Pharmacokinetics and Safety of Omadacycline in Subjects With Impaired Renal Function

Jolene K. Berg,[a] Evan Tzanis,[b] Lynne Garrity-Ryan,[b,#] Stephen Bai,[b] Surya Chitra,[b] Amy Manley,[b] Stephen Villano[b]

[a]DaVita Clinical Research, Minneapolis, MN, USA; [b]Paratek Pharmaceuticals Inc., King of Prussia, PA, USA

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[#]**Corresponding author:**

Lynne Garrity-Ryan, PhD

Paratek Pharmaceuticals, Inc.

75 Park Plaza 4th Floor

Boston, MA 02116

Phone: (617) 807-6628

E-mail: Lynne.Garrity-Ryan@ParatekPharma.com

ABSTRACT

Many antibiotics require dosing adjustments in patients with renal impairment and/or in those undergoing hemodialysis. Omadacycline, the first aminomethylcycline antibiotic in late-stage clinical development, displays activity against a broad-spectrum of bacterial pathogens, including resistant strains. Data from completed phase 3 acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP) studies showed intravenous (IV) to once-daily oral omadacycline to be clinically effective and well tolerated. To determine if dosing of omadacycline should be adjusted in patients with impaired renal function, a phase 1 study examining the pharmacokinetics (PK) and safety of IV (100 mg) omadacycline was conducted in subjects with end-stage renal disease (ESRD) on stable hemodialysis (n = 8) and in matched healthy subjects (n = 8). IV administration of omadacycline produced a similar plasma concentration-time profile in subjects with ESRD and healthy subjects. Further, in subjects with ESRD, similar PK parameters were observed when omadacycline was administered IV after or before dialysis. The mean $AUC_{0\text{-}inf}$ was 10.30 h•µg/mL when administered after dialysis, 10.20 h•µg/mL before dialysis, and 9.76 h•µg/mL in healthy subjects. The mean C_{max} in ESRD subjects was 1.88 µg/mL when administered after dialysis and 2.33 µg/mL when administered before dialysis, and in healthy subjects was 1.92 µg/mL. The 100-mg IV dose of omadacycline was generally safe and well-tolerated in both ESRD and healthy subjects. This study demonstrates that no dose adjustment is necessary for omadacycline in patients with impaired renal function or on days when patients are receiving hemodialysis.

INTRODUCTION

As of 2014, nearly 15% of adults in the United States had some form of chronic kidney disease (CKD) and the prevalence of the most severe form of renal disease, end stage renal disease (ESRD), continues to rise annually (1). According to the United States Renal Data System, there are almost 680,000 cases of ESRD in the United States, and 63% of these patients, about 427,000 individuals, receive hemodialysis (1). Community-acquired infections are of concern in this population; patients with CKD have nearly a 2-fold increase in risk of pneumonia (2), including community-acquired bacterial pneumonia (CABP). Further, 9.3% of patients who are hospitalized for acute bacterial skin and skin structure infections (ABSSSI) have moderate to severe renal disease (3) and 6% of community-acquired pneumonia patients present with renal disease as a co-morbidity (4). Hospitalization for infections in patients receiving hemodialysis increased 95% between 1993 and 2005 (5).

Omadacycline is the first aminomethylcycline antibiotic in late-stage clinical development. Aminomethylcyclines are semi-synthetic antibiotics related to tetracyclines (6, 7) (and reviewed in Chopra et al (8)). Similar to their tetracycline counterparts, aminomethylcyclines inhibit bacterial protein synthesis. Importantly, however, the 2 main mechanisms of tetracycline resistance, namely efflux pumps and ribosomal protection, are overcome by modifications present at the C-7 and C-9 position in the chemical structure of omadacycline (7, 9). Omadacycline has been shown to be active against a variety of bacterial pathogens: Gram-positive aerobes including methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant and multidrug-resistant *Streptococcus pneumoniae,* and vancomycin-resistant enterococcus (VRE);

Gram-negative aerobes; some anaerobes; and atypical bacteria such as *Legionella* spp. and *Chlamydia* spp, (6, 9).

