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Abstract (poster session)

Population pharmacokinetic (PPK) analyses of brilacidin using data from healthy subjects and patients with acute bacterial skin and skin structure infections (ABSSSI)

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Objectives: Brilacidin (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. The objectives of this analysis were to update a previously-developed PPK model for BRI using pooled data from Phase 1 and Phase 2 studies and to characterize interindividual and intraindividual variability in the pharmacokinetics (PK) and the influence of subject descriptors on PK. Methods: The data utilized for this analysis were obtained from three Phase 1 studies, designed to evaluate the safety, tolerability, and PK of single or multiple-dose BRI regimens in healthy subjects, and one Phase 2 study designed to assess the efficacy and safety of BRI in patients with ABSSSI. The final pooled PK analysis dataset consisted of 1582 concentrations from 75 healthy subjects and 773 concentrations from 153 patients with ABSSSI. Intravenously administered doses ranged from 0.016 to 2.5 mg/kg. After the base model was updated, covariate analysis was conducted using forward selection followed by backward elimination. Subject demographics, laboratory tests, and disease characteristics were evaluated for their ability to describe the interindividual variability in BRI PK parameters. The appropriateness of the structural and variance models was assessed throughout and refined as necessary. The final model was qualified using a prediction-corrected visual predictive check technique. Results: The previously-developed 3-compartment model with zero-order infusion and first-order elimination was successfully applied to pooled BRI concentration-time data. The only significant covariate relationships for BRI were between body surface area and clearance and between sex and central volume of distribution. The visual predictive check supported the robustness of the final PPK model. Final model parameter estimates and associated precision are reported in Table 1 below. Conclusions: A 3-compartment model with zero-order infusion and first-order elimination adequately described BRI PK. Given the predictive ability of the final PPK model, individual model predictions were deemed appropriate for subsequent pharmacokinetic-pharmacodynamic analyses of efficacy and safety using Phase 2 data from patients with ABSSSI and simulations of exposure to support BRI dose selection for future studies.

Table 1. BRI final PPK model parameter estimates and standard errors

Parameter	Population mean		Magnitude of interindividual variability (%CV)	
	Final estimate	%SEM	Final estimate	%SEM
CL (L/hr)	0.333	4.20	34.1	15.9
V_c (L)	5.21	7.10	55.1	16.6
V_{p1} (L)	2.46	6.10	NE	NA
Q_1 (L/h)	0.562	21.7	NE	NA
V_{p2} (L)	4.95	25.9	67.0	27.3
Q_2 (L/h)	0.083	17.3	165	17.7
Coefficient of power relationship between BSA and CL	1.10	17.1	NE	NA
Proportional shift in V_c for females	-0.289	24.4	NE	NA
Residual error (%CV)	14.9	10.1	NE	NA
Minimum value of the objective function = 32788.628				

CL: Systemic drug clearance (L/hr). V_c: Central volume of distribution (L). V_{p1}: First peripheral volume of distribution (L). V_{p2}: Second peripheral volume of distribution (L). Q_1: Inter-compartmental clearance between central and the first peripheral compartments (L/hr). Q_2: Inter-compartmental clearance between central and the second peripheral compartments (L/hr). BSA: body surface area. NE: Not evaluable. NA: Not applicable. %CV: coefficient of variation expressed as a percent. %SEM: Percent standard error of the mean.