Application of Pharmacokinetic-Pharmacodynamic Models for Brilacidin Dose Selection Support for Patients with Acute Bacterial Skin and Skin Structure Infections

INSTITUTE for CLINICAL PHARMACODYNAMICS

Sujata M. Bhavnani, Pharm.D., M.S.
Institute for Clinical Pharmacodynamics
242 Broadway
Schenectady, NY 12305
Telephone: (518) 429-2600/(518) 631-8100
E-mail: SBhavnani@ICPD.com

S.M. Bhavnani[1], J.P. Hammel[1], A. Forrest[1], S.A. Van Wart[1], P. Sager[2], K.J. Tack[3], R.W. Scott[4], D.M. Jorgensen[3], P.G. Ambrose[1]

[1]Institute for Clinical Pharmacodynamics, Schenectady, NY; [2]Stanford University, Palo Alto, CA; [3]Cellceutix Corp., Beverly, MA; [4]FoxChase Chemical Diversity Center, Doylestown, PA.

ABSTRACT

Objectives: Brilacidin (BRI) is a synthetic molecule of a novel class of agents that demonstrates potent antimicrobial activity against Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA). BRI is being developed for the treatment of patients with acute bacterial skin and skin structure infections (ABSSSI). Using population pharmacokinetic (PK) and pharmacokinetic-pharmacodynamic (PK-PD) models for efficacy and safety developed using data from two Phase 2 studies of BRI-treated patients with ABSSSI and Monte Carlo simulation (MCS), BRI dosing regimens were evaluated.

Methods: MCS was used to generate 5,000 patients with distributions for covariates of PK based on data included in the previous PK analysis population. MCS was carried out using the BRI population PK model. Individual post-hoc parameter estimates were used to generate plasma BRI concentration-time profiles for simulated patients following 8 BRI dosing regimens, 4 of which were single doses (0.4, 0.6, 0.8 and 1 mg/kg) and 4 of which were 3-day dosing regimens. These included 0.4 mg/kg on Day 1, followed by 0.2 mg/kg on Days 2 and 3; 0.5 mg/kg on Day 1, followed by 0.2 mg/kg on Days 2 and 3; 0.5 mg/kg on Day 1, followed by 0.3 mg/kg on Days 2 and 3; and 0.6 mg/kg on Day 1, followed by 0.3 mg/kg on Days 2 and 3. Daily AUCs were calculated. Using parameter estimates from PK-PD models for clinical response at test of cure (TOC) and systolic blood pressure (SBP) and appropriate distributions or assumptions for independent variables retained in multivariable models, average predicted % probabilities of these endpoints were determined for each BRI dosing regimen.

Results: Across BRI dosing regimens, % probabilities of clinical success averaged over a BRI MIC distribution for *S. aureus* ranged from 86.4 to 93.1%. During Days 1-7, the % of simulated patients with sustained SBP ≥160 and ≥180 mmHg over 24 h ranged from 1.44 to 4.06% and 0.02 to 0.10%, respectively. A single 0.6 mg/kg dose best balanced safety and efficacy considerations, with % probabilities of 89.2, 1.7, and 0.02% for these endpoints, respectively.

Conclusions: Application of PK-PD relationships for efficacy and safety to simulated data allowed for benefit/risk discrimination among the BRI dosing regimens assessed for patients with ABSSSI.

INTRODUCTION

- Brilacidin, a synthetic molecule from a novel class of antimicrobial agents that mimic the structure and function of host defense proteins, acts directly on the cell membrane, disrupting its integrity and causing bacterial death. Brilacidin demonstrates potent *in vitro* activity against Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA).
- To date, three Phase 1 studies in healthy volunteers and two Phase 2 studies in patients with acute bacterial skin and skin structure infections (ABSSSI) have been completed. Pharmacokinetic (PK) data from these studies were used to develop a population PK model to describe the disposition of the brilacidin [1].
- Use of individual predicted brilacidin exposures based on this population PK model for patients in the Phase 2 studies provided the opportunity to evaluate pharmacokinetic-pharmacodynamic (PK-PD) relationships for efficacy and safety of brilacidin [2]. Results of such analyses demonstrated that as brilacidin exposure increased, so too did the probability of efficacy and safety endpoints.
- As described herein, the application of PK-PD relationships for safety and efficacy endpoints provided the opportunity to evaluate the risk versus benefit for brilacidin dosing regimens to be used in future Phase 3 studies.

