SHORT REPORT

The effect of food and formulation on the population pharmacokinetics of cholesteryl ester transferase protein inhibitor DRL-17822 in healthy male volunteers

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We aimed to characterise the population pharmacokinetics of cholesteryl ester transferase protein inhibitor DRL-17822 in healthy males and explore the effect of food and formulation on the oral absorption of DRL-17822 in 4 phase I studies. DRL-17822 was dosed orally (2–1000 mg) in 2 different drug formulations (nanocrystal formulation and amorphous solid dispersion formulation) after either an overnight fast, or a low-fat, continental or high-fat breakfast. A 2-compartment model with 6 transit absorption compartments best characterised the data. Additionally, a strong interaction of food and formulation on bioavailability was observed and parsimoniously characterised in the model by binning combinations of food state and formulation with similar bio-availabilities. The final model adequately characterised the pharmacokinetic data of DRL-17822 in healthy males including the complex interaction of food and drug formulation. The amorphous solid dispersion formulation has a lower food effect on bioavailability compared with the nanocrystal formulation.

KEYWORDS
cardiovascular, cholesteryl ester transferase protein inhibitor, food/drug interaction, population pharmacokinetics

1 | INTRODUCTION

The levels of high-density lipoprotein (HDL)-cholesterol are an inverse predictor for the risk of atherosclerotic cardiovascular disease.[1] It was therefore proposed that increase in HDL-cholesterol levels may be beneficial in the treatment of cardiovascular disease.[2] An effective method to increase plasma HDL-cholesterol is the inhibition of cholesteryl ester transferase protein (CETP), which promotes the transfer of cholesteryl esters from HDL to low-density lipoproteins (LDL) and very-low-density lipoproteins.[3] In addition to the HDL increasing effect, CETP inhibitors have been shown to reduce levels of LDL-cholesterol.[4]

DRL-17822 is a strongly lipophilic (log$P$ = 8.86) CETP inhibitor currently in clinical development, which has been well tolerated in healthy volunteers in single doses (2–1000 mg) and once daily dosing for 2 weeks (50–450 mg).[5,6] In the multiple dose study in healthy

volunteers, DRL-17822 increased levels of HDL-cholesterol (51– to 111%), and reduced levels of LDL-cholesterol (−25 to −56%).

During the phase I studies, large differences in exposure were observed when the nanocrystal formulation of DRL-17822 was administered orally after an overnight fast *vs* a standard high-fat or continental breakfast.[7] An amorphous solid dispersion oral formulation of DRL-17822 was therefore developed to reduce the effect of food, and compared with the nanocrystal formulation in a randomised open-label, 4-way cross-over trial.[7]

The wide range of tested doses combined with the complex interaction of food and drug formulation complicated the interpretation of the phase I pharmacokinetic (PK) data. Therefore, in this study, we used population PK modelling to analyse the data from all phase I studies of DRL-17822 in an integrated manner, so that the resulting model may support future studies.

2 | METHODS

2.1 | Clinical studies

Data from 4 phase I studies were analysed, which were all conducted according to the principles of the Declaration of Helsinki and the European guidelines on Good Clinical Practice. All subjects provided written informed consent, prior to study enrolment. Studies 1, 2 and 3 were approved by the independent Medical review and Ethics Committee STEG/METC (The Netherlands). Study 4 was approved by independent Medical Review and Ethics Committee BEBO (The Netherlands). All studies were performed under sponsor responsibility of Dr Reddy's Laboratories, which provided the quality controlled raw data. Study 1 was the first-in-human single-dose phase I study, Study 2 was a single-dose food interaction study, Study 3 was a 2-week once-daily multiple-dose study, and Study 4 (parts A and B) was a single-dose food and formulation interaction study. In all studies, DRL-17822 concentrations were measured using validated liquid chromatography–tandem mass spectrometry methods.[7] Analyses were performed in compliance with Good Laboratory Practice regulations. Subject demographics by study are shown in Table S1, and show no large differences between the populations. Table S2 gives an overview of the 4 studies included in this analysis, including the doses, formulations and food intake before dosing in each study.[5–7]

