Use of Pharmacokinetics-Pharmacodynamics and Monte Carlo Simulation Analyses to Support Brilacidin Dose Selection for Patients with Acute Bacterial Skin and Skin Structure Infections

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

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

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

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). Using parameter estimates from a population pharmacokinetic (PK) model based on Phase 1 and 2 data, results of pharmacokinetic-pharmacodynamic (PK-PD) analyses for efficacy and safety based on Phase 2 data from BRI-treated patients with ABSSSI, and Monte Carlo simulations (MCS), the objective of this analysis was to evaluate BRI dosing regimens for future Phase 2/3 studies.

Methods: MCS, using SAS v 9.2, was conducted to generate a population of 2,000 patients. Appropriate demographic characteristics for the simulated relative to the observed Phase 2 ABSSSI population were maintained. Population PK fixed and random effects parameter estimates and MCS techniques were employed to generate individual parameter estimates for each simulated patient. These parameter estimates were used to generate plasma brilacidin concentration-time profiles for each simulated patient following administration of each of 12 brilacidin dosing regimens. AUC measures were calculated for all dosing regimens for each simulated patient. Using parameter estimates from univariable PK-PD models for efficacy and multivariable PK-PD models for systolic blood pressure (SBP) endpoints and appropriate distributions or assumptions for the MIC distribution for *S. aureus* for the efficacy models and other independent variables retained in the SBP models, average predicted percent probabilities of efficacy on Day 2, end of therapy (EOT; Day 7-8) and test of cure (TOC; Day 10-14) and SBP endpoints (Days 2-4) were determined for each BRI dosing regimen.

Results: Average predicted percent probabilities of response for efficacy and SBP endpoints for the 5 BRI dosing regimens of most interest are reported in Table 1. For each dosing regimen, high average predicted percent probabilities of success for the 3 efficacy endpoints evaluated were evident. The maximum among Days 2, 3, and 4 of the average predicted percent probabilities of change from baseline in SBP ≥20 and ≥35, and SBP ≥160 mmHg were low and ranged from 3.92 to 5.46% and 0.76 to 1.16%, and 0.98 to 1.26%, respectively.

Conclusions: Optimal benefit-to-risk ratios were evident for BRI dosing regimens with larger initial doses and short duration (1-3 days), including single dose therapy, which maximizes patient compliance. These data will be used to support BRI dose selection for future studies in patients with ABSSSI.

Table 1. Predicted percent probability of efficacy and change in SBP ≥20 and ≥35, and SBP ≥160 mmHg by BRI dosing regimen

BRI dosing regimens	Average predicted percent probability of response											
	Efficacy endpoints[a]			SBP (mmHg) by day endpoints[b]								
	≥20% reduction from baseline in erythema/ induration on Day 2	Clinical success		Change in SBP ≥20 mmHg			Change in SBP ≥35 mmHg			SBP ≥160 mmHg		
		EOT[c]	TOC[d]	Day			Day			Day		
				2	3	4	2	3	4	2	3	4
0.6 mg/kg on Day 1 (single dose)	65.9	91.6	90.9	3.92	3.06	3.38	0.76	0.38	0.34	0.98	0.61	0.54
0.8 mg/kg on Day 1 (single dose)	68.6	93.5	92.6	4.99	3.33	3.53	1.16	0.44	0.37	1.26	0.67	0.56
0.6 mg/kg on Day 1 and 0.4 mg/kg on Day 2	69.8	94.2	93.3	3.92	4.94	4.01	0.76	0.86	0.46	0.98	0.99	0.64
0.8 mg/kg on Day 1 and 0.2 mg/kg on Day 2	70.4	94.6	93.6	4.99	4.24	3.84	1.16	0.66	0.43	1.26	0.85	0.61
0.6 mg/kg on Day 1 and 0.3 mg/kg on Days 2 and 3	68.9	93.7	92.8	3.92	4.38	5.46	0.76	0.70	0.78	0.98	0.88	0.88

a. Using the MIC distribution for BRI against *S. aureus* based on surveillance data from N. America, S. America, Europe, Asia, and Australia and model-predicted response percent probabilities by MIC value, average predicted percent probabilities for each efficacy endpoint were calculated for the BRI dosing regimens evaluated.
b. Using the baseline SBP distribution for patients with PK data in the intent-to-treat population and model-predicted response percent probabilities by baseline SBP value, average predicted percent probabilities for each change in SBP by day endpoint were calculated for the BRI dosing regimens evaluated.
c. EOT = Day 7-8
d. TOC = Day 10-14

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 (Study PMX63-203) in patients with ABSSSI caused by *S. aureus* evaluating brilacidin have been completed.
- Application of parameter estimates from a previously-developed population pharmacokinetic (PPK) model for brilacidin based on Phase 1 and 2 data [ECCMID 2013, P917] and pharmacokinetic-pharmacodynamic (PK-PD) models for efficacy and safety based on Phase 2 data [ECCMID 2013, P916] provide the opportunity to evaluate brilacidin dosing regimens for future study.
- The objectives of these analyses were to use the above-described PPK and PK-PD models , together with Monte Carlo simulation, to evaluate candidate brilacidin dosing regimens for future Phase 2/3 studies.

