Clinical Trial Protocol: PTK0796-AP-17202

Study Title:	A Randomized, Double-Blinded, Adaptive Phase 2 Study to Evaluate the Safety and Efficacy of IV or IV/PO Omadacycline and IV/PO Levofloxacin in the Treatment of Adults with Acute Pyelonephritis
Study Number:	PTK0796-AP-17202
Study Phase:	2
Product Name:	Omadacycline (PTK 0796)
IND Number:	75,928 73,431
Indication:	Acute Pyelonephritis
Investigators:	Multicenter
Sponsor:	Paratek Pharma, LLC. A wholly-owned subsidiary of Paratek Pharmaceuticals, Inc. 75 Park Plaza, 4th Floor Boston, MA 02116 1000 First Ave Suite 200 King of Prussia, PA 19406
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Global Medical Monitor:	[redacted]
Regional Medical Monitor:	[redacted]

Original Protocol Version 1: 26 March 2018

Confidentiality Statement

The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the expressed, written consent of Paratek Pharma, LLC.

The study was in accordance with the International Council on Harmonisation Harmonised Tripartite Guidelines for Good Clinical Practice.

NCT Number: NCT03757234
This NCT number has been applied to the document for purposes of posting on clinicaltrials.gov

SYNOPSIS

Sponsor:
Paratek Pharma, LLC.

Name of Finished Product:
Omadacycline for injection, 100 mg lyophilized vial drug product
Omadacycline oral tablet, 150 mg

Name of Active Ingredient:
Omadacycline

Study Title:
A Randomized, Double-Blinded, Adaptive Phase 2 Study to Evaluate the Safety and Efficacy of IV or IV/PO Omadacycline and IV/PO Levofloxacin in the Treatment of Adults with Acute Pyelonephritis

Study Number:
PTK0796-AP-17202

Study Phase: 2

Study Rationale:
Omadacycline is the first member of the aminomethylcycline class of antibiotics, which are semi-synthetic derivatives of the tetracycline class. Omadacycline has *in vitro* activity against the most common bacterial pathogens associated with acute pyelonephritis (AP). Omadacycline has been shown to have a significant fraction of the administered dose excreted by the kidneys and is present as active drug in the urine. The safety, efficacy and pharmacokinetics (PK) of omadacycline have not been evaluated in adults with AP.

Primary Objective:
To evaluate the efficacy of intravenous (iv) and iv to oral (iv/po) dosing regimens of omadacycline and levofloxacin in the treatment of adults with AP.

Secondary Objectives:

- To evaluate the safety of omadacycline in the treatment of adults with AP.
- To evaluate the PK of omadacycline in adults with AP.

Study Design:

This is a randomized, double-blinded, adaptive designed Phase 2 study evaluating 4 once-daily iv or iv/po dosing regimens of omadacycline compared to levofloxacin in the treatment of adults with AP. The planned length of subject participation in the study is up to 30 days.

Initially, eligible subjects will be randomly assigned to receive either a once-daily dosing regimen of omadacycline or a once-daily regimen of levofloxacin. All subjects initially will receive at least 1 day of iv treatment, and will receive a total of 7 to 10 days of treatment (iv and oral combined). Subjects with baseline bacteremia (ie, confirmed from local blood culture drawn at screening) can receive up to 14 days of treatment.

Switch from active iv to active po study drug therapy is optional, and will occur based on treatment group assignment and the decision should be made by the investigator based on evaluation of the criteria below. Criteria will be confirmed and documented in the source documents. Upon decision to switch, subjects randomized to iv only treatment groups will begin to receive placebo po in addition to their active iv test article. Those randomized to an iv/po treatment group will begin to receive active po test article and placebo iv infusions.

- Afebrile for ≥ 24 hours (highest daily oral, tympanic, rectal, or core temperature < 37.8°C [100.0°F]) without the use of anti-pyretics,
- Improvement or resolution of the signs and symptoms of the index AP.
- Ability to tolerate and ingest oral therapy (eg, no nausea, vomiting), and
- For subjects with bacteremia identified at screening, follow-up blood cultures must be negative.