2.2 | PK model development

Model development was performed in NONMEM version 7.2 using a first-order conditional estimation with interaction method.[8] Data below the limit of quantitation were excluded (8.4% of total data points).[9] A systematic, stepwise approach was used to develop the model. First, 2- and 3-compartment models were explored with various absorption submodels: (i) first-order absorption; (ii) first-order absorption with absorption lag time and (iii) first-order absorption through a series of empirical transit compartments (models with

What is already known about the subject

- DRL-17822 is a novel cholesteryl ester transferase protein inhibitor, currently in clinical development.
- DRL-17822 is well tolerated and increases high-density lipoprotein-cholesterol levels, while decreasing low-density lipoprotein-cholesterol levels.
- Like several other cholesteryl ester transferase protein inhibitors, DRL-17822's oral absorption is influenced by food intake.

What this study adds

- A 2-compartment model with transit compartment absorption adequately characterises the pharmacokinetics of DRL-17822 in healthy males.
- Quantified the complex interaction of food and formulation on the oral absorption (rate and extent) of DRL-17822 using modelling.
- An oral amorphous solid dispersion formulation of DRL-17822 showed a lower food effect on bioavailability, compared with the nanocrystal formulation.

increasing number of transit compartments were tested). The effect of food and formulation on relative bioavailability was modelled by pooling the 7 possible combinations of food before dose and formulation in an optimal number of bins. The bioavailability was parameterised as relative to the food+formulation bin with the highest bioavailability ($F_{reference}$, fixed to 1.0). The base model started with 2 bins, 1 for all fasted doses and 1 for all doses after food. Both inter-individual (IIV) and interoccasion (IOV) variability were assumed to be log-normally distributed. The use of additive, proportional and combined residual error models were explored. Covariates (age, body weight, height and body mass index [BMI] that showed a Pearson's correlation ($R^2 > 0.5$) with the individual *posthoc* parameter estimates were formally tested during model development using a forward inclusion ($P < .05$) and backwards elimination ($P < .01$) procedure. Nested models were compared with the likelihood ratio test to determine whether the more complex model resulted in a significant ($P < .05$) improvement in model fit.

2.3 | Model evaluation

Models were assessed based on the relative standard error (RSE) of parameter estimates and several diagnostic plots: (i) observed and predicted concentrations *vs* time; (ii) observed concentrations *vs* population predicted concentration (PRED); (iii) observed concentrations *vs* individual predicted concentrations (IPRED); (iv) conditional

weighted residuals with interaction (CWRESI) *vs* PRED; and (v) CWRESI *vs* time.[10,11] A prediction-corrected visual predictive check (VPC) was performed to evaluate potential misspecification in the final model.[12]

2.4 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

3 | RESULTS

3.1 | PK model description

A total of 2816 DRL-17822 plasma concentrations in 95 subjects were available for analysis. After a stepwise development (Table S3), the final PK model for DRL-17822 is parameterised in terms of relative bioavailability (F), absorption rate constant (k_a), apparent volume of the central compartment (V_c), apparent volume of the peripheral compartment (V_p), intercompartmental clearance ($Q_{c/p}$) and first-order elimination rate constant (k_{el}). Parameter estimates are reported in Table 1, and final model code can be found in the Supplemental Material. A 3-compartment model did not improve the model fit and resulted in overparameterisation of the model and was thus not taken forward in the model development. An empirical absorption model

with 6 transit compartments between the dosing and central compartment was used, as it resulted in the lowest Akaike information criterion among the tested absorption models.

The best PK model for DRL-17822 consisted of 4 bins to characterise the interaction of food and formulation on relative bioavailability ($F_{reference}$, F_{medium}, $F_{medium-low}$, F_{low}). Adding a fifth bin did not result in improved model fit. This resulted in $F_{reference}$ (F = 1) being represented by the nanocrystal formulation after a high-fat or continental breakfast. F_{medium} represents the relative bioavailability (relative to $F_{reference}$) of the amorphous solid dispersion formulation after a low- or high-fat breakfast and the nanocrystal formulation after a low-fat breakfast. $F_{medium-low}$ represents the relative bioavailability of the amorphous solid dispersion formulation in fasted state. The lowest relative bioavailability, F_{low} represents the nanocrystal formulation in fasted state.

