Effect of Food on the Bioavailability of Omadacycline in Healthy Volunteers

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ABSTRACT

Background: Omadacycline is a first-in-class aminomethylcycline antibiotic that is being studied in Phase 3 studies as an oral and intravenous monotherapy for skin infections and community-acquired pneumonia. This study evaluated the effect of food consumption on the oral bioavailability of a single 300 mg dose.

Methods: This was a phase 1, randomized, open-label 4-period, crossover study. Healthy subjects were randomized to 1 of 4 treatments: A) standard 6-hour fast, B) standard, high fat, non-dairy meal 4 hours before dosing, C) standard, high fat, non-dairy meal 2 hours before dosing, and D) standard, high fat meal containing dairy 2 hours before dosing, separated by a 5 day washout period. Patients received a single 300 mg oral dose of omadacycline during each treatment period. Blood samples for pharmacokinetic (PK) analysis were collected at frequent intervals for 24 hours after each dose, and safety assessments included adverse events, clinical laboratory tests and vital signs. A linear mixed-effect model with treatment condition, sequence, and period as fixed effects and subject nested within sequence as a random effect was fitted to the natural log-transformed PK parameters for estimation of effects and 90% confidence intervals (CIs) for the fed states compared with the fasted state.

Results: Thirty-one subjects were included in the PK analysis. Fasted AUC_{0-inf}, AUC_{0-t}, and AUC_{0-24} were 10.2, 7.2, and 7.2 mcg*h/mL, respectively and C_{max} was 0.6 mcg/mL. Compared with a fasted dose, bioavailability was reduced by 15% to 17% for a nondairy meal 4 hours before dosing, 40% to 42% reduction for a nondairy meal 2 hours before dosing, and 59% to 63% reduction for a dairy meal 2 hours before dosing. The effect of food was more pronounced when a high-fat meal was consumed closer to dosing and when dairy was included in the meal. Across all treatment periods, mean $T_{1/2}$ ranged from 13.5 to 13.8 hours, and median T_{max} ranged from 2.5 to 2.9 hours. No treatment-related adverse events or clinically relevant changes in laboratory values, or vital signs occurred.

Conclusions: A single oral dose of omadacycline was well tolerated. Administration of a 300 mg dose within 2 to 4 hours of food reduced the bioavailability compared with the fasted state. Once daily oral omadacycline should be administered at least 6 hours following a meal.

INTRODUCTION

- Omadacycline is a first-in-class aminomethylcycline antibiotic that is characterized by improved *in vitro* antimicrobial activity (Honeyman et al, 2015).
- Omadacycline demonstrates *in vitro* activity against a broad range of Gram-positive and Gram-negative aerobes, many anaerobes, and atypical pathogens including *Legionella* spp. and *Mycoplasma* spp. (Macone et al, 2014; Dubois et al, 2015; Kim et al, 2016).
- In patients with complicated skin and skin structure infection, omadacycline demonstrated clinical efficacy and tolerability that was comparable to linezolid (Noel et al, 2012; Noel et al, 2012a).
- Phase 3 studies are ongoing with omadacycline as oral and intravenous (IV) monotherapy in patients with acute bacterial skin and skin structure infection (ABSSSI) and community-acquired bacterial pneumonia (CABP).
- During the development process, oral omadacycline formulations have evolved from free-base in a capsule through a series of tablet and salt formulations in order to optimize oral bioavailability while improving tolerability.
- The current phase 3 tablet formulation is the tosylate salt of omadacycline, which has been shown to have an absolute bioavailability of 34.5% when administered under fasting conditions.
- The primary objective of this study was to evaluate the relative bioavailability of a single oral 300 mg dose of omadacycline (administered as the phase 3 tablet formulation) at various times after the consumption of food in healthy adult subjects.

METHODS

Study Design

- Phase 1, randomized, open-label, 4-period, crossover study.
- Subjects underwent screening evaluations to determine eligibility within 21 days before dosing in Period 1.
- Subjects were admitted to the clinical site on the day before dosing (Day −1) in each period for baseline evaluations.
- Before dosing on Day 1 of Period 1, subjects were randomized to one of four treatment sequences (**Table 1**).
- On Day 1 of each period, subjects received a single oral dose of 300 mg omadacycline (2 x 150 mg tablets) at various times after the consumption of food.
- There was a washout period of at least 5 days between each dosing period.
- A final study completion visit occurred 6 to 10 days after the last dose of omadacycline.

