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POPULATION PHARMACOKINETICS OF TIGECYCLINE IN PHASE 1 SUBJECTS

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ABSTRACT

Background:

TGC is the first glycylcycline antimicrobial agent in development and has potent in vitro activity against many multi-drug resistant organisms. Given observed differences in the PK profiles after single doses (SD) & multiple doses (MD) of TGC, separate PPK models were developed for SD & MD data pooled from 5 Phase 1 studies.

Methods:

TGC (12.5 to 300 mg) was infused over 1 hour twice daily for 9 to 10 days. Serial blood samples were collected after a SD (2030 samples, 174 subjects) and on Day 9 or 10 (203 samples, 13 subjects). Both 2- and 3-compartment (CMT) models were fit to the serum TGC data using NONMEM®. The models that best described the full-profile SD & MD data were evaluated on a PH 1 dataset reduced to the Phase 2/3 sparse sampling scheme and dose range (25 to 100 mg)

Results:

3-CMT models with 1st-order elimination best described the SD & MD data. Intersubject variability (IIV) of CL, distribution CL (Q1 & Q2), and volume (Vp1 & Vp2) for each peripheral CMT were described using an exponential error model. However, the IIV of Q2 & Vp2 could not be estimated for MD data and were removed from the MD model. A log error model best described residual variability (RV) for both the SD & MD models. The elimination half-life was longer following MD of TGC (115 hr) than a SD (51 hr). The MD Bayesian PK parameters were also used to predict SD data (reverse superpositioning), revealing that the SD AUC0-12 was underpredicted for most subjects. Thus, the full-profile SD & MD data were not pooled and fit with a single model. The reduced Phase 1 data collected out 12 hr for both SD & MD of TGC were adequately described using a 2-CMT model. The predicted SD & MD AUC0-12 values were unbiased relative to observed values; median prediction error (PE) and absolute PE were similar for both models and were ±1% and 3%, respectively.

Conclusions:

A 3-CMT model best described the serial TGC data following a SD or MD, however, an empiric 2-CMT model provides unbiased estimates of $AUC_{0\text{-}12}$ using the PK sampling strategy implemented in Phase 2/3.

INTRODUCTION

- Tigecycline (TGC), an analog of minocycline, is the first of the glycylcyclines to reach clinical trials and exhibits a broad spectrum of activity against many aerobic and anaerobic Gram-positive and Gram-negative organisms.
- TGC has demonstrated impressive activity against multiple-drug resistant organisms such as methicillin-resistant S. aureus (MRSA), penicillin-resistant S. pneumoniae (PRSP), and vancomycin-resistant enterococcal species (VRE).
- The goals of this analysis were to:
  - develop a population pharmacokinetic (PK) model that characterizes the PK of TGC in Phase 1 subjects for doses ranging from 12.5 to 300 mg; and
  - assess the ability of the population PK model to provide unbiased estimates of TGC exposure (e.g, AUC0-12) for the dose range and PK sampling scheme utilized in Phase 2/3 trials in patients.

METHODS

Data

- Data from five single-center, Phase 1 studies of TGC in healthy subjects were pooled for population PK analysis. TGC dosing and PK sampling times are provided in **Table 1**.
- Blood was placed immediately on ice until a clot formed (~1 hr) after which samples were centrifuged at 4˚C. Serum was collected and frozen at -80ºC until analyzed using an:
  - HPLC assay (LOQ of 25 ng/mL) for Studies 100, 101, and 102; or
  - LC/MS/MS assay (LOQ of 10 ng/mL) for Studies 103 and 109

METHODS *continued*

Table 1:
Treatment Administration and PK Sampling for Studies Included in the Population PK Analysis

Study	Title	# of Subjects	IV Dosing Regimen(s)	PK Sample Collection Times
100	Single,ascending dose study for safety, tolerance, and PK	66	12.5, 25, 50, 75, 100 or 200 mg over 1 hr	Day 1: Pre-dose, and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60, 72, and 96 hr post-dose
			200 or 300 mg over 4 hr	Day 1: Pre-dose, and at 0.5, 1, 1.5, 2, 3, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 60, 72, and 96 hr post-dose
101	Double-blind, randomized, placebo-controlled, ascending multiple-dose study for safety, tolerability, and PK	24	25, 50 or 100 over 1 hr BID for 9 or 10 Days	Days 1 & 10: Pre-dose, and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hr post-dose On Day 10 only: 16, 24, 36, 48, 60, 72, 96, 120, and 144 hr post-dose
102	Effects of age and gender on the safety, tolerability, and PK	45	100 mg over 1 hr	Day 1: Pre-dose, and at 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 30, 36, 48, 60, 72, 96, and 120 hr post-dose
103	PK in adult subjects with various degrees of renal function	20	100 mg over 1 hr	Day 1: Pre-dose, and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 36, 48, 60, 72, and 96 hr post-dose
109	Safety and tolerability of various concentrations and infusion rates	19	100 mg loading dose/50 mg over 0.5 hr BID for 5 days	Day 1: Pre-dose, and at 0.25 and 0.5 hr post-dose
			100 mg loading dose/50 mg over 0.5 hr BID for 5 days	Day 1: Pre-dose, and at 0.25, 0.5, 0.75, and 1 hr post-dose

