Population Pharmacokinetic Analyses of Omadacycline Using Phase 1 and 3 Data

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INTRODUCTION

- Omadacycline is a novel aminomethylcycline that is synthesized by chemical modification of minocycline.
  - Active against Gram-positive, Gram-negative, anaerobic, and atypical pathogens [1].
  - Overcomes efflux pump and ribosomal protection mechanisms of tetracycline resistance [1].
  - Currently in development for the treatment of patients with acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP).
- An omadacycline population pharmacokinetic (PK) model was previously developed using data from Phase 1 studies in healthy volunteers [2].
  - The model was able to characterize the impact of different oral formulations as well as the omadacycline food-effect.
  - Since the development of this population PK model, pharmacokinetic data from additional studies, including studies in infected patients, have become available.

OBJECTIVES

- The objectives of these analyses were the following:
  - To refine the previously-developed population PK model using data from additional Phase 1 studies, one Phase 1b uncomplicated urinary tract infection (uUTI) study, one Phase 3 CABP study, and two Phase 3 ABSSSI studies and;
  - To characterize relationships between patient-specific covariates and omadacycline PK parameters.

METHODS

Data

- 11 Phase 1 studies were used to construct previous population PK models [2, 3].
- Two additional Phase 1 studies:
  1. A study evaluating intravenous (IV) omadacycline adult subjects with end-stage renal disease (ESRD) on hemodialysis to matched healthy adult subjects.
  2. A healthy volunteer study comparing the pharmacokinetics of 300, 450, and 600 mg oral (PO) doses of oral omadacycline administered daily over 5 days.
- One Phase 1b uUTI study:
  - Group 1: 200 mg IV on Day 1 followed by 300 mg PO q24h Days 2-5.
  - Group 2: 300 mg PO q12h on Day 1 followed by q24h Days 2-5.
  - Group 3: 450 mg PO q12h on Day 1 followed by q24h Days 2-5.
  - Rich PK sampling on Days 1 and 5.
- One Phase 3 CABP study:
  - 100 mg IV q12h on Day 1 followed by 100 mg IV/ 300 mg PO q24h for up to a total of 14 days.
- Three Phase 3 ABSSSI studies:
  1. 100 mg IV q12h on Day 1 followed by 100 mg IV/ 300 mg PO q24h for up to a total of 14 days.
  2. 100 mg IV q24h for 4 -7 days followed by 300 mg PO q24h for up to a total of 14 days.
  3. 450 mg PO every q24h for 2 doses followed by 300 mg PO q24h up to a total of 14 days.
     - PK data from this study were only used for external model qualification as data were not available during model development.

Population PK Model

- Candidate population PK models were fit to the pooled PK data using NONMEM® Version 7.2, implementing the first-order conditional estimation method with η-ε interaction (FOCE-I).
- Interindividual variability for each PK parameter was described, where possible, using an exponential error model assuming a log-normal distribution.
- A combined additive plus constant coefficient of variation (CCV) error model was used to describe plasma residual variability, and a CCV error model was used to describe the epithelial lining fluid (ELF) residual variability.
- Model discrimination was performed by evaluating mean PK parameter estimates and their precision, graphical examination of standard goodness-of-fit plots, reduction in both residual variability (σ^2) and interindividual variability (ω^2), and comparison of the objective function for nested models.
- The ability of subject demographics (race, age, sex), various body size measures, albumin level, renal function, presence of cirrhosis, and presence of various infections to explain a portion of the interindividual variability (IIV) in selected omadacycline PK parameters was then explored using stepwise forward selection ($\alpha = 0.01$) and backward elimination ($\alpha = 0.001$) procedures.
- A prediction-corrected visual predictive check (PC-VPC) was used to evaluate the ability of the model to adequately describe the observed PK data used for model development.
- The final model was externally validated through a PC-VPC, and compared model-based predictions to observed data from the third Phase 3 ABSSSI study, which was not utilized for model development.

RESULTS

Data

- The final analysis dataset consisted of 11331 plasma PK samples collected from a total of 613 subjects.
  - 88.4% of plasma PK samples were collected from Phase 1 studies.
  - Of the 613 subjects, 180 (29.4%) were enrolled in Phase 3 studies, 31 (5.1%) were enrolled in the Phase 1b uUTI study, and the remaining subjects were enrolled in Phase 1 studies.
    - Of the 180 subjects enrolled in the Phase 3 studies, 50 were enrolled in the CABP study. The remaining were enrolled in one of the three Phase 3 ABSSSI studies.
- Summary statistics of baseline subject descriptors for the overall PK analysis population are presented in **Table 1**.

Table 1. Summary statistics of subject demographics and clinical laboratory measures for the overall PK analysis population

Variable		N (%)	Mean (SD)	Median	Minimum	Maximum
Age (yr)		613	39.3 (14.8)	37.0	18	88
Weight (kg)		613	78.4 (14.6)	77.5	36.0	148
Height (cm)		613	173 (9.2)	174	137	201
BSA (m^2)		613	1.92(0.19)	1.92	1.25	2.73
BMI (kg/m^2)		613	26.2 (4.5)	25.6	16.0	49.3
CLcr (mL/min/1.73 m^2)		613	99.8 (28.1)	113	5.5	185
Albumin (mg/dL)		613	4.33 (0.46)	4.40	2.20	5.30
Race	Caucasian	433 (70.6)	—	—	—	—
	Black	105 (17.1)	—	—	—	—
	Asian	12 (2.0)	—	—	—	—
	Other	63 (10.3)	—	—	—	—
Sex	Male	435 (71.0)	—	—	—	—
	Female	178 (29.0)	—	—	—	—
Presence of cirrhosis	No	595 (97.1)	—	—	—	—
	Yes	18 (2.9)	—	—	—	—

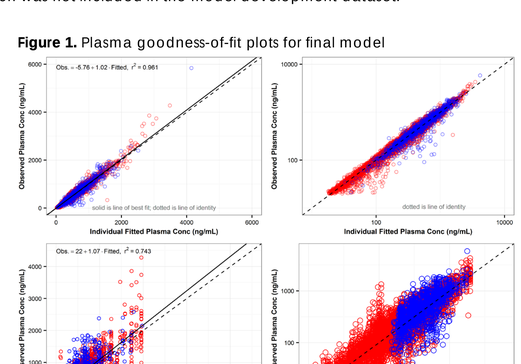
Note: SD = Standard deviation.

