P1319

Single and Multiple Dose Pharmacokinetics and Tolerability of Intravenous Omadacycline in Healthy Volunteers

S. Ken Tanaka, PhD; Stephen Villano, MD; Evan Tzanis
Paratek Pharmaceuticals, King of Prussia, Pennsylvania, USA

ABSTRACT

Background: A first in class aminomethylcycline antibiotic, omadacycline, is undergoing clinical development for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP) as a once daily oral and intravenous (IV) formulation. Two phase 1 studies in healthy volunteers examined the pharmacokinetic (PK) profile and tolerability of omadacycline after single- and multiple-dose administration.

Methods: Both studies were randomized, double-blind, and placebo-controlled in healthy male subjects. In Study 1, subjects were randomized to receive a single omadacycline dose of 25, 50, 100, 200, 300, 400 or 600 mg as a 30- or 60-minute IV infusion. In Study 2, subjects received a 30-minute IV infusion of omadacycline 200 mg once daily x 7 days. Blood samples were obtained pre-dose and at frequent intervals over 72 hours to determine plasma omadacycline levels for PK calculations. Monitoring consisted of adverse events, vital signs, physical examination, laboratory tests, and an electrocardiogram.

Results: In Study 1, 41 subjects were treated with omadacycline and had PK data available. After a single IV dose, a dose-dependent increase was exhibited for mean $AUC_{0\text{-}24}$ (0.9 to 24.9 mg*h/L) over the range from 25 to 600 mg. Mean C_{max} was 0.3 to 2.6 mg/L for 25 to 200 mg doses infused over 30 minutes and 2.6 to 4.5 mcg/mL for doses infused over 60 minutes, respectively. For the majority of doses, mean half-life ranged from 17 to 21 hours. In Study 2, 20 subjects were treated in 2 cohorts with omadacycline and had PK data available. Among the 2 cohorts, mean C_{max} on Day 1 was 2.9 and 2.7 mg/L and on Day 7 was 3.5 and 3.3 mg/L, and, mean $AUC_{0\text{-}24}$ on Day 1 was 12.1 and 11.0 mg*h/L and Day 7 was 17.8 and 17.2 mg*h/L. $AUC_{0\text{-}24}$ on Day 7 was approximately 1.5-1.6 fold higher than Day 1. For all of the AUC measures, the coefficient of variation ranged from 8.7% to 13.8%. In Study 1, no GI adverse events were recorded. In Study 2, 5 (12.2%) episodes of mild or moderate nausea and 1 (2.4%) of vomiting were reported, but there were no discontinuations due to any adverse event. No unexpected safety issues were reported.

Conclusion: After IV administration, omadacycline demonstrated a well-tolerated, dose-proportional, and linear PK profile over a dosage range from 25 to 600 mg together with a low incidence of GI adverse events, which contrasts with other tetracycline-derived antibiotics.

INTRODUCTION

- Omadacycline represents a first in class aminomethylcycline antibiotic with *in vitro* activity against Gram-positive and Gram-negative aerobes, anaerobes, and atypical bacteria including *Legionella* spp. and *Mycoplasma* spp. (Macone et al, 2014). Omadacycline is being developed as monotherapy for oral and intravenous (IV) treatment of serious community-acquired infections. In early clinical studies in patients with complicated skin infections, omadacycline demonstrated efficacy comparable to linezolid (Noel et al, 2012; Noel et al, 2012a). Phase 3 studies are underway with omadacycline for treating acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP).
- Phase 1 studies in healthy subjects have shown that omadacycline has low protein binding (21%), and that a 300 mg oral dose is bioequivalent to a 100 mg IV dose (Sun et al, 2012; Ting et al, 2010). The PK profile and tolerability of IV omadacycline across a range of doses were evaluated in a single ascending dose study and a multiple ascending dose study in healthy subjects.