Omadacycline is in clinical development for treatment of ABSSSI and CABP. In two phase 3 trials, IV to once-daily oral omadacycline was found to be effective and non-inferior to linezolid (for the treatment of ABSSSI in the Omadacycline in Acute Skin and Skin Structure Infections Study, OASIS-1; NCT02378480) or moxifloxacin (for the treatment of CABP in Omadacycline for Pneumonia Treatment in the Community, OPTIC; NCT02531438), with similar safety and tolerability (10, 11). In both studies the omadacycline dosing regimen was IV 100 mg Q12H for 2 doses followed by 100 mg Q24H for at least 3 days, followed by 300 mg orally Q24H. Once-daily oral omadacycline has also shown non-inferiority to twice-daily linezolid for the treatment of ABSSSI (OASIS-2, NCT02877927) (12).

While oral omadacycline is eliminated predominantly in the feces, an appreciable portion of the oral dose (14.4% in humans) is eliminated, primarily as unmetabolized omadacycline, in the urine (13). Therefore, understanding the effect of renal impairment on omadacycline is critical for its effective clinical use. This study examined the pharmacokinetics (PK) and safety of omadacycline in patients with ESRD, requiring hemodialysis, versus healthy subjects. We also examined the effect of hemodialysis on PK of omadacycline by administering omadacycline after or before hemodialysis in the ESRD subjects. The IV dose of omadacycline evaluated (100 mg) was the same that was utilized in the phase 3 studies described above. Results from this study provide insight to guide dosing regimens for patients with renal impairment and those receiving hemodialysis.

RESULTS

Subject Demographics—Safety and PK Populations

A total of 44 subjects were screened. Twenty-eight subjects failed screening and were not enrolled in the study. Sixteen subjects were enrolled with 8 subjects assigned to each of the 2 groups (healthy subjects and subjects with ESRD requiring dialysis). All subjects completed the study and were included in both the safety and PK populations. Subject baseline demographic characteristics are summarized in **Table 1**. The age range across both groups was 43 to 70 years with a median age of 58.5 years. Overall, 12 subjects (75.0%) were male and 4 subjects (25.0%) were female. A majority (87.5%) of healthy subjects were white, whereas race was more heterogeneous in subjects with ESRD.

Pharmacokinetic Assessment

Plasma Concentrations and PK Parameters of Omadacycline in ESRD and Healthy Subjects

The mean (± standard deviation) plasma concentrations of omadacycline over time profiles were nearly identical in all cohorts (**Fig. 1**). Subjects with ESRD displayed a similar plasma-time concentration profile as healthy subjects, irrespective of whether omadacycline was dosed after or before hemodialysis. Further, in all cohorts, omadacycline distributed rapidly in plasma (median time of maximum observed plasma omadacycline concentration [T_{max}] values ≤ 1 hour) and omadacycline plasma concentrations declined in a biphasic manner.

All plasma PK parameters were similar in ESRD subjects when dosed after or before hemodialysis versus healthy subjects (**Table 2**). In terms of total systemic exposure following IV administration of 100-mg omadacycline, the mean area under the concentration-time curve extrapolated to infinity in plasma ($AUC_{0\text{-}inf}$) was 10.30 h•µg/mL and 10.20 h•µg/mL in ESRD subjects when dosed after dialysis and before dialysis, respectively, compared to 9.76 h•µg/mL in healthy control subjects. Across all 3 cohorts, mean maximum observed plasma omadacycline concentration (C_{max}) ranged from 1.88 µg/mL to 2.33 µg/mL, mean terminal elimination half-life in plasma ($t_{1/2}$) ranged from 17.1 to 18.9 hours, mean total clearance (CL) ranged from 10.1 to 10.6 L/hr, and mean volume of distribution at steady state (V_{ss}) ranged from 194 to 214 L.

When PK parameters for ESRD subjects dosed after dialysis are statistically compared to PK parameters of healthy subjects, data showed that renal impairment did not affect overall exposure (area under the concentration-time curve from time zero to last quantifiable concentration in plasma [$AUC_{0\text{-}last}$] and $AUC_{0\text{-}inf}$) or CL, and had minimal effect on C_{max} (**Table 3**).

Omadacycline Plasma PK Parameters in ESRD Subjects Dosed After Hemodialysis Versus ESRD Subjects Dosed Before Hemodialysis

The effect of hemodialysis on the PK of omadacycline was evaluated by calculating the relative exposure of the 100-mg IV dose administered in ESRD subjects after and before hemodialysis (**Table 4**). Results indicate that hemodialysis did not have an effect on the overall extent of exposure ($AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$) and CL. While not statistically significant, C_{max} was slightly greater when subjects received omadacycline

before hemodialysis, compared to subjects receiving omadacycline after hemodialysis or healthy subjects.

