Pharmacokinetics, Safety, and Clinical Outcomes of Omadacycline in Women with Cystitis: Results from a Phase 1 Study

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ABSTRACT

Omadacycline, an aminomethylcycline antibiotic, is approved as once-daily intravenous and oral monotherapy for acute bacterial skin and skin structure infections, and community-acquired bacterial pneumonia, and is under development for treatment of urinary tract infection (UTI). This is a phase 1, randomized, open-label study of omadacycline in women with cystitis (defined as UTI symptoms and positive urine leukocyte esterase test). Patients received omadacycline for 5 days (Group 1: 200 mg intravenously on Day 1 then 300 mg orally every 24 hours [Q24h]; Group 2: 300 mg orally every 12 hours [Q12h] on Day 1 then 300 mg orally Q24h; Group 3: 450 mg orally Q12h on Day 1 then 450 mg orally Q24h). Blood and urine samples were collected over 5 days. Investigator-assessed clinical response was determined at end of treatment (EOT; Day 6) and post-treatment evaluation (PTE; 5–9 days after last dosing). Thirty-one women were treated. At steady-state (Day 5), mean omadacycline urine concentration over 24 hours across the groups (range) was 17.94–48.12 µg/mL. Most common treatment-emergent adverse events were gastrointestinal (including nausea [60%-73%] and vomiting [20%-40%]), and generally mild and transient. Investigator-determined clinical success was observed in 94% and 84% of patients at EOT and PTE, respectively, with similar results across groups. A favorable microbiological response at PTE was observed in 78% of patients who had a baseline pathogen. Omadacycline is partially excreted in urine and appears safe and well tolerated. These preliminary results indicate that omadacycline warrants further evaluation in larger controlled UTI studies.

KEYWORDS omadacycline, cystitis, urinary tract infection, women
INTRODUCTION

Urinary tract infection (UTI) poses a substantial problem in community- and hospital-based settings; approximately 150 million UTIs occur worldwide each year, accounting for ~US$6 billion in healthcare expenditures, as reported by the American Urological Association (AUA) [https://www.auanet.org/education/adult-uti.cfm]. UTIs are particularly common in women and the elderly. Among young, healthy women, nearly one in three will have had at least one episode of UTI requiring antimicrobial therapy by the age of 24 years, and almost one-third of these women will develop a second infection within 6 months of initial diagnosis [1, 2]. The annual estimated incidence of UTI in premenopausal women in the United States is 0.5 to 0.7 infections/person/year, and among Medicare beneficiaries aged ≥65 years, UTIs account for 1.8 million office visits each year [https://www.auanet.org/education/adult-uti.cfm]. UTIs are often categorized clinically as uncomplicated (e.g., cystitis in women with no known urological abnormalities) or complicated (e.g., pyelonephritis or UTI associated with an indwelling urinary catheter or structural urological abnormalities).

The majority of community-acquired UTIs manifest as uncomplicated bacterial cystitis, and mainly affect women [https://www.auanet.org/education/adult-uti.cfm]. Uncomplicated UTI (uUTI) is most commonly caused by Escherichia coli (~80% of cases) and Staphylococcus saprophyticus (~5% to 15% of cases), and substantial increases in antimicrobial resistance rates in E. coli have been reported [3]. Based on an analysis of changes in antimicrobial resistance patterns in the United States between 2000 and 2010 (N = 12,253,679), the largest increases in E. coli resistance were
reported for ciprofloxacin (3.0% to 17.1%) and trimethoprim/sulfamethoxazole (17.9% to 24.2%)

Omadacycline is approved as a once-daily intravenous (IV) and oral (PO) antibiotic for use as empiric monotherapy in acute bacterial skin and skin-structure infections (OASIS-1 Study [NCT02378480](4), OASIS-2 Study [NCT02877927]) and community-acquired bacterial pneumonia (OPTIC Study [NCT02531438](5)).

Omadacycline, the first aminomethylcycline antibiotic, is a semisynthetic derivative of the tetracyclines that exhibits activity against Gram-positive and Gram-negative aerobes, anaerobes, and atypical bacteria (6). It has been shown to be active against tetracycline-susceptible and tetracycline-resistant strains (7). The minimum inhibitory concentrations of omadacycline for at least 90% of isolates (MIC₉₀) are 0.25 μg/mL for *S. saprophyticus* and 2 μg/mL for *E. coli*(8), regardless of the presence of extended-spectrum beta-lactamases (ESBLs) (MD Huband, BS, unpublished data 2015; MD Huband *et al*. presentation P1253 27th European Congress of Clinical Microbiology and Infectious Diseases, Vienna, Austria, 22-25 April 2017). A phase 1 absorption, distribution, metabolism, and excretion study in healthy human volunteers demonstrated partial renal excretion of omadacycline (9).

