Pharmacokinetic-Pharmacodynamic Analyses for Efficacy and Safety of Brilacidin Using Data From Patients with Acute Bacterial Skin and Skin Structure Infections

S.M. Bhavnani[1], J.P. Hammel[1], A. Forrest[1], M. Melhem[1], P. Sager[2], D. Jorgensen[3], P.G. Ambrose[1]

[1]ICPD, Latham, NY, [2]Scientific Programs Committee, Cardiac Safety Research, San Francisco, CA; [3]PolyMedix, Inc., Radnor, PA.

Sujata M. Bhavnani, Pharm.D., M.S.
Institute for Clinical Pharmacodynamics
43 British American Blvd.
Latham, NY 12110
Telephone: (518) 429-2600
E-mail: SBhavnani@icpd.com

ABSTRACT

Background: 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 infection (ABSSSI). Using Phase 2 data from BRI-treated patients with ABSSSI caused by *S. aureus*, the objective of these analyses was to characterize pharmacokinetic-pharmacodynamic (PK-PD) relationships for efficacy and safety.
Methods: PK-PD relationships for efficacy and safety endpoints were explored using clinical and PK data from patients in the per protocol (PP) and intent-to-treat (ITT) populations who received 1 of 3 BRI IV dosing regimens, 0.75, 0.4, and 1.0 mg/kg on Day 1 followed by 0.35, 0.3, 0.35 mg/kg Q24h for Days 2-5, respectively. Univariable relationships between AUC:MIC ratio and dichotomous efficacy endpoints, clinical and microbiological response at end-of-therapy (EOT; Day 7-8) and test-of-cure (TOC; Day 10-14), and change in area of erythema/induration on Days 1-6, were examined using Chi-square or Fisher's exact tests for categorical independent variables and logistic regression for continuous independent variables. Relationships between AUC:MIC ratio and time to cessation of spread or reduction from baseline in the area of erythema/induration were examined using log rank tests for categorical variables and Cox regression for continuous variables. Repeated measures multivariable logistic regression analyses evaluating relationships between change from baseline in systolic blood pressure (SBP) ≥20 and ≥35 mm Hg or SBP ≥160 mmHg and independent variables, including AUC in the previous dosing interval, observation time point (pre-dose, end of infusion, and 3 hours post-dosing), treatment day, and baseline SBP, were performed.
Results: 108 PP and 158 ITT patients were evaluable for efficacy and SBP endpoints, respectively. Statistically significant univariable relationships for efficacy were identified when AUC:MIC ratio was evaluated as a two-group variable (see Table 1). Increased AUC (p<0.001), increased days of treatment (p<0.001), and lower baseline SBP (p=0.001) were significantly associated with change from baseline in SBP ≥20 mmHg. Only increased AUC was statistically associated with change from baseline in SBP ≥35 and SBP ≥160 mmHg (p<0.001 for both).
Conclusions: Statistically significant PK-PD relationships for efficacy and safety of BRI were identified. Such data will be useful to support BRI dose selection for future studies in patients with ABSSSI.

Table 1. Summary of univariable PK-PD relationships for dichotomous efficacy endpoints

Efficacy endpoint	Magnitude of BRI AUC:MIC ratio associated with efficacy	Percentage of patients achieving the efficacy endpoint		p-value
		≥AUC:MIC ratio[b] (n/N)	<AUC:MIC ratio[b] (n/N)	
Clinical response at EOT	60	96.9 (94/97)	80 (8/10)	0.07
Clinical response at TOC	60	95.9 (93/97)	80 (8/10)	0.1
≥ 20% reduction from baseline in the area of erythema/induration on Day 2[a]	125	79.4 (54/68)	60 (24/40)	0.03

a. Represents an efficacy endpoint advocated by the US FDA. The magnitude of the AUC:MIC ratio associated with earlier time-to-event for this efficacy endpoint was closely similar to those required to achieve lower or higher thresholds for percent reductions in the area of erythema/induration.
b. Based on total-drug AUC:MIC ratio evaluated as a two-group variable. AUC represents total-drug $AUC_{0\text{-}48}$ divided by 2.