For the nanocrystal formulation of DRL-17822, a high-fat or continental breakfast before drug administration results in an 18-fold increase in bioavailability ($F_{reference}$), compared with a fasted state (F_{low}). This food effect appears to be dependent on the type of breakfast, as the bioavailability after a low-fat breakfast is 2-fold lower (F_{medium}) than after a high-fat or continental breakfast. The amorphous solid dispersion formulation lowers the food effect on bioavailability, for which the difference between fasted ($F_{medium-low}$) and high-fat breakfast (F_{medium}) dosing is 3.5-fold. Additionally, no difference in bioavailability of the amorphous solid dispersion formulation could be identified between a high-fat and low-fat breakfast (both in F_{medium}-bin).

A significantly lower k_a was identified for the amorphous solid dispersion formulation of DRL-17822 after a high-fat breakfast

TABLE 1 Parameter estimates and uncertainties of pharmacokinetic model

Parameter	Estimate [RSE%]	IIV (CV%)[a] [RSE%]	IOV (CV%) [RSE%]
k_a (h^{-1})	1.74 [2.5]	25.4 [16.3]	20.9 [16.2]
V_c (L)	86.7 [6.7]	26.7 [27.8]	
k_{el} (h^{-1})	0.100 [3.1]	23.8 [26.4]	
V_p (L)	599 [6.7]		
$Q_{c/p}$ (L/h)	5.11 [6.3]		
$F_{reference}$	1.0 [fixed]	69.2 [27.6]	44.8 [13.7]
F_{medium}	0.532 [3.2]	As $F_{reference}$	As $F_{reference}$
$F_{medium-low}$	0.151 [10.7]	As $F_{reference}$	As $F_{reference}$
F_{low}	0.056 [8.7]	As $F_{reference}$	As $F_{reference}$
COV$_{BMI, Vc}$	0.041 [16.3]		
$k_{a,asd,HF}$	0.599 [11.2]		
Cor. IIV V_c-k_a	0.707 [28.7]		
Cor. IIV F-k_a	−0.280 [35.7]		
Cor. IOV F-k_a	−0.089 [36.4]		
Proportional error (σ^2)	0.114 [4.8]		

[a]CV%, coefficient of variation, calculated as: $\sqrt{(e^{\omega^2} - 1)}$.

