Population Pharmacokinetics of Brilacidin in Healthy Subjects and Patients with Acute Bacterial Skin and Skin-Structure Infections

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ABSTRACT

Background: Brilacidin (BRI), which acts by disrupting bacterial cell membrane integrity, has potent antimicrobial activity against Gram-positive and -negative organisms, including methicillin-resistant *Staphylococcus aureus*. Using data from three Phase 1 and two Phase 2 studies in acute bacterial skin and skin-structure infection (ABSSSI) patients (Studies 203 and 204), a population pharmacokinetic (PPK) model for BRI was developed to describe the time-course of BRI in plasma and to identify significant predictors of BRI PK.

Methods: The PPK analysis was conducted in NONMEM 7.2 using 2960 plasma BRI concentrations from 75 healthy subjects and 316 ABSSSI patients administered a single IV dose (0.016 to 10 mg/kg infused over 1 h) or various front-loaded multiple dosing regimens. Various structural PK models were evaluated. Covariates were then analyzed using stepwise forward selection and backward elimination (α=0.001).

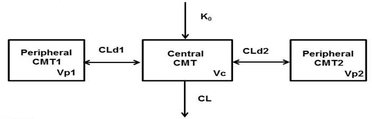
Results: A 3-compartment model with zero-order input and first-order elimination best described the plasma BRI PK data. Goodness-of-fit plots were unbiased with excellent agreement between the observed data and both the population predictions (r^2=0.75) and individual post-hoc predictions (r^2=0.94). Proportional residual variability was larger in ABSSSI patients (25.0% CV in Study 203; 18.2% CV in Study 204) relative to the Phase 1 studies (9.6% CV). The covariate analysis showed that males had a 21.5% faster clearance (CL) relative to females, and that body size (BSA or weight) was a significant predictor of the BRI volume of distribution (Vc) terms. ABSSSI patients had a substantially faster distribution CL than healthy subjects. Interestingly, patients in Study 204 had a larger Vc consistent with the slightly lower concentrations observed relative to Study 203. The median calculated alpha-, beta-, and gamma-phase half-lives were 1.4, 10.7, and 73.2 h, respectively. A prediction-corrected visual predictive check revealed no remaining biases between healthy subjects and ABSSSI patients.

Conclusions: A PPK model, developed using all BRI PK data collected to date, allowed for identification of significant covariate effects. Since CL did not appear to be weight-dependent, fixed BRI dosing may be an option. This model will be useful to generate individual PK exposures for the conduct of PK-PD analyses for safety and efficacy.

INTRODUCTION

- Brilacidin is a synthetic molecule that represents a novel class of antimicrobials agents that mimic the structure and function of host defense proteins.
- Brilacidin acts directly on the cell membrane, disrupting its integrity and causing bacterial death and has demonstrated potent antimicrobial activity against Gram-positive and Gram-negative organisms, including methicillin-resistant *Staphylococcus aureus*.
- Cellceutix Corporation is currently developing brilacidin for the treatment of patients with acute bacterial skin and skin structure infection (ABSSSI) caused by *S. aureus*.
- Plasma brilacidin concentrations exhibit a poly-exponential decline, with biliary clearance (CL), the predominant route of elimination and negligible (<1%) renal elimination or hepatic metabolism. The extent of fecal excretion of radiolabeled brilacidin was shown to be 40.2% in male rats and 25.5% in female rats suggesting sex-related differences in biliary CL [1].
- The pharmacokinetics (PK) of brilacidin have previously been studied in healthy subjects in three Phase 1 studies (Studies PMX63-101, PMX63-102, and PMX63-103) and patients with ABSSSI from a Phase 2 study (StudyPMX63-203) [2].
  - A linear three-compartment model with zero-order intravenous (IV) input and first-order elimination (**Figure 1**) was previously developed by ICPD to describe brilacidin PK.

Figure 1. Structural population PK model for brilacidin



Where:
K_0: Constant zero-order rate of drug infusion into plasma (mg/hr)
CL: Systemic drug clearance (L/hr)
Vc: Central volume of distribution (L)
Vp1: First peripheral volume of distribution (L)
Vp2: Second peripheral volume of distribution (L)
CLd1: Distribution clearance between central and first peripheral CMT (L/hr)
CLd2: Distribution clearance between central and second peripheral CMT (L/hr)

OBJECTIVES

- The objectives of these analyses were the following:
  - To refine a previously-developed population PK model for brilacidin using pooled data from three Phase 1 studies (Studies PMX63-101, PMX63-102, and PMX63-103) and the Phase 2 Study, Study PMX63-203, after including additional data from patients with ABSSSI in Study CTIX-BRI-204; and
  - To conduct a covariate analysis to examine the impact of patient demographics and clinical laboratory and disease-related covariates on interindividual variability (IIV) for brilacidin PK.