METHODS

Study Design

- Two randomized, double-blind, placebo-controlled studies were conducted in healthy male subjects aged 18 to 50 years.
  - Study 1
    - Subjects were randomized to receive a single dose of omadacycline 25, 50, 100, 200, 300, 400 or 600 mg as either a 30- or 60-minute IV infusion.
  - Study 2
    - Two separate cohorts of subjects received a 30-minute IV infusion of omadacycline 200 mg once daily x 7 days. This dosing regimen was repeated to expand the safety database for this dose.
    - [In other cohorts subjects received 100 mg IV once daily for 7 or 14 days, but PK samples were obtained with improper blood collection tubes so PK data are not available for these subjects]

Study Assessments

- Blood samples were obtained pre-dose and at frequent intervals over 72 hours to determine plasma omadacycline levels for PK calculations.
- Safety monitoring consisted of adverse events, vital signs, physical examination, laboratory tests, and electrocardiograms (ECG).

RESULTS

Study 1

- 41 subjects were enrolled, received omadacycline, and completed all PK analyses.
- Baseline demographic characteristics were comparable between treatment groups (**Table 1**).

Table 1. Demographic Characteristics

	Omadacycline Single IV Dose (mg)							
	25 (N=6)	50 (N=6)	100 (N=5)	200 A (N=6)	200 B (N=5)	300 (N=5)	400 (N=6)	600 (N=2)
Age, year[a]	30.3 (10.5)	34.3 (9.4)	33.0 (12.9)	29.5 (8.8)	36.6 (12.4)	31.0 (10.2)	28.7 (9.7)	38.0 (4.2)
Caucasian, n	6	6	5	5	5	3	5	2
Weight, kg[a]	70.3 (7.2)	77.5 (11.6)	73.7 (10.3)	77.3 (7.1)	74.7 (6.0)	76.4 (14.6)	84.5 (9.3)	89.1 (18.7)
BMI, kg/m^2[a]	22.8 (2.2)	25.0 (3.3)	25.2 (2.8)	24.0 (1.4)	23.4 (2.3)	25.1 (2.7)	26.5 (2.2)	26.4 (2.3)

[a]Values are mean (standard deviation).
A: 0.5 mg/mL infused over 30 minutes; B: 1 mg/mL infused over 30 minutes.

Pharmacokinetics

After a single IV dose, a dose-dependent increase was observed for mean $AUC_{0\text{-}24}$ (0.9 to 24.9 mg*h/L) over the dose range from 25 to 600 mg (**Table 2**).

- Mean C_{max} ranged from 0.3 to 4.5 mg/L across the dose range.
- For the majority of doses, mean half-life ranged between 17 to 21 hours.
- Mean plasma omadacycline concentrations decreased rapidly after IV administration, and concentrations were less than 0.5 mg/L for all doses by 36 hours post-dose (**Figure 1**).
- Omadacycline exposure was linear across the dose range (**Figures 2** and **3**).
- The volume of distribution was large and ranged from 333 to 640 L.

Table 2. Mean (SD) Pharmacokinetic Parameters after Single IV Omadacycline Doses

	Mean (standard deviation)							
Dose (mg)	C_{max} (mg/L)	T_{max} (h)[a]	$AUC_{0\text{-}inf}$ (mg*h/L)	$AUC_{0\text{-}24}$ (mg*h/L)	$AUC_{0\text{-}12}$ (mg*h/L)	$T_{1/2}$ (h)	CL (L/h)	Vd (L)
Dose infused over 30 minutes								
25 (N=6)	0.28 (0.06)	0.5	0.9 (0.2)	0.9 (0.2)	1.3 (0.3)	11.7 (3.4)	20.9 (5.3)	333 (39)
50 (N=6)	0.79 (0.35)	0.3	2.6 (0.6)	2.4 (0.6)	3.5 (1.4)	20.5 (20.5)	15.8 (4.5)	380 (191)
100 (N=5)	1.13 (0.35)	0.3	5.4 (0.9)	4.3 (0.8)	6.0 (0.8)	14.1 (2.8)	17.1 (2.5)	353 (114)
200A (N=6)	2.01 (0.80)	0.4	10.3 (2.4)	7.5 (1.8)	11.1 (2.5)	18.7 (4.1)	18.8 (4.0)	506 (153)
200B (N=5)	2.60 (0.36)	0.3	11.7 (2.1)	9.1 (1.3)	13.3 (2.0)	19.0 (4.5)	15.3 (2.3)	412 (84)
Dose infused over 60 minutes								
300 (N=5)	2.46 (0.68)	0.5	17.4 (3.4)	12.8 (2.7)	18.4 (3.4)	19.3 (3.5)	16.7 (3.1)	467 (119)
400 (N=6)	3.21 (0.71)	1.1	21.5 (3.5)	14.7 (2.2)	24.1 (3.8)	26.0 (4.5)	17.0 (2.9)	640 (164)
600 (N=2)	4.51 (0.11)	0.8	34.3 (2.4)	24.9 (0.9)	36.0 (2.4)	17.1 (0.11)	16.7 (1.1)	411 (30)