Table 1. Treatment Sequences

Sequence	Period 1	Period 2	Period 3	Period 4
ADBC	A	D	B	C
BACD	B	A	C	D
CBDA	C	B	D	A
DCAB	D	C	A	B

A: subjects fasted overnight (no food or drink except for water for at least 6 hours before dosing); a standard high-fat (nondairy) meal was served 3 hours after dosing
B: a standard high-fat (nondairy) meal completed at 4 hours before dosing
C: a standard high-fat (nondairy) meal completed at 2 hours before dosing
D: a standard high-fat meal including dairy completed at 2 hours before dosing

- The high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal followed Food and Drug Administration guidance recommendations, and provided approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively (FDA Guidance, 2002).
- These meals were to be consumed within 20 minutes.
- Dose administration for Treatments B, C, and D was based off of the end time of the meal.
- During all 4 treatment periods, subjects received no food or drink except water for at least 3 hours after dosing and no dairy products, antacids or multivitamins for 4 hours after dosing.

Subject Selection

- Male and female subjects ages 18 to 55 years (inclusive)
- Body mass index ≥18 to ≤30 kg/m^2
- In good health based on general medical assessment
- Afebrile and vital signs within normal ranges
- Women were required to have a negative serum pregnancy test and use a highly effective form of contraception during the study.
- Subjects were excluded for
  - Use of other investigational drugs within 30 days of screening or any prescription drugs, herbal supplements or OTC drugs within 2 to 4 weeks of baseline
  - Recent smoking history or history of bronchospastic disease
  - History of autonomic dysfunction
  - History of clinically significant cardiac rhythm abnormality
  - History or evidence of immunodeficiency
  - Hypersensitivity or allergic reaction to any tetracycline

Study Assessments

- Blood samples for PK assessments of omadacycline were collected before dosing (predose) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 hours after dosing in each period.
- PK parameters included:
  - Area under the plasma concentration-time curve (AUC) from time 0 to 24 hours after dosing (AUC_{0-24})
  - AUC from time 0 to the last quantifiable concentration (AUC_{0-t})
  - AUC time 0 extrapolated to infinity (AUC_{0-inf})
  - Maximum (peak) observed plasma concentration (C_{max})
  - Time to reach C_{max} (T_{max})
  - Terminal elimination half-life ($T_{1/2}$)
  - Terminal phase rate constant (λz)
- Safety and tolerability was assessed by
  - Adverse events (AEs)
  - Vital sign measurements at multiple time-points within 24 hours post-dose in each treatment period
  - Clinical laboratory tests 24 hours post-dose in each treatment period

Statistical Analysis

- Individual PK parameters for omadacycline were summarized with descriptive statistics.
- Geometric means were determined for AUC and C_{max}.
- PK parameters were evaluated using noncompartmental analysis using Phoenix® WinNonlin® (Pharsight Corp, St. Louis, Missouri), Version 6.2.1.
- Confidence intervals (CI) for test treatments (fed states: Treatments B, C, and D) compared with the reference treatment (fasted state: Treatment A) were constructed for AUC_{0-24}, AUC_{0-t}, AUC_{0-inf}, and C_{max}.
- Absence of the effect of food was concluded if the 90% CI for the test-to-reference ratios (B/A, C/A, or D/A) of geometric means were contained within the criterion interval of 80% to 125% for AUC_{0-24}, AUC_{0-t}, AUC_{0-inf}, and C_{max}.
- For T_{max}, the Wilcoxon signed rank test was performed.
- p≤0.05 was considered statistically significant.

RESULTS

- 32 subjects were enrolled and dosed in at least one treatment period.
- Overall mean age was 32.3 years, with a range of 21 to 50 years; 47% were male (**Table 2**).
- One subject was discontinued from the study because of a positive alcohol screen at baseline of period 3 and did not receive Treatments A and D.
- One subject requested withdrawal and did not receive Treatments B and C.
- PK data were available for 31 subjects for each treatment condition.

Table 2. Baseline Demographics

	Subjects N=32
Age, years[a]	32.3 (8.0)
Age range, years	21–50
Male, n (%)	15 (46.9)
Race, n (%)	
White	24 (75.0)
Black/African American	8 (25.0)
Hispanic/Latino	12 (37.5)
Height, cm[a]	168.0 (9.5)
Weight, kg[a]	71.5 (13.4)
BMI, kg/m^2 [a]	25.2 (3.2)

BMI = body mass index
[a]Mean (standard deviation)

Pharmacokinetic Analysis

- Fasted AUC_{0-inf}, AUC_{0-t}, and AUC_{0-24} were 10.2, 7.2, and 7.2 mcg*h/mL, respectively and C_{max} was 0.6 mcg/mL (**Table 3**). These data are consistent with the PK profile of this tablet formulation in other studies.

