Population Pharmacokinetics of Plazomicin and Use of Therapeutic Drug Management in Critically-Ill Patients

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INTRODUCTION

- Plazomicin is a novel aminoglycoside antibiotic that has potent bactericidal activity against Enterobacteriacae isolates that possess a broad range of resistance mechanisms such as aminoglycoside-modifying enzymes, carbapenemases, extended-spectrum β-lactamases and fluoroquinolone target-site mutations.
- Plazomicin was well tolerated in Phase 1 studies and a Phase 2 study in patients with complicated urinary tract infections (cUTI) or acute pyelonephritis (AP).
- A Phase 3 study (CARE) was conducted to evaluate the efficacy and safety of plazomicin compared with colistin in critically-ill patients with bloodstream infections (BSI), hospital- or ventilator-acquired bacterial pneumonia (HABP or VABP), cUTI or AP due to CRE.
  - Initial plazomicin dosing guidelines in CARE were designed to achieve a mean steady-state AUC_{0-24} of 262 mg/L•h which is comparable to that predicted for adult patients with normal renal function administered 15 mg/kg/day.
  - An enzyme immunoassay to determine plasma plazomicin concentrations was developed to allow for implementation of therapeutic drug management (TDM) to guide dose adjustments.
  - TDM was used to help achieve plazomicin steady-state AUC_{0-24} exposures within a reasonably precise target range of 200–400 mg/L•h.

OBJECTIVES

- To utilize interim pharmacokinetic (PK) data from CARE to update a previously-developed population PK model; and
- To assess the performance and adequacy of the plazomicin dosing guidelines used for assigning the initial dose and to adjust the dose during treatment for patients who participated in CARE.

METHODS

Plazomicin Dosing, TDM Dose Adjustment and PK

- Plazomicin-treated patients were assigned an initial dose and dosing interval (**Table 1**) based on adjusted body weight, and creatinine clearance (CLcr) or the use of CRRT. Plazomicin was to be given as a 30 minute IV infusion daily for approximately 7 to 14 days.
- After the initial dose, additional plazomicin doses may have been adjusted based on changes in renal function and measured plazomicin concentrations obtained from TDM using protocol-specified dose adjustment equations.
- PK samples were assayed for plazomicin via a central lab using an LC/MS/MS assay.

Table 1. Initial plazomicin dosing guidelines and PK sampling scheme

CLcr (mL/min)	Plazomicin dose (mg/kg/dose)[a]	Frequency of dosing	PK sampling times after start of infusion on Day 1 and at steady-state[b]	TDM sampling times after start of infusion (Days 1, 4, and/or 8±1)
> 70	15			
> 60 to 70	14			
> 50 to 60	12	q24h	0.75, 1.5, 6, 10, 18 and 24 h	1.5 ±0.25 and 10 ±0.5 h
> 40 to 50	10			
> 30 to 40	8			
> 25 to 30	12			
> 20 to 25	10	q48h	0.75, 1.5, 12, 18, 36 and 48 h	1.5 ±0.25 and 18 ±0.5 h
> 15 to 20	8			
Slow CRRT[c]	11	q24h	0.75, 1.5, 6, 10, 18 and 24 h	1.5 ±0.25 and 10 ±0.5 h
Fast CRRT[d]	10	q12h	0.75, 1.5, 3, 6, 8 and 12 h	1.5 ±0.25 and 8 ±0.5 h

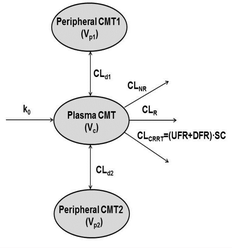
a. In protocol amendments #1 and 2, all patients with CLcr >60 mL/min received 15 mg/kg/dose.
b. In protocol amendments #1 and 2, the number of PK samples was reduced and were collected on Days 1 and 4 (±1 day) of treatment at 1.5, 4, and at either 8, 10 or 18 h (patients on q12h, q24h or q48h dosing regimens, respectively).
c. Ultrafiltrate flow rate of 5–15 mL/min and blood flow rate of 150 mL/min.
d. Ultrafiltrate flow rate of 30–40 mL/min and blood flow rate of 150 mL/min.

