Safety and Pharmacokinetics of the Aminomethylcycline Antibiotic Omadacycline Administered to Healthy Subjects in Oral Multiple Dose Regimens

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ABSTRACT

Omadacycline, a first-in-class aminomethylcycline antibiotic, is related to tetracyclines, but structurally modified to circumvent mechanisms of resistance to tetracyclines. Omadacycline demonstrates potent activity against a broad range of pathogens, including drug-resistant strains, and is in late-stage development for treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia. Previous studies support an intravenous-to-oral transition regimen with 300 mg once-daily oral dosing. This phase 1 study investigated the pharmacokinetics and safety/tolerability of multiple oral omadacycline doses higher than 300 mg. Using a 3-period crossover design, healthy adults were randomized to receive oral omadacycline 300, 450, and 600 mg in variable sequence (n = 26) or placebo (n = 7) once daily for 5 consecutive days per period. In plasma, omadacycline maximum concentration and total exposure increased with increasing dose, but were less than dose proportional. The kinetics of omadacycline plasma accumulation were similar between dose levels; exposure on Day 5 was ~50% higher than on Day 1. Omadacycline plasma concentrations on Day 1 of 450-mg dosing were similar to those on Day 5 of 300-mg dosing. All doses were generally well tolerated, but the 600-mg dose was associated with more gastrointestinal adverse events.

INTRODUCTION

Omadacycline is a potent semisynthetic antibiotic that represents a new class of tetracycline-related compounds, the aminomethylcyclines (reviewed in (1, 2)). Like that of tetracyclines, the antibacterial activity of omadacycline stems from its ability to bind to the tetracycline binding site on the 30S subunit of the bacterial ribosome and inhibit bacterial protein synthesis (3, 4). Notably, however, structural modifications at the C7 and C9 positions allow omadacycline to overcome the 2 main mechanisms of resistance to tetracyclines, efflux pumps and ribosomal protection (2, 4, 5). These modifications result in an improved spectrum of activity compared with earlier-generation tetracyclines. Omadacycline demonstrates potent *in vitro* activity against Gram-positive and Gram-negative aerobes, anaerobes, and atypical pathogens, which include *Legionella* and *Chlamydia* spp. Omadacycline also displays *in vitro* activity against drug resistant pathogens common in community-acquired infections such as methicillin-resistant *Staphylococcus aureus* (MRSA), multidrug-resistant *Streptococcus pneumoniae*, vancomycin-resistant *Enterococcus* spp. (VRE), and extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* (2, 6).

Omadacycline is currently in late-stage development as a monotherapy for treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP), both of which may involve pathogens resistant to current standard-of-care drugs. Both intravenous (IV) and oral formulations of omadacycline are in development and have been evaluated in more than 20 phase 1 trials. These phase 1 trials established pharmacokinetic profiles, proved general safety

and tolerability at therapeutic doses, and demonstrated that a 300-mg oral dose provides exposure comparable with a 100-mg IV dose (2, 7). Phase 3 trials evaluating IV-to-once-daily oral dosing have been completed for both ABSSSI (ClinicalTrials.gov ID, NCT02378480) and CABP (ClinicalTrials.gov ID, NCT02531438).

In completed clinical studies, single IV and single oral doses up to 600 mg have been investigated (1, 2). Multiple IV doses of 100 mg or 200 mg once daily for up to 14 and 7 consecutive days, respectively, and multiple oral doses of 200 mg or 300 mg once daily for up to 10 consecutive days have also been evaluated (1, 2). Based on the results of these studies, the once-daily oral dose selected for use in the phase 3 ABSSSI and CABP trials was 300 mg (following at least 3 days of IV omadacycline administration). In both of these trials, IV-to-once-daily oral omadacycline met primary endpoints and was non-inferior to the IV-to-oral comparator antibiotics, with a favorable overall safety and tolerability profile (8, 9). It is possible that a higher oral dose could be used as a “loading dose” to eliminate the need for an initial IV infusion phase of treatment for ABSSSI and CABP. A higher oral dose might also be important for additional potential indications involving bacterial infections in organs/tissues other than skin or lungs. Therefore, this phase 1 study was designed to compare the pharmacokinetics and safety of multiple oral doses of 300, 450, or 600 mg omadacycline when administered to healthy adults once daily for 5 consecutive days. Within this dose range, we hypothesized that the oral pharmacokinetics of omadacycline were linear and that multiple doses of omadacycline would be generally safe and well tolerated.