METHODS

Data

- Data for these analyses were obtained from 75 intensively-sampled healthy subjects in three Phase 1 studies (PMX63-101, PMX63-102, and PMX63-103) and 316 sparsely-sampled patients with ABSSSI in two Phase 2 studies (PMX63-203 and CTIX-BRI-204) where IV brilacidin was infused over 1 hour as a single dose or as repeated doses either every 24 (q24h) or 48 hours (q48h):
  - PMX63-101 (N=19) was a single ascending dose (0.016 to 10 mg/kg) study.
  - PMX63-102 (N=40) was a multiple-dose (0.1 or 0.2 mg/kg q48h, or 0.1 to 0.7 mg/kg q24h, for a total of 5 doses) study.
  - PMX63-103 (N=16) was a multiple-dose study evaluating a front-loaded dosing regimen (1 mg/kg on Day 1 and 0.35 mg/kg q24h on Days 2 to 14).
  - PMX63-203 (N=157) evaluated different front-loaded dosing regimens consisting of 0.75 or 1 mg/kg followed by 0.35 mg/kg q24h for 4 days, or 0.4 mg/kg followed by 0.3 mg/kg q24h for 4 days.
  - CTIX-BRI-204 (N=159) evaluated a single-dose of either 0.6 or 0.8 mg/kg, and a front-loaded dosing regimen (0.6 mg/kg) followed by 0.3 mg/kg q24h on Days 2 and 3.
- Subject demographics (sex, age, body weight, height, body mass index and body surface area [BSA]), estimated creatinine clearance (CLcr) normalized to a BSA of 1.73 m^2, patient status (healthy subjects vs. ABSSSI patients) and study were evaluated to explain a portion of the IIV (ω^2) in key PK parameters.

Population PK Analysis

- The PK analysis was conducted using NONMEM® software Version 7.2 implementing the first-order conditional estimation method with interaction.
  - A previously-developed three-compartment model with zero-order IV input and first-order elimination [2] was re-fit to the pooled brilacidin concentration-time data across studies. A two-compartment model was also evaluated for comparison purposes.
  - ω^2 for each PK parameter was initially modeled assuming log-normal distributions while residual variability (σ^2) was modeled separately by population using a proportional error model.
  - Model fit was assessed using standard statistical and graphical goodness-of-fit (GOF) criteria and the population PK model was refined as necessary.
  - Following selection of an appropriate structural population PK model for brilacidin, a formal covariate analysis was undertaken using stepwise forward selection (α=0.001) followed by stepwise backward elimination (α=0.001) procedures.
  - The final population PK model, including all statistically significant covariate effects, was qualified through evaluation of the distribution of normalized prediction distribution errors (NPDE) and by performing a prediction-corrected visual predictive check (PC-VPC).

RESULTS

Data Description

- A total of 2,960 plasma brilacidin concentrations collected from 391 individuals were used to construct the population PK model.
- The PK analysis population was 73.2% male and had a median (min, max) weight of 78.0 (42.0, 145) kg, age of 40.0 (18, 79) years, BSA of 1.91 (1.34, 2.56) m^2, and CLcr of 97.3 (21.0, 190) mL/min/1.73 m^2.

Population PK Analysis

- A three-compartment model with zero-order input and first-order elimination best described brilacidin PK in both healthy subjects and patients with ABSSSI.
- The final population PK model parameter estimates and associated standard errors are provided in **Table 1** and selected GOF plots stratified by study are shown in **Figure 2**.
  - The observed brilacidin concentrations were in good agreement with both the population predicted concentrations (r^2=0.75) and individual post-hoc predicted concentrations (r^2=0.94) and did not exhibit any noticeable biases. Plots of the conditional weighted residuals also did not show any biases with respect to time since last dose, study, or brilacidin dose.
  - Residual variability was described using a constant coefficient of variation (CCV) error model and was estimated to be significantly larger in Study PMX63-203 (25.0% CV) and Study CTIX-BRI-204 (18.2% CV) relative to the well-controlled Phase 1 studies (9.58% CV).

RESULTS

- The covariate analysis indicated the following:
  - Males had a 21.5% faster brilacidin CL relative to females throughout the entire range of each body size measure; however, it cannot be completely ruled out that CL is not related to body size given the co-linearity between sex and body size.
  - Body size was a significant predictor of both Vc (BSA) and Vp1 (body weight).
  - Patients with ABSSSI had a faster CLd2 than healthy subjects, which may be an artifact of sparse PK sampling.
  - Patients with ABSSSI in Study CTIX-BRI-204 also had a 23.1% larger Vc than both healthy Phase 1 subjects and patients with ABSSSI in Study PMX63-203. After including these patient covariate effects, the model adequately described the data from Study CTIX-BRI-204 (**Figure 3**).
- Individual post-hoc parameters were used to calculate the alpha-, beta-, and gamma-phase half-lives ($T_{1/2,\alpha}$, $T_{1/2,\beta}$, and $T_{1/2,\gamma}$, respectively). The median (5th to 95th percentiles) $T_{1/2,\alpha}$ was 1.4 (0.9 to 2.1) h, $T_{1/2,\beta}$ was 10.7 (7.1 to 18.6) h, and $T_{1/2,\gamma}$, was 73.2 (34.5 to 410) h.
- A PC-VPC (**Figure 4**) and a histogram of the NPDE stratified by population, demonstrated that the model provided an adequate description of both the fixed and random effects and there were no remaining biases with respect to healthy subjects and patients with ABSSSI.
- Lack of a substantial relationship between brilacidin CL and body weight in this analysis suggests that capping weight-based dosing for patients ≥90 kg, or using fixed dosing, will provide a more consistent area under the concentration-time curve (AUC) range, as shown for patients administered 0.6 mg/kg in **Figure 5**.

