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Abstract (poster session)

Use of pharmacokinetics-pharmacodynamics (PK-PD) and Monte Carlo simulation (MCS) analyses to support brilacidin (BRI) dose selection for patients with acute bacterial skin and skin structure infections (ABSSSI)

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Objectives: BRI, a small synthetic mimic of host defense proteins with activity against Gram-positive organisms including methicillin-resistant S. aureus, is currently being developed for the treatment of patients with ABSSSI. Using parameter estimates from a population PK model based on Phase 1 and 2 data, results of PK-PD analyses for efficacy and safety based on Phase 2 data from BRI-treated patients with ABSSSI, and MCS, the objective of this analysis was to evaluate BRI dosing regimens for future Phase 2/3 studies. Methods: MCS, using SAS v9.2, 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. Average predicted percent probabilities of change from baseline in SBP >= 20, >= 35 and SBP >= 160 mmHg were low and ranged from 3.06 to 5.46%, 0.34 to 1.16% and 0.54 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 or ≥ 35 or 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		
				Day			Day			Day		
		EOT[c]	TOC[d]	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 North America, South. 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