Population Pharmacokinetic Analyses of Brilacidin Using Data from Healthy Subjects and Patients with Acute Bacterial Skin and Skin Structure Infections

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ABSTRACT

Objectives: Brilacidin (BRI), a small synthetic mimic of host defense proteins with activity against Gram-positive organisms including methicillin-resistant *Staphylococcus aureus*, is currently being developed for the treatment of patients with acute bacterial skin and skin structure infections (ABSSSI). The objectives of this analysis were to update a previously-developed population pharmacokinetic (PPK) model for BRI using pooled data from Phase 1 and Phase 2 studies and to characterize inter-individual and intra-individual variability in the pharmacokinetics (PK) and the influence of subject descriptors on PK.
Methods: The data utilized for this analysis were obtained from three Phase 1 studies, designed to evaluate the safety, tolerability, and PK of single or multiple-dose BRI regimens in healthy subjects, and one Phase 2 study designed to assess the efficacy and safety of BRI in patients with ABSSSI. The final pooled PK analysis dataset consisted of 1582 concentrations from 75 healthy subjects and 773 concentrations from 153 patients with ABSSSI. Intravenously administered doses ranged from 0.016 to 2.5 mg/kg. After the base model was updated, covariate analysis was conducted using forward selection followed by backward elimination. Subject demographics, laboratory tests, and disease characteristics were evaluated for their ability to describe the inter-individual variability in BRI PK parameters. The appropriateness of the structural and variance models was assessed throughout and refined as necessary. The final model was qualified using a prediction-corrected visual predictive check technique.
Results: The previously-developed 3-compartment model with zero-order infusion and first-order elimination was successfully applied to pooled BRI concentration-time data. The only significant covariate relationships for BRI were between body surface area and clearance and between sex and central volume of distribution. The visual predictive check supported the robustness of the final PPK model. Final model parameter estimates and associated precision are reported in Table 1 below.
Conclusions: A 3-compartment model with zero-order infusion and first-order elimination adequately described BRI PK. Given the predictive ability of the final PPK model, individual model predictions were deemed appropriate for subsequent pharmacokinetic-pharmacodynamic analyses of efficacy and safety using Phase 2 data from patients with ABSSSI and simulations of exposure to support BRI dose selection for future studies.

Table 1. BRI final PPK model parameter estimates and standard errors

Parameter	Population mean		Magnitude of interindividual variability (%CV)	
	Final estimate	%SEM	Final estimate	%SEM
CL (L/hr)	0.333	4.20	34.1	15.9
V_c (L)	5.21	7.10	55.1	16.6
V_{p1} (L)	2.46	6.10	NE	NA
Q_1 (L/h)	0.562	21.7	NE	NA
V_{p2} (L)	4.95	25.9	67.0	27.3
Q_2 (L/h)	0.083	17.3	165	17.7
Coefficient of power relationship between BSA and CL	1.10	17.1	NE	NA
Proportional shift in V_c for females	-0.289	24.4	NE	NA
Residual error (%CV)	14.9	10.1	NE	NA
Minimum value of the objective function = 32788.628				

CL: Systemic drug clearance (L/hr). V_c: Central volume of distribution (L). V_{p1}: First peripheral volume of distribution (L). V_{p2}: Second peripheral volume of distribution (L). Q_1: Inter-compartmental clearance between central and the first peripheral compartments (L/hr). Q_2: Inter-compartmental clearance between central and the second peripheral compartments (L/hr). BSA: body surface area. NE: Not evaluable. NA: Not applicable. %CV: coefficient of variation expressed as a percent. %SEM: Percent standard error of the mean.