RESULTS

Demographics, baseline characteristics, and disposition of study subjects. Of the 33 subjects enrolled in the study, 26 were assigned to receive omadacycline and 7 were assigned to receive placebo. Demographic and baseline characteristics were generally similar between omadacycline and placebo treatment groups (**Table 1**) and across all omadacycline treatment sequences (data not shown). The majority of subjects in the study were white (57.6%) and male (81.8%). The overall mean age of subjects was 36.9 years, with a range of 21 to 55 years.

All 33 subjects received at least 1 dose of study drug (omadacycline or placebo) and were included in the safety analysis population. Twenty-five of the 26 omadacycline-treated subjects (96.2%) were included in the pharmacokinetic (PK) analysis population (1 subject was excluded from this population due to vomiting after dosing). Five subjects (15.2%) discontinued the study early, including 4 omadacycline-treated subjects (15.4%) and 1 placebo-treated subject (14.3%). Four subjects (12.1%) discontinued due to treatment emergent adverse events (TEAEs), including 3 omadacycline-treated subjects (11.5%) and 1 placebo-treated subject (14.3%), as detailed below. In addition, 1 omadacycline-treated subject was lost to follow-up. Thus, 22 subjects received all 5 doses of 300, 450, and 600 mg omadacycline and 6 subjects received all 5 doses of placebo in Periods 1, 2, and 3. These subjects were considered to have completed the study.

Plasma pharmacokinetics. At all tested omadacycline dose levels, on both Day 1 and Day 5 of each 5-day treatment period, mean plasma omadacycline

concentrations peaked 2.5 h after dosing (T_{max}) and omadacycline was measurable in plasma for up to 24 h after dosing (the last sampling time). Omadacycline total exposure (AUC_{0-24} and AUC_{last}) and peak concentrations (C_{max}) increased with increasing omadacycline dose (300 vs 450 vs 600 mg) on both Day 1 and Day 5, and were higher on Day 5 than on Day 1 for corresponding doses (**Fig. 1 and Table 2**). The mean $t_{1/2}$ of omadacycline in plasma was similar across the 3 tested dose levels, ranging from 13.03 to 13.66 h on Day 1 and from 15.49 to 16.83 h on Day 5. Steady-state conditions appeared to have been reached by Day 5, because the concentrations at t = 0 and t = 24 following the Day 5 dose were similar. Between-subject variability in systemic omadacycline exposure was low and was similar at all 3 tested dose levels, with coefficients of variation (CVs) ranging from 23.2% to 26.6% for C_{max}, AUC_{0-24}, and AUC_{last} on Day 1 and from 25.0% to 27.1% for C_{max}, AUC_{0-24}, and AUC_{last} on Day 5 (**Table 2**).

Although omadacycline AUC_{0-24}, AUC_{last}, and C_{max} increased with increasing omadacycline dose, the observed increases in exposure were less than dose proportional on both days of analysis (**Tables 3, 4**). Statistical analyses showed that with an increase in dose from 300 mg to 600 mg, omadacycline exposure (based on dose-normalized AUC_{0-24}) on Day 1 was 76% of that predicted if exposure were perfectly dose proportional; on Day 5, the observed increase in omadacycline exposure was 88% of predicted (**Table 3**). Analyses using a power model showed that the slope between 300-mg and 600-mg dosing on Day 5 was 0.824 (90% CI: 0.607-1.041) for AUC_{0-24}, falling outside the limits for dose proportionality (**Table 4**). Analysis of C_{max} values, using ANOVA and a power model, similarly demonstrated that omadacycline

concentrations were dose linear, but less than dose proportional, in this study (**Tables 3, 4**).

