Population Pharmacokinetics of Omadacycline Following Intravenous and Oral Administration and Evaluation of Phase 3 Sparse PK Sampling Strategies

Scott A. Van Wart[1], Amy Manley[2], Sujata M. Bhavnani[1], Ken Tanaka[2], Evan Loh[2], Evan Tzanis[2], Paul G. Ambrose[1]

[1]Institute for Clinical Pharmacodynamics, Schenectady, NY; [2]Paratek Pharmaceuticals, Inc. Boston, MA

ICPD INSTITUTE for CLINICAL PHARMACODYNAMICS

Scott A. VanWart, M.S., Ph.D.
Institute for Clinical Pharmacodynamics
242 Broadway
Schenectady, NY 12305
Telephone: (518) 429-2600 / (518) 631-8100
E-mail: SVanWart@ICPD.com

ABSTRACT

Background: Omadacycline is a first-in-class aminomethylcycline antibiotic currently being developed to treat acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia. A population PK model for omadacycline developed using Phase 1 data was used to evaluate potential Phase 3 sparse PK sampling strategies.

Methods: A 3-compartment model with zero-order IV input, or first-order oral absorption with transit compartments, best described plasma PK data from 281 subjects. Clearance (CL) was a function of creatinine clearance; bioavailability (F) was estimated based upon the timing of a meal relative to dosing. Using this model, PK data were simulated for 2000 patients and were administered 100 mg IV q12h on Day 1, followed by 100 mg q24h thereafter. Patients were randomly switched to 300 mg oral omadacycline q24h between Days 4 and 7. Maximum a-posteriori (MAP) Bayesian estimation was performed in NONMEM for various PK datasets with 2 samples each on Days 1 and 7. Absolute prediction error percent (|PE%|) for the Bayesian PK estimates relative to the true values were calculated for CL, steady-state volume of distribution, F, and the maximum concentrations after IV and oral dosing. The median |PE%| for each parameter within each sparse PK sampling scheme was calculated.

Results: The simulated patient data, with circles depicting suggested PK sampling times, are shown in **Figure 4** using an interactive R-Shiny app. Based on a composite ranking of |PE%| across parameters, PK samples should be collected 3 to 5 h and at 12 h after first IV dose on Day 1, and pre-dose and 1 to 3 h after oral dosing on Day 7.

Conclusions: A population PK model for omadacycline developed using Phase 1 data was used to recommend a Phase 3 sparse PK sampling strategy.

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 patients with acute bacterial skin and skin structure (ABSSSI) infections or community-acquired bacterial pneumonia.
- A population pharmacokinetic (PK) analysis was previously conducted to characterize the time-course of omadacycline in plasma and excretion into the urine of healthy volunteers, followed by 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 [1].
- During development of this population PK model for omadacycline, the model was used to evaluate potential sparse PK sampling strategies for use in planned Phase 3 trials in which patients with skin and skin structure infections were to be switched from IV to oral treatment.

OBJECTIVE

- To utilize a population PK model for omadacycline, which was developed using Phase 1 data to evaluate potential sparse PK sampling strategies for use in Phase 3 trials in patients with ABSSSI who switched from IV to oral treatment.

METHODS

Population Pharmacokinetic Model

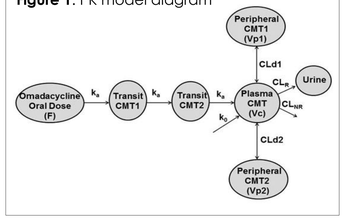
- The population PK model for omadacycline was constructed in NONMEM 7.2 using plasma PK data from 319 subjects (including 18 with cirrhosis) who participated in 10 Phase 1 clinical trials. Urine PK data was also available in a small subset of subjects (N=6).
- The population PK analysis population (N=319) was 81.2% male and 75.2% Caucasian. The mean (SD) age was 32.8 (11.0) years, and weight was 75.8 (10.9) kg. Creatinine clearance (CLcr) was 107 (19.6) mL/min/1.73 m^2 and ranged from 52.8 to 185 mL/min/1.73 m^2.
- 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 four-hour window prior to or after oral dosing.

