Population Pharmacokinetics of Omadacycline Following Intravenous or Oral Administration to Phase 1 Subjects

S.A. Van Wart[1], A. Manley[2], S.M. Bhavnani[1], K. Tanaka[2], E. Loh[2], C.M. Rubino[1], E. Tzanis[2], P.G. Ambrose[1]

[1]ICPD, Latham, NY; [2]Paratek Pharmaceuticals, Inc., Boston, MA

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Introduction

- Omadacycline, a novel aminomethylcyline synthesized by chemical modification of minocycline, is active against both Gram-positive and Gram-negative organisms.
- Omadacycline is available for both intravenous (IV) and oral administration and is currently in phase 3 of development for treatment of acute bacterial skin and skin structure infections or community-acquired bacterial pneumonia.
- A population pharmacokinetic (PPK) analysis was conducted to characterize the time-course of omadacycline in plasma and excretion into the urine of healthy volunteers following IV and/or oral administration, as well as to evaluate the impact of formulation differences and food on the rate and extent of omadacycline absorption.

Materials and Methods

Data

- The population PK analysis was conducted in NONMEM 7.2 using plasma PK data from 319 subjects (including 18 with cirrhosis) who participated in 10 Phase 1 clinical trials.
- Subjects were administered omadacycline freebase or tosylate salt as IV (50 or 100 mg), oral capsule (50 to 600 mg) or tablet (150 to 300 mg) doses; food was consumed at varying times within a 4 hour window prior to or after oral dosing across studies.
- Serial PK samples collected in each study were assayed using LC-MS/MS (lower limit of quantitation of 20 ng/mL) to determine plasma omadacycline concentrations.

Population Pharmacokinetic Analysis

- Both 2- and 3-compartment (CMT) models with zero-order input and first-order elimination were first evaluated using only IV data.
  - ❑ The models were parameterized using total clearance (CL), central volume (Vc), distribution clearances (CLd1 and CLd2), and peripheral volumes (Vp1 and Vp2).
  - ❑ Interindividual variability (IIV) for PK parameters was described using an exponential model; an additive plus constant coefficient of variation model was used for residual error.
- The population PK model was then modified to simultaneously fit the data obtained after IV or oral dosing
  - ❑ Oral bioavailability (F) and first-order absorption rate (k_a) and their IIV were estimated.
  - ❑ An absorption lag-time or transit absorption compartments were also explored to better account for the delay in the onset of oral absorption.
  - ❑ Interoccasion variability (IOV) was also estimated for k_a.
  - ❑ Omadacycline oral formulation differences, as well as the timing of meals relative to dose administration, were explored as covariates on both F and k_a.
  - ❑ Subject covariates such as age, weight, BMI, creatinine clearance (CLcr), etc. were then analyzed using stepwise forward selection (α=0.01) and backward elimination (α=0.001).
- Lastly, plasma and urine PK data (6 subjects only) were co-modeled to independently estimate renal (CL_R) and non-renal (CL_{NR}) clearance, and a prediction corrected visual predictive check (PC-VPC) was performed to evaluate final model fit.

Results

Pharmacokinetic Analysis Population

- The PK analysis population (N = 319) was 81.2% male and 75.2% Caucasian. The mean (SD) age was 32.8 (11.0) years, weight was 75.8 (10.9) kg, and CLcr was 107 (19.6) mL/min/1.73 m^2 and ranged from 52.8 to 185 mL/min/1.73 m^2.

Final Population Pharmacokinetic Model

- A 3-CMT model with zero-order IV input, or first-order oral absorption with 2 transit CMTs to provide delayed absorption, best characterized omadacycline PK (**Figure 1** and **Table 1**).