Statistical analyses also revealed accumulation of omadacycline in plasma following once-daily dosing for 5 consecutive days. Depending on dose, accumulation ratios between Day 5 and Day 1 ranged from 1.40 to 1.62 for AUC_{0-24} and from 1.24 to 1.35 for C_{max} (data not shown). These findings are consistent with the long $t_{1/2}$ of omadacycline in plasma.

Safety and tolerability. Overall, 12 of the 33 subjects in the safety population reported a total of 36 TEAEs during the study (**Table 5**). TEAEs were reported by 38.5% of subjects who received omadacycline and by 28.6% of subjects who received placebo. The highest percentage of TEAEs was classified as gastrointestinal (GI) disorders. The most frequently reported TEAE was nausea, which was reported in ≤ 7.7% of subjects during 300-mg and 450-mg omadacycline dosing and by 16.7% of subjects during 600-mg dosing.

There were no serious TEAEs reported during the study. Four subjects experienced TEAEs leading to study discontinuation, including 1 subject during each of the 3 omadacycline dose levels and 1 subject in the placebo group.

There were no clinically significant findings in vital sign measurements, physical examination, ECG results, hematology, or urinalysis parameters. Serum chemistry analyses showed that between baseline and Day 5 of each dosing period, the median change in alanine aminotransferase (ALT) concentration was –2.0, 5.0, and 19.5 IU/L in subjects dosed with 300 mg, 450 mg, and 600 mg omadacycline, respectively. The corresponding changes in placebo groups ranged from –5.0 to –1.0 IU/L. No substantial

changes in median aspartate aminotransferase (AST), bilirubin, or other serum chemistry parameters were noted. The highest individual ALT value was 150 IU/L (2.7-fold above the upper limit of normal [ULN]), which occurred in a subject who first received 450 mg omadacycline in Period 1, then 300 mg in Period 2, and then was discontinued due to the liver enzyme changes; this subject's bilirubin values remained within the normal range at all time points assessed.

DISCUSSION

Although a number of phase 1-3 studies support once-daily 300 mg oral omadacycline as a safe and effective therapeutic dosing regimen, it is possible that greater drug exposure from higher oral doses could be beneficial in some clinical situations. However, multidose regimens of oral omadacycline using doses higher than 300 mg have not been previously investigated. The goal of this study was to understand the pharmacokinetics and safety of oral omadacycline at doses higher than 300 mg. A 3-period crossover study was used to investigate the pharmacokinetics and safety and tolerability of oral omadacycline when administered once daily at dose levels of 300, 450, or 600 mg for 5 consecutive days. The highest dose level was selected based on a previous study in which single oral doses up to 600 mg were administered to humans and showed an acceptable safety profile, although there was some increased incidence of GI adverse events at doses over 400 mg (Paratek, data on file). The crossover study design was intended to control for intrasubject variability and, based on previous indications of a ~17-h $t_{1/2}$ for oral omadacycline (7), a 5-day washout interval between dosing periods was expected to be sufficient to prevent observation of any carryover effects of the study drug between treatment periods. It is recommended that oral omadacycline be administered in a fasted state, due to reduced oral bioavailability when omadacycline is administered within 2 to 4 hours of food (10). As such, this study was conducted in fasted subjects.

Twenty-six healthy adult subjects received omadacycline in this study and 7 subjects received matching placebo. Analysis of plasma samples collected from

omadacycline-treated subjects at various time points on Days 1 and 5 of each 5-day dosing period showed that mean concentrations of omadacycline peaked at 2.5 h and remained measurable up to 24 h (the last tested time point) at all omadacycline dosing levels (300, 450, and 600 mg). Two subjects experienced vomiting before reaching PK steady state on Day 5 and were excluded from the Day 5 analysis. On Day 5, mean steady-state exposure (AUC_{0-24}) in subjects dosed with 300 mg omadacycline was 9267 ng•h/mL, which is consistent with results of previous studies with 300-mg oral dosing (1, 7). Both AUC_{0-24} and C_{max} increased with increasing dose and were nearly, but somewhat less than, dose-proportional (ranging from 76% to 96% of expected across all dose comparisons for AUC_{0-24} and from 74% to 91% of expected across all dose comparisons for C_{max}). This was the case on both Day 1 and Day 5 of dosing. Due to its relatively long $t_{1/2}$ (mean = ~13 h on Day 1, ~16 h on Day 5), omadacycline accumulated in plasma over the course of 5 consecutive days of dosing. Thus, at all tested dose levels, systemic exposure on Day 5 was ~50% higher than on Day 1. This degree of accumulation is also consistent with that observed following multiple once-daily dosing of IV or oral formulations of omadacycline in early pharmacology studies (1).