COV$_{BMI, VC}$, covariate effect of BMI on V_C; Cor., correlation; HF, high-fat; IIV, interindividual variability; IOV, interoccasion variability; $k_{a,asd,HF}$, fraction of k_a for the amorphous solid dispersion formulation after a high-fat breakfast; RSE, relative standard error.
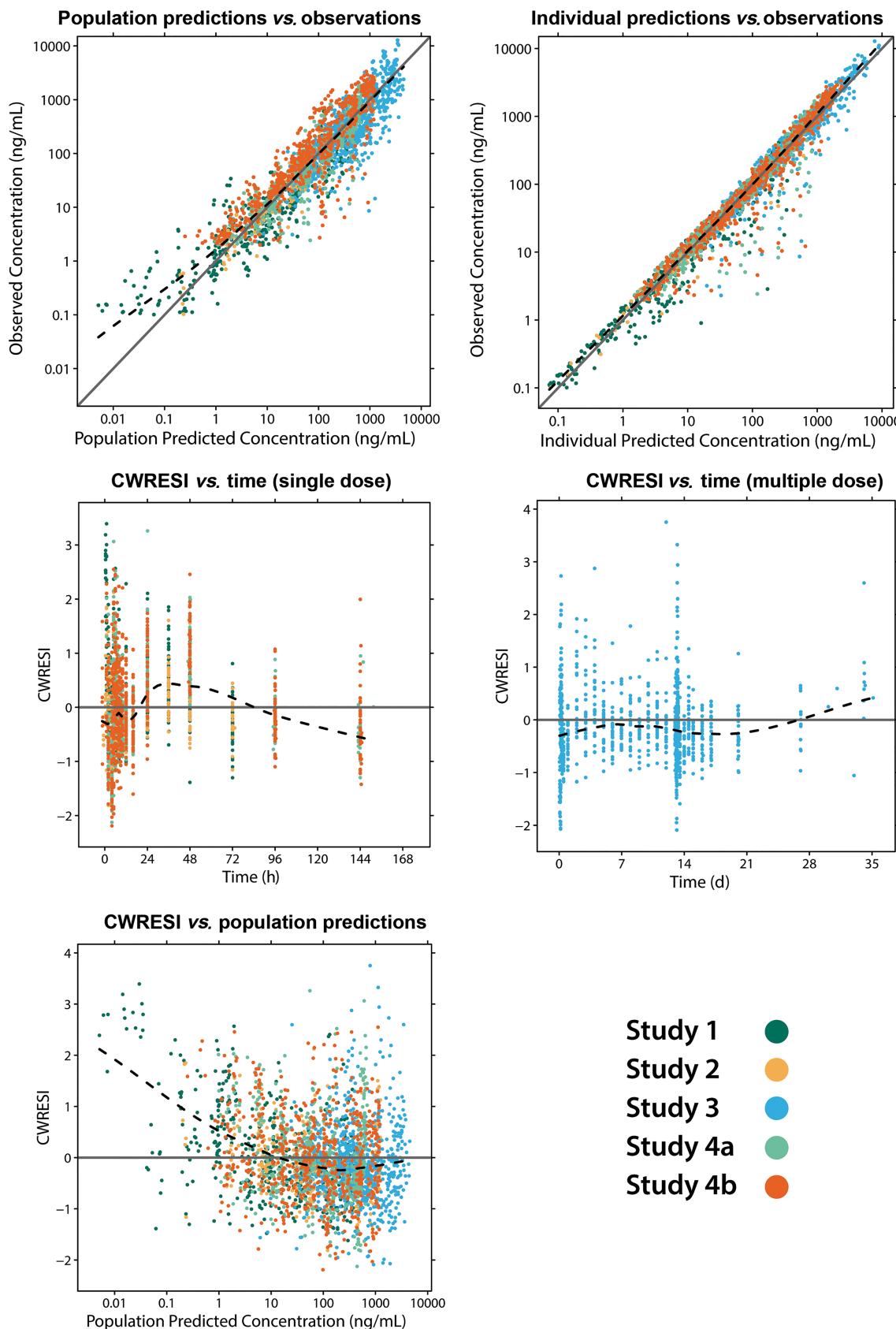
FIGURE 1 Goodness-of-fit plots. Line of unity (straight grey line) and a LOESS smoother curves (dashed black line) are shown to aid interpretation. The conditional weighted residuals (CWRESI) over time plot is shown separately for the single dose studies (studies 1, 2 and 4) and the multiple dose study (study 3). The lower limit of quantification