METHODS

Population PK and PK-PD Models

- Parameter estimates from a PPK model based on data from three Phase 1 studies in healthy subjects and one Phase 2 study in patients with ABSSSI caused by *S. aureus* [ECCMID 2013, P917] and results of PK-PD analyses for efficacy and safety based on the Phase 2 study [ECCMID 2013, P916] were utilized.
- PK-PD relationships between efficacy endpoints and AUC:MIC ratio utilized are shown in **Table 1**.

Table 1. 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 end-of-therapy (EOT)	60	96.9 (94/97)	80 (8/10)	0.07
Clinical response at test-of-cure (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_{0-24} divided by 2.

- PK-PD relationships for safety were based on repeated measures multivariable logistic regression models for change from baseline in systolic blood pressure (SBP) ≥20 and ≥35 mmHg, and SBP ≥160 mmHg.
- Independent variables evaluated were total-drug AUC for brilacidin of the previous dosing interval, observation time point (pre-dose, end of infusion, and 3 hours post-dosing), treatment day, and baseline SBP.
  - 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).

Monte Carlo Simulation

- Using SAS V9.2, Monte Carlo simulation was carried out to generate a population of 2,000 patients. The following patient characteristics were incorporated into the simulations:
  - Given that body surface area (BSA) and sex were statistically significant predictors of clearance and volume of the central compartment respectively [ECCMID 2013, P917], distributions for these covariates were considered:
    - Sex was simulated according to a uniform distribution to provide equal numbers of males and females.
    - Height was simulated separately by sex according to a Gaussian distribution based on observed distributions for patients included in the Study PMX63-203 dataset.
  - Ideal body weight (IBW) in kg was calculated separately by sex using the simulated patient heights in cm to generate some correlation between height in cm (HTCM) and weight using **Equations 1** and **2**:

    For males: IBW = 50+2.3*(HTCM/2.54-60) **(1)**

    For females: IBW = 45.5+2.3*(HTCM/2.54-60) **(2)**
  - Fractional body fat (FBF) was simulated according to a Gaussian distribution with a mean (SD) of 0.2 (0.05).
  - Total body weight was calculated using **Equation 3**:

    Total body weight = IBW*(1+FBF) **(3)**
  - Increasing IBW by a fraction equal to the simulated FBF was carried out to mimic the trend of observing heavier subjects in the general population relative to their IBW values.

Generation of Brilacidin Exposure for Simulated Patients

- Using the above-described demographics for the simulated patient population, final PPK fixed and random effects parameter estimates and Monte Carlo simulation techniques employed using NONMEM, individual post-hoc parameter estimates were generated for each simulated patient.

METHODS

Generation of Brilacidin Exposure for Simulated Patients

- These parameters were used to generate plasma brilacidin concentration-time profiles for each simulated patient following the administration of each of the five brilacidin dosing regimens listed in **Table 1**.
- AUC measures were calculated for all dosing regimens for each simulated patient.

Table 2. Brilacidin dosing regimens simulated

No.	Brilacidin dosing regimen
1	0.6 mg/kg on Day 1 (single dose)
2	0.8 mg/kg on Day 1 (single dose)
3	0.6 mg/kg on Day 1 followed by 0.4 mg/kg on Day 2
4	0.8 mg/kg on Day 1 followed by 0.2 mg/kg on Day 2
5	0.6 mg/kg on Day 1 followed by 0.3 mg/kg Q24h on Days 2 and 3

Application of PK-PD Relationships for Efficacy and Safety

- Using parameter estimates from PK-PD models for efficacy and safety endpoints and appropriate distributions or assumptions for other independent variables retained in each model, average predicted percent probabilities of response among simulated patients were determined for each dosing regimen.
- For PK-PD models for efficacy, average predicted percent probabilities of response were determined assuming fixed MIC values and using the MIC distribution for brilacidin against *S. aureus* based on recent surveillance data (the MIC_{50}, MIC_{90}, and range, which were 0.5, 1, and 0.5 to 2 mg/L, respectively) [Data on file, PolyMedix, Inc.].
  - The weighted average across the MIC distribution was derived for a simulated patient for a given dosing regimen by multiplying the predicted percent probability of the efficacy endpoint at each fixed MIC value with the probability of occurrence of that MIC value.
  - The sum of these percentages was then the MIC weighted average percent for that simulated patient.
  - The average of the MIC weighted average percentages from among all simulated patients was then determined.

RESULTS

Simulated Patient Population

- The mean (SD) height for males and females from this population and the simulated population was 176.1 (7.14) and 163.1 (6.61) and 176 (7.36) and 163 (6.59) cm, respectively, thus demonstrating that the simulated data compared well to the observed data.
- The distribution of post-hoc PK parameters values from simulated patients agreed well with those for the original population PK model.