[a]Median.
A: 0.5 mg/mL infused over 30 minutes; B: 1 mg/mL infused over 30 minutes.

Figure 1. Mean Omadacycline Plasma Concentrations Over Time by Dose

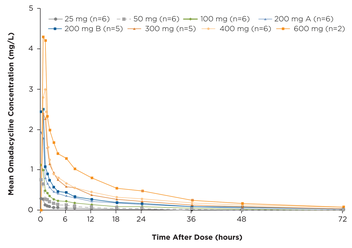


Figure 2. Correlation Between Omadacycline Dose and $AUC_{0\text{-}inf}$

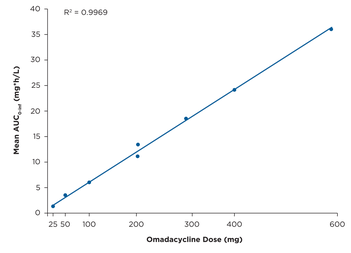
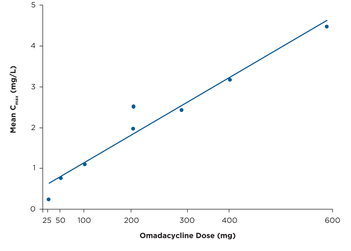


Figure 3. Correlation Between Omadacycline Dose and C_{max}



Study 2

Demographics

- 20 subjects received omadacycline 200 mg IV once daily x 7 days (in 2 separate cohorts) and had PK data available.

Table 3. Demographic Characteristics

	Omadacycline 200 mg IV Once Daily x 7 Days	
	Cohort 1 (N=10)	Cohort 2 (N=10)
Age, years[a]	27.1 (8.5)	31.5 (8.3)
Age range, years	19–43	21–45
Caucasian, n	7	10
Weight, kg[a]	73.9 (11.7)	75.8 (7.2)
BMI, kg/m^2[a]	22.8 (2.5)	23.8 (1.3)

[a]Values are mean (standard deviation)

Pharmacokinetics

- Mean C_{max} on Day 1 was 2.8-3.0 mg/L and on Day 7 was 3.4-3.6 mg/L (**Table 4**).
- Mean $AUC_{0\text{-}24}$ on Day 1 was 11.2-12.2 mg/h/L and Day 7 was 17.4-18.0 mg*h/L.
- $AUC_{0\text{-}24}$ on Day 7 was approximately 50% higher than Day 1.
- For all of the AUC measures, the coefficient of variation was low (ranging from 8.7% to 13.8%).

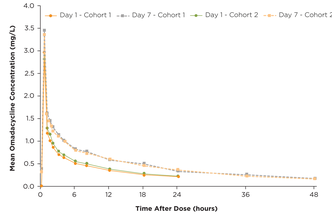
Table 4. Summary of PK Parameters for Cohorts 1 and 2 After Omadacycline 200 mg IV Once Daily X 7 Days