Figure 2. Selected GOF plots for the final population PK model fit to data from healthy subjects and patients with ABSSSI

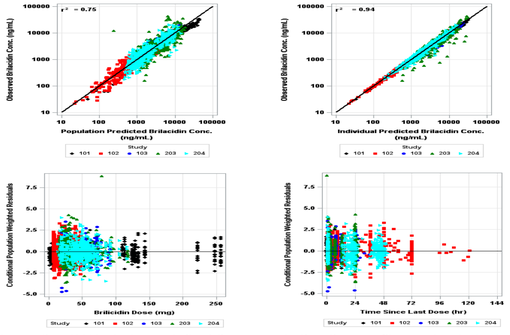
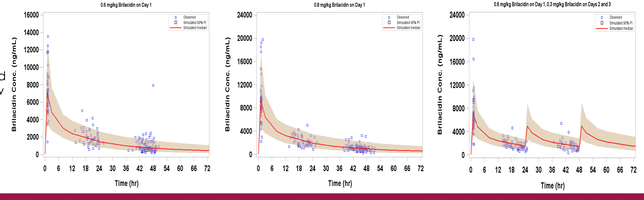


Figure 3. Median (90% PI) plasma brilacidin concentration-time profile constructed using Monte Carlo simulation and the final population PK model overlaid upon observed data from patients with ABSSSI in Study CTIX-BRI-204



RESULTS

Table 1. Final population PK model parameter estimates and associated precision (%SEM)

Parameter	Final estimate	%SEM
CL (L/h)		
Females	0.279	5.42
Proportional increase for males	0.215	28.0
Vc (L)		
Coefficient (Vc at a median BSA of 1.91 m^2)	4.91	3.76
Power term for Vc-BSA relationship	0.805	26.0
Proportional increase for Study CTIX-BRI-204 ABSSSI patients	0.231	24.1
Vp1 (L)		
Coefficient (Vp1 at a median weight of 78 kg)	3.32	4.45
Power term for Vp1-weight relationship	0.892	26.9
CLd1 (L/h)	0.889	6.15
Vp2 (L)	9.92	15.3
CLd2 (L/h)		
Healthy Phase 1 subjects	0.0310	13.8
Proportional increase for ABSSSI patients	5.77	19.0
ω^2 for CL	0.123 (35.0% CV)	9.99
ω^2 for Vc	0.180 (42.4% CV)	4.87
ω^2 for Vp1	0.094 (30.7% CV)	30.7
ω^2 for CLd1	0.140 (37.4% CV)	24.0
ω^2 for Vp2	1.33 (115% CV)	21.3
ω^2 for CLd2	0.149 (38.6% CV)	60.7
Covariance between CL and Vc	0.123 (r^2=0.681)	7.80
Residual error (σ^2)		
Healthy Phase 1 subjects	0.00918 (9.58% CV)	1.72
Study CTIX-BRI-204 ABSSSI patients	0.0332 (18.2% CV)	7.95
Study PMX63-203 ABSSSI patients	0.0626 (25.0% CV)	4.87

Figure 4. PC-VPC using the final population PK model for brilacidin

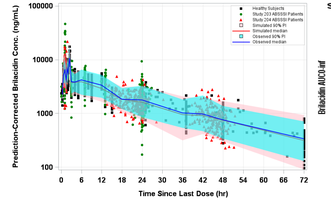
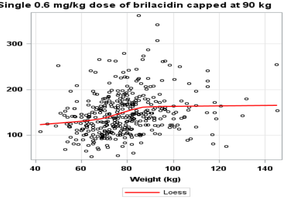


Figure 5. Relationship between brilacidin $AUC_{0\text{-}inf}$ (mg•h/L) and weight



CONCLUSIONS

- A three-compartment model with zero-order input and first-order elimination best described the plasma brilacidin concentration-time profile in both healthy subjects and patients with ABSSSI.
- The most statistically significant parameter-covariate relationship identified was the impact of sex on brilacidin CL, for which the 21.5% faster CL in males was of marginal clinical significance, while as expected, body size was predictive of the overall Vc.
- Lack of a substantial relationship between brilacidin CL and body weight in this analysis suggests that capping weight-based dosing for patients ≥90 kg, or using fixed dosing, is expected to help ensure brilacidin AUC are maintained within a safe and effective window.

REFERENCES

1. Data on file, Cellceutix Corporation.
2. Melhem M, Rubino CM, Bhavnani SM, Forrest A, Reynolds DK, Jorgensen D, Korczak B, Ambrose PG. Population pharmacokinetic analyses of brilacidin using data from healthy subjects and patients with acute bacterial skin and skin structure infections. 52nd European Congress of Clinical Microbiology and Infectious Diseases. Berlin, Germany. April 27-30, 2013. [Abstract No. P 917].

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