As would be expected for most pharmacologic agents, increasing omadacycline dosing beyond a certain point appears to have adverse effects in terms of safety and tolerability. Multiple doses of 300, 450, and 600 mg were all generally well tolerated in this study (all TEAEs were either mild or moderate in severity); however, there were some differences between doses. The frequency of treatment-related TEAEs did not increase with an increase in omadacycline dose from 300 to 450 mg (15.4% vs 8.3%), but such events were more frequent with 600-mg dosing (25.0%). Within the most

frequent class of TEAEs, GI disorders, the only 2 reports of diarrhea in this study occurred with 600-mg dosing, and nausea occurred with an incidence at least 9% higher at the 600-mg dose level than at the lower doses. In addition, serum chemistry analyses showed a small, but notable, dose-dependent increase in median ALT concentrations. Although no individual ALT values exceeded 3-fold above the ULN, the higher median at 600 mg suggests an increased chance of more significantly elevated serum transaminase levels with this dose. Based on these observations, for situations in which an oral dose above 300 mg may be beneficial, 450 mg is the oral dose most likely to provide higher omadacycline exposure with favorable safety and tolerability.

In terms of optimizing systemic exposure, this study showed that omadacycline plasma concentrations on Day 1 of 450-mg dosing were similar to those on Day 5 of 300-mg dosing (mean AUC_{0-24} = 8976.5 and 9267.2 ng•h/mL, respectively). For indications in which the therapeutic dosing regimen incorporates 300-mg daily oral dosing, these data support a strategy of using an initial oral “loading dose” of 450 mg once daily for 1 to 2 days, followed by 300-mg once-daily oral dosing. Such a strategy could potentially eliminate the need for an IV phase of treatment and was evaluated in a recently completed phase 3 trial of oral-only omadacycline treatment in patients with ABSSSI (ClinicalTrials.gov ID, NCT02877927).

In summary, these data indicate that systemic drug exposure to omadacycline increases with increasing once-daily oral dosing from 300 mg to 450 mg or 600 mg, but the exposure is not dose proportional. There were no substantial differences in the safety or tolerability of 300- and 450-mg doses, but increasing the dose to 600 mg appears to have less favorable safety and tolerability. Overall, these data provide

information about the pharmacokinetics and safety of oral omadacycline at doses greater than 300 mg and support the potential clinical utility of a 450-mg oral dose of omadacycline, either as part of a “loading dose” strategy or for indications where systemic exposure higher than that achieved with a 300-mg oral dose is necessary.

METHODS

This study was conducted in accordance with International Council for Harmonisation harmonised tripartite guideline E6(R1): Good Clinical Practice. All aspects of the study complied with all national, state, and local laws and regulations. The study protocol was reviewed and approved by the Institutional Review Board at the study center. Each participating subject provided written informed consent prior to enrollment.

Study design. This was a phase 1, randomized, double-blind, 3-period, crossover study in healthy adult subjects aimed at evaluating the pharmacokinetics (PK) (primary objective) and safety and tolerability (secondary objective) of multiple once-daily oral doses of omadacycline (at dose levels of 300, 450, and 600 mg). Placebo-treated subjects were included in the study to minimize potential bias in assessing tolerability. The study was performed at a single center, viz., PPD Phase I Clinic in Austin, TX, USA. The study consisted of a screening period (Day –21 through Day –2), three baseline periods (Day –1 of each period), 3 treatment periods (Day 1 through Day 6 of each period), and a study completion visit (within 6 to 10 days after the last dose of study drug in Period 3). Washout periods of at least 5 days were included between the last dose in one period and the first dose in the next period. Subjects were confined to the study site from Day –1 of Period 1 until discharge on Day 6 of Period 3, after the 24-h blood sampling and safety assessments were completed.