Omadacycline Urine PK Parameters in Healthy Subjects

The cumulative amount of omadacycline excreted in the urine of healthy subjects following dosing with 100 mg of omadacycline IV was 27±3.49 mg (mean ± standard deviation). Hence, the fraction of the total omadacycline dose excreted in urine (Fe_u) was 27.0±3.49%. The mean (±standard deviation) renal clearance (CL_R) was 3.06±0.69 L/h in these subjects.

Omadacycline Dialysate PK Parameters in ESRD Subjects Dosed Before Hemodialysis

During dialysis in ESRD subjects, the mean percentage of the omadacycline cleared by hemodialysis, following dosing with 100 mg of omadacycline IV, compared to the total clearance of omadacycline was 47.8%. However, due to low total systemic clearance (10.1 to 10.6 L/h, across cohorts) and large volume of distribution (194 to 214 L, across cohorts) of omadacycline, the actual percent of the omadacycline dose recovered in the dialysate during dialysis was only 7.89% (7.89 mg).

Safety

Overall, 5 of 16 subjects enrolled in the study (31.3%) experienced at least 1 treatment emergent adverse event (TEAE) during the study (**Table 5**). There were no serious adverse events (SAE) or deaths reported. Further, no subjects withdrew from

the study due to adverse event (AE), and no AEs resulted in study drug discontinuation or interruption.

Three TEAEs involved respiratory tract infections and all 3 were considered by the Investigator to be not related to the study treatment. The Investigator indicated that all of these respiratory tract infections occurred during cold season, resolved spontaneously, and were likely to be of viral origin. The event of bronchospasm occurred in an ESRD subject with a history of asthma. Only 1 subject experienced any TEAE considered to be drug-related. This subject had ESRD and experienced 2 drug-related TEAEs (dizziness and rash papular) in association with the dosing of omadacycline after dialysis. All subjects experiencing an AE recovered, and all AEs resolved.

There was a transient increase in heart rate that typically peaked within 2 hours post dose in all groups. The largest median increase in heart rate at any measured timepoint within 24 hours (9.5 bpm) was observed in healthy subjects. There were no clinically relevant adverse trends in blood pressure other than a transient increase observed around the time of initiation of hemodialysis in the ESRD subjects when dosed before hemodialysis. No changes in vital sign parameters were reported as AEs. There were no clinically relevant trends in the hematology, clinical chemistry, or 12-lead ECG results.

DISCUSSION

A comparison of the PK data for omadacycline for ESRD subjects versus healthy subjects in the present study suggests that dose adjustment is not necessary in patients with any degree of renal impairment including those receiving hemodialysis. Intravenous administration of omadacycline produced similar plasma concentration-time profiles and PK parameters in ESRD subjects on hemodialysis and in matched healthy subjects. Despite 27% of the dose being eliminated in the urine of healthy subjects, overall clearance and volume of distribution were similar in ESRD subjects and healthy subjects. Pharmacokinetic findings (including clearance, volume of distribution, and fraction excreted unchanged in urine) from the healthy subjects cohort in the present study were similar to those reported previously (13-15). When subjects with ESRD received IV omadacycline after or before hemodialysis, no significant differences were observed. There was no effect on overall extent of exposure ($AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$), CL, V_{ss}, or $t_{1/2}$. The effect on C_{max} was considered small and not clinically relevant. Omadacycline was generally safe in healthy subjects, as has been previously observed (13, 16), and in subjects with ESRD. Only 1 subject presented with mild TEAEs related to omadacycline, and no SAE was reported.

The present finding with omadacycline is significant considering that the PK of many antibiotics is altered in patients with renal impairment or undergoing hemodialysis. Appropriate antibiotic dosing is an appreciated clinical challenge in these patient populations (17). Administration of drugs with significant renal clearance to patients with renal impairment, without dosage adjustment, may lead to overdosing, wherein the

decreased drug clearance leads to an increase in the overall exposure and potential increase in adverse events. In turn, this can potentially lead to increased mortality and a greater burden on the healthcare system in the form of increased hospitalizations, length of hospital stay, and increased clinical investigations (18). Conversely, drugs that are hydrophilic and usually subject to renal clearance may be filtered out during hemodialysis, thus decreasing overall exposure and increasing the opportunity for underdosing. Underdosing may lead to decreased efficacy of treatment and allows for the possibility of antibiotic resistance to develop. To avoid this, patients frequently need supplemental dosing during or following hemodialysis, or adjustment of time of antibiotic administration relative to hemodialysis treatment. Thus, modifications in dosing regimens for the renally impaired patient population and patients undergoing hemodialysis are often required to maintain the appropriate therapeutic concentrations of drug in serum, maximizing the therapeutic potential of the drug while minimizing side effects and adverse events.