Statistical Analysis

- PK analyses were performed using NONMEM®, version 5.1.1 using the first-order conditional estimation method (FOCE) with interaction. For each analysis, the minimum value of the objective function (MVOF) was computed.
  - MVOF is proportional to minus twice the log likelihood of the data.
  - The change in MVOF is asymptotically distributed as χ^2 for hierarchical models.
- Goodness-of-fit (GOF) of each NONMEM® analysis was assessed by examining the precision of PK parameter estimates (%SEM), changes in both the IIV and RV, and scatterplots of:
  - population and individual predicted concentrations vs. measured concentrations;
  - weighted residuals vs. predicted concentrations and time since last dose;
  - individual weighted residuals and their absolute values vs. individual predicted concentrations.

Structural Model Development Using Full-Profile SD and MD Data

- Examination of the individual TGC concentration-time profiles revealed:
  - TGC concentrations generally exhibited a multi-phasic decline; and
  - secondary peaks were visible in the PK profiles following the termination of the IV infusion.
- Both 2- and 3-compartment (CMT) models were evaluated seperately for the SD and MD data. IIV for each parameter was described with an exponential error model; RV was described using a log error model.
- To determe the feasibility of combining all of the data together and fitting with a linear model, reverse superpositioning was performed
  - Bayesian PK parameter estimates from the 3-CMT model fit to the MD data were used to predict TGC concentrations at observed sampling times from 0 to 12 hr following a SD.
  - $AUC_{0\text{-}12}$ was calculated for both the observed and the predicted SD data (mixed trapezoidal rule), and assessed graphically for bias.

Evaluation of the Phase 2/3 Sparse Sampling Scheme

- The ability to obtain unbiased estimates of TGC exposure (e.g, $AUC_{0\text{-}12}$) using the Phase 2/3 sparse sampling scheme (0, 1, 3, 6, and 12 hr post start of infusion) and dose range (25-100 mg) was evaluated.

METHODS *continued*

- Select models were evaluated using the reduced data.
  - Bayesian PK parameters from these models were used to predict TGC concentrations at each of the full-profile sampling times.
  - $AUC_{0\text{-}12}$ was calculated for both the observed and predicted TGC data (mixed trapezoidal rule) and assessed graphically for bias
  - Prediction error percents (PE% = [observed $AUC_{0\text{-}12}$-predicted $AUC_{0\text{-}12}$]
- 100/observed $AUC_{0\text{-}12}$) and |PE|% were also evaluated as measures of bias and precision, respectively.

RESULTS

Data

- A total of 2030 samples from 174 subjects following a SD and 203 samples from 13 subjects following 9 or 10 days of BID dosing were available for PK analysis.
- The Phase 1 population for all studies combined was:
  - 86% male, and was 60% White, 16% Black, and 22% Hispanic
  - median age = 35 yr (ranged from 18 to 84 yr)
  - median weight = 76 kg (ranged from 50 to 112 kg)
  - median CrCL = 94 mL/min (ranged from 5 to 186 mL/min)

Structural Model Development Using Full-Profile SD and MD Data

- A 3-CMT model with zero-order input and first-order elimination adequately described both the SD and MD data.
  - Final population PK parameter estimates for both the SD and MD models are provided in **Table 2**.
  - The population mean predicted concentration-time profile from the fit of the model to the SD data is shown for the 100 mg dose group only in Figure 1.
  - An individual predicted concentration-time profile for a subject in the MD dataset with secondary peaks is shown in **Figure 2**.
- Comparing the results from the SD and MD models:
  - substantial differences were noted for several of the model-estimated parameters (with the exception of CL and Vc);
  - elimination half-life ($t_{1/2}$-gamma) was longer following MD of TGC (mean of 115 hr and range of 79 to 189 hr in 13 subjects) than a SD (mean of 51 hr and range of 23 to 106 hr in 171 subjects); and
  - reverse superpositioning revealed that the SD $AUC_{0\text{-}12}$ was underpredicted for most subjects.
- Based upon these PK differences, SD and MD data were always fit separately to avoid any biases that may have resulted from trying to fit a model to all data combined.