OBJECTIVE

- Using a previously-developed population PK model and PK-PD models for efficacy and safety [2], *in vitro* surveillance data, and Monte Carlo simulation (MCS), the objective of these analyses was to evaluate brilacidin dosing regimens for future study in patients with ABSSSI were evaluated.

METHODS

- As described below, simulations to evaluate brilacidin dosing regimens were conducted using a previously-developed population PK model and PK-PD models for efficacy and safety, *in vitro* surveillance data, and MCS.

Population Pharmacokinetic Model

- The previously-described population PK model for brilacidin [1] demonstrated that a three-compartment model with zero-order input and first-order elimination best described the plasma brilacidin concentration-time profile in both healthy Phase 1 subjects and in Phase 2 ABSSSI patients.
- This model was used to generate individual brilacidin exposures for simulated patients, following administration of different brilacidin dosing regimens.

METHODS

Pharmacokinetic-Pharmacodynamic Models for Efficacy

- Previously-conducted PK-PD analyses for brilacidin efficacy [2] demonstrated univariable relationships between each of Sponsor-defined success at end of therapy (EOT) and test of cure/short-term-follow-up (TOC/STFU) and ≥20% and ≥50% reduction in lesion area from baseline on Days 2 and 3, respectively, and AUC:MIC ratio evaluated as a continuous variable. These relationships demonstrated that as AUC:MIC ratio increased so too did the probability of the efficacy endpoint.

Pharmacokinetic-Pharmacodynamic Models for Safety

- Previously-conducted PK-PD analyses for brilacidin safety [2] resulted in the development of the following multivariable models for systolic blood pressure (SBP) and the probability of numbness or tingling events of any severity or events that were moderate or severe in nature.
  - Repeated measures multiple linear regression for SBP.
  - Multivariable autoregressive logistic regression for numbness/tingling.
- The above-described models demonstrated that as AUC increased so too did SBP and the probability of numbness/tingling.

Brilacidin *In Vitro* Activity

- Brilacidin MIC distributions for *Staphylococcus aureus* were based on surveillance data for isolates collected worldwide (n= 263) [data on file, Cellceutix Corp.].
- The MIC_{50}, MIC_{90}, and minimum to maximum values for the overall distribution were 0.5, 1, and 0.5 to 2 mg/L, respectively [Data on File, Cellceutix Corp.].

Evaluation of Candidate Brilacidin Dosing Regimens

- MCS was carried out to generate a population of 5,000 patients with distributions for sex, height, and weight based on the observed data for Phase 2 patients with ABSSSI included in the population PK dataset [1].
- Using the simulated patient population, MCS was performed using the final fixed and random effects parameter estimates for the population PK model for brilacidin [1].
- Using individual post-hoc parameter estimates for each simulated patient, plasma brilacidin concentration-time profiles were generated following the administration of the eight brilacidin dosing regimens shown in **Table 1**.