The primary objective of the current study, which is the first study of omadacycline in patients with UTI, was to evaluate the plasma and urine pharmacokinetics (PK) of omadacycline in women with cystitis. Safety was a secondary objective and clinical efficacy an exploratory objective. The results of this study were intended to determine the potential utility of omadacycline for the treatment of UTI, and to aid in the selection of dosing regimens for use in possible future UTI studies.
RESULTS

Patient disposition. Between May and September 2016, a total of 31 patients (11 in Group 1 and 10 each in Groups 2 and 3) were randomized and received study medication for 5 days at three study sites in the United States. Patients in Group 1 received 200 mg IV on Day 1 followed by 300 mg PO every 24 hours [Q24h]. Patients in Group 2 received 300 mg PO every 12 hours [Q12h] on Day 1 followed by 300 mg PO Q24h; and patients in Group 3 received 450 mg PO Q12h on Day 1 followed by 450 mg PO Q24h. In line with the reduced oral bioavailability of omadacycline when administered with food, patients in this study were fasted of food and drink (except water) for at least 6 hours prior to oral dosing and for 2 hours after oral dosing; patients also had no dairy products, antacids, or multivitamins for 4 hours after oral dosing (10). All but one patient completed the intended 5 days of study treatment (one patient in Group 1 withdrew consent on study Day 2 and did not complete the Day 5 PK assessment or end of treatment visit).

Baseline demographics and disease characteristics. Patient demographics and disease characteristics were well balanced (Table 1). Patients ranged in age from 19 to 75 years (median, 38 years). Patients were generally in good health otherwise, without significant comorbidities that would affect study participation. A total of nine (29.0%) patients were postmenopausal and three (9.7%) had diabetes mellitus. Baseline cystitis symptoms were reported as moderate or severe by most patients. No patients had a fever (temperature >100.4°F) at baseline or during the study. At baseline, 27 (87.1%) patients had growth of one or more bacterial organisms in urine cultures, and 18 (58.1%) had one or more bacterial species that met the definition of a urinary
pathogen ($\geq 1 \times 10^5$ CFU/mL in urine and considered a potential cause of UTI; Table 2).

The most common urinary pathogens at baseline were *E. coli* (55.6%), *Proteus mirabilis* (22.2%), and *Klebsiella pneumoniae* (16.7%); *S. saprophyticus* was detected in one patient (5.6%). There were no patients with positive blood cultures in this study.

**Pharmacokinetics.** Steady-state concentrations of omadacycline were achieved by the end of Day 1 using either a single IV dose of 200 mg, or a PO dose of 300 mg or 450 mg every 12 hours (Fig. 1a).

After a single 200-mg IV dose of omadacycline, the mean maximum (peak) observed plasma concentration ($C_{max}$) was 2.16 µg/mL (Table 3). The AUC from 0 to 24 hours ($\text{AUC}_{0-24}$) for IV omadacycline was 16.02 µg•h/mL on Day 1. The mean clearance and volume of distribution values were 10.27 L/h and 167.57 L, respectively. Using the omadacycline PO loading dose paradigm on Day 1, the mean $C_{max}$ and area under concentration-time curve (AUC) from 0 to 12 hours for 450 mg every 12 hours (0.99 µg/mL and 6.85 µg•h/mL, respectively) were only modestly higher than for 300 mg every 12 hours (0.88 µg/mL and 6.26 µg•h/mL). At steady-state (Day 5), $C_{max}$ and $\text{AUC}_{0-24}$ values in patients in Groups 1 and 2 (both receiving 300 mg PO once daily) varied by only approximately ~3% ($C_{max}$ was 1.12 µg/mL in both groups; $\text{AUC}_{0-24}$ was 13.16 µg•h/mL in Group 1 and 13.50 µg•h/mL in Group 2), whereas in Group 3 (450 mg PO once daily), the $C_{max}$ and $\text{AUC}_{0-24}$ values (1.49 µg/mL and 19.83 µg•h/mL, respectively) were ~33% and 46% higher, respectively, compared with values in Groups 1 and 2. The median time to reach $C_{max}$ ($T_{max}$) was 0.75 hours for the IV dose and 3.0 hours for the PO doses (Table 3).

The highest omadacycline concentration in urine (mean, 65.4 µg/mL) was
observed in Group 1 between 0 and 4 hours after administration of the 200-mg IV dose on Day 1 (Fig. 1b). Mean values across all other groups and time intervals ranged from 11.7 µg/mL to 48.1 µg/mL. After dosing on Day 1, mean values for the cumulative amounts of drug excreted unchanged in urine from 0 to 24 hours (Ae₀-2₄) were similar in each group (35.95 to 40.70 mg; Table 3). At steady-state (Day 5), the mean urine concentration for 0-24 hours ranged from 17.94 to 48.12 µg/mL across the three groups; mean Ae₀-2₄ values were similar in Groups 1 and 2 (32.27 mg and 38.21 mg) following administration of 300 mg PO once daily, and higher in Group 3 (54.87 mg) following administration of 450 mg PO once daily. Mean values for the fraction of the dose excreted unchanged in urine from 0 to 24 hours after dosing (fₑ₀-2₄) at steady-state (Day 5) ranged from 10.8% to 12.7%. After the PO dose on Day 5, mean renal clearance values were also similar in each group (range, 2.42 L/h to 2.80 L/h).

