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Population Pharmacokinetics of Tigecycline in Patients with Complicated Intra-abdominal or Skin and Skin-Structure Infections

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ABSTRACT

Purpose
Tigecycline is a novel glycylcycline antibiotic demonstrating broad-spectrum *in vitro* activity. A previously developed population pharmacokinetic (PK) model was utilized to generate individual predicted $AUC_{0\text{-}12}$ estimates in patients with complicated skin and skin-structure infections (cSSSI) or complicated intra-abdominal infections (cIAI) in Phase 3 studies for use in future exposure-response analyses of safety and efficacy.

Methods
In 4 Phase 3 studies, tigecycline was infused over 0.5 hour (cIAI patients, n=155) or 1 hour (cSSSI patients, n=24) as a 100-mg loading dose followed by 50 mg every 12 hours for up to 14 days. A population PK model (2-compartment, zero-order input and first-order elimination; clearance as a function of creatinine clearance, weight, and sex) was previously developed using steady-state data from Phase 2 studies of patients with cSSSI and cIAI. The final Phase 2 parameter estimates were used as population priors. The model was applied separately to the Phase 3 cSSSI and cIAI data in NONMEM® to estimate empirical Bayesian PK parameters. Model performance was evaluated for both datasets by assessing goodness-of-fit, bias (PE%), and precision (|PE|%) for individual predicted tigecycline concentrations and steady-state $AUC_{0\text{-}12}$ values.

Results
The patient populations in Phase 2 and 3 cSSSI and cIAI studies had similar demographic characteristics and steady-state tigecycline concentrations. Goodness-of-fit plots revealed that the Phase 2 model provided a relatively unbiased fit to both Phase 3 datasets: the median PE% was ± 3% and 4%, while |PE|% was within 10% and 4% for the individual predicted tigecycline concentrations and $AUC_{0\text{-}12}$ values, respectively.

Conclusions
The feasibility of using a previously developed population PK model to predict individual $AUC_{0\text{-}12}$ in a new population with similar demographic and pharmacokinetic characteristics was explored. The Phase 2 population PK model for tigecycline provided an acceptably precise and relatively unbiased fit to the Phase 3 data, and resulted in unbiased estimates of $AUC_{0\text{-}12}$, without the need for further model refinement.

BACKGROUND

- Tigecycline (Tygacil™) is a first-in-class glycylcycline that exhibits a broad spectrum of activity against many aerobic and anaerobic gram-positive and gram-negative organisms, as well as atypical pathogens, including many multiple-drug resistant organisms.
- Tigecycline has a large steady-state volume of distribution, indicating extensive tissue distribution.
- Pharmacokinetic/pharmacodynamic (PK/PD) analyses in experimental animal models of infection have indicated that AUC:MIC ratio is the index that is most likely to correlate with the efficacy of tigecycline (AAC 44:943-949, 2000).
- Results from Phase 2/3 clinical trials demonstrated that tigecycline was efficacious and well tolerated in the treatment of complicated skin and skin-structure infections (cSSSI) and complicated intra-abdominal infections (cIAI).
- The Food and Drug Administration approved tigecycline for the treatment of these infections in June 2005, including cSSSI due to methicillin-resistant *Staphylococcus aureus*.
- A previously developed population pharmacokinetic (PK) model was used in the current analysis to generate individual predicted estimates of the area under the curve during the dosing interval at steady-state ($AUC_{0\text{-}12}$) in patients with cSSSI and cIAI in Phase 3 studies.

METHODS

Data
- Data from two Phase 3 studies in patients with cSSSI, or data from two Phase 3 studies in patients with cIAI, were used to assess the predictive performance of a population PK model previously developed using data from two Phase 2 studies (one each cIAI and cSSSI).
  - The study designs and tigecycline dosing regimens administered over 14 days are summarized in **Table 1**.
    - Based on the clinical judgment of the investigator, patients enrolled in these studies could have been discharged from the hospital after 3 days of inpatient therapy and received IV tigecycline doses at home.
    - The actual time of infusion termination was only recorded for the Phase 2 studies; the protocol-specified duration of infusion was therefore assumed for each Phase 3 study.
  - Blood (5 mL) was generally collected prior to dosing, at the end-of-infusion (either 0.5 or 1 h), and at 3 and 6 h post-start of infusion on the day before or day of discharge from the study unit.
  - Serum tigecycline concentrations were determined using a validated LC/MS/MS method with an LLOQ of 10 ng/mL.

Population PK Model
- The population PK model was a 2-compartment model with zero-order input and first-order elimination and clearance modeled as a function of creatinine clearance (CrCL), weight, and gender (**Table 2**).