Many antibiotics commonly used for the treatment of community-acquired bacterial infections such as ABSSSI and CABP require dosing adjustments in patients with renal impairment. In patients with any level of renal dysfunction (CrCl, creatinine clearance, <90 mL/min), vancomycin, very commonly considered a gold standard drug for ABSSSI infections involving MRSA, requires dosing adjustment (19). Telavancin, ceftaroline, levofloxacin, and cefpodoxime all require dosing modifications in patients with moderate renal impairment (CrCL <50 mL/min) (20-23). In patients with the most severe renal impairment (CrCL <30 mL/min), daptomycin, dalbavancin, trimethoprim-sulfamethoxazole, clarithromycin, and amoxicillin require dosing adjustments (24-28).

Additionally, some antibiotics, such as the beta-lactams, including ceftaroline and cefpodoxime, are filtered out during hemodialysis (21, 23). Thus, efficient dosing of these drugs in this setting is problematic.

In contrast, data from the present study demonstrate that changes to the dosing regimen of omadacycline are not necessary in patients with ESRD on hemodialysis and therefore dose adjustment is not necessary for any degree of renal impairment. Taken together with previous studies, which report that omadacycline does not require dosage adjustment on the basis of age, sex, or level of hepatic function (29, 30), along with its availability as a once-daily oral administration, these latest findings further support omadacycline as a safe antibiotic that is convenient to dose in diverse patient populations.

MATERIALS AND METHODS

Study Design

This was a phase 1, open-label, single dose, two-period, parallel group study. The primary objective of the study was to compare the PK of omadacycline in adult subjects with ESRD on hemodialysis to matched healthy adult subjects. Secondary objectives were to evaluate the safety and tolerability of single IV doses of omadacycline administered to subjects with ESRD, to determine the proportion of omadacycline removed by hemodialysis, and to determine the urine concentration of omadacycline after IV administration in healthy subjects. Subjects were assigned to a treatment group depending on renal function status. IntegReview (Austin, Texas, USA) Institutional Review Board (IRB) reviewed and approved this study and its conduct at the clinical site. The IRB was appropriately constituted in accordance with the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP), and local requirements, as applicable. All participants were informed verbally and in writing of the objectives, procedures, and risks of study participation. Participants voluntarily provided written, informed consent prior to undergoing any study-related procedures. The study was conducted from November 2015 (first subject enrolled) to May 2016 (last subject completed).

Subject Selection

Key Inclusion Criteria: Subjects who fulfilled the following criteria were eligible for inclusion in the study: male or female, 18 years of age or older, and body weight ≥50 kg.

Healthy subjects were required to have adequate creatinine clearance as calculated by the Cockcroft-Gault formula of ≥90 mL/min, and be in good general health as determined by medical history, physical examination, vital signs, ECG, and laboratory tests. Subjects with ESRD were required to be on a stable hemodialysis program (defined as a urea clearance by time divided by urea volume [Kt/V] urea above 1.2 within the past 4 weeks without significant change in the past 3 months), and have acceptable vital signs, and a stable ECG. Further, there should have been no evidence of hepatic decompensation, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 times the upper limit of normal (ULN) and bilirubin ≤ 1.5 times the ULN. Healthy adult subjects were matched to adult subjects with ESRD based on sex, age (±5 years), and weight (±10 kg).