Subjects meeting the criteria for enrollment in the study (see below) were randomly assigned to 1 of 3 treatment sequences using a Latin Square design.

Sequences designated which omadacycline dose was administered in each period: 300/600/450 mg, 450/300/600 mg, or 600/450/300 mg in periods 1, 2, and 3, respectively. Subjects assigned to omadacycline received omadacycline during all 3 periods and at all tested dose levels. Subjects assigned to placebo received placebo during all 3 periods. Investigators and subjects were blind to whether the subject received omadacycline or placebo. The study was planned for 30 subjects (24 omadacycline, 6 placebo) divided equally among the 3 treatment sequences (8 omadacycline, 2 placebo per sequence).

Subjects received the appropriate dose of omadacycline or placebo once daily on Day 1 through Day 5 of each period. Omadacycline 150-mg tablets were used in the study; thus, doses consisted of 2, 3, or 4 tablets (for 300-, 450-, and 600-mg doses, respectively). An equal number of placebo tablets were administered to corresponding placebo groups. All doses of study drug were administered in the morning with no food or drink except for water at least 6 h before dosing. Subjects had no food or drink except water for at least 2 h after dosing and no dairy products, antacids, or multivitamins for 4 h after dosing.

Subject selection. Healthy, nonsmoking, male and female subjects were eligible for participation in the study if they were between 18 and 55 years of age (inclusive), weighed ≥ 50 kg, had a body mass index between 18 and 30 kg/m^2 (inclusive), met all eligibility criteria during screening (performed within 21 days before dosing in Period 1) and at baseline (Day –1) for Period 1, and provided written informed consent. Health status was determined by past medical history, clinical laboratory tests, vital signs (oral body temperature, systolic blood pressure, diastolic blood pressure, and heart rate),

12-lead electrocardiogram (ECG), and physical examination at screening. Eligibility criteria included ability to swallow up to 4 tablets in succession. Subjects were excluded from participation in the study for prior treatment with omadacycline, recent use of other investigational drugs; ECG abnormalities; inability to tolerate oral medications; pregnancy or breastfeeding; use of tobacco products, prescription drugs, herbal supplements, or over-the-counter medications or intake of xanthine (eg, caffeine)–containing food or beverages within a specified time frame before study initiation; blood loss/donation; low hemoglobin levels; high creatinine or blood urea nitrogen levels; urinary obstruction/difficulty voiding; positive alcohol or drug test; hypersensitivity or allergy to any tetracycline; signs of liver disease or liver injury; significant illness within 2 weeks of study initiation; any planned medical intervention that might interfere with the study; or a history of diseases or medical conditions as specified in the study protocol.

Study assessments: plasma pharmacokinetics. Serial blood samples for PK analysis of omadacycline were collected prior to dosing (predose) and at the following time points after dosing on Day 1 and Day 5 of each period: 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 h. In each period, the 24-h blood sample for Day 1 was collected before administration of the Day 2 dose. The PK analysis population consisted of subjects who received omadacycline and had at least 1 evaluable PK parameter. Subjects were excluded from PK analysis on a given day if they missed doses, had diarrhea, or had vomiting within twice the median T_{max} of omadacycline.

Non-compartmental PK parameters were determined from plasma omadacycline concentration and actual time data using Phoenix® WinNonlin® (Certara, Princeton, NJ, USA) Version 6.2.1., including area under the plasma concentration-versus-time curve

(AUC) from time 0 to 24 h after dosing (AUC_{0-24}), AUC from time 0 to the last quantifiable concentration (AUC_{last}), maximum observed plasma concentration (C_{max}), time to reach maximum observed plasma concentration (T_{max}), terminal elimination half-life ($t_{1/2}$), terminal phase rate constant (λ_z) and the accumulation factor of AUC_{0-24} and C_{max}.