**Efficacy.** Patient-reported clinical success at end of treatment (EOT) occurred in 72.7% of patients in Group 1, 100% in Group 2, and 90.0% in Group 3. Investigator-determined clinical success was ≥90.0% in all groups at EOT (Table 4). At post-treatment evaluation (PTE), these rates were 100% in Group 1, 70.0% in Group 2, and 80.0% in Group 3. Four patients had clinical failure across Groups 2 and 3, of whom two patients had no known baseline pathogens, one patient had *K. pneumoniae* (omadacycline MIC = 2 µg/mL) with a favorable microbiological response and *A. urinae* (omadacycline MIC ≤0.06 µg/mL) with a favorable microbiological response, and one patient had *E. coli* (omadacycline MIC = 1 µg/mL) with an unfavorable microbiological response and *P. mirabilis* (omadacycline MIC = 8 µg/mL) with a favorable microbiological response. Among patients with a baseline pathogen, favorable
microbiological responses at PTE occurred in 100% in Group 1, 80.0% in Group 2, and 57.1% in Group 3 (Table 5). Four patients had unfavorable microbiological responses across Groups 2 and 3, three patients had baseline *E. coli* with MIC values of 0.5 to 1 µg/mL, and one patient had *K. pneumoniae* with an MIC of 2 µg/mL. Data for favorable microbiological response and clinical success at PTE by baseline pathogen and MIC are provided in Table 6.

Urinalysis was notable only for leukocyte esterase testing, which shifted from positive at baseline (trace to 3+) to a less severe category or negative at EOT for most patients. This finding is consistent with what was expected, as all patients had to have a positive leukocyte esterase test at screening to qualify for the study, and it would be expected that this would improve or become negative if the infection was improving/resolving.

**Safety.** The percentage of patients with any treatment-emergent adverse event (TEAE) was comparable in each group (80.0% to 90.0%; Table 7). The percentage of patients with treatment-related TEAEs was similar in each treatment group (Group 1, 81.8%; Group 2, 90.0%; Group 3, 80.0%). There were no severe or serious TEAEs, or TEAEs resulting in premature treatment discontinuation. Gastrointestinal events were the most common TEAEs in each group, most notably nausea (60.0% to 72.7%), vomiting (20.0% to 40.0%), and diarrhea (0.0% to 20.0%); all were mild or moderate in intensity and generally transient. No patients discontinued omadacycline because of these TEAEs. However, seven (23.0%) received the antiemetic/antinauseant medication ondansetron during the study.

Clinically asymptomatic elevations in pulse rate were observed in each treatment
group. The largest median increase in pulse rate (20 beats per minute) was observed in Group 1 after the 200-mg IV dose. The largest median increase in pulse rate in Groups 2 and 3 after PO doses of 300 mg or 450 mg was approximately 15 beats per minute. These changes were transient, generally occurring between 1 and 3 hours post dose, and then resolving over several hours. There were no clinically relevant changes in blood pressure, 12-lead electrocardiogram parameters, or physical examination results. Laboratory testing was notable only for a small increase from baseline in serum alanine aminotransferase (ALT) values at the end of treatment in Group 3 following 450-mg PO dosing (median change, 18 U/L). The corresponding median changes in ALT in Groups 1 and 2 were ≤6.0 U/L. The highest individual ALT value (92 U/L; 2.8-fold > upper limit of normal [ULN]) occurred at EOT in a patient in the 450-mg PO dose group, but the ALT value subsequently declined to 40 U/L at PTE. There were no clinically meaningful changes from baseline or differences between groups in other laboratory parameters.

**DISCUSSION**

This study, the first evaluation of omadacycline in patients with UTI, demonstrated that the PK of omadacycline in women with cystitis are similar to the PK previously observed in healthy subjects (9-12). In previous studies, C_{max} varied across doses and infusion time, with a mean of 1.8 µg/mL for 100 mg IV administration and 0.7 µg/mL for 300 mg oral. The mean terminal elimination half-life was 17 hours, although this varied across doses, and mean clearance was 17.1 L/h, independent of the dose used (11). In a mass balance study 14.4% of a 300 mg oral dose of omadacycline, corresponding to approximately 40% of the absorbed dose, was excreted by the
In the current study, at steady-state the fraction of omadacycline excreted in urine over 24 hours after PO dosing was ~12%, which, based on an established PO bioavailability of 35% (13), translates to ~34% of the absorbed dose.

In the current study, both IV and PO administration of omadacycline resulted in urine concentrations that exceeded peak plasma concentrations and were sustained over the 24-hour dosing interval. At steady-state, the PO dosing regimens of 300 mg or 450 mg once daily provided mean omadacycline concentrations in urine (range, 17.94 µg/mL to 48.12 µg/mL) that compare favorably to the omadacycline MIC<sub>90</sub> values for common UTI pathogens such as <i>E. coli</i> (MIC<sub>90</sub> = 2 µg/mL) (8) and <i>S. saprophyticus</i> (MIC<sub>90</sub> = 0.25 µg/mL) (MD Huband, BS, unpublished data 2015). These data indicate that once-daily PO dosing can achieve concentrations of omadacycline (sustained over the 24-hour dosing period) that will exceed the MIC<sub>90</sub> for common UTI pathogens. The proportion of the administered PO dose excreted in the urine, together with the extensive tissue distribution demonstrated in earlier PK studies, suggest that omadacycline may also have clinical utility in complicated UTI, including acute pyelonephritis.

