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PK-PD Target Attainment with Monte Carlo Simulation as Decision Support of Phase 2 / 3 Dosing Strategies for the Clinical Development of Doripenem

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ABSTRACT

Background: Integration of Phase 1 pharmacokinetic (PK) and non-clinical data provides for the potential to optimize antimicrobial dosing regimens for Phase 2/3 studies. A murine-thigh infection model identified the pharmacokinetic-pharmacodynamic (PK-PD) measure associated with efficacy (T>MIC) and the magnitude of T>MIC predictive of response (27, 35, and 43% for *S. pneumoniae*, *S. aureus*, and Gram-negative bacilli, respectively). MCS was applied to Phase 1 PK and non-clinical data to forecast doripenem (DOR) dosing strategies that maximize therapeutic benefit while minimizing drug exposure.

Methods: Using Phase 1 data from 24 subjects that received 1 of 4 regimens, 500 or 1000 mg given q12h or q8h, a population PK model was developed. Blood samples (n) were collected on days 1 (12), 4-6 (6), 7 (13), 8 (1), and 11 (1). Mean PK parameter estimates and a covariance matrix were used for a 5000 patient Monte Carlo Simulation (MCS) to evaluate PK-PD target attainment (based on free drug concentrations) for >100 different regimens (doses of 250, 500, 750, 1000, 2000, 3000 mg; intervals of q6h, q8h, q12h, q24h; infusion durations of 1-6 & 24 h). A range of doubling MIC dilutions from 0.25-16 mg/L was considered.

Results: Using a 2-compartment model with linear elimination and an additive plus proportional residual error model, CL (14.5 L/h), Vc (9.43 L), and $t_{1/2}$ (0.5 h) were estimated. A subset of the results (below) demonstrate the impact of varying dose, interval, and infusion durations on PK-PD target attainment (%) at MICs of 2, 4, and 8 mg/L.

Dosing Regimen	MIC	Duration of Infusion (hrs)	Percent of Patients Achieving T>MIC Target	
			35% T>MIC	40% T>MIC
500 mg q8h	2	1/2/3	99/100/100	77/100/100
500 mg q8h	4	3/4/5	100/100/99	84/99/99
1000 mg q12h	4	4/5/6	100/100/100	92/100/100
1000 mg q8h	4	1/2/3	99/100/100	77/100/100
1000/2000/3000 mg q24h	4	24	0/98/100	0/98/100
1000 mg q8h	8	3/4/5	100/100/99	84/99/99
1000/2000/3000 mg q24h	8	24	0/0/46	0/0/46

Conclusions: Prolonged infusion of DOR may allow for the treatment of infections caused by organisms with higher MICs, with little or no increase in drug exposure.

INTRODUCTION

- DOR is a synthetic, parenteral carbapenem that is structurally related to β–lactam antibacterial agents. It has a broad spectrum of *in vitro* and *in vivo* microbiological activity, including most clinically relevant Gram-negative and -positive pathogens.
- The clinical safety of DOR has been supported by several Phase I trials conducted in the United Kingdom and Japan and Phase II trials in Japan. Further clinical development has been undertaken by Peninsula Pharmaceuticals, Inc. in order to make this new carbapenem available in the US for the treatment of serious infections with resistant or difficult-to-treat pathogens.
- The integration of Phase 1 PK and non-clinical data from infection models provides for the potential to optimize antimicrobial dosing regimens for Phase 2/3 studies.
- A murine-thigh infection model identified the PK-PD measure associated with efficacy (T>MIC) and the magnitude of T>MIC predictive of response (27, 35, and 43% for *S. pneumoniae, S. aureus*, and Gram-negative bacilli, respectively) (See Poster A-308 for details).
- By applying MCS to Phase 1 PK and non-clinical data, DOR dosing strategies that maximize the therapeutic benefit while minimizing drug exposure may be forecasted.
- The objectives of these analyses were the following:
  - to develop a population PK model to describe the disposition of DOR using PK data collected from a Phase I double-blind, dose escalation study conducted in healthy subjects;
  - to assess the performance of various dosing regimens of DOR in attaining PK-PD targets over a range of MIC values using MCS; and
  - to identify optimal dosing regimens for consideration for Phase 2/3 studies.