Parameter	Mean (Standard Deviation)			
	Cohort 1 (N=10)		Cohort 2 (N=10)	
	Day 1	Day 7	Day 1	Day 7
C_{max} (mg/L)	3.0 (0.5)	3.6 (0.8)	2.8 (0.7)	3.4 (0.4)
	CV 11.7%	CV% 14.8%	CV 16.7%	CV 8.4%
$AUC_{0\text{-}24}$ (mg*h/L)	12.2 (1.7)	18.0 (2.9)	11.2 (2.0)	17.4 (3.0)
	CV 8.7%	CV 9.9%	CV 10.8%	CV 11.0%
$AUC_{0\text{-}inf}$ (mg*h/L)	ND	30.9 (6.6)	ND	28.9 (6.1)
		CV 13.8%		CV 13.4%
T_{max} (h)	0.25 (0.0)	0.28 (0.1)	0.25 (0.0)	0.25 (0.0)
$T_{1/2}$ (h)	14.2 (2.5)	25.2 (3.6)	15.6 (3.9)	23.7 (2.7)
CL (L/h)	ND	11.3 (1.6)	ND	11.8 (1.9)
Vd (L)	ND	413.6 (90.8)	ND	401.4 (64.3)
V_{ss} (L)	ND	285.4 (50.1)	ND	282.3 (36.1)

ND: not done; parameters calculated only following the last dose.

- Mean plasma omadacycline concentrations over time were comparable between the cohorts and reflect accumulation following once daily dosing through Day 7 (**Figure 4**).

Figure 4. Mean Plasma Omadacycline Concentrations Over Time on Day 1 and Day 7 of a 200 mg IV Dose



Safety and Tolerability

Treatment-emergent adverse events for the combined cohorts in each study are shown in **Table 5**.

- No serious adverse events or discontinuations for adverse events were reported in either study.

Table 5. Treatment-Emergent Adverse Events Reported in at Least 2 Subjects in Either Study

Event	Number (%) of Subjects	
	Study 1 25-600 mg IV SD N=41	Study 2 200 mg IV QD x 7 N=20
Subjects with any AE	18 (44)	12 (60)
Cannula site reaction	9 (22)	0
ALT increased	5 (12)	4 (20)
Headache	2 (5)	4 (20)
Dizziness	2 (5)	3 (15)
Nausea	0	3 (15)
Abdominal pain	0	2 (10)
Venipuncture site bruise	2 (5)	0
Venipuncture site reaction	2 (5)	0

SD: single dose.

Study 1

- IV cannula site reactions were not related to dose.
- No gastrointestinal AEs were reported.
- ALT increases were dose-related: no events up to 200 mg; 3/11 subjects at 300-400 mg; 2/2 subjects at 600 mg [therefore no further subjects dosed at 600 mg]. In 4 cases, peak ALT was ~2x upper limit of normal (ULN), occurred 2-5 days after dosing and then resolved. In 1 case peak ALT was 3.8xULN and occurred 7 days after dosing, following alcohol consumption. There were no clinically significant changes in serum bilirubin or alkaline phosphatase.
- Asymptomatic transient increases in heart rate were observed, typically within 6 hours post-dose. Compared to baseline, median peak increase in heart rate was 7-12 bpm for doses ≤100 mg IV and 18-24 bpm for doses ≥200 mg IV. Changes resolved by 24 hours post-dose.

Study 2

- All ALT increases reported as AEs were of mild intensity, with no clinically significant changes in serum bilirubin.
- Heart rate changes were observed comparable to those in Study 1; findings were generally consistent with subsequent doses.

SUMMARY AND CONCLUSIONS

- Following administration of single IV doses from 25 to 600 mg, omadacycline demonstrated a dose-proportional and linear PK profile, with a large volume of distribution.
- The mean terminal elimination half-life of omadacycline is ~17 h.
- After 7 days of dosing with omadacycline 200 mg IV once daily, the steady-state $AUC_{0\text{-}24}$ was approximately 50% higher compared with Day 1. [With once-daily dosing, steady-state is generally achieved by Day 4].
- IV omadacycline was well tolerated over the dose range evaluated; ALT increases were dose-limiting at the dose of 600 mg IV.
- Dose-related increases in heart rate occurred for several hours after dosing but were asymptomatic and transient.
- Gastrointestinal AEs were uncommon in these studies.
- A loading dose of 200 mg IV and then 100 mg IV once daily is being evaluated in Phase 3 studies of ABSSSI and CABP.

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PARATEK