METHODS

Population Pharmacokinetic Analysis

- A population PK model previously developed using NONMEM® 7.2 based on data from 3 studies conducted in healthy volunteers and 1 study in cUTI/AP patients who received IV plazomicin once daily [1] was updated using the interim CARE data.
- Data from 22 patients enrolled in CARE, including 5 patients undergoing slow continuous renal replacement therapy (CRRT), were included in the interim PK analysis.
- A 3-compartment (CMT) model with zero-order input (k_0) and first-order elimination was used (**Figure 1**). Clearance (CL), central volume of distribution (Vc), and the distribution CL and volume of peripheral CMTs 1 (CLd1 and Vp1) and 2 (CLd2 and Vp2) were estimated.
- Prior covariate-parameter relationships (time-varying CLcr on CL; body size on CL, Vp1 and CLd2; and infection type on Vc) were retained in the model and expanded where needed (e.g., by adding infection type categories for BSI and HABP/VABP).
- The CL due to CRRT (CL_{CRRT}) was set to the sum of the actual patient-specific dialysate flow rate (DFR) and ultrafiltrate flow rate (UFR), multiplied by an estimated sieving coefficient (SC); dialysis CL was set to 0 when CRRT was not utilized.
- Both interindividual (ω^2) and interoccasion variability (IOV) was included in the updated PK model to allow for random differences in plazomicin PK on different PK sampling days.
- Residual variability (σ^2) was modeled using an additive plus proportional error model and was allowed to differ for studies in patients relative to well-controlled Phase 1 studies.

Figure 1. Plazomicin PK model diagram



RESULTS

Population Pharmacokinetic Analysis

- The updated population PK model (**Table 2**) provided an adequate fit to all the data. There were no observed biases in the population PK model fit (**Figure 2**) after accounting for increased CL in VABP patients, random IOV and differences in residual variability across different phases of clinical development.
- After including the additional CL due to CRRT, by incorporating the recorded UFR and DFR plus estimating a sieving coefficient (46.2%), plazomicin PK was adequately predicted in those patients undergoing CRRT.
- As a model check, individual post-hoc estimates of CL for patients in CARE who were not on CRRT were generally within the 90% prediction interval for CL created using the prior population PK model when examined by CLcr (**Figure 3**).

RESULTS

Table 2. Plazomicin population PK model parameters estimates

Parameter	Final Estimate	%SEM
CL (L/hr) CL_{NR} (L/h)	0.523	10.8
CL_{Crmax} (L/h)	5.15	7.59
$CLCf_{50}$ (mL/min/1.73 m²)	64.3	6.73
Hill coefficient	2.48	12.2
CL-Height power	0.830	46.0
Fractional increase for VABP patients	0.584	35.8
Vc (L)[a] Healthy subjects	8.34	4.47
Fractional increase for AP patients	0.440	32.1
Fractional increase for cUTI patients	0.888	19.9
Fractional increase for BSI patients	2.36	20.5
Fractional increase for VABP patients	3.48	17.5
CLd1 (L/h)	7.77	8.49
Vp1 (L) Coefficient	7.10	4.94
Vp1-BSA power	0.996	33.3
Vp1-Age slope	0.0757	17.4
CLd2 (L/h) Coefficient	0.175	4.38
CLd2-Height power	4.14	13.7
Vp2 (L)	6.86	7.83
CL_{CRRT} (L/h) Sum of UFR and DFR	~1.14 to 1.8 L/hr	Fixed to Patient Value
Sieving Coefficient	0.462	43.7
ω^2_{CL}	0.0857 (29.3 % CV)	24.5
ω^2_{Vc}	0.209 (45.7% CV)	35.3
ω^2_{CLd1}	0.185 (43.0% CV)	34.2
ω^2_{Vp1}	0.0762 (27.6% CV)	38.2
ω^2_{CLd2}	0.0444 (21.1% CV)	55.9
ω^2_{Vp2}	0.182 (42.7% CV)	41.9
IOV for CL	0.00352 (5.90% CV)	43.4
IOV for Vc	0.0120 (11.0% CV)	117
IOV for Vp1	0.0314 (7.80% CV)	239
σ^2_{CV} for Phase 1 Studies	0.0210 (14.5 % CV)	16.2
σ^2_{CV} for Phase 2 Study	0.140 (37.4% CV)	17.1
σ^2_{CV} for Phase 3 Study (CARE)	0.0472 (21.7% CV)	22.7
σ^2_{ADD}	0.0000169 (0.00770 mg/L)	177