RESULTS

Population PK Model

- The structural model was a linear, three-compartment model with zero order IV input and first-order absorption using transit compartments to account for a delay in oral absorption following administration of the tablet or capsule formulations.
  - ELF concentrations were modeled as a subcompartment of peripheral compartment 1 [3].
    - In the model, omadacycline distributes between the central compartment and peripheral compartment 1 in a similar manner as the central compartment and ELF compartment; however, ELF concentrations are scaled using "FRAC" term (**Table 2**).
  - Oral bioavailability decreased when food was administered before or after oral dosing. This effect was greater when food was taken prior to oral administration of omadacycline or when the food contained dairy products.
  - Sex was the only significant covariate identified.
- The final parameter estimates and their associated precision (%SEM) for the final population PK model describing the time course of omadacycline plasma and ELF PK profiles are provided in **Table 2**.
  - The mean (percent coefficient of variation [%CV]) of the clearance (CL) was 10.3 (22.3%) and 8.69 L/hr (22.3%) for males and females, respectively.
- Goodness-of-fit diagnostics indicated an unbiased fit to the data as seen in **Figure 1**.
  - There was excellent agreement between the observed plasma omadacycline concentrations and both the population predicted ($r^2 = 0.743$) and individual predicted ($r^2 = 0.961$) concentrations.
- Using an omadacycline protein binding value of 21% and the final population PK model, the total-drug ELF:free-drug plasma penetration ratio was estimated to be 2.06 [4].
- As shown in **Figure 2**, the final model was also able to predict the central tendency and distribution of concentration-time profiles using data for a Phase 3 ABSSSI study, which was not included in the model development dataset.

Figure 1. Plasma goodness-of-fit plots for final model



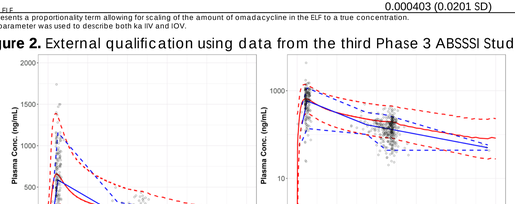
RESULTS

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

Parameter	Final estimate	%SEM
CL (L/hr)	10.3	0.682
Proportional change in females	-0.156	12.0
Vc (L)	21.1	2.20
CLd1 (L/hr)	101	2.20
Proportional change in females	0.500	27.6
Vp1 (L)	79.9	0.0842
Proportional change in females	-0.176	16.9
CLd2 (L/hr)	21.3	0.242
Vp2 (L)	129	1.45
Proportional change in females	-0.271	9.45
ka (hr^{-1})	1.74	1.55
F_0	0.00663	4.99
F_{max}	0.252	0.996
Proportional decrease for Capsugels or freebase capsules > 200 mg	-0.280	21.8
$AMTIME_{50}$ (hr)	0.568	0.0567
Proportional increase for consuming food pre-dose	1.68	8.15
Proportional increase for consuming food w/dairy products pre-dose	3.59	4.48
γ	1.73	0.484
ELF Frac[a]	1.63	5.69
ω^2 for CL	0.0497 (22.3% CV)	7.72
ω^2 for Vc	0.885 (94.1% CV)	10.9
ω^2 for CLd1	0.423 (65.0% CV)	10.8
ω^2 for Vp1	0.0776 (27.9% CV)	10.6
ω^2 for Vp2	0.0759 (27.5% CV)	9.59
ω^2 for F	0.154 (39.2% CV)	5.28
ω^2 for ka	0.0599[b] (24.5% CV)	4.79
IOV for ka	0.0599[b] (24.5% CV)	4.79
IOV for F	0.0495 (22.2% CV)	3.21
Covariance(CL,CLd1)	-0.0415 ($r^2 = 0.0819$)	23.3
Covariance(CL,Vp2)	0.0258 ($r^2 = 0.176$)	16.4
$\sigma^2_{CCV, plasma}$	0.0217 (14.7% CV)	0.0399
$\sigma^2_{Additive, plasma}$	0.00145 (0.0381 SD)	0.163
$\sigma^2_{CCV, ELF}$	0.206 (45.4% CV)	24.5
$\sigma^2_{Additive, ELF}$	0.000403 (0.0201 SD)	Fixed

a. Frac represents a proportionality term allowing for scaling of the amount of omadacycline in the ELF to a true concentration.
b. A single parameter was used to describe both ka IIV and IOV.

Figure 2. External qualification using data from the third Phase 3 ABSSSI Study



CONCLUSIONS

- A population PK model describing omadacycline PK in healthy subjects and infected patients was successfully developed.
- This model supported subsequent assessments of pharmacokinetic-pharmacodynamic (PK-PD) relationships for efficacy and PK-PD target attainment [5].

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Poster No. SATURDAY 628

American Society for Microbiology Microbe 2018, Atlanta, GA. June 7-11, 2018

Funding for this analysis was provided by Paratek Pharmaceuticals, Inc., King of Prussia, PA, USA