of the pharmacokinetic assay ranged from 0.1 to 20 ng/mL among the different studies (see Table S2 for more details)
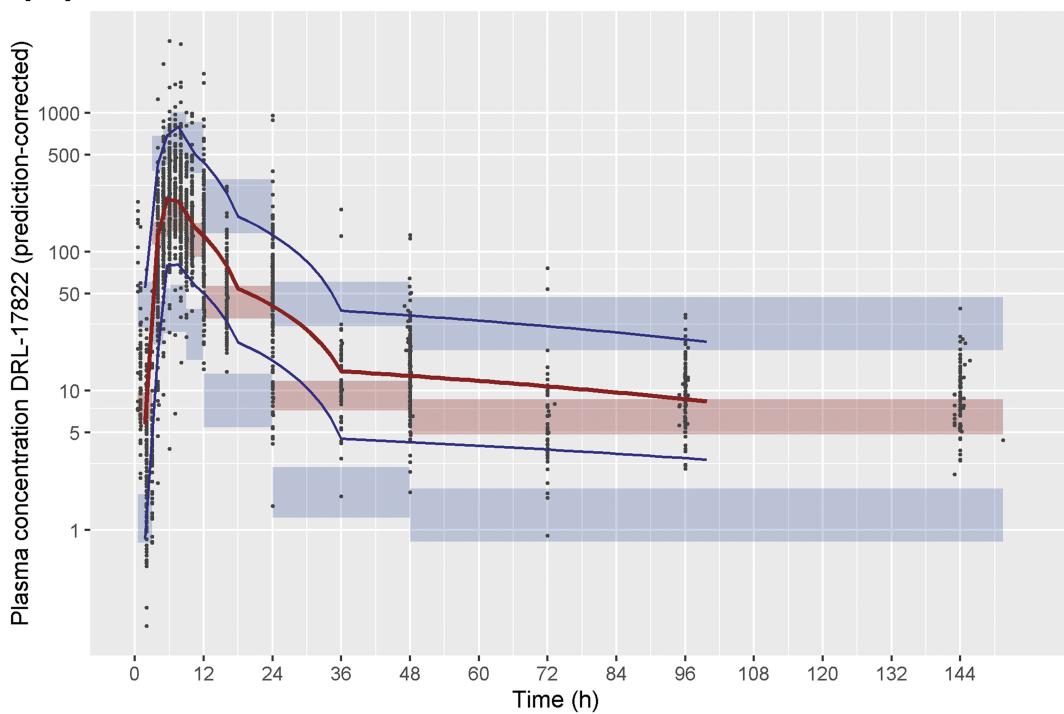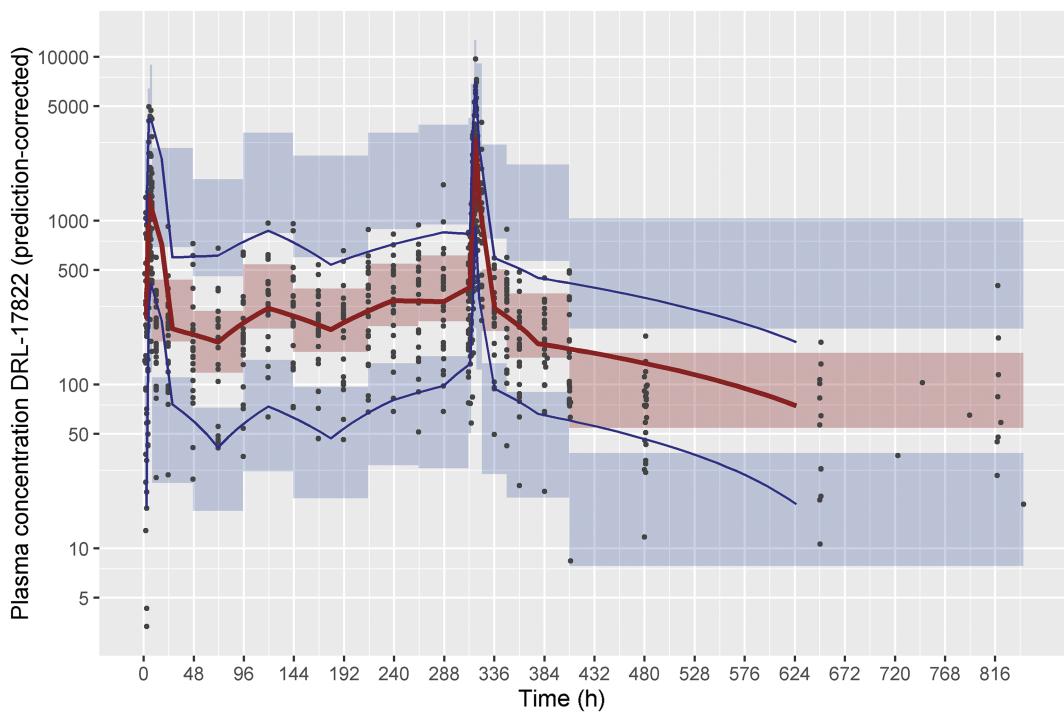
FIGURE 2 Prediction-corrected visual predictive check (1000 samples) of the single (A) and multiple dose (B) studies using the final parameter estimates (Table 1). Observations are shown as solid circles. The median of the binned observations is shown as a red solid line, while the 5 and 95% percentiles are shown as a blue solid line. The 90% confidence interval of the simulated median, and the 5 and 95% percentile are depicted with red and blue shaded rectangles