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 infection (ABSSSI).
- To date, three Phase 1 studies in healthy subjects and one Phase 2 study (Study PMX63-203) in patients with ABSSSI caused by *S. aureus* evaluating brilacidin have been completed.
- Results of population pharmacokinetic (PPK) analysis based on the above-described data resulted in a final model that demonstrated good predictive ability [ECCMID 2013, P917], thus providing appropriate individual predictions of exposure for patients from Study PMX63-203 for future pharmacokinetic-pharmacodynamic (PK-PD) analyses.
- Using data from Study PMX63-203 in which patients received three different front-loaded brilacidin dosing regimens, the objective of these analyses was to characterize PK-PD relationships for efficacy and safety.

METHODS

Study Design

- Patients in Study PMX63-203 were randomized to one of the following IV doses of brilacidin administered over 1 h:
  - 0.75 mg/kg on Day 1 followed by 0.35 mg/kg Q24h x 4 days;
  - 0.4 mg/kg on Day 1 followed by 0.30 mg/kg Q24h x 4 days; and
  - 1.0 mg/kg on Day 1 followed by 0.35 mg/kg Q24h x 4 days.
- Blood samples for PK evaluation were collected post-dose on Day 1, pre- and post-dose at early-treatment-assessment (ETA, Day 3), and Day 5.
- Lesion assessments were conducted daily during therapy, at end-of-therapy (EOT, Day 7/8), test-of-cure (TOC, Day 10-14), and at follow-up (Week 4).
- Blood pressure was measured at pre-dose, end of infusion, 3 h post-dose daily during therapy, and at EOT, TOC, and follow-up visits.

Determination of Exposure

- For the PK-PD analyses for efficacy, the PK-PD index of interest was AUC:MIC ratio which has been demonstrated to be most predictive of brilacidin efficacy based on pre-clinical data [Data on file, PolyMedix, Inc.]. AUC represented the average daily exposure based on the first 2 days of therapy and was calculated by taking the total-drug AUC from time zero to 48 h ($AUC_{0\text{-}48}$) divided by 2.
- For the PK-PD analyses for safety, daily between-dose total-drug AUC values were determined.
- AUC was determined using the final population PK model [ECCMID 2013, P917], dosing history, and post-hoc PK parameter estimates for each patient. A PK simulation was performed to generate individual total-drug plasma concentration-time profiles from 0 to 168 h post-first dose.
  - For PK-PD analyses of efficacy, $AUC_{0\text{-}48}$ was calculated by integrating the total-drug plasma concentration-time profile over 0 to 48 h.
  - For the PK-PD analyses of safety, the AUC from the administration of the previous dose to the administration of the dose on the day of the measurement of the safety endpoint was used to represent the between-dose AUC.

PK-PD Analyses for Efficacy

- Patients in the per-protocol population and for whom PK data were available were considered for the PK-PD analyses for efficacy.
- Efficacy endpoints evaluated included clinical and microbiological response at ETA, EOT, and TOC (dichotomous endpoints) and change in area of erythema/induration from baseline on Days 1-6, EOT, and TOC (dichotomous and time-to-event endpoints).
- Independent variables considered were AUC, MIC, and AUC:MIC ratio
- Univariable relationships for dichotomous efficacy endpoints were examined using Chi-square or Fisher's exact tests for categorical independent variables and logistic regression for continuous independent variables.
- Relationships for time to cessation of spread or reduction from baseline in area of erythema/induration were examined using log rank tests for categorical variables and Cox regression for continuous variables.
- Univariable analyses of other independent variables (e.g., demographic and underlying medical characteristics) and multivariable analyses were considered if statistically significant univariable relationships between efficacy endpoints and AUC:MIC ratio, AUC, and/or MIC were identified.

PK-PD Analyses for Safety

- Patients in the intent-to-treat population and for whom PK data were evaluated were considered for the PK-PD analyses for safety.
- The following dependent variables were evaluated:
  - Change in systolic blood pressure (SBP) from baseline of ≥20 mmHg;
  - Change in SBP from baseline of ≥35 mmHg; and
  - SBP ≥160 mmHg.
- Independent variables included the AUC in the previous dosing interval , treatment day, and baseline SBP.
- Repeated measures multiple logistic regression was carried out with generalized estimating equations to estimate model parameters.