Table 1. Summary of simulated brilacidin dosing regimens evaluated

	Dosing regimen
1	0.4 mg/kg on Day 1
2	0.6 mg/kg on Day 1
3	0.8 mg/kg on Day 1
4	1.0 mg/kg on Day 1
5	0.4 mg/kg on Day 1, followed by 0.2 mg/kg on Days 2 and 3
6	0.5 mg/kg on Day 1, followed by 0.2 mg/kg on Days 2 and 3
7	0.5 mg/kg on Day 1, followed by 0.3 mg/kg on Days 2 and 3
8	0.6 mg/kg on Day 1, followed by 0.3 mg/kg on Days 2 and 3

- Cumulative AUC measures for all dosing regimens were calculated for each simulated patient, using numerical integration up to selected times (prior to dosing, and at 0.15, 1, 3, 8, and 12 hours post-dose) on each day for 7 consecutive days, following the start of treatment.
- Using parameter estimates from the final PK-PD models for efficacy and safety endpoints, and appropriate distributions or assumptions for other independent variables retained in PK-PD models for safety endpoints; average predicted percent probabilities of efficacy and safety endpoints among simulated patients were determined for each brilacidin dosing regimen evaluated.

RESULTS

Application of Pharmacokinetic-Pharmacodynamic Relationships for Efficacy

- The average predicted percent probabilities of patients achieving of Sponsor-defined clinical success at EOT ranged from 84.3 to 94.1% for the brilacidin single-dose regimen evaluated and 87.8 to 92.3% for the three-day dosing regimens over the MIC distribution.

RESULTS

- Average predicted percent probabilities of clinical success at TOC/SFU ranged from 86.4 to 93.1% for the brilacidin single-dose Sponsor-defined regimens evaluated and 88.5 to 91.6% for the three-day dosing regimens.
- **Table 2** shows average predicted percent probabilities of Sponsor-defined clinical success at EOT and TOC/STFU, and achieving dichotomous lesion size reduction endpoints by MIC, and averaged over the MIC distribution for simulated patients following brilacidin single-doses of 0.6 and 0.8 mg/kg.

Table 2. Average predicted percent probabilities of Sponsor-defined clinical success at EOT and TOC/STFU and achieving dichotomous lesion size reduction endpoints by MIC for simulated patients after administration of brilacidin in single dosing regimen(n=5,000)

Efficacy endpoint	MIC (mg/L)	Average predicted percent probability of response (95% CI) by brilacidin single dose regimen	
		0.6 mg/kg	0.8 mg/kg
Sponsor-defined clinical success at EOT	0.5	92.9 (88.4, 96.9)	95.7 (91.5, 98.9)
	1.0	84.6 (75.4, 92.4)	88.1 (82.1, 93.3)
	2.0	77.5 (51.2, 91.1)	80.1 (60.7, 91.7)
	Averaged[a]	88.9 (83.5, 93.8)	92.0 (87.9, 95.7)
Sponsor-defined clinical success at TOC/STFU	0.5	91.7 (87.3, 96.0)	94.0 (89.9, 97.8)
	1.0	86.4 (77.9, 93.9)	88.5 (82.3, 94.1)
	2.0	82.7 (65.6, 93.5)	84.0 (70.5, 93.5)
	Averaged[a]	89.2 (83.5, 94.4)	91.4 (87.0, 95.5)
≥20% reduction from baseline in lesion area on Day 2	0.5	62.2 (54.8, 69.4)	66.5 (58.6, 73.3)
	1.0	55.3 (45.2, 65.0)	57.6 (48.7, 66.2)
	2.0	51.7 (39.2, 63.8)	52.9 (41.2, 64.1)
	Averaged[a]	58.9 (50.8, 67.1)	62.3 (55.0, 69.3)
≥50% reduction from baseline in lesion area on Day 3	0.5	55.2 (47.6, 62.9)	59.4 (51.4, 68.0)
	1.0	48.7 (39.0, 58.9)	50.9 (42.0, 60.2)
	2.0	45.4 (32.5, 57.7)	46.5 (35.0, 58.1)
	Averaged[a]	52.2 (43.9, 60.9)	55.4 (47.9, 63.0)

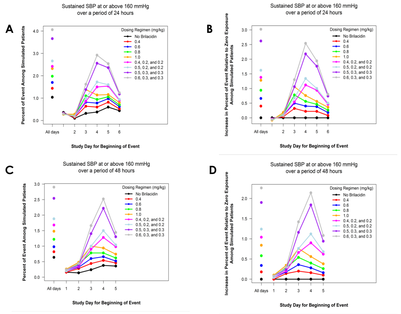
a. Using the brilacidin MIC distribution for *S. aureus* based on surveillance data and AUC_{0-48}:MIC ratio, average predicted percent probabilities of a successful response over the MIC distribution were averaged.