It was encouraging that exploratory analyses of efficacy demonstrated high clinical response rates, with investigator-determined clinical success in 94% and 84% of patients at EOT and PTE, respectively, across all 31 treated patients. Clinical failure and unfavorable microbiological response were not correlated, and no factor was identified that could explain the unfavorable clinical or microbiological response in all patients. However, given the small sample size and the relatively high clinical response
rates, no conclusions can be drawn with respect to potential efficacy differences between the dosing regimens evaluated. The safety profile of omadacycline in the female patients with cystitis in the current study was comparable with that observed in other study populations receiving similar omadacycline dosing regimens (6, 9, 10, 12). The only notable exception was the incidence of gastrointestinal TEAEs, especially nausea and vomiting, which was higher than expected in the current study. However, no patient required study treatment discontinuation for TEAEs. Lower incidences of nausea (8% and 4%) and vomiting (8% and 0%) had been observed in a phase 1, PO, multi-dose study in healthy volunteers at 300-mg and 450-mg omadacycline doses, respectively (10). The reason for the higher incidences of nausea and vomiting in the current study is not clear, and the study design and small sample size make this challenging to interpret. The observations in some patients of transient, asymptomatic changes in heart rate or serum ALT have been observed in prior studies of omadacycline in healthy subjects (9, 10, 12).

Antibiotic resistance rates to current standard therapies have increased for outpatient UTI E. coli isolates, and multi-drug resistant E. coli and ESBL-positive E. coli are being isolated from community-acquired infections more frequently than has been observed previously (3, 14). There is a particular need for new antimicrobials with appropriate coverage of UTI pathogens that are orally bioavailable and thus can be used primarily for outpatient treatment or transition from IV to PO therapy upon hospital discharge. The antibacterial spectrum of omadacycline, in particular its activity against ESBL-positive E. coli, development of both IV and PO formulations, its plasma and urine PK, and its safety and tolerability profile suggest that omadacycline has the
potential to be a useful antibiotic for the treatment of UTI. As this was a small scale study, the findings are limited by the small number of patients included, and associated variation in PK parameters. The observed variation in parameters such as $C_{\text{max}}$, should be used to estimate the required sample sizes for future larger-scale studies. In addition, larger studies that focus on specific UTI patient populations, such as uUTI and complicated UTI (i.e., acute pyelonephritis), and/or a specific spectrum of bacterial pathogens, are needed to better understand the potential role and appropriate dose of omadacycline for the treatment of UTI.

**MATERIALS AND METHODS**

**Patient population.** Adult (≥18 years of age) women who had an onset of ≥2 cystitis symptoms (dysuria, urgency, frequency, or suprapubic pain) within ≤72 hours before randomization were eligible. Patients were required to have a positive urine leukocyte esterase test and to provide a clean-voided midstream urine sample for microbiological analysis at screening. Patients were excluded for a known or suspected complicated UTI, previous treatment with a systemic antibiotic ≤48 hours before randomization, history or evidence of severe renal disease or a calculated creatinine clearance of <30 mL/minute using the Cockcroft-Gault equation, or the need for any form of dialysis (e.g., hemodialysis or peritoneal dialysis). Also excluded were patients with a known history of unstable cardiac disease (e.g., unstable angina, myocardial infarction, acute congestive heart failure, or unstable cardiac arrhythmia) within 3 months before screening. Additionally, patients with elevated levels of ALT (≥3 × ULN),
aspartate aminotransferase ($\geq 3 \times \text{ULN}$), or total bilirubin ($>1.5 \times \text{ULN}$) were not eligible.

Complete study entry criteria are provided in the supplementary appendix.

The study was designed, conducted and reported in accordance with the ethical principles laid down in the Declaration of Helsinki. All patients provided written informed consent prior to participation. The study was approved by a properly constituted institutional review board/independent ethics committee/research ethics board (Quorum Review IRB, Seattle, WA, USA) before study start. The patients were enrolled from May 1, 2016 (first patient enrolled) to September 26, 2016 (last patient completed).

**Study design.** In this phase 1b, open-label, randomized (1:1:1), parallel-group study, patients received one of three omadacycline regimens for 5 days (Fig. S1 in the supplementary appendix). All patients were to remain housed at the clinical site from the start of treatment (Day 1) through the EOT assessment on Day 6.