Subjects will be randomized to one of the following treatment groups, dosing in all treatment groups is once-per-day:

Group	Test Article	Study Day 1	Study Days 2 to 7	Study Days 8 to 10[a]
1	Omadacycline	200 mg iv	200 mg iv	200 mg iv
2	Omadacycline	200 mg iv	100 mg iv	100 mg iv
3	Omadacycline	200 mg iv	300 mg po or 100 mg iv	300 mg po or 100 mg iv
4	Omadacycline	200 mg iv	450 mg po or 100 mg iv	450 mg po or 100 mg iv
5	Levofloxacin	750 mg iv	750 mg po or 750 mg iv	750 mg po or 750 mg iv

iv = intravenous, po = per oral

[a] The total duration of treatment for subjects is 7-10 days, up to 14 days of treatment for subjects with bacteremia.

Dosing blinded iv and oral double-blind, double-dummy:

Dosing		**Group 1 omadacycline**	**Group 2 omadacycline**	**Group 3 Omadacycline**	**Group 4 omadacycline**	**Group 5 Levofloxacin**
Day 1		omadacycline 200 mg iv in 150 mL NS	omadacycline 200 mg iv in 150 mL NS	omadacycline 200 mg iv in 150 mL NS	omadacycline 200 mg iv in 150 mL NS	levofloxacin 750 mg iv in 150 mL saline
Days2 to 7-10[a, b, c]	**continue iv**	omadacycline 200 mg iv in 150 mL NS	omadacycline 100 mg iv in 150 mL NS	omadacycline 100 mg iv in 150 mL NS	omadacycline 100 mg iv in 150 mL NS	levofloxacin 750 mg iv in 150 mL saline
	switch to po[b]	omadacycline 200 mg iv in 150 mL NS **and** three placebo tablets resembling omadacycline **and** three over-encapsulated placebo tablets resembling levofloxacin	omadacycline 100 mg iv in 150 mL NS **and** three placebo tablets resembling omadacycline **and** three over-encapsulated placebo tablets resembling levofloxacin	150 mL NS **and** two 150 mg omadacycline tablets, one placebo tablet resembling omadacycline, **and** three over-encapsulated placebo tablets resembling levofloxacin	150 mL NS **and** three 150 mg omadacycline tablets **and** three over-encapsulated placebo tablets resembling levofloxacin	150 mL NS **and** three placebo tablets resembling omadacycline **and** three over-encapsulated 250 mg levofloxacin tablets

Dosing in all treatment groups is once-per-day.
All iv doses will be administered as continuous infusions over 90 minutes.
All oral doses will be taken in a fasted state (no food, antacids or multivitamins containing multivalent cations [eg, aluminum, magnesium, calcium, bismuth, iron, or zinc] or drink except water for at least 6 hours prior to dosing; after dosing, no food for 2 hours, no dairy products, antacids or multivitamins containing multivalent cations for 4 hours).
iv = intravenous, NS = normal saline, po = per oral.

[a] The total duration of treatment is 7-10 days, Subjects with bacteremia can continue treatment for up to 14 days .
[b] Starting on Day 2, per investigator's discretion, subjects may be switched to oral dosing per oral switch criteria.
[c] All therapy may be discontinued after the seventh day of treatment, when the infection is considered clinically cured (based on normalization of the clinical signs and symptoms of infection and the investigator's clinical assessment that continued systemic antibacterial therapy is no longer needed).

During the study period, blood and urine samples will be collected for safety analysis, microbiological analysis and for omadacycline PK analysis. Safety assessments will include monitoring of adverse events (AEs), clinical laboratory test results, vital sign measurements, pregnancy testing (for women only) and physical examination findings.