Application of Pharmacokinetic-Pharmacodynamic Relationships for Safety

Systolic Blood Pressure

- Of the SBP endpoints evaluated, sustained SBP ≥160 or ≥180 mmHg over 24 or 48 hours represented those of greatest clinical interest. **Figure 1** shows the percentage of simulated patients with these former SBP endpoints over 24 or 48 hours during any of Days 1 to 6

Figure 1. Percent of simulated patients with sustained SBP ≥160 mmHg over a period of 24 hours (A) relative to zero brilacidin exposure (B) and over a period of 48 hours (C) relative to zero brilacidin exposure (D) by study day and brilacidin dosing regimen



RESULTS

- Sustained elevations of SBP ≥160 mmHg over 24 or 48 hours during any of Days 1 to 6 among simulated patients who received 0.6 and 0.8 mg/kg single-dose regimens compared to the no brilacidin dosing regimen are shown in **Table 3**.
- The percentage of simulated patients with sustained SBP ≥180 mmHg over 24 or 48 hours during any of Days 1 to 6 among those who received the 0.6 and 0.8 mg/kg single-dose regimens was negligible (≤0.02%; relative to no brilacidin, the increase was 0%).

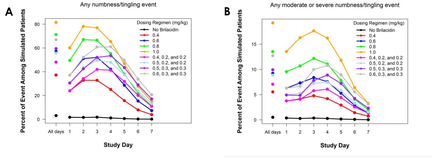
Table 3. Sustained elevations of SBP ≥160 mmHg over 24 or 48 hours during the observation period among simulated patients who received the 0.6 and 0.8 mg/kg single-dosing regimens compared to the no brilacidin dosing regimen

Dosing regimen	Time window	Day	Simulated patients achieving SBP endpoint (%)	Difference from no brilacidin regimen (%)
0.6 mg/kg on Day 1	24 hour	All Days	1.70	0.66
		Day 1	0.30	-0.06
		Day 2	0.18	0.08
		Day 3	0.82	0.50
		Day 4	0.78	0.40
		Day 5	0.98	0.38
		Day 6	0.62	0.18
	48 hour	All Days	0.98	0.34
		Day 1	0.20	0.04
		Day 2	0.32	0.18
		Day 3	0.60	0.36
		Day 4	0.66	0.28
		Day 5	0.52	0.16
0.8 mg/kg on Day 1	24 hour	All Days	1.98	0.94
		Day 1	0.28	-0.08
		Day 2	0.22	0.12
		Day 3	1.10	0.78
		Day 4	0.94	0.56
		Day 5	1.06	0.46
		Day 6	0.70	0.26
	48 hour	All Days	1.22	0.58
		Day 1	0.26	0.10
		Day 2	0.42	0.28
		Day 3	0.78	0.54
		Day 4	0.78	0.40
		Day 5	0.62	0.26

Numbness/Tingling

- The average percent probability of a numbness/tingling event of any severity during Days 1 to 7 ranged from 39.0 to 81.9% across all brilacidin dosing regimen evaluated (**Figure 2A**) while the average percent probability of a numbness/tingling event that was moderate or severe in nature during this period ranged from 5.52 to 19.0% across these dosing regimens (**Figure 2B**).
- The average number of days that simulated patients experienced a numbness/tingling event across Days 1 to 7 ranged from 1.48 to 3.69 days while the average number of days with a moderate or severe event ranged from 0.22 to 0.84 days.