**Dose selection.** Previous clinical data suggested that 300 mg was the lowest daily PO dose of omadacycline that would maintain favorable urine concentrations to treat common uUTI pathogens (9). The omadacycline half-life of approximately 18 hours suggested that once-daily dosing would be justified (9). Given this half-life, between 72 and 90 hours would be required to achieve steady-state conditions at a constant dosing rate. To reduce the time required to achieve target concentrations, a "loading dose" strategy was employed. Group 1 used an initial dose of 200 mg IV on Day 1, followed by once-daily doses of 300 mg PO. The 300-mg PO dose is bioequivalent to a 100-mg IV dose; hence, 200 mg IV was expected to be comparable with 600 mg PO. Because early studies demonstrated an increased incidence of gastrointestinal AEs at doses $\geq 400$ mg PO (11), the 200-mg IV dose was evaluated as a potential means of providing...
a rapid and better tolerated “loading dose”. Group 2 used two doses of 300 mg PO (separated by 12 hours) on Day 1, followed by once-daily doses of 300 mg PO. Group 3 evaluated higher doses of omadacycline—initial dosing with two doses of 450 mg PO (separated by 12 hours) on Day 1, followed by once-daily doses of 450 mg PO—with the goal of achieving greater exposure that may be required in future studies. Based on prior phase 1 studies, the 450-mg PO dose was considered near the upper end of the dose range for providing acceptable tolerability in treating UTI (10).

**Study assessments.** Blood and urine samples were collected on Days 1 and 5 for PK and safety analyses. Plasma and urine samples were analyzed for determination of omadacycline concentrations using a validated liquid chromatography-mass spectrometry/mass spectrometry analytical method at Q2 Solutions, formerly Quintiles BioSciences (Ithaca, New York, USA). Safety assessments included adverse events, 12-lead electrocardiogram recordings, clinical laboratory testing, vital sign measurements, and physical examinations. Efficacy assessments consisted of investigator-assessed clinical response and microbiologic outcome at EOT (Day 6) and at PTE (5 to 9 days after the last dose). Urine cultures were performed at baseline, daily through EOT, and at PTE. Cystitis symptoms (including frequency, urgency, pain, incomplete voiding, fever, hypothermia, and blood in urine) were assessed by patients using the Urinary Tract Infection Symptoms Assessment questionnaire (15).
Statistical analysis. The safety population comprised all randomized patients who received any amount of omadacycline; the PK population comprised all randomized patients who received omadacycline and had evaluable PK parameter data. Descriptive statistics were presented for the PK parameter estimates for AUC, $C_{\text{max}}$, and $T_{\text{max}}$ after treatment on Days 1 and 5. The concentration, amount excreted in urine over a dosing interval, urinary excretion rate, and renal clearance of omadacycline after Day-1 and Day-5 doses were summarized by treatment group.

Adverse events were coded using Medical Dictionary for Regulatory Activities terminology. The incidence of TEAEs was presented by system organ class and preferred term, relationship to study medication, severity, and those that were serious or led to premature treatment discontinuation. Descriptive statistics for continuous-variable safety parameters were provided for each treatment group by visit and change from baseline.

The number and percentage of patients with investigator-assessed outcomes of clinical success, clinical failure, and indeterminate were presented for EOT and PTE by treatment group. Clinical success was defined as resolution of signs and symptoms of UTI at the EOT visit and no use of additional systemic antimicrobial therapy for the UTI. Clinical failure was defined as persistence of (or reappearance of) signs and symptoms, or use of additional systemic antimicrobial therapy for the UTI. If the EOT or PTE visit was not completed, the response was considered indeterminate. Patient-reported clinical response at EOT was programmatically determined; clinical success was defined as improvement from baseline by at least one number score in at least two of...
the key symptoms (dysuria, frequency, urgency, suprapubic pain), with no worsening in any of the other symptoms.

Microbiological outcomes at PTE were defined as eradication, persistence, or indeterminate. Eradication indicated that each baseline pathogen found at $\geq 10^5$ CFU/mL in urine was reduced to $< 10^4$ CFU/mL, and were not present in a blood culture (16). Microbiological failures did not meet that criterion and, if no follow-up urine culture was obtained, the response was considered indeterminate.

SUPPLEMENTAL MATERIAL

A supplementary appendix for this article may be found at [journal to add url].

SUPPLEMENTAL FILE 1
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All authors contributed to the design, analysis and interpretation of the study.

Authors L.G-R., J.S., S.B., S.C., A.M., and E.T. are employees of Paratek Pharmaceuticals. J.S.P and P.B. have no conflicts of interest to declare.
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TABLE 1 Demographics and baseline characteristics (safety population)

| Parameter                      | Group 1     | Group 2      | Group 3      | All patients |
|--------------------------------|-------------|--------------|--------------|--------------|
|                                | IV<sup>a</sup> 200 mg → PO<sup>b</sup> 300 mg | Group 2 PO 300 mg | Group 3 PO 450 mg | All patients |
|                                | (n = 11)    | (n = 10)     | (n = 10)     | (N = 31)     |
| Race, n (%)                    |             |              |              |              |
| White                          | 4 (36.4)    | 3 (30.0)     | 4 (40.0)     | 11 (35.5)    |
| Black or African American      | 6 (54.5)    | 7 (70.0)     | 6 (60.0)     | 19 (61.3)    |
| Asian                          | 1 (9.1)     | 0            | 0            | 1 (3.2)      |
| Female, n (%)                  | 11 (100.0)  | 10 (100.0)   | 10 (100.0)   | 31 (100.0)   |
| Age, years                     |             |              |              |              |
| Median (range)                 | 51 (20 to 60) | 31 (25 to 54) | 41 (19 to 75) | 38 (19 to 75) |
| Weight, kg                     |             |              |              |              |
| Median (range)                 | 72 (47 to 95) | 75 (54 to 121) | 69 (51 to 111) | 72 (47 to 121) |
| Body mass index, kg/m<sup>2</sup> |             |              |              |              |
| Median (range)                 | 27 (20 to 39) | 28 (20 to 43) | 27 (21 to 41) | 27 (20 to 43) |
| Medical history, n (%)         |             |              |              |              |
| Condition                     | Number | Percentage |
|------------------------------|--------|------------|
| Postmenopausal               | 5      | 45.5%      |
| Diabetes mellitus            | 0      | 0%         |
| 1 (10.0)                     | 1 (10.0) |
| 2 (20.0)                     | 3 (30.0) |
| 3 (30.0)                     | 3 (30.0) |