Study assessments: safety and tolerability. Safety assessments included monitoring of adverse events (AEs), clinical laboratory test results, vital sign measurements, 12-lead ECG results, and physical examination findings. All randomly assigned subjects who received at least 1 dose of any study drug (omadacycline or placebo) were included in the safety analysis population. Adverse events were coded by preferred term and system organ class using MedDRA Version 17.1.

Statistical analysis. Plasma concentration data were summarized by day and time point for each treatment using descriptive statistics (number of subjects, mean, standard deviation, coefficient of variation, median, minimum, and maximum). All further statistical analyses were performed using SAS® software (SAS Institute, Cary, NC. USA), Version 9.2. A linear, mixed-effect, ANOVA model (SAS PROC MIXED) with treatment (300, 450, 600 mg), sequence, and treatment period as fixed effects and subject nested within sequence as a random effect were fitted to the natural log-transformed dose-normalized PK parameters AUC_{0-24}/dose, AUC_{last}/dose, and C_{max}/dose after dosing on Day 1 and Day 5 of each period for use in estimation of effects and construction of confidence intervals (CIs). Point estimates and 90% CIs for differences on the log scale were exponentiated to obtain estimates for the ratios of

329 geometric means and respective 90% CIs on the original scale. No adjustment was
330 made for multiplicity.

331 Dose linearity across all 3 dose levels was assessed by fitting omadacycline
332 C_{max}, AUC_{last}, and AUC_{0-24} after both the Day 1 and Day 5 doses to a power model (11):
333 ln(*PK*) = *a* + *b* × ln(*Dose*) + error, where *PK* was the PK parameter, *a* was the intercept,
334 and *b* was the slope. The estimates of slope *b* were reported along with the
335 corresponding 2-sided 90% CIs. If the 90% CIs of the slope, defined by the power
336 model, were contained within the dose proportionality bounds of 0.80-1.25 (0.68-1.32,
337 when adjusted for dose), dose proportionality over the 300 to 600 mg dosing range was
338 concluded.

339 For statistical analysis of accumulation of omadacycline, a linear mixed-effect
340 model with day as a fixed effect and subject as random effect was fitted to the natural
341 log-transformed C_{max} and AUC_{0-24} to construct 90% CIs for Day 5 compared with Day 1
342 (at each dose level separately).
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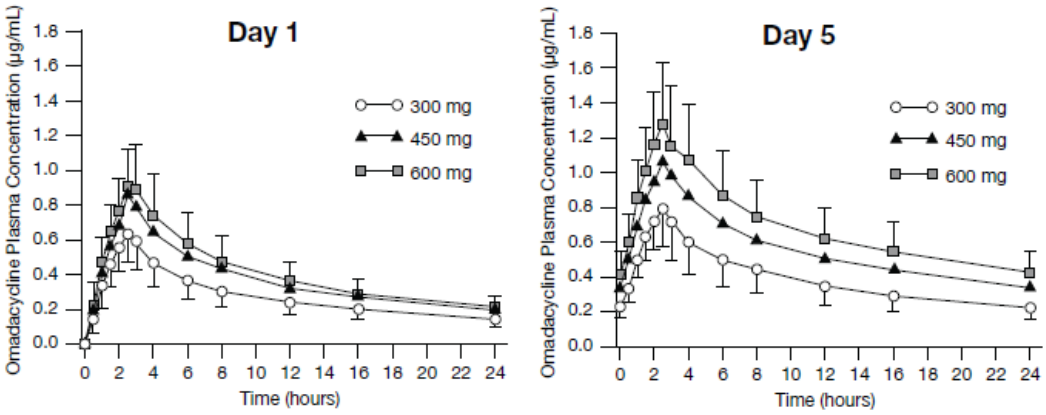

FIG 1 Plasma concentration-versus-time curves of omadacycline after oral administration. Mean (± SD) plasma concentrations of omadacycline versus time are shown by omadacycline dose group (300, 450, or 600 mg) for the PK population. Oral omadacycline doses were administered at time 0 on each of 5 consecutive days of dosing in each of 3 periods. Blood samples were collected for PK analysis on Day 1 (left panel) and Day 5 (right panel). Data were pooled by omadacycline dose for all subjects regardless of the period in which they received a particular dose. SD, standard deviation.