Figure 2. Goodness-of-fit plots from CARE patients

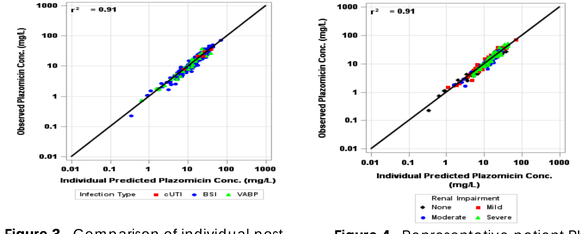
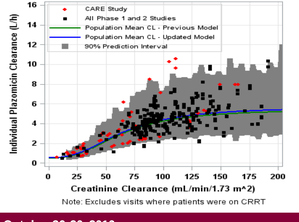


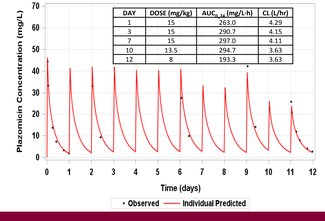
Figure 3. Comparison of individual post-hoc CL values from CARE to other studies



Note: Excludes visits where patients were on CRRT

Figure 4. Representative patient PK profile from CARE

DAY	DOSE (mg/kg)	AUC_{0-24} (mg/L·h)	CL (L/hr)
1	15	263.0	4.29
3	15	290.7	4.15
7	15	297.0	4.11
10	13.5	294.7	3.63
12	8	193.3	3.63



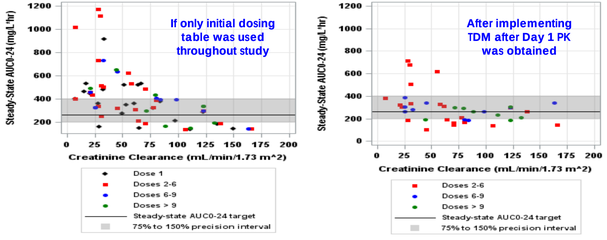
Evaluation of TDM Performance

- Individual post-hoc estimates of CL on each day of PK sampling were used along with the plazomicin dose (DOSEMGKG, in mg/kg/dose), the dosing weight (DWTKG), and the dosing interval (*Tau*) to estimate a steady-state AUC_{0-24}, as shown below, in order to assess performance of achieving the AUC_{0-24} target.

$$AUC_{0\_24} = \frac{DOSEMGKG \cdot DWTKG}{CL} \cdot \frac{24}{Tau}$$

- Observed plazomicin PK profiles were consistent with those predicted by the population PK model (**Figure 4**).
- Use of TDM appeared to reduce the inter-day differences in AUC_{0-24} and ensured that more patients achieved reasonably precise AUC_{0-24} values than what would have been achieved had only the initial dosing table been utilized (**Figure 5**).

Figure 5. Performance for targeting a steady-state AUC_{0-24} if the initial dosing table had been used on all PK sampling days versus using TDM to adjust dose



CONCLUSIONS

- A previously-developed population PK model was refined in order to describe plazomicin PK, and to provide an interim assessment of plazomicin exposures in critically-ill patients with CRE infections.
- Use of TDM to adjust plazomicin dose contributed to a substantially larger percentage of PK profiles producing a steady-state AUC_{0-24} within a reasonably precise range than what could have been achieved using the initial dosing table.

REFERENCES

1. Van Wart SA *et al.*. Pharmacokinetic-pharmacodynamic analysis predicts a high probability of efficacy for plazomicin against serious infections caused by carbapenem-resistant Enterobacteriaceae. ECCMID 2013, Abstract P-914.

ACKNOWLEDGMENTS

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