IV, intravenous. PO, oral.
### TABLE 2 Baseline pathogens (safety population)

| Parameter | Group 1 | Group 2 | Group 3 | All patients |
|-----------|---------|---------|---------|-------------|
|           | IV<sup>a</sup> 200 mg | PO<sup>b</sup> 300 mg | PO 300 mg | PO 450 mg | (N = 31) |
|           | (n = 11) | (n = 10) | (n = 10) | (n = 10) |           |
| Patients with culture growth at baseline, n (%) | 8 (72.7) | 9 (90.0) | 10 (100.0) | 27 (87.1) |
| Patients with pathogen growth at baseline,<sup>c,d</sup> N1 (%) | 6 (54.5) | 5 (50.0) | 7 (70.0) | 18 (58.1) |
| Patients with Gram-negative pathogens,<sup>e</sup> n (%) | 6 (100.0) | 4 (80.0) | 6 (85.7) | 16 (88.9) |
| Escherichia coli | 3 (50.0) | 3 (60.0) | 4 (57.1) | 10 (55.6) |
| Klebsiella pneumoniae | 0 | 1 (20.0) | 2 (28.6) | 3 (16.7) |
| Proteus mirabilis | 3 (50.0) | 1 (20.0) | 0 | 4 (22.2) |
| Patients with Gram-positive pathogens,<sup>e</sup> n (%) | 1 (16.7) | 1 (20.0) | 2 (28.6) | 4 (22.2) |
| Aerococcus urinae | 0 | 0 | 1 (14.3) | 1 (5.6) |
| Enterococcus faecalis | 1 (16.7) | 0 | 0 | 1 (5.6) |
| Staphylococcus saprophyticus | 0 | 0 | 1 (14.3) | 1 (5.6) |
| Streptococcus agalactiae | 0 | 1 (20.0) | 0 | 1 (5.6) |
(Group B)

N1 = number of subjects with organism growth at baseline

IV, intravenous.

PO, oral.

Baseline pathogens were defined as bacteria identified in urine at ≥1 × 10^5 CFU/mL and considered a potential cause of urinary tract infection. Patients may have had more than one pathogen.

Percentages were calculated as 100 × (N1/N).

Percentages were calculated as 100 × (n/N1).
| Parameter (unit) | Day 1 | Day 5 |
|------------------|-------|-------|
|                  | Group 1 | Group 2 | Group 3 | Group 1 | Group 2 | Group 3 |
|                  | IV² 200 mg → | PO³ 300 mg | PO 300 mg | PO 450 mg | PO 300 mg | PO 450 mg |
|                  | PO³ 300 mg | PO 300 mg | PO 450 mg | PO 300 mg | PO 300 mg | PO 450 mg |
|                 | (n = 11) | (n = 10) | (n = 10) | (n = 10) | (n = 10) | (n = 10) |
| **Plasma**       |         |         |         |         |         |         |
| C_{max} {µg/mL}  | 2.16 (59.0) | 0.88 (25.6) | 0.99 (30.8) | 1.12 (58.8) | 1.12 (37.2) | 1.49 (36.2) |
| T_{max} {h}      | 0.75 | 3.0 | 3.0 | 3.0 | 3.0 | 3.0 |
|                  | (0.72, 1.60) | (2.0, 4.0) | (0.97, 4.0) | (0.0, 4.0) | (2.0, 8.0) | (0.50, 8.0) |
| AUC_{0-24} {µg•h/mL} | 16.02 (28.7) | ND | ND | 13.16 (59.7) | 13.50 (33.7) | 19.83 (30.8) |
| AUC_{0-12} {µg•h/mL} | ND | 6.26 (18.9) | 6.85 (23.2) | ND | ND | ND |
| T_{1/2} {h}      | 11.38 (13.6) | ND | ND | ND | ND | ND |
| Clearance, L/h   | 10.27 (15.1) | ND | ND | ND | ND | ND |
| V_{e} {L}        | 167.57 (17.6) | ND | ND | ND | ND | ND |
| C_{min} {µg/mL}  | ND | ND | ND | 0.29 (60.4) | 0.32 (35.4) | 0.48 (27.6) |
### Urine