Key Exclusion Criteria: Healthy subjects were excluded if there was a history of clinically significant cardiac rhythm abnormalities, lab tests indicating liver disease or injury, history or presence of impaired renal function, signs of urinary obstruction/difficulty voiding at screening, recent or recurrent history of acute or chronic bronchospastic disease, or any surgical or medical condition which the investigator felt may alter the absorption, distribution, metabolism, or excretion of drugs. Subjects with ESRD were excluded from the study if they had history of congestive heart failure, significant coronary artery disease or unstable angina within 6 months prior to screening; emergency room visit or hospitalization for chest pain or shortness of breath within 2 months of screening, or history or evidence of autonomic dysfunction within the preceding 1 year not related to hemodialysis. Key exclusion criteria for both groups

included use of other investigational drugs within 5 half-lives or within 30 days prior to the first dose of study drug, history of hypersensitivity or allergic reaction to any tetracycline; history of malignancy of any organ system (other than localized basal cell carcinoma of the skin) within the last 5 years, known HIV infection, and history of drug or alcohol abuse within 12 months.

Treatments

Each subject with ESRD participated in the study for approximately 65 days. This included a screening period (not exceeding 28 days), a 1-day baseline period, a 4-day treatment period (first treatment period), a washout period of 10 to 20 days, followed by a second 1-day baseline period and 4-day treatment period (second treatment period). After the second treatment period, there was a study completion evaluation which occurred approximately 1 week (±3 days) after the last dose of study drug. In the first treatment period, all ESRD subjects received a single dose of 100 mg omadacycline via IV infusion over approximately 30 minutes on Day 1 at 0 to 2 hours after dialysis. This dose was given in association with either the Friday or Saturday dialysis session to ensure a 72-hour gap from the start of omadacycline infusion before the next dialysis session. After the washout period, ESRD subjects received a second dose of omadacycline (second treatment period) approximately 60 to 90 minutes before dialysis. In both treatment periods, blood samples were collected at specified times through 68 hours post dose. During the second treatment period, dialysate samples were collected at specified times through 4 hours post dose.

Each healthy subject participated in the study for approximately 40 days. This included a screening period (not exceeding 28 days), a 1-day baseline period, a 4-day treatment period and a study completion evaluation which occurred approximately 1 week (±3 days) after the last dose of study drug. The healthy subjects received a single IV dose of 100 mg omadacycline on Day 1. Healthy subjects did not receive a second dose of omadacycline. Blood and urine were collected at specified time points through 72 hours post dose. All subjects (ESRD and healthy) were confined to the clinical research unit during the baseline and treatment periods.

Study Assessments

Pharmacokinetic Analysis

The PK population consisted of all subjects who received the intended dose of omadacycline for a given treatment period and for whom PK parameters could be calculated. This population was used for the PK concentration and PK parameter data summaries. Plasma, urine, and dialysate samples were analyzed for determination of omadacycline concentration using a validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) analytical method at Q2 Solutions, formerly Quintiles BioSciences, (Ithaca, New York). The following PK parameters were calculated using WinNonlin PK software (V5.0 or later) in this population: $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max}, T_{max}, $t_{1/2}$, CL, and V_{ss}.

Pharmacokinetic Statistical Analysis

For estimation of PK parameters of 2 groups, the statistical analysis of PK parameters was carried out by using an Analysis of Variance (ANOVA) model on log transformed PK parameters $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max}, and CL as response variable with fixed effect terms ESRD status (matched healthy subjects and subjects on hemodialysis [after dialysis dosing]) and matched pair as a random effect. The estimated mean difference and their associated 90% confidence intervals (CI) were constructed for the differences of dialysis for ESRD subjects on hemodialysis (after dialysis dosing) versus matched healthy subjects. The estimated mean difference and 90% CI were then back-transformed to give estimates and 90% CI for the ratio of the parameters in both categories, ESRD subjects versus matched healthy subjects.

In addition, to evaluate the effect of dialysis on omadacycline, the log transformed PK parameters ($AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max}, and CL) values for dosing before hemodialysis (test) versus dosing after hemodialysis (reference) in ESRD subjects was carried out by using an ANOVA model with period as factor, body weight at baseline, age and gender as covariates and subject as random effect. The 2-sided 90% CI for the estimated ratio of test versus reference was calculated for all PK parameters ($AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max}, and CL). The ratio of geometric means and its CI were obtained by back-transforming the estimated mean difference and its corresponding CI.

Safety Assessment

The safety and tolerability of omadacycline was assessed in terms of adverse events (AEs), serious adverse events (SAEs), vital signs, 12-lead electrocardiogram

(ECG), physical examination, and standard clinical laboratory safety tests (hematology and blood chemistry tests, coagulation, and urinalysis [healthy subjects]). The safety population consisted of all enrolled subjects who received any dose of omadacycline. All AEs were listed individually for each subject and summarized by system organ class (SOC) and preferred term (PT) assigned to the AEs, and were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 or later.