The iv treatment phase and oral treatment phase will be blinded and the oral treatment phase is double-dummy. All subjects should remain in a hospital setting during treatment. However, subjects may receive iv treatment in certain outpatient centers in circumstances where the principal site investigator has identified that sufficient resources are available to complete all study procedures as defined in the protocol and the sponsor or sponsor's designee has reviewed and approved the process for outpatient iv test article administration.

Subject visits occur on Days 1 to 7. If treatment extends beyond 7 days, subject visits may occur on Days 8 to 10. If treatment extends beyond 10 days for cases of bacteremia, visits will occur on Days 11 to 13. An end of treatment (EOT) visit will be conducted on the day of or within 2 days following the last dose. Subjects will return to the study site for a Post Therapy Evaluation (PTE) on Day 21 (± 2 days). A Final Follow-up visit (Final Follow-up) will be conducted on Day 28 (± 2 days) following the first dose of test article. The Final Follow-up assessment may be conducted via telephone contact or by another interactive technology for subjects who were considered to be clinical successes and had no AEs or clinically significant laboratory or electrocardiogram (ECG) abnormalities noted at or after the PTE visit. Otherwise, this assessment is to be performed with an in-person study visit. During the Follow up call/visit if the subject reports symptoms of potential recurrence, additional procedures will be performed. See Appendix 1 for the full schedule of events.

Rationale for Omadacycline Dose Regimen Selection:

The dosing regimen of omadacycline selected for this study is based on the nonclinical and clinical experience to date, including *in vitro* antibacterial activity, PK characteristics, clinical efficacy in prior studies, and the overall safety and tolerability profile. Key considerations in dose selection are summarized below:

- In PTK0796-SDES-0501, the PK of omadacycline iv were linear over the entire dose range (25 mg to 600 mg) as assessed by area under the concentration time curve (AUC). Therefore, the loading dose given on Day 1 in the pivotal Phase 3 trials, 100 mg iv every 12 hours (q12h), is from an exposure perspective comparable to the 200 mg iv loading dose on Day 1 to be utilized in this study.
- In PTK0796-MDES-0601, 200 mg iv for seven days was safe and well tolerated. Alanine aminotransferase (ALT) was reported as increased in 26% of subjects however the post-baseline change was approximately 30 IU/L on the last day of infusion. A heart rate model demonstrated that the post-baseline increase in heart rate for a 200 mg dose could be minimized to 15 beats per minute with infusion over 60 minutes.
- In PTK0796-UUTI-15103, omadacycline dosed as 200 mg iv on Day 1 followed by 300 mg po daily for 5 days, 300 mg po q12h on Day 1 followed by 300 mg po daily for 5 days and 450 mg po q12h on Day 1 followed by 450 mg po daily for 5 days demonstrated high urinary concentration on Day 1 and Day 5. For the 200 mg iv load

followed by 300 mg daily dosing group, mean urinary concentrations ranged from 22 to 65 μg/mL on Day 1 and 21 to 42 μg/mL on Day 5. For the 300 mg dosing group, mean urinary concentrations ranged from 14 to 20 μg/mL on Day 1 and 17 to 30 μg/mL on Day 5. For the 450 mg dosing group, mean urinary concentrations ranged from 11 to 25 μg/mL on Day 1 and 30 to 48 μg/mL on Day 5.

- The driver of efficacy for omadacycline in urinary tract infection (UTI) is not known, however the extensive tissue distribution of omadacycline suggests that plasma levels may not be the best predictor of efficacy for every indication. Extensive tissue distribution is likely essential for the eradication of susceptible bacteria in the intracellular compartment of peripheral tissues. In the BAL-15104 study examining lung tissue concentrations following iv administration of 100 mg omadacycline in healthy subjects, at steady-state, the concentration of omadacycline was 25.79-fold higher in alveolar cells (AC, 302.46 h·μg/mL) than in plasma, and 1.47-fold higher in epithelial lining fluid (ELF, 17.23 h·μg/mL) than in plasma.
- A pragmatic assumption was made in the recently completed Phase 1 study of uncomplicated UTI (PTK0796-UUTI-15103) that maximizing the time of omadacycline concentration in urine above the pathogen minimum inhibitory concentration (MIC) (ideally, throughout the dosing interval) would be desirable. In addition, the omadacycline concentrations in urine determined in the phase 1 study demonstrated that the urine concentrations were above the *E. coli* MIC_{90} of 2 μg/mL. It is appropriate to determine the optimal iv and oral dose for AP to achieve clinical success similar to a standard comparator. Therefore, both the standard 100 mg iv dose as well as the higher 200 mg iv dose will be explored. Oral doses of 300 mg and 450 mg will be explored as was done in the PTK0796-UUTI-15103 and is being explored for the uncomplicated UTI (acute cystitis) in PTK0796-UUTI-17201.