| $A_{0-24}$, mg | 40.70 (44) | 39.24 (34) | 35.95 (33) | 32.27 (79) | 38.21 (52) | 54.87 (67) |
|----------------|------------|------------|------------|------------|------------|------------|
| Total dose within 24 hours, mg | 200 IV | 600 PO | 900 PO | 300 PO | 300 PO | 450 PO |
| $f_{e_{0-24}}$, % | 20.4 | 6.5 | 4.0 | 10.8 | 12.7 | 12.2 |
| Concentration, µg/mL | | | | | | |
| 0–4 h | 65.36 (53.02) | 14.00 (9.69) | 23.01 (29.94) | 42.71 (43.37) | 30.90 (18.90) | 35.99 (24.12) |
| 4–8 h | 43.55 (31.52) | 19.09 (9.47) | 20.54 (19.19) | 26.09 (18.06) | 29.11 (21.37) | 48.12 (46.01) |
| 8–12 h | 32.41 (20.32) | 19.98 (19.23) | 11.70 (6.82) | 33.24 (34.55) | 25.35 (16.69) | 30.47 (25.84) |
| 12–24 h | 22.41 (17.75) | 20.77 (11.92) | 25.71 (16.24) | 21.48 (21.97) | 17.94 (12.00) | 30.28 (23.57) |

| $CL_r$, L/h | 2.64 (1.21) | ND | ND | 2.42 (0.92) | 2.71 (1.01) | 2.80 (2.29) |

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*IV, intravenous.

*PO, oral.

One patient in Group 1 withdrew consent on study Day 2 and did not complete the Day 5 PK assessment.
Arithmetic mean (percent coefficient of variation [%CV]) is shown for all parameters except $T_{\text{max}}$, which is shown as median and range (minimum, maximum).

$C_{\text{max}}$, mean maximum (peak) observed plasma concentration.

$T_{\text{max}}$, median time to maximum (peak) observed plasma concentration.

$AUC_{0-24}$, area under concentration-time curve from 0 to 24 h.

ND, not determined.

$AUC_{0-12}$, area under concentration-time curve from 0 to 12 h.

$T_{1/2}$, half-life.

$V_d$, volume of distribution.

$C_{\text{min}}$, mean minimum observed plasma concentration.

$Ae_{0-24}$, amount excreted unchanged in urine from 0 to 24 h.

Mean (%CV).

$fe_{0-24}$, fraction of dose excreted in urine from 0 to 24 h.

Mean (SD).

CLR, renal clearance.
TABLE 4 Investigator assessment of clinical response (safety population)

| Parameter                  | Omadacycline dose | Group 2 | Group 3 |
|----------------------------|-------------------|---------|---------|
|                            | IV* 200 mg →      | PO 300 mg | PO 450 mg |
|                            | (n = 11)          | (n = 10) | (n = 10) |
| End of treatment, n (%)    |                   |         |         |
| Clinical success           | 10 (90.9)         | 10 (100)| 9 (90.0)|
| Clinical failure           | 0                 | 0       | 1 (10.0)|
| Indeterminate              | 1 (9.1)           | 0       | 0       |
| Post-treatment evaluation, n (%) |         |         |         |
| Clinical success           | 11 (100)          | 7 (70.0)| 8 (80.0)|
| Clinical failure           | 0                 | 2 (20.0)| 2 (20.0)|
| Indeterminate              | 0                 | 1 (10.0)| 0       |

*IV, intravenous.

*PO, oral.

Clinical success indicates resolution of signs and symptoms and no use of additional systemic antimicrobial therapy for the urinary tract infection.

Clinical failure indicates no apparent response to therapy, persistence of signs and symptoms of infection at the end-of-treatment visit, or use of additional systemic antimicrobial therapy for the current infection.

Indeterminate indicates the visit was not completed.
TABLE 5  Microbiological response at the post-treatment evaluation visit in patients with a baseline pathogen (safety population)

| Omadacycline dose | Group 1 | Group 2 | Group 3 |
|-------------------|---------|---------|---------|
| Parameter         | IV a 200 mg → PO b 300 mg | PO 300 mg (n = 10) | PO 450 mg (n = 10) |
| Patients with pathogen growth at baseline, c N1 (%) | 6 (54.5) (n = 11) | 5 (50.0) | 7 (70.0) |
| Favorable, d,e n (%) | 6 (100.0) | 4 (80.0) | 4 (57.1) |
| Unfavorable, f n (%) | 0 (0.0) | 1 (20.0) | 3 (42.9) |
| Indeterminate g | 0 (0.0) | 0 (0.0) | 0 (0.0) |