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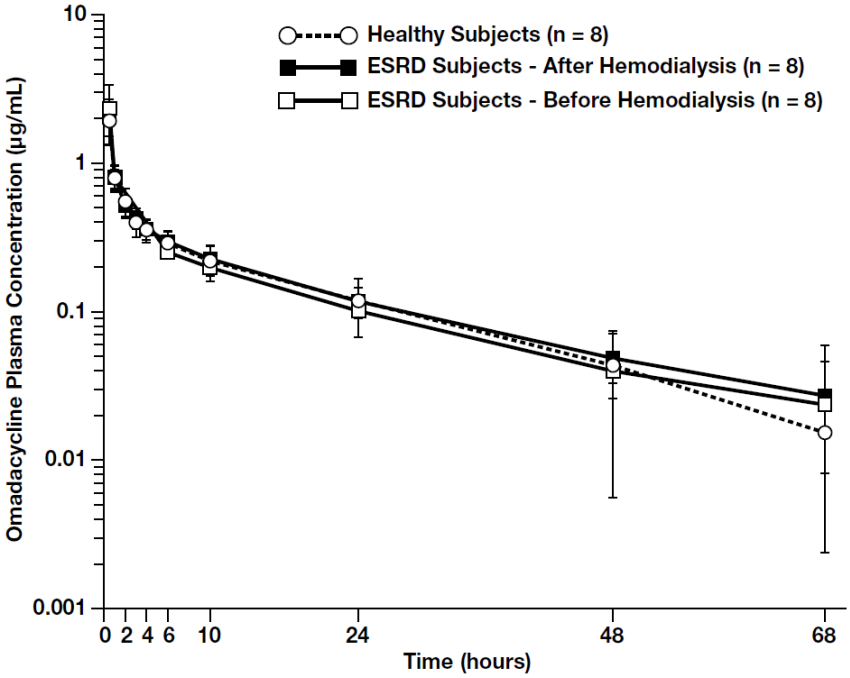

Fig 1 Plasma concentrations of omadacycline in ESRD subjects and healthy subjects (PK population). Subjects were dosed with 100 mg omadacycline IV. Healthy subjects were dosed once. Subjects with ESRD were dosed after hemodialysis and before hemodialysis, with a 10-20 day washout period between doses.

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TABLE 1 Baseline demographic characteristics

Characteristic	ESRD Subjects (n = 8)	Healthy Subjects (n = 8)	Total (N = 16)
Age, years			
Median (range)	58.5 (43-70)	56.5 (45-67)	58.5 (43-70)
Sex, n (%)			
Female	2 (25.0)	2 (25.0)	4 (25.0)
Male	6 (75.0)	6 (75.0)	12 (75.0)
Race, n (%)			
White	4 (50.0)	7 (87.5)	11 (68.8)
Black/African American	3 (37.5)	1 (12.5)	4 (25.0)
Other	1 (12.5)	0	1 (6.3)
Ethnicity, n (%)			
Hispanic or Latino	1 (12.5)	1 (12.5)	2 (12.5)
Not Hispanic or Latino	7 (87.5)	7 (87.5)	14 (87.5)
Weight, kg			
Median (range)	87.5 (52.9, 129.7)	91.7 (61.2, 129.3)	88.9 (52.9, 129.7)
BMI, kg/m^2			
Median (range)	28.0 (21.5, 39.2)	28.5 (20.9, 41.7)	28.5 (20.9, 41.7)

BMI, body mass index; ESRD, end-stage renal disease; N, number of subjects; n, non-missing observations.

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TABLE 2 Summary of omadacycline PK parameters in ESRD and healthy subjects

	ESRD Subjects n = 8		
Parameter	**Dose After Hemodialysis**	**Dose Before Hemodialysis**	**Healthy Subjects n = 8**
$AUC_{0\text{-last}}$, h•µg/mL	9.40 (2.10)	9.25 (1.80)	9.08 (1.86)
$AUC_{0\text{-inf}}$, h•µg/mL	10.30 (2.35)	10.20 (1.99)	9.76 (1.77)
C_{max}, µg/mL	1.88 (0.74)	2.33 (1.02)	1.92 (0.41)
T_{max}, h	0.58 (0.58, 1.08)	0.59 (0.58, 0.77)	0.58 (0.58, 0.68)
$t_{1/2}$, h	18.6 (5.21)	18.9 (6.34)	17.1 (2.60)
CL, L/h	10.1 (2.24)	10.1 (2.05)	10.6 (1.99)
V_{ss}, L	214 (56.1)	194 (69.2)	204 (47.6)

Arithmetic mean (standard deviation) is shown for all parameters except T_{max}, where median and range (minimum, maximum) are shown.