Table 3. Plasma Pharmacokinetic Parameters for Omadacycline After a Single 300 mg Oral Dose

Parameter	Mean (Coefficient of Variation)			
	Treatment A N=31	Treatment B N=31	Treatment C N=31	Treatment D N=31
AUC_{0-24}, mcg*h/mL	7.2 (28.1)	6.1 (26.3)	4.2 (23.4)	2.8 (44.3)
AUC_{0-t}, mcg*h/mL	7.2 (28.1)	6.1 (26.3)	4.2 (23.4)	2.8 (44.4)
AUC_{0-inf}, mcg*h/mL	10.2 (27.0)[b]	8.8 (29.2)	6.0 (25.4)	4.0 (44.1)
C_{max}, mcg/mL	0.6 (25.3)	0.6 (25.0)	0.4 (22.4)	0.3 (42.6)
T_{max}, h[a]	2.5 (1.5, 4.1)	2.9 (1.0, 6.0)	2.9 (1.0, 6.0)	2.9 (1.0, 6.0)
$T_{1/2}$, h	13.8 (10.3)[b]	13.6 (12.7)	13.6 (12.2)	13.5 (14.7)

[a]Median (minimum, maximum) values
[b]N=30

- A significant reduction in systemic exposure to omadacycline was observed for all three treatments (Treatments B, C, and D) vs. Treatment A (**Figure 1** and **Table 4**).

Figure 1. Plasma Concentration-Time Curve for Omadacycline

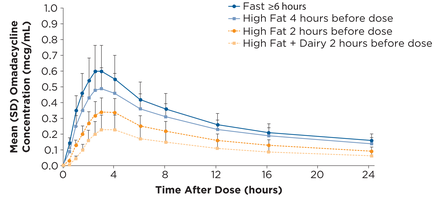

Table 4. Statistical Analysis of the Effect of Food on Plasma Pharmacokinetic Parameters of Omadacycline (N=31)

Parameter	Treatment	Geometric LS Mean	Treatment Comparison	Ratio of Geometric LS Mean (%)	90% CI of Ratio (%)
AUC_{0-24}, mcg*h/L	A	7.4			
	B	6.2	B/A	83.4	74.9, 92.7
	C	4.3	C/A	57.7	51.9, 64.2
	D	2.8	D/A	37.3	33.6, 41.5
AUC_{0-t}, mcg*h/L	A	7.4			
	B	6.2	B/A	83.3	74.9, 92.7
	C	4.3	C/A	57.7	51.9, 64.1
	D	2.8	D/A	37.3	33.5, 41.4
AUC_{0-inf}, mcg*h/L	A*	10.6			
	B	9.0	B/A	84.7	75.8, 94.6
	C	6.2	C/A	58.4	52.3, 65.3
	D	4.0	D/A	37.9	34.0, 42.3
C_{max}, mcg/L	A	0.66			
	B	0.56	B/A	84.5	75.9, 94.1
	C	0.39	C/A	60.1	54.0, 66.9
	D	0.27	D/A	40.7	36.5, 45.2

*N=30, a terminal mono-exponential phase could not be identified for one subject.
CI, confidence interval; LS, least squares

- The effect of food was more pronounced when a high-fat meal was consumed closer to dosing and when dairy was included in the meal.
- Compared with a fasted dose, omadacycline exposure (C_{max} and AUC) was
  - Reduced by 15% to 17% for a nondairy meal 4 hours before dosing
  - Reduced by 40% to 42% for a nondairy meal 2 hours before dosing
  - Reduced by 59% to 63% for a dairy meal 2 hours before dosing
- The between-subject variability in systemic exposure to omadacycline was similar for Treatments A, B and C (CV 22.4- 29.2%) for C_{max} and AUC. By contrast, for Treatment D the CV was 42.6- 44.4% for these parameters.

Safety and Tolerability

- Two subjects experienced treatment emergent AEs (one reported nausea, one reported somnolence); both events were of mild intensity and considered unrelated to study drug.
- No subject discontinued the study for an AE, and no subject experienced a serious AE.
- A slight increase from baseline in heart rate (median 8 to 10 bpm at 4 to 6 hours post dose) was observed for Treatment A (i.e., the group with highest omadacycline exposure). In all other treatment groups, the median change from baseline in heart rate was ≤3 bpm at all measured time points.
- No notable changes in blood pressure were observed.
- There were no clinically significant changes in clinical laboratory tests.

CONCLUSIONS

- A reduction in exposure was observed when oral omadacycline 300 mg was administered in various fed states compared with the fasted state.
- The food effect was more pronounced when a meal was consumed closer to oral dosing, with an even greater effect when dairy was included in the meal.
- These findings are consistent with the known tetracycline characteristic of binding to calcium as well as other multivalent cations (Agwuh and MacGowan, 2006).
- These results support the current recommendation that oral omadacycline tablets should be taken in a fasted state.

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