Application of the Population PK Model to the Phase 3 Data
- The population PK model was applied separately to the pooled Phase 3 data from patients with cSSSI or cIAI.
  - All population mean parameters were fixed to the final Phase 2 estimates.
  - Bayesian PK parameter estimates were obtained for each patient in both datasets.
- Goodness-of-fit was assessed graphically for both datasets.

Predictive Performance Assessment
- Model performance was evaluated for each dataset by comparing the bias and precision of the steady-state $AUC_{0\text{-}12}$ values computed from individual predicted concentrations relative to steady-state $AUC_{0\text{-}12}$ values computed from observed concentrations.
- Patients were included in this assessment provided they:
  - contributed at least four observed concentrations per patient;
  - had a sample collected prior to dosing (e.g., trough) and another sample collected within 0.25 h of termination of the infusion; and
  - had a trough sample collected at 12 ± 0.5 h following a dose (trough concentrations were duplicated for use as an observed concentration at the end of the dosing interval).
- Bayesian PK parameter estimates were used to predict tigecycline concentrations at each of the observed sampling times.
- Observed and individual predicted steady-state $AUC_{0\text{-}12}$ values were calculated using the mixed log-linear trapezoidal rule and were plotted to assess potential biases.
- The difference between the observed and individual predicted $AUC_{0\text{-}12}$ was also calculated as a percentage of the observed $AUC_{0\text{-}12}$. The distributions of these prediction error percents (PE%) and the |PE|% were evaluated as measures of bias and precision, respectively.

RESULTS

Table 1: Tigecycline Study Designs, Dosing Regimens, and Number of Patients Included in the PK Analysis

Study	Description	No. of Patients	Dosage Regimen(s)[a]	Infusion Duration
1	Multicenter, randomized, open-label, Phase 2 study of tigecycline safety and efficacy in hospitalized patients with cSSSI	43 35	50 mg + 25 mg q12h 100 mg + 50 mg q12h	1 h
2	Multicenter, open-label, Phase 2 study of tigecycline safety and efficacy in hospitalized patients with cIAI	68	100 mg + 50 mg q12h	1 h
3 & 4	Multicenter, randomized, Phase 3, double-blind comparisons of the safety and efficacy of tigecycline to that of vancomycin and aztreonam in hospitalized patients with cSSSI	24	100 mg + 50 mg q12h	1 h
5 & 6	Multicenter, randomized, Phase 3, double-blind comparisons of the safety and efficacy of tigecycline to that of imipenem and cilastatin in hospitalized patients with cIAI	155	100 mg + 50 mg q12h	0.5 h

[a] Tigecycline was administered for up to 14 days

Table 3: Baseline Characteristics for Each Analysis Dataset

Parameter	Phase 2 Model Development Patients (n=146)	Phase 3 cSSSI Patients (n=24)	Phase 3 cIAI Patients (n=155)
Age (yr)[a]	45.7 (15.6), 18-82	41.8 (16.7), 21-78	47.5 (17.7), 18-85
Weight (kg)[a]	84.3 (25.8), 47-227	83.7 (32.9), 57-200	73.9 (14.6), 45-122
CrCL (mL/min/1.73 m²)[a]	91.9 (36.9), 24.2-278	90.5 (25.6), 40.2-152	83.0 (27.1), 22.1-186
Gender, n (%)			
Male	103 (70.6)	18 (75.0)	95 (61.0)
Female	43 (26.9)	6 (25.0)	60 (39.0)
Ethnicity, n (%)			
Caucasian	63 (43.2)	21 (87.5)	141 (91.0)
Black	20 (14.1)	0 (0)	9 (5.8)
Hispanic	60 (41.1)	3 (12.5)	0 (0)
Other	3 (2.1)	0 (0)	5 (3.2)

[a] Values presented as Mean (SD), minimum-maximum

Table 4: Summary Statistics for PE% and |PE|% of the Steady-State $AUC_{0\text{-}12}$, by Dataset

Parameter	Phase 2 Model Development Dataset (n=130)	Phase 3 cSSSI Dataset (n=16)	Phase 3 cIAI Dataset (n=107)
PE%[a]			
Mean (SD)	-3.47 (9.14)	-1.44 (5.76)	-5.54 (7.32)
Median	-1.60	-2.00	-3.78
Min-Max	-59.8-14.3	-10.9-13.6	-48.5-3.76
|PE|%			
Mean (SD)	5.25 (8.24)	4.34 (3.91)	5.99 (6.96)
Median	2.94	3.37	3.78
Minimum-Maximum	0.021-59.8	0.005-13.6	0.114-48.5

[a] PE%=[(observed $AUC_{0\text{-}12}$-individual predicted $AUC_{0\text{-}12}$)/observed $AUC_{0\text{-}12}$]·100

Figure 1: Semilog Plot of Serum Tigecycline Concentration Versus Time Since Last Dose for Patients Administered 100 mg + 50 mg q12h