METHODS

Population Pharmacokinetic Model (continued)

- A 3-compartment (CMT) model with zero-order IV input, or first-order oral absorption with 2 transit CMTs to provide delayed absorption, was used to characterize the omadacycline plasma PK data from these studies (**Table 1** and **Figure 1**).
- The model was parameterized using total clearance (CL), central volume of distribution (Vc), distribution clearances (CLd1 and CLd2), peripheral volumes of distribution (Vp1 and Vp2), oral bioavailability (F), and a first-order oral absorption rate (k_a).
- Interindividual variability (IIV) for PK parameters was described using an exponential model; interoccasion variability (IOV) was also estimated for k_a.
- Separate additive plus constant coefficient of variation models were used to describe residual error for the plasma and urine PK data.

Figure 1. PK model diagram



- For the final population PK model, the observed plasma concentrations agreed well with the population (r^2=0.74) and individual post-hoc (r^2=0.96) predictions and prediction-corrected visual predictive checks showed a reasonable fit by formulation.
- Non-renal CL (CL_{NR}) was 5.72 L/hr, while the renal component of CL (CL_R) 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 at dosing time(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; 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[1]	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

METHODS

Monte Carlo Simulations to Assess Phase 3 Sparse Pharmacokinetic Sampling Strategies

- Monte Carlo simulation (MCS) was performed to generate 2000 patients, with CLcr values derived from a normal distribution based upon the Phase 1 subjects.
- To reflect the potential dosing scheme utilized in Phase 3 trials, simulated patients received 100 mg of IV omadacycline infused over 0.5 h q12h on Day 1, followed by 100 mg of IV omadacycline infused over 0.5 h once-daily thereafter.
- Simulated patients were to be switched to oral once-daily omadacycline tablets, with 25% switching on Day 4, 50% by Day 5, 75% by Day 6, and 100% by Day 7.
- The population PK model was applied to the simulated patient population to generate "true" individual PK parameter estimates, and output simulated plasma omadacycline concentrations at selected PK sampling times for each patient.

Evaluation of the Phase 3 Sparse Pharmacokinetic Sampling Strategies

- Maximum a posteriori (MAP) Bayesian estimation was performed using the population PK model for omadacycline, and 143 possible datasets comprised of different combinations of four-PK sample schemes per patient . Only those time points considered to be both informative of omadacycline PK and clinically convenient were evaluated(**Table 2**).

Table 2. Various combinations of four-sample sparse PK sampling schemes evaluated

Options for sample time 1	Sample time 2	Sample time 3	Options for sample time 4
0.75 hr	12 hr	24 hr	0.5 hr (Time = 144.5 hr)
1 hr	(Time = 12 hr)	(Time = 144 hr)	1 hr (Time = 145 hr)
1.5 hr			1.5 hr (Time = 145.5 hr)
2 hr			2 hr (Time = 146 hr)
2.5 hr			2.5 hr (Time = 146.5 hr)
3 hr			3 hr (Time = 147 hr)
4 hr			4 hr (Time = 148 hr)
5 hr			5 hr (Time = 149 hr)
6 hr			6 hr (Time = 150 hr)
7 hr			7 hr (Time = 151 hr)
8 hr			8 hr (Time = 152 hr)
			9 hr (Time = 153 hr)
			10 hr (Time = 154 hr)

- Since free-drug AUC:MIC ratio is expected to be the most relevant clinical index for efficacy, when evaluating the utility of the various sparse PK sampling schemes priority was given to the ability to generate precise estimates of CL and F in order to be able to estimate individual patient AUC values after either IV or oral dosing. Therefore, samples number 2 and 3 were forced to be PK samples toward the end of the IF or oral dosing interval.
- Individual PK parameters were obtained for each of the 2000 simulated patients within each dataset. The prediction error percent (%PE) and absolute prediction error (|PE%|) for the individual PK parameter estimates relative to the "true" simulated PK parameters for each subject were calculated for CL, steady state volume of distribution (Vss), F, and the maximum plasma concentration (C_{max}) after an IV dose (Day 1) or an oral dose at steady-state (Day 7).
- The median PE% and |PE%| across all 2000 subjects for each sparse PK sampling scheme evaluated was calculated separately for each PK parameter (CL, Vss, F, and C_{max} after an IV or oral dose). An average composite score across all five parameters was then used to rank the utility of each sparse PK sampling scheme based upon median |PE%|.
- An interactive R-Shiny app was also created to show an overlay of the selected PK sampling times relative to the expected PK for dosing regimens of interest.