Study Population:

Approximately 200 subjects will be enrolled at approximately 35 sites. Initially, subjects will be randomized (1:1:1:1:1) to 1 of 5 treatment groups. Enrollment of a total of approximately 200 subjects is planned to achieve at least 150 evaluable subjects. If required, to improve the precision of the interim or projected final analysis estimates of overall success, enrollment may be increased above the approximate 200 subjects.

Adaptive Design:

This is an adaptive dose-response finding study. Initially, allocation to treatment arms will be equal between treatment arms. During the course of the study, Bayesian analysis will be used to adaptively allocate new subjects to one of the treatment arms, conditional on the availability of primary efficacy endpoint data (overall response comprised of clinical and microbiologic response). When there is sufficient information available about the dose-response, results from the Bayesian analysis will be reviewed by a Data Monitoring Committee (DMC) to determine if enrollment in any omadacycline treatment group(s) should be initiated, stopped, or modified. Modifications to omadacycline treatment groups may also be based on safety and tolerability. It is possible that not all treatment arms will be enrolling

subjects at the same time. Arms may be dropped based on the Bayesian analysis or initiated based on the Bayesian analysis of the ongoing treatment arms. There will always be at least one omadacycline arm and the levofloxacin arm open.

Modifications to the total number of subjects enrolled may also be based on the evaluability rate for the microbiological intent-to-treat (micro-ITT) population.

Bayesian analyses will be conducted after efficacy data (overall response at PTE) are available for approximately 40, 80 and 100 subjects in the micro-ITT population in order to:

- Determine omadacycline treatment group(s) that can be initiated or dropped from the trial, or
- Modify the randomization ratios among the treatment groups to improve the precision of the selected dose groups comparison of overall success to that of the levofloxacin group.

Additional analyses may be carried out for the same purposes. Response criteria are targeted towards estimating the probability that the overall success rate (proportion of subjects) for each omadacycline treatment group is within 10% of that of the levofloxacin group. If at the interim analyses, that probability falls below 30% for a particular treatment group, recruitment for that treatment group may be stopped or curtailed. If that probability exceeds 70% for a particular treatment group, recruitment for that treatment group may be stopped or increased to improve the precision of the estimate. Concurrent bacteremia are higher among adults >65 years of age. After approximately 100 subjects have been enrolled, the inclusion of females >65 years of age may be allowed based on review of interim analysis.

Main Criteria for Inclusion:

1. Written and signed informed consent must be obtained before any assessment is performed.
2. a. Females age 18-65 years.

   b. Females age 18 years or older.

