Population Pharmacokinetic Analyses for Arbekacin After Administration of ME1100 Inhalation Solution

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INTRODUCTION

- Arbekacin has activity against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus*, and Gram-negative bacteria, including *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.
- ME1100, as an inhalational formulation of arbekacin, is being developed for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP).

OBJECTIVE

- The objective of these analyses was to develop a population pharmacokinetic (PK) model to describe the arbekacin concentration-time profile in plasma and epithelial lining fluid (ELF), following ME1100 administration.

METHODS

- Data were obtained from the following studies:
  - A post-marketing study for an intravenous (IV) formulation of arbekacin in 180 Japanese patients
    - A wide range of dosing regimens was utilized
  - Phase 1 single-dose study of ME1100 in 42 healthy volunteers
    - Studied doses: 90 and 450 mg
  - Phase 1b study of ME1100 in patients with mechanically ventilated bacterial pneumonia (MVBP)
    - Treatment Arm A (n=12): ME1100 300 mg twice daily (BID) for 5-14 days plus Best Available MVBP Therapy
    - Treatment Arm B (n=12): ME1100 600 mg BID for 5-14 days plus Best Available MVBP Therapy
- Data from the post-marketing study were utilized to develop a structural PK model following IV administration and to subsequently conduct a covariate analysis utilizing stepwise forward selection (α = 0.05) and backward elimination (α = 0.001).
- This model was utilized as the foundation for development of the model characterizing arbekacin disposition in plasma and ELF following inhalation of ME1100.
- All model development was conducted using NONMEM 7.2.

RESULTS

Table 1. Summary statistics of subject demographics

	Post-marketing study[a]		Phase 1 Study		Phase 1b Study	
Demographic	**Median**	**Range**	**Median**	**Range**	**Median**	**Range**
Age (yr)	73	16 – 98	33	21 – 55	59	21 – 76
BMI(kg/m^2)	20.1	13 – 36.7	26.5	20.4 – 30	26.5	12.4 – 59.7
BSA (m^2)	1.55	1.12 – 2.29	1.95	1.54 – 2.41	1.89	1.43 – 3.22
Height (cm)	162	138 – 180	175	152 – 193	174	152 – 192
Weight (kg)	52.2	30 – 110	78	55.5 – 111	77.5	38.1 – 220
CLCRN (mL/min/1.73 m^2)	77.1	5.32 – 178	90.8	59.2 – 136	71.9	23.4 – 160
Demographic	**N (%)**		**N (%)**		**N (%)**	
Gender						
Male	107 (74.8)		28 (66.7)		14 (58.3)	
Female	36 (25.2)		14 (33.3)		10 (41.7)	
Race						
White	N/A		24 (57.1)		21 (87.5)	
Black	N/A		11 (26.2)		2 (8.3)	
Asian	143 (100)		4 (9.5)		1 (4.2)	
Other	N/A		3 (7.1)		0	

Abbreviations: BMI = body mass index, BSA = body surface area, CLCRN = normalized creatinine clearance
a. Subjects with missing demographic information (n=37) excluded.

- The final PK dataset was derived from subjects with a wide range of renal function, body size, and age (**Table 1**).
- The final model was developed using 873 plasma samples and 59 ELF samples collected from 209 and 59 subjects, respectively.
- As depicted in **Figure 1**, the final population PK model utilized linear two-compartment models for both plasma and ELF disposition. Final model parameter estimates are displayed in **Table 2**.
  - The movement of arbekacin between the ELF and plasma was parameterized using linear first-order rate constants.
  - A bioavailability term was included for the inhalational route of administration, which was estimated to be 19.5% for a typical patient. The final model included CLCRN and weight as covariates on arbekacin clearance.
  - The model simultaneously described arbekacin PK following both IV and inhaled administration and provided acceptable fits to the plasma and ELF data (**Figure 2** and **Figure 3**, respectively).
  - The median (min, max) total-drug plasma:total-drug ELF penetration ratio was 0.392% (<0.01%, 9.57%), indicating that arbekacin exposures are substantially higher in ELF relative to plasma.

Table 2. Population PK parameter estimates for the final population PK model

Exposure matrix	Parameter	Population mean		Interindividual variability (%CV)	
		Final estimate	%SEM	Final estimate	%SEM
Plasma	CL (L/h)[a]	—	—	32.1	18.6
	CL-weight power	0.855	15.2	—	—
	CL-CLCRN slope	0.0289	7.37	—	—
	CL coefficient	2.32	5.30	—	—
	Vc (L)	13.8	4.43	19.3	41.9
	CLd1(L/h)	0.901	26.3	—	—
	Vp1 (L)	17.5	30.5	113	50.7
	Additive error[b]	0.000669 (0.026)	290	—	—
	Proportional error[b]	0.0603 (0.246)	5.17	—	—
ELF	Logit_bioavailability	-1.42[c]	8.38	0.460[d]	24.2
	V_{Lung}	0.0255	22.6	—	—
	k_{31}	0.893	14.6	75.6	28.3
	k_{13}	0.186	23.2	—	—
	k_{34}	0.102	68.5	223	53.1
	k_{43}	0.226	28.5	—	—
	Additive Error[b]	2050 (45.3)	1702	—	—
	Proportional Error[b]	0.695 (0.834)	71.2	—	—
Minimum Value of the Objective Function = 1302.8					

Abbreviations: CL = clearance; Vc = volume of the central compartment; CLd1 = distributional clearance to peripheral compartment 1;Vp1 = volume of distribution for peripheral compartment 1; V_{lung} = volume of central lung compartment; k_{13}, k_{31} = rate constants between Vc and V_{lung}; k_{43}, k_{43} = rate constants between V_{Lung} and peripheral lung compartment; %SEM = standard error of the mean; %CV = coefficient of variation.
a. CL = (WTKG/52.2)$^{0.855}$ ·((CLCRN – 77)·0.0289 + 2.32)
b. Population mean residual variability terms reported as variance (standard deviation).
c. Translates to 19.5%.
d. IIV is additive rather than proportional. Listed value is a standard deviation rather than a %CV.