INTRODUCTION/OBJECTIVES

- Brilacidin, a small synthetic mimic of host defense proteins with activity against Gram-positive organisms including methicillin-resistant *Staphylococcus aureus*, is currently being developed for the treatment of patients with acute bacterial skin and skin structure infections (ABSSSI).
- To date, three Phase 1 studies in healthy subjects and one Phase 2 study in patients with ABSSSI evaluating brilacidin have been completed.
- Results of previous population pharmacokinetic (PPK) analyses based on data from two of the Phase 1 and all three Phase 1 studies [1, 2] demonstrated that a linear three-compartment model with zero-order infusion and first-order elimination adequately described the individual brilacidin PK data.
- Given that the above-described PPK model did not consider the Phase 2 PK data, the objectives of this analysis were the following:
  - To refine the previously-developed PPK model for brilacidin using pooled data from three Phase 1 studies and one Phase 2 study; and
  - To characterize inter-individual and intra-individual variability in PK and the influence of subject descriptors on PK.

METHODS

Data

- Data for the analyses were obtained from three Phase 1 studies in healthy subjects (PMX63-101, PMX63-102, and PMX63-103) and one Phase 2 study (PMX63-203) in patients with ABSSSI.
  - PMX63-101 was a single ascending dose study.
  - PMX63-102 was a multiple-dose study.
  - PMX63-103 was a multiple-dose study of a front-loaded dosing regimen.
  - PMX63-203 was a multiple-dose study of three different front-loaded dosing regimens on Day 1 followed by 0.35 or 0.3 mg/kg QD for the next 4 days.
- Data preparation and presentation were conducted using SAS® V9.1.3.

Subject Demographic and Disease Characteristics

- Subject demographic and disease characteristics were used to describe the analysis population and evaluate their ability to explain a portion of the interindividual variability (IIV) in key PK parameters.
- Demographic information included age, weight, body surface area (BSA), and sex. Serum creatinine was used to calculate creatinine clearance (CLcr).

Population Pharmacokinetic Analysis

- A previously-developed three-compartment model with zero-order infusion and first-order elimination [1, 2] was applied to brilacidin concentration-time data and modified as necessary.
- IIV in PK parameters was initially modeled assuming log-normal distributions while residual variability was modeled using a proportional error model.
- All PPK analyses were conducted using NONMEM®, V7, Level 1.2.
- The first order conditional estimation method with the interaction option was implemented for all model development.
- Assessment of the goodness-of-fit of each NONMEM analysis included, but was not limited to, examination of the following:
  - Outcome (convergence) of the estimation and covariance routines;
  - Reasonableness and precision of the parameter estimates based upon the known PK of the compound;
  - Agreement in scatterplots of population and individual predicted versus measured concentrations; and
  - Lack of trend or pattern in scatterplots of the conditional weighted residuals and individual residuals over time and range of predictions (stratified and/or differentiated by dose level and significant covariates).

Covariate Analysis

- Following the identification of an appropriate base structural model, PPK covariate analysis was undertaken using stepwise forward selection procedure ($\alpha = 0.01$, one degree of freedom).
- The resulting full multivariable model was then refined by examining the post-hoc distribution of IIV, estimating IIV on other PK parameters, and testing other residual variability error structures.
- If more than two covariates were included in the full multivariable model, stepwise backward elimination was employed ($\alpha = 0.001$, one degree of freedom).

Final Model Evaluation/Qualification

- A prediction-corrected visual predictive check (pcVPC) was used to evaluate the ability of the model to describe the observed PK data.
- Summary measures of the distribution of predictions and observations were compared visually.

RESULTS

Data

- The final dataset contained 228 subjects and 2,355 plasma concentrations of which 1,582 samples were from 75 healthy subjects and 773 samples were from 153 patients with ABSSSI.
  - Less than 3% of the subjects contributed only one sample while approximately 7% contributed 27 samples from different sampling occasions.
  - Subjects received a wide range of brilacidin doses, 0.3 to 256.6 mg (0.016 to 2.5 mg/kg).

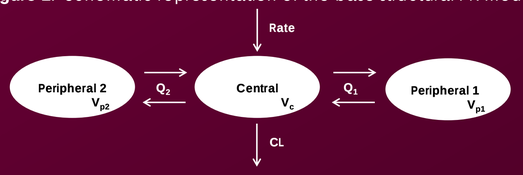
Subject Demographic and Disease Characteristics

- The analysis population was predominantly male (76.4%) with a wide range of renal function (CLcr 34.7 to 198 mL/min/1.73 m^2).
- Age, BSA, and weight ranged from 18 to 79 yrs, 1.34 to 2.37 m^2, and 42.0 to 118 kg, respectively.