   Inclusion 2a will be followed for first 100 subjects enrolled. Following an interim analysis, see adaptive design section for additional information, inclusion 2b may be allowed. An administrative memo will be issued to sites to formally notify them if/when Inclusion 2b will be followed. No subjects >65 years may be enrolled until an administrative memo is received and acknowledged by the investigator.
3. Clinical signs and symptoms of acute uncomplicated pyelonephritis with onset or worsening within 96 hours prior to randomization. Clinical signs and symptoms are defined as:
   - Flank pain or costovertebral angle tenderness on physical examination plus at least one of the following:
     - Chills or rigors or warmth associated with fever (oral, tympanic, rectal or core temperature > 38°C [> 100.4°F], which must be observed and documented by a health care provider), or
     - Nausea or Vomiting
4. A clean-catch midstream urine sample with dipstick analysis positive (at least ++) for leukocyte esterase or pyuria (white blood cell [WBC] count > 10/µL in unspun urine or ≥ 10 per high power field in spun urine sediment).
5. Female subjects must have a negative pregnancy test at Screening, and agree to comply with using an acceptable form of birth control (eg, abstinence, oral contraceptive, intrauterine device [IUD], barrier contraception [condom], tubal ligation, hysterectomy, bilateral oophorectomy, postmenopausal or vasectomized partner) from Screening through PTE.
6. Ability to communicate well with the investigator, to understand and comply with the requirements of the study.

Main Criteria for Exclusion:

1. Pregnant or nursing (breastfeeding) women.
2. Receipt of any dose of a potentially therapeutic antibacterial agent (with potential activity against uropathogens in the urinary tract) from 72 hours prior to randomization until the first dose of test article. [NOTE: Subjects who developed the current pyelonephritis while receiving prophylactic antibacterial therapy (for any reason) may be eligible if all prophylactic antibacterials are stopped (no further dosing after randomization) and approved by the study medical monitor.]
3. Anticipated need for systemic antibacterial therapy other than test article (for treatment or prophylaxis) during the study period.
4. Infection at baseline that in the Investigator's judgment would require more than 10 days of antibacterial therapy (subjects determined to have bacteremia based on blood cultures collected at screening can be treated for up to 14 days).

5. Symptoms of AP present longer than 7 days prior to randomization.
6. Confirmed or suspected AP caused by a pathogen that is resistant to tetracyclines or fluoroquinolones, including infection caused by fungi (eg, Candida spp.) or mycobacteria (eg, urogenital tuberculosis).
7. Known or suspected rapidly-progressing or life-threatening illness including septic shock. Septic shock can be identified using the clinical criteria of hypotension requiring vasopressor therapy to maintain mean arterial blood pressure of 65mmHg or greater and having a serum lactate level greater than 2 mmol/L after adequate fluid resuscitation.
8. Use of an indwelling urinary catheter, nephrostomy tubes or other indwelling urinary tract device within the 30 days prior to randomization.
9. Confirmed or suspected urinary retention (≥ 100 mL of residual urine after voiding) from any cause, including neurogenic bladder or obstruction.
10. History of surgically modified or abnormal urinary tract anatomy (eg, bladder diverticula or redundant urine collection system).
11. Confirmed or suspected complete or partial obstruction of the urinary tract, or obstructive uropathy that is scheduled to be medically or surgically relieved during the study therapy period (eg, renal calculi, urethral or ureteral stricture).
12. Confirmed or suspected renal disease or condition that, in the opinion of the investigator, may confound the assessment of efficacy, including but not limited to the following:
    - Perinephric or intrarenal abscess
    - Emphysematous pyelonephritis
    - Chronic pyelonephritis, including xanthogranulomatous pyelonephritis
    - Polycystic kidney disease
    - Renal carcinoma
13. History of renal transplant or a surgically created intestinal conduit for urinary diversion.
14. Suspected or confirmed non-renal source of infection (eg, prostatitis, epididymitis, orchitis, endocarditis, osteomyelitis, abscess, meningitis, pneumonia).
15. Confirmed or suspected vaginitis or sexually transmitted infection or lower UTI (ie, cystitis) without symptoms/signs of AP.
16. Has any of the following at Screening:
    - ALT or aspartate aminotransferase (AST) ≥ 3 × Upper Limit of Normal (ULN)
    - total bilirubin > 1.5 × ULN
    - suspected or confirmed clinical evidence of end-stage liver disease (eg, ascites, hepatic encephalopathy)
17. History of unstable cardiac disease (eg, unstable angina, myocardial infarction, acute congestive heart failure, unstable cardiac arrhythmia, etc.) within the 3 months prior to randomization.
18. Significant immunological disease determined by any of the following:
    - Current or anticipated neutropenia defined as less than 500 neutrophils/mm^3
    - Known infection with Human Immunodeficiency Virus (HIV) and a cluster of differentiation 4 (CD4) count that is unknown or documented to be less than 200 cells/mm^3 within the last year, or other Acquired Immune Deficiency

Syndrome (AIDS)-defining illness as determined by the investigator.