RESULTS

Figure 1. Final structural arbekacin population PK model

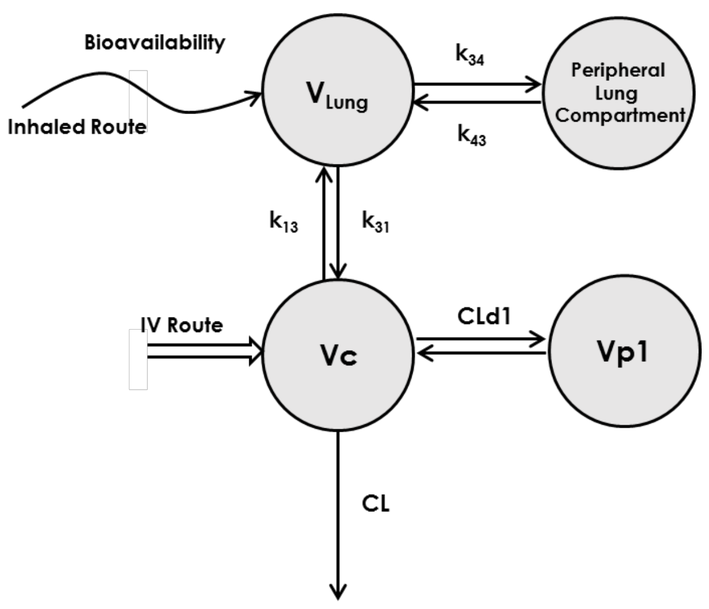


Figure 2. Plasma goodness-of-fit plots for final model

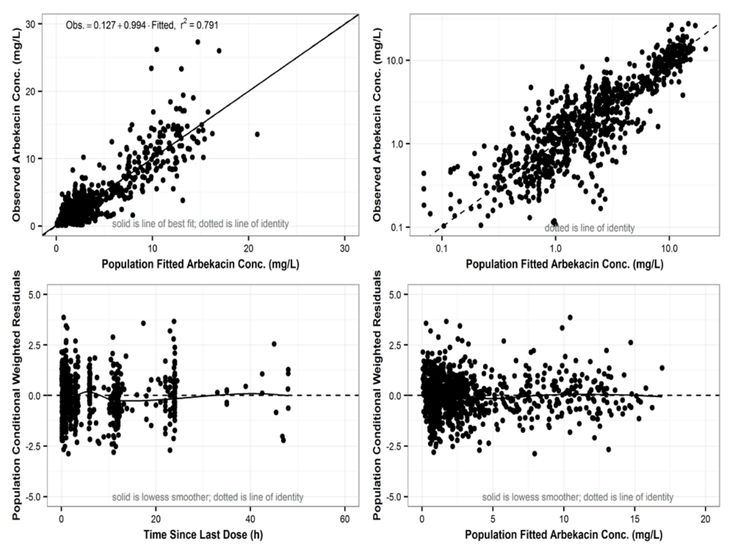
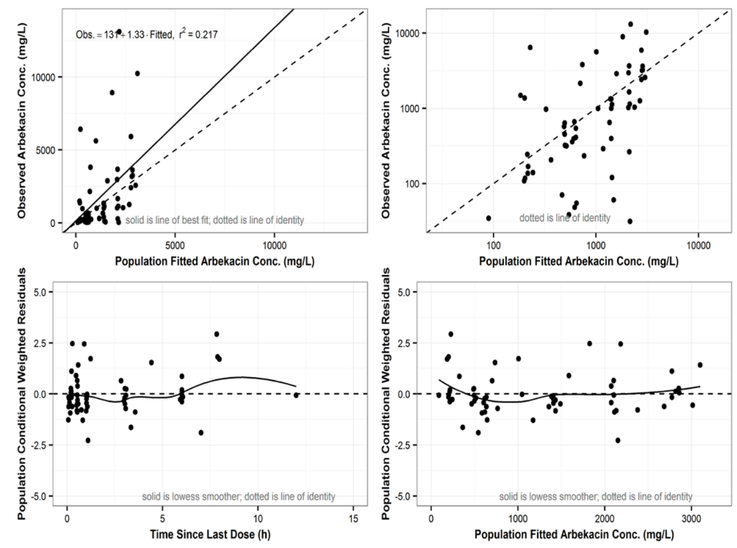


Figure 3. ELF goodness-of-fit plots for final model



CONCLUSIONS

- A population PK model was successfully developed which describes the time course of arbekacin concentrations in both plasma and ELF after either IV infusion or inhalation.
- This model will be useful for pharmacokinetic-pharmacodynamic target attainment analyses to support ME1100 dose selection.