Evaluation of the Phase 2/3 Sparse Sampling Scheme

- A 2-CMT model with zero-order input and first-order elimination (**Table 2**) best described the sparse PK data.
- CL was parameterized in the SD model as a nonlinear function of dose (i.e., power function) since:
  - GOF plots revealed a slight underprediction bias for population mean predicted concentrations with dose groups ≤ 50 mg;
  - boxplots of the empiric Bayesian PK parameters by dose group showed CL increased less than proportionally with dose; and
  - the addition of a dose effect on CL to the model resulted in a statistically significant decrease in the MVOF (43 units) and reduced the bias in the GOF plots.
- Plots of the individual predicted versus observed AUC0-12 values were unbiased for both SD and MD data (**Figure 3**)
- $AUC_{0\text{-}12}$ was unbiased (median PE% ± 1%) and was reasonably precise (median PE% < 3%) for both the SD and MD data.

RESULTS

Table 2:
Population Mean PK Parameter Estimates and Standard Errors for Select Models

Parameter	3-CMT fit to full-profile SD Data		3-CMT fit to full-profile SD Data		2-CMT fit to sparse SD Data[a,b]		2-CMT fit to sparse MD Data	
Mean Estimate	Population Mean Estimate	%SEM	Population Mean Estimate	%SEM	Population Mean Estimate	%SEM	Population Mean Estimate	%SEM
CL (L/hr)	16.3	3.2	16.8	4.2	Coeff = 7.69 Power = 0.294	15.7 12.8	16.3	4.6
Vc (L)	23.9	3.2	27.8	9.1	46.4	4.9	57.7	7.7
Q1 (L/hr)	18.9	5.0	3.02	15.2	86.1	5.6	74.7	11.3
Vp1(L)	523	6.7	388	31.4	248	3.6	1030	19.5
Q2 (L/hr)	106	3.0	100	5.9	---	---	---	---
Vp2(L)	226	3.4	439	6.0	---	---	---	---
IIV of CL (%CV)	33.9%	16.0	14.9%	39.8	24.9%	15.7	13.1%	50.1
IIV of Vc (%CV)	---	---	---	---	---	---	56.8%	34.7
IIV of Q1 (%CV)	47.8%	21.3	36.2%	61.9	55.5%	31.2	---	---
IIV of Vp1 (%CV)	36.7%	24.1	40.5%	65.9	35.5%	18.7	---	---
IIV of Q2 (%CV)	34.4%	16.6	---	---	---	---	---	---
IIV of Vp2 (%CV)	28.0%	15.1	---	---	---	---	---	---
RV (Loge SD)	0.13	14.5	0.15	11.5	0.09	19.1	0.11	21.4

[a] TVCL (L/hr) = 7.69•DOSE0.294 and was calculated to be 19.8, 24.3, 27.4 and 29.8 L/hr for the 25, 50, 75, and 100 mg dose groups, respectively.

[b] Covariances between CL and Vp (r2 = 0.434), CL and Q (r2 = 0.372), and Q and Vp (r2 = 0.727) were estimated.

DISCUSSIONS & CONCLUSIONS

- Both the SD and MD full-profile data were adequately described using an empiric 3-CMT model with zero order input and first-order elimination despite the presence of secondary peaks in some of the PK profiles.
- The SD and MD data were always fit separately to avoid any biases that may have resulted from trying to fit a model to all data combined. The following evidence supported the decision not to fit the combined data together with a simple linear PK model:
  - substantial differences for several of the model-estimated parameters (with the exception of CL and Vc);
  - longer elimination half-life values for MD versus SD data (mean values of 115 vs. 51 hr); and
  - reverse superpositioning demonstrated that the MD model consistently underpredicts the observed data from 0 to 12 hr following a SD.
- A mechanistic PK model would be required to fit SD and MD data together and properly characterize the attainment of steady-state conditions. This approach was not implemented given the lack of supportive data (e.g., limited number of subjects who had both SD and MD data, recording of meal times, etc.).
- A 2-CMT model provided unbiased and reasonably precise estimates of $AUC_{0\text{-}12}$ using the Phase 2/3 sparse sampling strategy and dose range.
- This work will support the development of a population PK model to characterize sparse TGC data in patients with cSSSI and cIA. The model may then be used to determine individual patient exposures for exposure-response analyses of safety and efficacy.

Fig. 1:
Population Mean Profile for the 3-CMT Model Fit to the Full-Profile SD Data (100 mg Dose Group only)

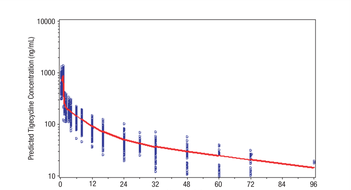
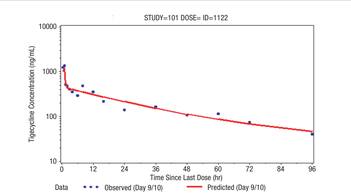


Fig. 2:
Semilog Plot of TGC Concentration versus Time Since Last Dose for a Subject in the MD Dataset with Secondary Peaks Post-Infusion



Figures 3a and 3b:
Plots of the Individual Predicted versus Observed AUC0-12 for the Reduced SD (Top) and MD (Bottom) Data