19. Receipt of cancer chemotherapy, radiotherapy, or potent, non-corticosteroid immunosuppressant drugs (eg, cyclosporine, azathioprine, tacrolimus, immune-modulating monoclonal antibody therapy, etc.) within the 3 months prior to randomization, or the receipt of systemic corticosteroids equivalent to or greater than 40 mg of prednisone per day (see equivalent corticosteroid doses in Appendix 2) or 40 mg of prednisone per day for more than 14 days in the 30 days prior to randomization.
20. History of hypersensitivity or allergic reaction (eg, anaphylaxis, urticaria, other significant reaction) to any tetracycline (eg, minocycline, doxycycline or tigecycline) or fluoroquinolone (eg, levofloxacin, ciprofloxacin, moxifloxacin) antibiotic.
21. Inability to swallow 6 tablets in succession.
22. History of pseudotumor cerebri, or prior (within 2 weeks prior to randomization) or planned concomitant use of isotretinoin.
23. History of systemic lupus erythematosus or lupus-like syndrome.
24. Has current evidence of pancreatitis.
25. History of myasthenia gravis.
26. Screening calculated creatinine clearance (CrCl) < 50 mL/minute, using the Cockcroft-Gault equation (see equation in Appendix 2), requires any form of dialysis (eg, hemodialysis, peritoneal dialysis, or continuous veno-venous hemofiltration), or other evidence of severe renal disease.
27. History of tendinitis, tendon rupture, arthralgia, myalgia, peripheral neuropathy, or central nervous system effects (eg, hallucinations, anxiety, depression, insomnia, severe headaches, and confusion). *
28. Has a QT interval > 500 msec, or known long QT syndrome. *
29. Current use of antiarrhythmic agents of Class IA (eg, quinidine, procainamide) or Class III (eg, amiodarone, sotalol). *
30. Use of other investigational drugs within 5 half-lives or 30 days prior to randomization, whichever is longer.
31. Has previously been treated with omadacycline or previously enrolled in this study.
32. Unable or unwilling, in the opinion of the investigator, to comply with the protocol requirements, or has any concomitant condition or planned medical intervention that, in the opinion of the investigator, is likely to interfere with evaluation of the response of the infection under study, determination of AEs, or completion of the expected course of treatment.

* Exclusions required due to fluoroquinolone comparator

Test Article; Dose; and Mode of Administration:

Group 1: Omadacycline 200 mg iv every 24 hours (q24h)
Group 2: Omadacycline 200 mg iv × 1 day followed by 100 mg iv q24h
Group 3: Omadacycline 200 mg iv × 1 day followed by mg iv q24h or 300 mg po q24h
Group 4: Omadacycline 200 mg iv × 1 day followed by 100 mg iv q24h or 450 mg po q24h
Group 5: Levofloxacin 750 mg iv q24h × 1 day followed by 750 mg iv or 750 mg po q24h

Duration of Treatment:

The total duration of therapy for subjects will be 7 to 10 days, with the exception of subjects with bacteremia confirmed from local blood culture drawn at screening can receive up to 14 days of treatment.

Pharmacokinetic Assessments

Blood collection (plasma):

Blood samples will be collected and analyzed for omadacycline concentration at the following times:

- Just prior to the dose on Day 3 and just prior to last dose of test article;
- 2 to 3 hours after dose on Day 3 and 2 to 3 hours after last dose of test article.

Urine Collection:

Urine will be collected, the volume recorded, and analyzed for omadacycline concentration at the following times:

- Day 3 to 4: pooled total urine from 0 to 24 hours after the Day 3 dose;
- Day 6 to 7: pooled total urine from 0 to 24 hours after the Day 6 dose.