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TABLE 1 Demographics and baseline characteristics of subjects in the study[a]

	Omadacycline (*n* = 26)	**Placebo (*n* = 7)**	**Overall (*N* = 33)**
Age, years			
Mean (± SD)	35.6 (±10.4)	41.9 (±11.6)	36.9 (±10.8)
Min, max	21, 55	25, 53	21, 55
Sex, n (%)			
Male	21 (80.8)	6 (85.7)	27 (81.8)
Female	5 (19.2)	1 (14.3)	6 (18.2)
Race, n (%)			
White	15 (57.7)	4 (57.1)	19 (57.6)
Black or African American	9 (34.6)	3 (42.9)	12 (36.4)
Asian	2 (7.7)	0	2 (6.1)
Height, cm			
Mean (± SD)	173.12 (±9.17)	172.89 (±4.31)	173.07 (±8.32)
Min, max	155.2, 192.4	165.6, 177.4	155.2, 192.4
Weight, kg			
Mean (± SD)	78.67 (±10.33)	83.77 (±4.80)	79.75 (±9.60)
Min, max	62.7, 101.4	76.7, 90.4	62.7, 101.4
Body mass index, kg/m^2			
Mean (± SD)	26.25 (±2.72)	28.04 (±1.45)	26.63 (±2.59)
Min, max	19.4, 29.8	25.8, 29.9	19.4, 29.9

[a] Results for safety population.

SD, standard deviation.

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TABLE 2 Plasma pharmacokinetic parameters of omadacycline, by dose, on days 1 and 5 of dosing[a]

	Omadacycline dose					
	Day 1			**Day 5**		
Parameter	**300 mg (*n* = 25)**	**450 mg (*n* = 24)**	**600 mg (*n* = 24)**	**300 mg (*n* = 23)**	**450 mg (*n* = 24)**	**600 mg (*n* = 23)**
Mean $AUC_{0\text{-}24}$, ng•h/mL (CV)	6644.8 (25.3)	8976.5 (26.6)	10020.5 (25.7)	9267.2 (26.8)	13366.7 (26.0)	16420.3 (27.1)
Mean AUC_{last}, ng•h/mL (CV)	6634.2 (25.3)	8962.5 (26.6)	10004.5 (25.7)	9270.2 (26.8)	13368.3 (25.9)	16424.6 (27.1)
Mean C_{max}, ng/mL (CV)	648.8 (24.0)	874.2 (26.6)	954.5 (23.2)	808.8 (25.9)	1077.3 (25.0)	1305.5 (26.6)
Mean T_{max}, h (Min, max)	2.50 (1.50, 3.00)	2.50 (1.50, 3.00)	2.51 (1.00, 3.00)	2.50 (1.00, 3.00)	2.50 (1.50, 4.00)	2.50 (2.00, 4.00)
Mean $t_{1/2}$, h (CV)	13.66 (12.5)[b]	13.45 (12.9)[c]	13.03 (11.8)[c]	15.49 (10.7)[d]	16.83 (8.1)[c]	16.75 (6.8)[d]

[a] Results for PK population.

[b] n = 24 ($t_{1/2}$ was not estimable for 1 subject).

[c] n = 23 ($t_{1/2}$ was not estimable for 1 subject).

[d] n = 21 ($t_{1/2}$ was not estimable for 2 subjects).

CV, coefficient of variation.

Note: One subject during 300-mg omadacycline dosing and 1 subject during 600-mg omadacycline dosing vomited before reaching PK steady state on Day 5. These subjects met criteria for exclusion from PK analyses and are not included in the Day 5 summary.