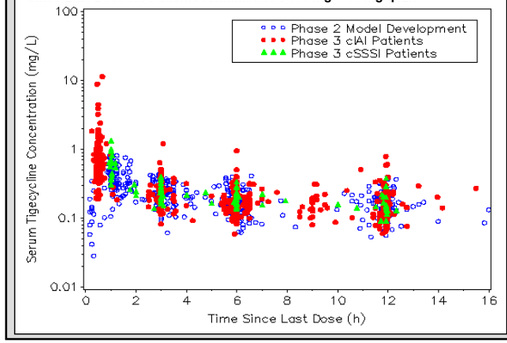

Figure 2: Individual Predicted Versus Observed Steady-State Tigecycline $AUC_{0\text{-}12}$ Values for the Phase 2 Model Development (Top), and Both the Phase 3 cSSSI (Bottom Left) and Phase 3 cIAI (Bottom Right) Datasets

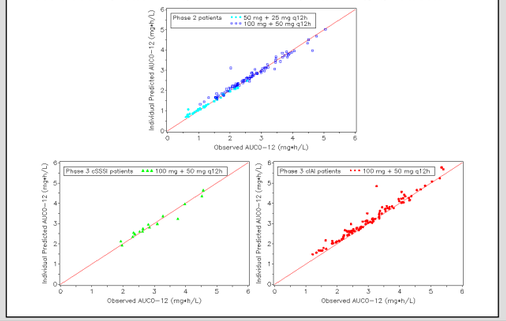

Table 2: Population Mean (%SEM) of the PK Parameters for the Population PK Model

Parameter	Final Model[a,b]
CL (L/h)	15.7 (8)
CL-WTKG slope	0.0943 (28)
CL-CrCL power	0.250 (38)
Additive Shift on CL for Males	3.23 (37)
Vc (L)	115 (7)
Q (L/h)	70.9 (7)
Vp (L)	644 (20)
IIV of CL (%CV)	35.1 (19)
IIV of Vc (%CV)	43.2 (27)
IIV of Q (%CV)	49.3 (35)
IIV of Vp (%CV)	NE
RV (%CV)	21.0 (13)

[a] Population mean CL_i (L/h)=15.7·(CrCL/88.3)$^{0.250}$+0.0943·(WTKG-80)+3.23·MALE; $CrCL_i$ is the creatinine clearance (mL/min) of the i^{th} patient, $WTKG_i$ is the weight (kg) of the i^{th} patient, and MALE is 1 if the i^{th} patient is male and 0 if the i^{th} patient is female

[b] Covariances between η_{CL},η_{Vc} (r^2=0.385), η_{CL},η_Q (r^2=0.095), and η_Q,η_{Vc} (r^2=0.666) were estimated

NE=not estimated

Data
- The Phase 3 cSSSI dataset consisted of 84 serum tigecycline concentrations obtained from 24 patients; the cIAI patient dataset consisted of 583 serum tigecycline concentrations from 155 patients.
- Patient demographics (**Table 3**) and the range of tigecycline serum concentrations and sampling times (**Figure 1**) were similar between the two Phase 3 datasets and the Phase 2 model development dataset.

Application of the Population PK Model to the Phase 3 Data
- The population PK model provided an adequate and relatively unbiased fit to both Phase 3 datasets based upon examination of goodness-of-fit plots.
- The model had a slightly higher tendency to under predict concentrations at the end of the infusion for both Phase 3 datasets than for the model development dataset. This may be due to the fact that the actual infusion duration was not recorded and required making the assumption that tigecycline was infused over the protocol-specified time period.

Predictive Performance Assessment
- Individual predicted $AUC_{0\text{-}12}$ values were in general agreement with the observed $AUC_{0\text{-}12}$ values, and no strong biases were observed over the range of observed $AUC_{0\text{-}12}$ values for each dataset (**Figure 2**).
- Summary statistics for PE% and |PE|% for $AUC_{0\text{-}12}$ were calculated for each dataset and are provided in **Table 4**.
- Although the population PK model appeared to slightly under predict $AUC_{0\text{-}12}$ for patients in each dataset, $AUC_{0\text{-}12}$ was generally unbiased (median PE% ranged from -1.60 to -3.78%) and acceptably precise (median |PE|% ranged from approximately 3 to 4%) across datasets.

CONCLUSIONS

- A previously developed population PK model for tigecycline based on Phase 2 data provided an acceptably precise and relatively unbiased fit to the sparse-sampling data from Phase 3 trials of patients with cIAI and cSSSI without the need for further model refinement.
- Individual predicted steady-state $AUC_{0\text{-}12}$ estimates in Phase 3 patients were also acceptably precise and unbiased and will be utilized in additional exposure-response analyses for safety and efficacy in the respective patient populations.