Average Predicted Percent Probabilities of Response for Efficacy and Safety Endpoints

- The average predicted percent probability of response for efficacy and SBP endpoints by brilacidin dosing regimen is shown in **Table 3**.
- Average predicted percent probabilities of patients achieving clinical success at EOT, clinical success at TOC, and a ≥20% reduction from baseline in the area of erythema/induration on Day 2 ranged from 91.6 to 94.6%, 90.9 to 93.6%, and 65.9 to 70.4%, respectively, for the five dosing regimens.
- **Figure 1** shows the average predicted percent probability of response for efficacy endpoints by MIC by brilacidin dosing regimen overlaid on the MIC distribution for brilacidin against *S. aureus* based on recent surveillance data.
- The maximum among Days 2, 3, and 4 of the average predicted percent probabilities of change from baseline in SBP ≥20 and ≥35, and SBP ≥160 mmHg were low and ranged from 3.92 to 5.46% and 0.76 to 1.16%, and 0.98 to 1.26%, respectively.

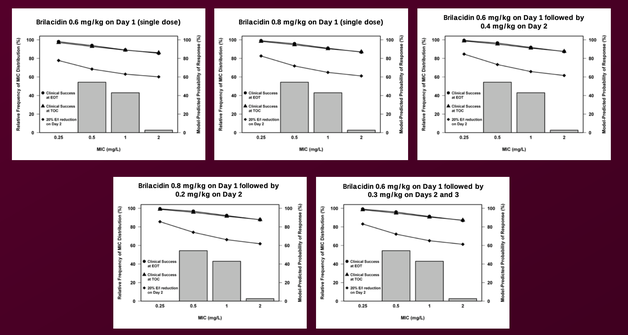
RESULTS

Table 3. Predicted percent probability of efficacy and change in SBP ≥20 and ≥35, and SBP ≥160 mmHg by brilacidin dosing regimen

Brilacidin dosing regimens (mg/kg)	Average predicted percent probability of response											
	Efficacy endpoints[a]			SBP (mmHg) by day endpoints[b]								
	≥20% reduction in erythema/ induration on Day 2	Clinical success		Change in SBP ≥20 mmHg			Change in SBP ≥35 mmHg			SBP ≥160 mmHg		
		EOT	TOC	Day			Day			Day		
				2	3	4	2	3	4	2	3	4
0.6 on Day 1(single dose)	65.9	91.6	90.9	3.92	3.06	3.38	0.76	0.38	0.34	0.98	0.61	0.54
0.8 on Day 1(single dose)	68.6	93.5	92.6	4.99	3.33	3.53	1.16	0.44	0.37	1.26	0.67	0.56
0.6 on Day 1 and 0.4 on Day 2	69.8	94.2	93.3	3.92	4.94	4.01	0.76	0.86	0.46	0.98	0.99	0.64
0.8 on Day 1 and 0.2 on Day 2	70.4	94.6	93.6	4.99	4.24	3.84	1.16	0.66	0.43	1.26	0.85	0.61
0.6 on Day 1 and 0.3 on Days 2 and 3	68.9	93.7	92.8	3.92	4.38	5.46	0.76	0.70	0.78	0.98	0.88	0.88

a. Using the MIC distribution for brilacidin against *S. aureus* based on surveillance data from N. America, S. America, Europe, Asia, and Australia and model-predicted response % probabilities by MIC value, average predicted % probabilities for each efficacy endpoint were calculated for the brilacidin dosing regimens evaluated.
b. Using the baseline SBP distribution for patients with PK data in the intent-to-treat population and model-predicted response % probabilities by baseline SBP value, average predicted % probabilities for each change in SBP by day endpoint were calculated for the brilacidin dosing regimens evaluated.

Figure 1. Average predicted percent probability of response for efficacy endpoints by MIC for brilacidin for the five dosing regimens evaluated overlaid on MIC distribution for brilacidin against *S. aureus*



CONCLUSIONS

- Using the parameters from PK-PD models for efficacy and safety and Monte Carlo simulation, average predicted percent probabilities for efficacy and change from baseline in SBP endpoints were calculated for 2,000 simulated patients who each received five different brilacidin dosing regimens.
  - Average predicted percent probabilities of patients achieving clinical success at EOT, clinical success at TOC, and a ≥20% reduction from baseline in the area of erythema/induration on Day 2 ranged from 91.6 to 94.6%, 90.9 to 93.6%, and 65.9 to 70.4%, respectively, for the five dosing regimens.
  - The maximum among Days 2, 3, and 4 of the average predicted percent probabilities of change from baseline in SBP ≥20 and ≥35, and SBP ≥160 mmHg were low and ranged from 3.92 to 5.46% and 0.76 to 1.16%, and 0.98 to 1.26%, respectively.
- Optimal benefit-to-risk ratios were evident for brilacidin dosing regimens with larger initial doses and short duration (1-3 days), including single dose therapy, which maximizes patient compliance.

Poster No. P 915

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