Results (continued)

- Observed plasma concentrations agreed well with the population (r^2=0.74) and individual post-hoc (r^2=0.96) predictions (**Figure 2**) and PC-VPCs (**Figure 3**) showed a reasonable fit by formulation.
- Non-renal CL was 5.72 L/hr, while renal CL was linearly related to CLcr (4.62 L/hr at the median of 109 mL/min/1.73 m^2) for the range of renal function studied.
- Body size was not predictive of Vc (24.3 L) but steady-state volume of distribution (225 L) indicated extensive tissue distribution.
- Cirrhosis did not impact total CL, although Vc was 74.4% lower relative to healthy subjects.
- F was determined using absolute time of food consumption relative to dosing (AMTIME) via a Hill-type function which estimated F for consuming food exactly at dosing (F_0) , the maximal increase in F in the absence of food (F_{max}) and the AMTIME at which F_{max} decreased by 50% ($AMTIME_{50}$)
- F was more sensitive to food consumption pre-dose (**Figure 4**); F was <3% when omadacycline was administered just prior to a meal and 27-30% when meals were restricted to 2-4 hours post-dose.

Table 1. Parameter estimates for the final population PK model

Parameter	Final Estimate	%SEM
CL_{NR} (L/hr)	5.72	1.28
CL_R (L/hr) coefficient at CLcr = 109 mL/min/1.73 m^2	4.62	1.85
Vc (L) for healthy subject	24.3	3.97
Vc for hepatic cirrhosis subject (L)	6.23	27.6
CLd1 (L/hr)	92.0	0.27
Vp1 (L)	76.3	0.16
CLd2 (L/hr)	22.1	1.05
Vp2 (L)	124	0.82
ka (hr^{-1})	1.77	1.98
F_0	0.00680	1.02
F_{max} for Tablets and freebase capsules ≤ 200 mg	0.293	1.96
Decrease for Capsugel/freebase capsules >200 mg	-36.9%	9.87
$AMTIME_{50}$ (hr)	0.581	0.03
Increase for food pre-dose	158%	7.36
Increase for food with dairy pre-dose	346%	4.00
γ	1.68	1.85
ω^2 for total CL	0.0428 (20.7% CV)	14.1
ω^2 for Vc	0.955 (97.7% CV)	23.2
ω^2 for CLd1	0.512 (71.6% CV)	8.40
ω^2 for Vp1	0.0437 (20.9% CV)	20.0
ω^2 for Vp2	0.0418 (20.4% CV)	13.9
ω^2 for F+	0.0514 (22.7% CV)	13.5
ω^2 for ka	0.0679 (26.1% CV)	6.53
IOV for ka	0.0679 (26.1% CV)	6.53
IOV for F	0.0350 (19.5% CV)	7.49
Covariance (CL,Vc)	0.146 (r^2 = 0.521)	21.9
Covariance (CL,Vp2)	0.0326 (r^2 = 0.594)	17.0
Covariance (Vc,Vp2)	0.117 (r^2 = 0.343)	23.6
$\sigma^2_{CCV, plasma}$	0.0210 (14.5% CV)	0.88
$\sigma^2_{Additive, plasma}$	0.00395 (0.0628 SD)	6.77
$\sigma^2_{Additive, urine}$	0.466 (0.683 SD)	19.5

Figure 1. Population PK model diagram

Figure 2. Goodness-of-fit plots for final model

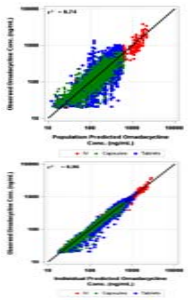


Figure 3. PC-VPC by formulation

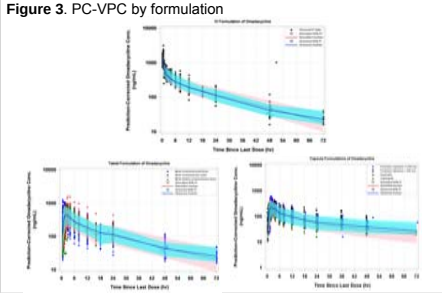
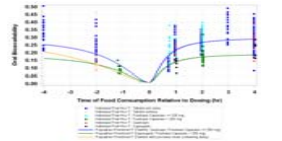


Figure 4. Food effect on relative F



Conclusions

- A PPK model including significant covariate effects for omadacycline was developed using Phase 1 data. This model provided the basis for recommending food consumption be restricted to at least 4 hours prior to or 2 hours after administration of an oral omadacycline dose.
- Although only a limited range of renal function has been studied to date, this PPK model will be further updated after including additional omadacycline PK from individuals with moderate or severe renal impairment and used to support dosing guidelines for renal impairment.