Population Pharmacokinetic Analysis

- A three-compartment model with zero-order infusion and first-order elimination provided the most robust fit to the PK data. A schematic representation of the model structure is shown in **Figure 1**.

Figure 1. Schematic representation of the base structural PK model



- IIV in CL and Vc were estimated per a log-normal distribution while the residual error was modeled as a proportional error structure.
- Significant covariate relationships for brilacidin were identified between BSA and CL and between subject sex and Vc.
- Parameter estimates and standard errors for the final model are shown in **Table 1**.
  - As evidenced by low to moderate %SEM, parameters were estimated with high to moderate precision.
  - The residual variability was 14.9%, which indicated a low extent of unexplained residual variability in the model fit.
  - The magnitude of the IIV was relatively modest for CL and V_c. However, the magnitude of the IIV was relatively high for Q_2 and extremely high for V_{p2}.

Table 1. Final PPK model parameter estimates and standard errors

Parameter	Population mean		Magnitude of IIV (%CV)	
	Final estimate	%SEM	Final estimate	%SEM
CL (L/h)	0.333	4.20	34.1	15.9
V_c (L)	5.21	7.10	55.1	16.6
V_{p1} (L)	2.46	6.10	NE	NA
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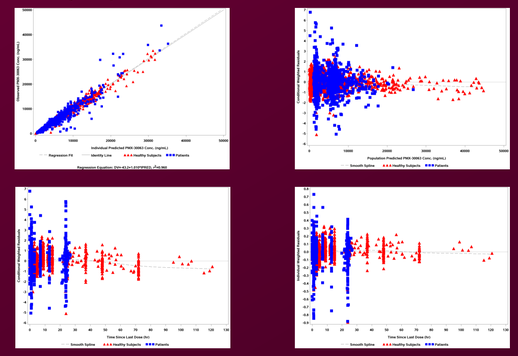
- **Figure 2** shows the goodness-of-fit plots for the final PPK model
  - Excellent agreement was obtained between observed and individual predicted concentrations.
  - No impressive trends or patterns for plots of residuals versus time or range of predicted values were evident, thus indicating lack of prediction bias.

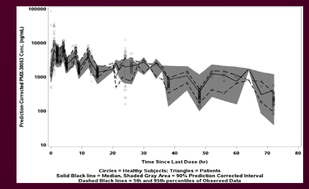
Figure 2. Goodness-of-fit plots for the final PPK model fit to pooled data from healthy subjects and patients with ABSSSI



Final Model Evaluation/Qualification

- A graphical display of the pcVPC for the final PPK model for brilacidin is provided in **Figure 3**.
  - Given that the majority of the prediction-corrected observed data were contained within the prediction-corrected prediction interval, this was indicative of negligible prediction bias in predicted concentrations.

Figure 3. pcVPC for the final PPK model for brilacidin in pooled data from healthy subjects and patients with ABSSSI



CONCLUSIONS

- The previously-developed three-compartment model with zero-order infusion and first-order elimination was successfully applied to pooled brilacidin concentration-time data from healthy subjects and patients with ABSSSI.
- Significant covariate relationships for brilacidin were identified between BSA and CL and between subject sex and Vc.
- The pcVPC supported the robustness of the final PPK model for brilacidin.
- Given the predictive ability of the final PPK model for brilacidin, individual model predictions were deemed appropriate for subsequent pharmacokinetic-pharmacokinetic analyses of efficacy and safety using data from patients in Study PMX63-203 [ECCMID 2013, P916].

REFERENCES

1. Melhem M *et al*. Population pharmacokinetics of PMX-30063 after single and multiple intravenous douses. ICAAC 2010 A1-025.
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