can change rapidly in patients with phenylketonuria and are impacted upon by multiple factors. The timing of phenylalanine determinations relative to pharmacokinetic sampling was not known.

Conclusion

The results of this study show that BH4 concentrations in the peripheral circulation increase rapidly after oral administration of sapropterin and that the pharmacokinetics of sapropterin support once-daily administration at doses of 5–20 mg/kg.

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