(difference in objective function value, ΔOFV = −62.04, $P < 10^{-14}$), parameterised as fraction of the population k_a ($k_{a,asd,HF}$). The same degree of IIV and IOV of k_a was estimated for all food +formulation bins.

IIV was identified for F, k_a, V_c and k_{el}. IOV on F and k_a significantly improved the individual fit of the data and was therefore included in the model. Individual BMI explained part of the IIV of the V_c (ΔOFV = −12.23, $P < .001$), and was therefore included in the final model. Correlations were identified between 3 pairs of variability: (i) IIV of V_c and k_a; (ii) IIV of F and k_a; (iii) IOV of F and k_a.

3.2 | PK model evaluation

The goodness-of-fit was graphically assessed (Figure 1). Above the lowest lower limit of quantification (0.1 ng/mL), there is no clear bias in plots of the population or individual predictions *vs* the observations. Some time-dependent bias can be observed in the CWRESI of the single-dose studies (underprediction of concentrations at 24–48 hours after dose). This bias is largely absent in the multiple dose study, although there appears to be an underprediction of DRL-17822 concentrations at 3 weeks after the last dose. A minor bias was observed in the CWRESI of population predictions below 0.1 ng/mL (the limit of quantification of Study 1). The prediction-corrected VPC (Figure 2) indicates that the data are, overall, well characterised by the model. However, just like the CWRESI over time plot, there is some bias towards underprediction of concentrations in the single dose studies between 24–48 hours after dose. Additionally, the observed 95% percentile is below the 90% confidence interval of the simulated 95% percentile in several of the bins in the multiple dose study (Figure 2b). The observed 5% percentile is above the 90% confidence interval of the simulated 5% percentile in most of the bins of the single dose study (Figure 2a).

4 | DISCUSSION

The population pharmacokinetics of DRL-17822 were best characterised with a 2-compartment model, and with 6 transit compartments to empirically describe the complex time-course of oral absorption. Additionally, we quantified the interaction of food and formulation on the pharmacokinetics of DRL-17822, a poorly soluble, highly lipophilic CETP inhibitor. While both formulations show an influence of food or fat content on the bioavailability of DRL-17822, this effect is larger in the nanocrystal formulation than with the amorphous solid dispersion formulation. This reduced impact of food on the absorption of the amorphous solid dispersion has been suggested to originate from the solubility-enhancing effect of the water-insoluble polymers in this formulation.[7]

We identified BMI as a covariate on the V_c, with an estimated 4.1% increase in V_c per point increase BMI, which might be explained by high lipophilicity of DRL-17822. Future studies should assess whether the DRL-17822 pharmacokinetics are similar for subjects with BMI values above 30 kg/m^2, women and patients, as only healthy male volunteers with BMI values between 18.8–29.9 kg/m^2 were included in this study.

The diagnostics (Figures 1 and 2) reveal some misspecifications of the model that could not be resolved during model development, especially in single dose studies after 24 hours or more after dose. However, the multiple-dose data are better characterised, and since DRI-17822 is expected to be chronically dosed once daily, the model is likely fit-for-purpose. In the prediction-corrected VPC, there is over-prediction of the 95% percentile of the multiple dose study (Figure 2). This suggests that the IIV of DRL-17822's bioavailability did not perfectly follow a log-normal distribution. However, the use of semi-parametric distribution with estimated shape parameters did not solve this issue.[13] The limitations of the model should be taken into account when using the model for simulations.

Although research on the therapeutic window of DRL-17822 in patient populations is ongoing, the effect of food on oral absorption can have potential impact on the compounds effect and safety in the patient population. For further clinical studies with DRL-17822, the selection of drug intake instructions (with or without food) might be just as important as the dose. The timing of the dose (morning or at night) could also affect patient compliance with these instructions, depending on their usual breakfast routine. Patient compliance with drug intake instructions will be likely to affect DRL-17822 exposure, and possibly also its safety and efficacy profile. The reduced food effect of the amorphous solid dispersion is therefore a beneficial trait.

In conclusion, we developed a population PK model for DRL-17822, a novel CETP inhibitor. The model adequately characterises the pharmacokinetics of DRL-17822 and quantifies the impact of a potentially clinically significant interaction between food and oral drug formulation on absorption. The model can serve as a starting point for a PK model in the patient population or for PK-PD models. Additionally, simulations with the model can guide design of future clinical trials. The impact of patient compliance with drug intake instructions—which could be relevant for clinical outcomes due to the strong food effect—should also be considered in such simulations.

CONTRIBUTORS

S.C.G. and J.S. performed the population pharmacokinetic analyses and interpreted the data. A.C.K. and I.M.C.K. designed the study, acquired the data/executed the clinical study 4, and interpreted the data. J.B., A.G. and S.A. designed the study and interpreted the data.

All authors were involved in drafting and reviewing the manuscript and approved the final version.

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