N1 = number of subjects with organism growth at baseline

aIV, intravenous.
bPO, oral.
cPercentages were calculated as 100 × (N1/N).
dPercentages were calculated as 100 × (n/N1).
fFavorable indicates each baseline pathogen was reduced to <10⁴ CFU/mL.
gUnfavorable indicates any baseline pathogen was not reduced to <10⁴ CFU/mL.
Indeterminate indicates that follow-up cultures were not obtained.
| Baseline pathogen                  | Omadacycline MIC (µg/mL) | Favorable microbiological response at PTE<sup>a</sup> n/N2 (%) | Clinical success at PTE<sup>b</sup> n/N2 (%) |
|-----------------------------------|--------------------------|---------------------------------------------------------------|-----------------------------------------------|
| **Gram-negative pathogens**       |                          |                                                               |                                               |
| *Escherichia coli*, n/N1          | 0.5                      | 2/3 (66.7)<sup>c</sup>                                        | 3/3 (100.0)                                   |
|                                  | 1.0                      | 4/6 (66.7)<sup>d,e</sup>                                      | 1/6 (16.7)<sup>c</sup>                        |
|                                  | 2.0                      | 1/1 (100.0)                                                   | 1/1 (100)                                     |
| *Klebsiella pneumoniae*, n/N1     | 1.0                      | 1/1 (100.0)                                                   | 1/1 (100)                                     |
|                                  | 2.0                      | 1/2 (50.0)<sup>f</sup>                                        | 1/2 (50.0)<sup>g</sup>                        |
| *Proteus mirabilis*, n/N1         | 8.0                      | 2/2 (100.0)                                                   | 1/2 (50.0)<sup>d</sup>                        |
|                                  | 16.0                     | 2/2 (100.0)                                                   | 2/2 (100.0)                                   |
| **Gram-positive pathogens**       |                          |                                                               |                                               |
| *Aerococcus urinae*               | ≤0.06                    | 1/1 (100.0)                                                   | 0/1 (0)<sup>g</sup>                           |
| *Enterococcus faecalis*           | ≤0.06                    | 1/1 (100.0)                                                   | 1/1 (100.0)                                   |
| Pathogen                      | MIC  | n (100.0) | N2 (100.0) |
|-------------------------------|------|-----------|------------|
| Staphylococcus saprophyticus  | 0.25 | 1/1       | 1/1        |
| Streptococcus agalactiae (Group B) | 0.12 | 1/1       | 1/1        |

MIC, minimum inhibitory concentration; n, number of patients in the specific category; N1, number of patients with the baseline pathogen; N2, number of patients with the baseline pathogen at the specified MIC; PTE, post-treatment evaluation.

Percentages are based on the number of patients with the baseline pathogen at the specified MIC.

*a* Favorable microbiological response indicates the baseline pathogen was reduced to $<10^4$ CFU/mL at PTE.

*b* Clinical success indicates resolution of signs and symptoms and no use of additional systemic antimicrobial therapy for the urinary tract infection; clinical failure indicates no apparent response to therapy, persistence of signs and symptoms of infection at the end-of-treatment visit, or use of additional systemic antimicrobial therapy for the current infection.

*c* One patient in Group 3 had an unfavorable microbiological response at PTE.

*d* One patient in Group 2 had *E. coli* with an unfavorable microbiological response at PTE and *P. mirabilis* with a favorable microbiological response PTE. The patient was assessed as a clinical failure at PTE.

*e* One patient in Group 3 had an unfavorable microbiological response at PTE.

*f* One patient in Group 3 had an unfavorable microbiological response at PTE.

*g* One patient in Group 3 had *K. pneumoniae* with a favorable microbiological response at PTE and *A. urinae* with a favorable microbiological response at PTE. The patient was assessed as a clinical failure at PTE.
TABLE 7 Treatment-emergent adverse events in >1 patient (safety population)

| Parameter                          | Omadacycline dose | Group 1 | Group 2 | Group 3 | All patients (N = 31) |
|------------------------------------|-------------------|---------|---------|---------|-----------------------|
|                                    | IV\(^a\) 200 mg   | (n = 11)|         |         |                       |
|                                    | PO\(^b\) 300 mg   |         | (n = 10)|         |                       |
| Patients with any TEAE,\(^c\) n (%)| 9 (81.8)          | 9 (90.0)| 8 (80.0)| 26 (83.9)          |
| Nausea                             | 8 (72.7)          | 6 (60.0)| 6 (60.0)| 20 (64.5)          |
| Vomiting                           | 4 (36.4)          | 4 (40.0)| 2 (20.0)| 10 (32.3)          |
| Headache                           | 3 (27.3)          | 2 (20.0)| 1 (10.0)| 6 (19.4)           |
| Amylase increased                  | 0                 | 3 (30.0)| 1 (10.0)| 4 (12.9)           |
| Vulvovaginal mycotic infection     | 1 (9.1)           | 1 (10.0)| 2 (20.0)| 4 (12.9)           |
| Diarrhea                           | 0                 | 2 (20.0)| 1 (10.0)| 3 (9.7)            |
| Gastroesophageal reflux disease    | 1 (9.1)           | 0       | 1 (10.0)| 2 (6.5)            |
| Pruritus                           | 2 (18.2)          | 0       | 0       | 2 (6.5)            |

\(^a\)IV, intravenous.

\(^b\)PO, oral.

\(^c\)TEAE, treatment-emergent adverse event.
FIG 1 (A) Mean (± standard deviation) concentrations of omadacycline in plasma; (B) mean (± standard deviation) concentrations of omadacycline and amount excreted in urine (pharmacokinetic population).