METHODS

Data

- Phase I data were obtained from a double-blind, dose escalation study of intravenous DOR in 24 healthy subjects between 18 and 65 years of age who received 1 of 4 regimens for 7 days, 500 or 1000 mg given q12h or q8h (See Poster A-21 for details).
- Blood samples (n) were collected at pre-specified time points on days 1 (12), 4-6 (6), 7 (13), 8 (1), and 11 (1).

Population PK Model Development

- Population PK analyses were performed using NONMEM®, version 5.1.1.
- Goodness-of-fit of each NONMEM analysis was assessed by examination of the following:
  - scatterplots of population and individual predicted concentrations versus measured concentrations;
  - scatterplots of weighted residuals versus predicted concentrations;
  - scatterplots of individual weighted residuals and their absolute values versus individual predicted concentrations;
  - precision of the PK parameter estimates as measured by the standard error / parameter estimate 100% (%SEM); and
  - changes in the estimates of the interindividual and residual variability.

Monte Carlo Simulation

- Mean PK parameter estimates and a covariance matrix obtained from the final population PK model were used for a 5000 patient MCS to evaluate PK-PD target attainment (based on free drug concentrations) for >100 different regimens (doses of 250, 500, 750, 1000, 2000, 3000 mg; intervals of q6h, q8h, q12h, q24h; infusion durations of 1-6 & 24 h).
- A range of doubling MIC dilutions from 0.25-16 mg/L was considered.
- Random number generation, simulation of plasma concentrations based on the population PK model, and PK-PD target attainment calculations were performed using SAS®, version 8.2.
- Plots of plasma concentration-time profiles comparing durations of infusion for doses of 250, 500, 750, and 1000 mg, and comparing 750, 1000, 2000, and 3000 mg doses administered every 24 hours and as continuously infused doses, were generated in S-plus, version 6.0.1.
- Sensitivity analyses were carried out to assess the magnitude of deviations in PK-PD target attainment for simulations based on the upper and lower confidence bounds vs central estimates for 4 PK parameters (clearance, CL; volume of the central compartment, Vc; volume of the peripheral compartment, Vp; and intercompartmental clearance, Q).

RESULTS

- PK data were accurately described by a 2-compartment model with linear elimination. Interindividual variability and the covariance between parameters were estimated for CL, Vc, and Vp and an additive plus proportional residual error model was utilized.
- Figure 1 demonstrates the fit of the population PK model for observed concentrations following the first dose of the 500 mg TID dosing regimen.
- PK parameter estimates and measures of interindividual variability are shown in Table 1. The estimated terminal half-life ($t_{1/2}$) of DOR was approximately 0.95 hours.
- As shown in Table 1, precision of final parameter estimates was reasonable for all parameters except the magnitude of interindividual variability in Vp (%SEM = 69.4).
- The magnitude of residual variability ranged from 20.5 %CV at predicted DOR concentrations of 1000 ng/mL to 10.9 %CV at predicted DOR concentrations of 2000 ng/mL and higher.
- Figures 2 and 3 demonstrate the plasma concentration-time profiles for different durations of infusion for a 500 mg and 1000 mg dose, respectively. Figure 4 demonstrates the plasma concentration-time profiles for 750, 1000, 2000, and 3000 mg doses administered as a continuous infusion.
- Results of MCS showed high proportions of patients achieving PK-PD targets for organisms with lower MIC values (0.5 μg/mL or less) across the majority of regimens evaluated, including those as low as 250 mg q8h.
- A subset of the MCS results comparing PK-PD target attainment (%) by varying dose, interval, and duration of infusion at MIC values of 2, 4, and 8 mg/L is shown in Table 2.
- Sensitivity analyses demonstrated that the PK-PD target attainment results of the simulations were not substantially affected by uncertainty in the estimation of PK parameter typical values or interindividual variabilities.

Figure 1: Population Mean Predicted (Line) and Observed Concentrations (*) versus Time Since Last Dose