RESULTS

Analysis Population

- 108 and 158 patients were included in the PK-PD analyses for efficacy and safety, respectively.
- Summary statistics for patients characteristics for the PK-PD dataset for efficacy and safety populations are shown in **Table 1**.

Table 1. Summary statistics for patient characteristics for the PK-PD analysis populations

Baseline characteristic	Mean (SD) or % (n/N)	
	Efficacy population	Safety population
Age (yr)	45.4 (16.0)	46.0 (16.5)
Ethnicity – Hispanic	0 (0/107)	0 (0/156)
Race		
White	98.2 (106/108)	98.1 (155/158)
Asian	1.85 (2/108)	1.90 (3/158)
Sex (male)	72.2 (78/108)	70.3 (111/158)
Weight (kg)	79.1 (14.9)	78.0 (14.5)
Prior antibacterial therapy	26.9 (29/108)	
Presence of diabetes	11.1 (12/108)	
Methicillin-resistant *S. aureus*	8.33 (9/108)	
Type of infection		
Major cutaneous abscess	44.4 (48/108)	
Post-surgical wound	5.56 (6/108)	
Post-traumatic wound	49.1 (53/108)	
Other	0.93 (1/108)	
Prior antihypertensive therapy		18.4 (29/158)
Baseline SBP (mmHg)		127 (10.7)

- **Table 2** shows the summary statistics for AUC, MIC, and AUC:MIC ratio for patients in the analysis population for efficacy.

Table 2. Summary statistics for AUC, MIC, and AUC:MIC ratio for patients included in the PK-PD analysis population for efficacy

Variable	Median or $MIC_{50/90}$ (min, max)			
	0.75 mg on Day 1 followed by 0.35 mg/kg Q24h x 4 days (N=33)	0.4 mg/kg on Day 1 followed by 0.30 mg/kg Q24h x 4 days (N=39)	1.0 mg/kg on Day 1 followed by 0.35 mg/kg Q24h x 4 days (N=36)	Total (N = 108)
AUC (mg•h/L)[a]	99.4 (44.1, 143)	61.3 (37.1, 255)	115 (58.5, 150)	88.5 (37.1, 255)
MIC (mg/L)	0.5/1.0 (0.5, 1.0)	0.5/1.0 (0.25, 2.0)	0.5/1.0 (0.25, 1.0)	0.5/1.0 (0.25, 2.0)
AUC:MIC ratio[b]	141 (57.4, 287)	110 (26.7, 509)	187 (58.5, 413)	141(26.7, 509)

a. AUC represents the total-drug $AUC_{0\text{-}48}$ divided by 2.
b. AUC:MIC ratio is calculated using total-drug $AUC_{0\text{-}48}$ divided by 2.

PK-PD Analyses for Efficacy

- **Table 3** shows the summary of univariable PK-PD relationships for dichotomous efficacy endpoints and AUC:MIC ratio evaluated as a two-group variable.
  - Evaluation of univariable relationships between dichotomous cessation of spread or α ≥10, 20, 30, 50, and 70% reduction from baseline in the area of erythema/induration on Days 2 to 5 endpoints and AUC:MIC ratio evaluated as two-group variable revealed the following:
    - On Day 2, the relationship for ≥20% reduction from baseline in the area of erythema/induration was the most statistically impressive (p=0.03).
    - On Days 3 to 5, univariable relationships for α ≥70% reduction from baseline in the area of erythema/induration were the most impressive statistically (p=0.021to 0.049) with AUC:MIC ratio thresholds ranging from 78.2 to 246.
- Univariable time-to-event analyses for cessation of spread and α ≥10, 20, 30, 50, and 70% reduction from baseline in the area of erythema/induration revealed borderline-significant to significant relationships for AUC:MIC ratio evaluated as a two-group variable, with p values ranging from 0.005 to 0.11.
  - AUC:MIC ratio thresholds ranged from 129 for cessation of spread in the area of erythema/induration to 237 to 247 for ≥10, 20 30, 50, and 70% reduction from baseline in the area of erythema/induration endpoints.
  - For each of these endpoints, time to 75% of the population achieving the event was from 1 day earlier in the higher compared to the lower AUC:MIC ratio group for cessation of spread, and as much as 3 days earlier in the higher compared to the lower AUC:MIC ratio group for the ≥70% reduction from baseline in the area of erythema/induration endpoint.
- Given the limited number of clinical failures at EOT and TOC, multivariable analyses based on the univariable relationships shown in **Table 3** for these endpoints were not considered. Multivariable analyses for the lesion size endpoints are planned.