AUC, area under the concentration-time curve; C_{max}, maximum observed concentration of omadacycline in plasma; CL, Total body clearance; ESRD, end-stage renal disease; PK, pharmacokinetics; $t_{½}$, terminal elimination half-life in plasma; T_{max}, time of maximum observed plasma concentration; V_{ss}, volume of distribution at steady state.

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TABLE 3 Statistical comparison of PK parameters for ESRD subjects dosed after hemodialysis versus healthy subjects

PK Parameter	Cohort	Geometric Mean	Ratio of Geometric Mean	90% Confidence Interval for Ratio of Geometric Mean
$AUC_{0\text{-last}}$, h•µg/mL	ESRD[a]	9.21	1.03	0.86-1.24
	Healthy[b]	8.91		
$AUC_{0\text{-inf}}$, h•µg/mL	ESRD[a]	10.10	1.05	0.87-1.26
	Healthy[b]	9.61		
C_{max}, µg/mL	ESRD[a]	1.78	0.94	0.72-1.23
	Healthy[b]	1.88		
CL, L/h	ESRD[a]	9.91	0.95	0.79-1.14
	Healthy[b]	10.4		

[a] ESRD subjects dosed after hemodialysis served as test cohort for this analysis.

[b] Healthy subjects served as reference cohort for this analysis.

The ANOVA model included log transformed PK parameters as response variable, fixed effect term as ESRD status and matched pair as random effect.

AUC, area under the concentration-time curve; C_{max}, maximum observed concentration of omadacycline in plasma; CL, total body clearance; ESRD, end-stage renal disease; PK, pharmacokinetics.

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TABLE 4 Statistical comparison of PK parameters for ESRD subjects dosed after versus before hemodialysis

PK Parameter	Cohort	Geometric Mean	Ratio of Geometric Mean	90% Confidence Interval for Ratio of Geometric Mean
$AUC_{0\text{-last}}$,h•µg/mL	Before[a]	9.09	0.988	0.948-1.029
	After[b]	9.21		
$AUC_{0\text{-inf}}$, h•µg/mL	Before[a]	10.00	0.995	0.961-1.030
	After[b]	10.10		
C_{max}, µg/mL	Before[a]	2.18	1.230	0.983-1.536
	After[b]	1.78		
CL, L/h	Before[a]	9.95	1.000	0.971-1.040
	After[b]	9.91		

[a] ESRD subjects dosed before hemodialysis served as the test cohort.

[b] ESRD subjects dosed after dialysis served as the reference cohort for this analysis.

The ANOVA model included log transformed PK parameters as response variable, fixed effect term as period and weight at baseline, age and gender as covariates and subject as random effect.

AUC, area under the concentration-time curve; C_{max}, maximum observed concentration of omadacycline in plasma; CL, total body clearance; ESRD, end-stage renal disease; PK, pharmacokinetics.

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TABLE 5 Overall summary of treatment emergent adverse events

	ESRD Subjects (n = 8)		Healthy Subjects (n = 8)	Total (N = 16)
	Dose After Hemodialysis	Dose Before Hemodialysis		
Subjects with any TEAE, n (%)	3 (37.5%)	2 (25.0%)	1 (12.5%)	5 (31.3%)
Types of TEAE observed, n (%)				
Upper RTI	2 (25.0)	0	0	2 (12.5)
Viral upper RTI	1 (12.5)	0	0	1 (6.3)
Dizziness	1 (12.5)	0	0	1 (6.3)
Headache	0	1 (12.5)	0	1 (6.3)
Infusion site erythema	0	0	1 (12.5)	1 (6.3)
Bronchospasm	0	1 (12.5)	0	1 (6.3)
Rash papular	1 (12.5)	0	0	1 (6.3)

ESRD, end-stage renal disease; N, number of subjects in group; n, number of subjects; RTI, respiratory tract infection; TEAE, treatment emergent adverse event.

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