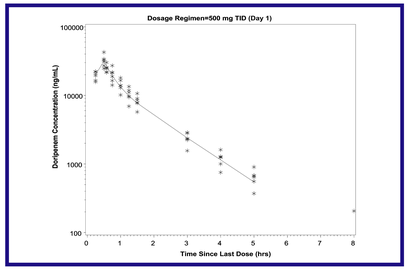

Figure 2: Simulated Concentration-Time Profiles for a 500 mg Dose

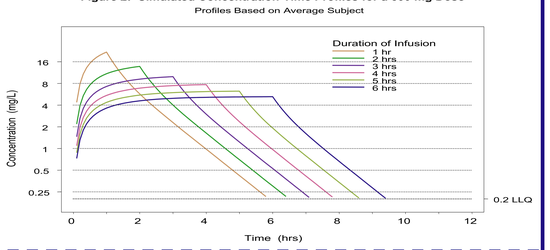

Figure 3: Simulated Concentration-Time Profiles for a 1000 mg Dose

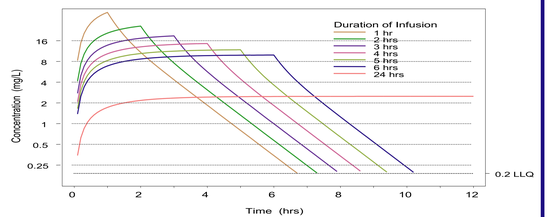

Figure 4: Simulated Concentration-Time Profiles for 24-hr Continuous Infusion Doses

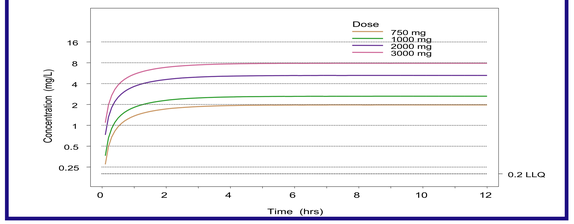

Table 1: Population PK Parameter Estimates for the Final Model Developed using Phase I Data from 24 Subjects

Parameter	Final Parameter Estimates		Magnitude of Interindividual Variability (%CV)	
	Final Estimate	%SEM	Final Estimate	%SEM
CL (L/hr)	14.5	2.6	13.19	32.5
Vc (L)	9.43	6.4	14.39	23.6
Q (L/hr)	9.69	20.3	NE[a]	NE[a]
Vp (L)	5.88	6.7	10.39	69.4
Residual Variability (%CV)	20.5% - 10.9%[b]	10.3, 39.3	– –	– –

[a]Not able to estimate.
[b]This represents the estimate of residual variability magnitude for predicted DOR concentrations ranging from 1000 – 20 000 ng/mL and higher.

Table 2: Comparison of PK-PD Target Attainment by Dosing Regimen, MIC, and Duration of Infusion

Dosing Regimen	MIC	Duration of Infusion (hrs)	Percent of Patients Achieving T>MIC Target			
			30% T>MIC	35% T>MIC	40% T>MIC	45% T>MIC
500 mg q8h	2	1/2/3	100/100/100	99/100/100	77/100/100	25/90/100
500 mg q8h	4	3/4/5	100/100/100	100/100/99	84/99/99	26/90/95
1000 mg q12h	4	4/5/6	100/100/100	100/100/100	92/100/100	23/96/100
1000 mg q8h	4	1/2/3	100/100/100	99/100/100	77/100/100	25/90/100
1000/2000/3000 mg q24h	4	24	0/98/100	0/98/100	0/98/100	0/98/100
1000 mg q8h	8	3/4/5	100/100/100	100/100/99	84/99/99	26/90/95
1000/2000/3000 mg q24h	8	24	0/0/46	0/0/46	0/0/46	0/0/46

DISCUSSION & CONCLUSIONS

- Among *Enterobacteriaceae*, the weighted MIC_{90} for DOR approximated 0.12 mg/L for *E. coli*, 0.12 mg/L for *K. pneumoniae*, 0.5 mg/L for *E. cloacae*, and 4 mg/L for *Serratia marcescens*. For *P. aeruginosa*, this value was < 4 mg/L or less.[1] PK-PD target attainment for organisms with MIC values of 0.5 mg/L was excellent (90%) for 45% T > MIC for all evaluated doses administered as q8h, regardless of the length of infusion.
- For organisms with higher MIC values, prolonged infusion of DOR should allow for the treatment of infections caused such organisms with little or no increase in drug exposure.
- Given that these analyses were based upon PK data from healthy volunteers, PK-PD target attainment results best reflect those for a patient population with normal renal function. Since DOR is largely renally eliminated (i.e., more than 75% of unchanged DOR is recovered in the urine irrespective of dose),[1] PK-PD target attainment results likely represent a conservative estimate of what would be expected in a renally-compromised population receiving the same doses.
- Results of these analyses will serve to support dose selection in future Phase 2/3 clinical trials.

REFERENCES

1. Doripenem Investigator's Brochure, Peninsula Pharmaceuticals, Inc., October 2002.