Figure 2. Percent probability of a numbness/tingling event of any severity (A) or moderate or severe (B) among simulated patients



RESULTS

- The probabilities of numbness/tingling events for simulated patients administered the 0.6 and 0.8 mg/kg single-dosing regimens are shown in **Table 4**. Given that the observed data for patients with severe numbness/tingling events were limited (n=2), the model-based predictions for simulated patients with moderate/severe numbness/tingling are more representative of moderate numbness/tingling.

Table 4. Probability of numbness/tingling events for simulated patients administered brilacidin 0.6 and 0.8 mg/kg single-dose regimens

Dosing Regimen	Study Day	Average percent probability of numbness/tingling (95% CI)	
		Any severity	Moderate or severe
0.6 mg/kg on Day 1	1	37.1 (31.4, 43.0)	6.28 (3.68, 9.65)
	2	51.8 (43.6, 58.4)	7.40 (4.45, 11.5)
	3	52.1 (45.4, 58.8)	8.42 (5.16, 12.4)
	4	42.2 (36.0, 49.2)	7.53 (4.69, 11.4)
	5	28.2 (22.6, 35.1)	5.25 (2.99, 8.57)
	6	15.5 (10.8, 21.0)	2.74 (1.34, 5.29)
	7	7.73 (4.60, 11.4)	1.16 (0.47, 3.44)
	All days[a]	56.7 (50.0, 63.9)	9.24 (6.02, 13.3)
	Number of days with numbness/tingling across all days	2.35 (2.01, 2.70)	0.39 (0.24, 0.60)
0.8 mg/kg on Day 1	1	49.5 (42.7, 56.0)	9.55 (5.64, 14.9)
	2	67.6 (59.5, 74.3)	10.6 (5.80, 17.3)
	3	67.5 (59.8, 73.1)	12.1 (7.37, 18.7)
	4	56.5 (48.5, 62.8)	11.4 (6.57, 17.1)
	5	39.4 (30.8, 45.2)	8.16 (4.23, 13.0)
	6	22.5 (16.4, 29.0)	4.47 (1.71, 8.08)
	7	11.6 (7.49, 16.3)	2.20 (0.56, 5.02)
	All days[a]	72.4 (64.5, 77.5)	13.8 (8.37, 20.0)
	Number of days with numbness/tingling across all days	3.16 (2.71, 3.45)	0.59 (0.32, 0.90)

a. Numbness/tingling on at least 1 day.

CONCLUSIONS

- The application of PK-PD relationships to data from simulated patients allowed for discrimination among the single and three-day brilacidin dosing regimens evaluated.
- Data from simulated patients demonstrated high average predicted percent probabilities of Sponsor-defined clinical success across the brilacidin dosing regimens evaluated. Application of the multivariable models for safety allowed for the brilacidin dosing regimens that best balanced the need for high efficacy and good safety to be identified.
- A brilacidin 0.6 mg/kg single-dosing regimen appeared to best balance these objectives.
  - This dosing regimen demonstrated a high average predicted percent probability of Sponsor-defined clinical success at TOC/STFU (88.9%), and low percent probabilities of sustained SBP ≥160 and ≥180 mmHg over 24 or 48 hours during any of Days 1 to 7 (≤1.7 and ≤0.02%, respectively).
  - The percent probability of a numbness/tingling event that was moderate or severe in nature during Days 1 to 7 was 9.24%.
- These data will be useful to support selection of a brilacidin dosing regimen for evaluation in future Phase 3 studies in patients with ABSSSI.

REFERENCES

1. Van Wart SA, *et al*. Population pharmacokinetics of brilacidin in healthy subjects and patients with acute bacterial skin and skin structure infections. [Abstract A-038] 55th Interscience Conference on Antimicrobial Agents and Chemotherapy. San Diego, CA. September 17-21, 2015.
2. Bhavnani SM, *et al*. Pharmacokinetic-pharmacodynamic analyses for efficacy and safety of brilacidin using data from patients with acute bacterial skin and skin structure infections. [Slide Session: 247] American Society of Microbiology Microbe 2016, Boston, MA June 16-20, 2016.