Table 3. Summary of univariable PK-PD relationships for dichotomous efficacy endpoints

Efficacy endpoint	Magnitude of brilacidin AUC:MIC ratio associated with efficacy	% of patients achieving the efficacy endpoint		p-value
		≥AUC:MIC ratio[b] (n/N)	<AUC:MIC ratio[b] (n/N)	
Clinical response at EOT	60	96.9 (94/97)	80 (8/10)	0.07
Clinical response at TOC	60	95.9 (93/97)	80 (8/10)	0.1
≥20% reduction from baseline in the area of erythema/induration on Day 2[a]	125	79.4 (54/68)	60 (24/40)	0.03

a. Represents an efficacy endpoint advocated by the US FDA. The magnitude of the AUC:MIC ratio associated with earlier time-to-event for this efficacy endpoint was closely similar to those required to achieve lower or higher thresholds for percent reductions in the area of erythema/induration.
b. Based on total-drug AUC:MIC ratio evaluated as a two-group variable. AUC represents total-drug $AUC_{0\text{-}48}$ divided by 2.

PK-PD Analyses for Safety

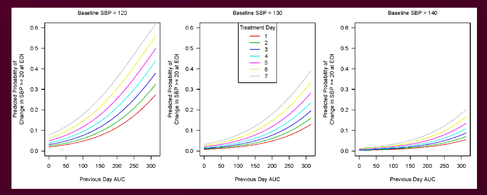
- The repeated measures multiple logistic regression model for change from baseline in SBP ≥20 mmHg based on data from the PK-PD analysis population for safety is shown in **Table 4.**
- **Figure 1** shows the relationships between predicted probability of change from baseline in SBP ≥20 mmHg and AUC by baseline SBP value based on data from the PK-PD analysis population for safety.

Table 4. Repeated measures multiple logistic regression model for change from baseline in SBP ≥20 mmHg based on data from the PK-PD analysis population for safety

Variable	Odds ratio (95% CI)	p-value
Treatment Day (per 1 day)[a]	1.27 (1.13, 1.43)	< 0.001
Observation time point		0.33
Pre-dose	0.89 (0.71, 1.13)	
End of infusion	1.05 (0.83, 1.32)	
3-hr post-dose	1	
Previous day AUC (per 10 mg•h/L units)	1.10 (1.05, 1.15)	< 0.001
Baseline SBP (per 1 mmHg unit)	0.91 (0.86, 0.96)	0.001

Note: Treatment Day/AUC interaction: p=0.37; Baseline SBP/AUC interaction: p=0.35; Time point/AUC interaction: p=0.70
a. Treatment Day was evaluated as a continuous variable.

Figure 1. Relationships between predicted probability of change from baseline in SBP ≥20 mmHg and AUC by baseline SBP value based on data from the PK-PD analysis population for safety.



- For the repeated measures multiple logistic regression models for change from baseline in SBP ≥35 and SBP ≥160 mmHg, only AUC on the previous day of treatment was statistically associated with outcome (p<0.001 for both); day of treatment and baseline SBP had no predictive value for these endpoints.
- These analyses are limited by the lack of consideration of concomitant antihypertensive agents
  - Concomitant antihypertensive medication histories were frequently complex with a subset having multiple agents that were started and stopped during study drug therapy. Analyses considering these data were attempted but without success; more sophisticated models will be needed to describe the data but are recommended after more data are available from future studies.

CONCLUSIONS

- Using data from patients with ABSSSI enrolled in Study PMX63-203, statistically significant PK-PD relationships for efficacy and safety of brilacidin were identified.
- Such data were useful for subsequent analyses to support brilacidin dose selection for future studies in patients with ABSSSI [ECCMID 2013, P915].

Poster No. P 916

23rd European Congress of Clinical Microbiology and Infectious Diseases, Berlin, Germany. April 27-30, 2013