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TABLE 3 Statistical analysis of dose-normalized omadacycline pharmacokinetic parameters on days 1 and 5 of dosing[a]

Parameter	Treatment	*n*	Geometric LS means	Treatment comparison	Ratio of geometric LS means (%)	90% CI of ratio (%)
Day 1						
AUC_{0-24}/dose,	300 mg	25	21.32			
ng•h/mL/mg	450 mg	24	18.64	450/300	87.44	(77.41-98.77)
	600 mg	24	16.18	600/450	86.79	(76.71-98.20)
				600/300	75.89	(67.20-85.71)
C_{max}/dose,	300 mg	25	2.09			
ng/mL/mg	450 mg	24	1.81	450/300	86.71	(76.17-98.71)
	600 mg	24	1.54	600/450	85.26	(74.76-97.23)
				600/300	73.92	(64.95-84.14)
Day 5						
AUC_{0-24}/dose,	300 mg	23	30.09			
ng•h/mL/mg	450 mg	24	28.83	450/300	95.82	(90.39-101.59)
	600 mg	23	26.46	600/450	91.78	(86.58-97.30)
				600/300	87.95	(82.96-93.25)
C_{max}/dose,	300 mg	23	2.62			
ng/mL/mg	450 mg	24	2.32	450/300	88.58	(83.19-94.32)
	600 mg	23	2.11	600/450	90.72	(85.20-96.60)
				600/300	80.36	(75.47-85.58)

[a] Results for PK population.

ANOVA analysis; see Materials and Methods for details.

CI, confidence interval; LS, least squares.

Note: One subject during 300-mg omadacycline dosing and 1 subject during 600-mg omadacycline dosing vomited before reaching PK steady state on Day 5. These subjects met criteria for exclusion from PK analyses and are not included in the Day 5 summary.

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TABLE 4 Dose linearity assessment of omadacycline pharmacokinetic parameters on Day 5 of dosing[a]

Parameter	*n*	Estimated Intercept (*a*)	Estimated Slope (*b*)	Standard Error of Slope	90% CI of Slope
AUC_{0-24}, ng•h/mL	70	4.406	0.824	0.130	0.607–1.041
C_{max}/dose, ng/mL	70	2.740	0.687	0.129	0.472–0.902

[a] Results for PK population.

CI, confidence interval.

Note: One subject during 300-mg omadacycline dosing and 1 subject during 600-mg omadacycline dosing vomited before reaching PK steady state on Day 5. These subjects met criteria for exclusion from PK analyses and are not included in the Day 5 summary.

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Table 5. Summary of treatment-emergent adverse events[a]

	Omadacycline dose			Omadacycline overall (n = 26)	Placebo overall (n = 7)
	300 mg (n = 26)	450 mg (n = 24)	600 mg (n = 24)		
n (%) of subjects with:					
Any TEAE	5 (19.2)	3 (12.5)	6 (25.0)	10 (38.5)	2 (28.6)
Treatment-related TEAE	4 (15.4)	2 (8.3)	6 (25.0)	9 (34.6)	1 (14.3)
Most frequent TEAEs (seen in > 1 study subject), n (%)					
Nausea	2 (7.7)	1 (4.2)	4 (16.7)	6 (23.1)	0
Vomiting	2 (7.7)	0	1 (4.2)	3 (11.5)	0
Diarrhea	0	0	2 (8.3)	2 (7.7)	0
Dizziness	2 (7.7)	0	1 (4.2)	3 (11.5)	0
ALT increased	0	1 (4.2)	1 (4.2)	2 (7.7)	0
TEAEs leading to early discontinuation of study drug, n (%)					
All	1 (3.8)	1 (4.2)	1 (4.2)	3 (11.5)	1 (14.3)
Nausea	1 (3.8)	0	0	1 (3.8)	0
Vomiting	1 (3.8)	0	0	1 (3.8)	0
ALT increased	0	1 (4.2)	0	1 (3.8)	0
Lipase increased	0	0	1 (4.2)	1 (3.8)	0
Syncope	0	0	0	0	1 (14.3)[b]

[a] Results for safety population.

[b] Vasovagal syncope following a blood draw.

ALT, alanine aminotransferase; TEAE, treatment-emergent adverse event.

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