RESULTS

- Based upon ranking the average composite score across all five PK parameters for CL, Vss, F, and C_{max} after an IV or oral dose, the top 10% of the four-sample sparse PK sampling schemes , as shown in **Table 3**, had a sample collected at the following times:
  - Between 3 and 8 hours and at 12 hours after the first IV dose on Day 1.
  - Pre-dose and between 1 and 3 hours after an oral dose at steady-state (Day 7).
- The median PE% and |PE%| for all five PK parameters were reasonably acceptable (**Table 4**) regardless of whether the samples were collected between 3 to 5 hours or 5 to 8 hours after the first IV dose in Day 1; therefore, the earlier window was selected for clinical convenience.

RESULTS

Table 3. Top 10% of PK sampling schemes based upon composite average rank of median |PE%|

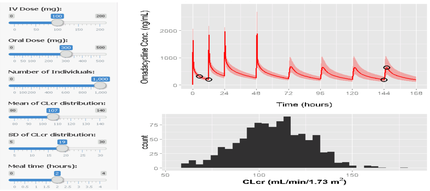
PK sample times (hr)	Median |PE%| rank by parameter						Median |PE%| by parameter				
	CL	Vss	F	IV C_{max}	Oral C_{max}	Average rank	CL	Vss	F	IV C_{max}	Oral C_{max}
8, 12, 144, 146	12	22	35	28	29	25.2	5.73	8.78	11.0	17.8	9.50
8, 12, 144, 145	5	17	124	9	15	34.0	5.70	8.72	13.3	17.2	9.25
8, 12, 144, 145.5	6	33	107	16	14	35.2	5.70	8.82	11.9	17.4	9.23
5, 12, 144, 146.5	42	25	22	54	37	36.0	5.87	8.80	10.9	18.4	10.7
8, 12, 144, 146.5	8	77	18	37	42	36.4	5.71	9.04	10.8	18.0	10.8
7, 12, 144, 145.5	17	35	117	14	3	37.2	5.76	8.83	12.5	17.3	9.10
6, 12, 144, 145	30	12	122	6	20	38.0	5.82	8.66	13.2	17.1	9.31
7, 12, 144, 145	14	40	128	2	16	40.0	5.75	8.86	13.4	16.7	9.26
3, 12, 144, 146.5	60	20	21	61	40	40.4	6.03	8.76	10.9	18.7	10.7
3, 12, 144, 146	62	29	46	43	25	41.0	6.04	8.81	11.1	18.2	9.43
3, 12, 144, 145	52	13	129	8	4	41.2	5.92	8.67	13.4	17.2	9.11
5, 12, 144, 147	22	23	2	99	62	41.6	5.78	8.79	10.1	19.2	12.0
6, 12, 144, 145.5	34	36	112	20	11	42.6	5.84	8.83	12.1	17.5	9.21
5, 12, 144, 146	48	28	60	52	26	42.8	5.90	8.81	11.2	18.4	9.44
8, 12, 144, 146	10	94	3	45	63	43.0	5.72	9.13	10.1	18.2	12.0

Table 4. Bias and precision of PK parameters when using various PK sampling windows

PK sample times (hr)	Median PE% by parameter					Median |PE%| by parameter				
	CL	Vss	F	IV C_{max}	Oral C_{max}	CL	Vss	F	IV C_{max}	Oral C_{max}
3 to 5, 12, 144, 145 to 147	0.63	1.39	-1.18	-0.18	-0.41	6.06	8.93	11.5	18.2	9.99
5 to 8, 12, 144, 145 to 147	0.54	1.50	-1.11	-0.44	-0.59	5.81	8.90	11.5	18.0	10.0

- Simulations were then conducted using an interactive R-Shiny app, as shown in **Figure 2** with the sparse PK sample collection times recommended added. This helps illustrate how the PK sampling scheme aligns with the median and 90% prediction interval for patients with varying degrees of renal function given various omadacycline dosing regimens, and when a meal was consumed at various times post-dose (2 hours post-dose was used for illustration).

Figure 2. MCS performed within an interactive R-Shiny app using the final population PK model, with circles depicting the exact time or midpoint of proposed sample collection window



CONCLUSIONS

- A previously-developed population PK model for omadacycline was used to design an informative and clinically useful four-sample sparse PK sampling scheme for inclusion in Phase 3 trials in which an oral switch was planned.
- The recommended sparse sampling scheme included a sample collected between 3 to 5 hours and at 12 hours after the first IV dose on Day 1, and immediately prior to and 1 to 3 hours after an oral dose at steady-state.

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