Omadacycline urine concentration data will be used to determine the 24-hour average urinary concentration and amount of drug excreted in the urine in a dosing interval at steady-state.

Safety Assessments:

- Physical examinations;
- Vital signs (body temperature, blood pressure, heart rate),
- Height and body weight;
- Laboratory tests (hematology, serum chemistry, urinalysis);
- AEs and serious adverse events (SAEs);
- AEs of interest (nausea and vomiting);
- Concomitant medications;
- Pregnancy assessments (for women only).

Efficacy Assessments:

- Investigator's assessment of clinical response (Clinical success is defined as resolution of signs and symptoms of the infection to the extent that further antibacterial therapy is not necessary);
- Microbiological assessment of the infection;
- Modified Patient symptom assessment questionnaire (mPSAQ)

Statistical Methods:

Enrollment of approximately 200 subjects is planned to achieve at least 150 subjects in the micro-ITT population. The Bayesian posterior probability that the overall success rate at the PTE Visit is within 0.10 of that of the levofloxacin group will be estimated for each omadacycline treatment group. The target probability is 0.70. If the true underlying overall success rates for the levofloxacin and omadacycline treatment groups are 0.69, then the sample size of N = 30 per treatment group has approximately 65% power/probability to yield the target probability (N = 80 per treatment group for 80% power). If the true underlying overall success rates for the levofloxacin and omadacycline treatment groups are 0.78, then the sample size of N = 30 per treatment group has approximately 68% power/probability to yield the target probability (N = 64 per treatment group for 80% power). The sample size may be increased for a particular omadacycline treatment group by changing the randomization ratio and/or dropping a treatment group to have improved power/probability of achieving the target probability that overall success rates for an omadacycline treatment group is within 0.10 of that of the levofloxacin group. If–required to improve the precision of the interim or projected final analyses estimates of overall response rates or posterior probabilities, the sample size may be increased to a maximum sample size provided in the Statistical Analysis Plan (SAP).

The following subject analysis populations have been defined:

- Intent-to-treat (ITT): all randomized subjects.
- Safety: all randomized subjects who receive any amount of test article.
- The micro-ITT population will consist of subjects in the ITT population who have an appropriately collected pretreatment baseline urine culture with at least 1 uropathogen at $\geq 10^5$ colony forming units (CFU)/mL and not more than 2 bacterial isolates at any count. If more than 2 bacterial isolates are identified, the culture will be considered contaminated regardless of colony count, unless 1 of the isolates that grows in the urine at $\geq 10^5$ CFU/mL is also isolated from a blood culture at the same visit.
- The clinically evaluable (CE) population will consist of all ITT subjects who received test article, have acute uncomplicated pyelonephritis, an assessment of outcome, and meet all other evaluability criteria detailed in the SAP.
- The microbiologically evaluable (ME) population will include subjects in the CE and micro-ITT populations who have an appropriately collected post-baseline urine sample and an interpretable post-baseline urine sample. An interpretable post-baseline urine culture is one that has a clearly identified pathogen or one where the baseline pathogen(s) can be excluded (ie, there is no growth of the baseline pathogen).

All safety data will be summarized by treatment group and the incidence of AEs will be presented by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA), relationship to the test article, and severity. Descriptive statistics of clinical laboratory results and vital signs and the change from baseline will be presented as will a summary of clinically notable values.

The primary efficacy outcome is overall response at the PTE Visit in the micro-ITT population, which is a composite of per-subject microbiologic response and investigator

assessment of clinical response.

The number and percentage of subjects within each category of overall response, investigator assessment of clinical response, and microbiological response will be presented at each time point measured by treatment group. Exact 95% confidence intervals (CIs) will be determined for the point estimates of the overall, clinical and microbiologic success rates. A comparison of overall success at PTE between each omadacycline treatment group and the levofloxacin group will be conducted using a beta distribution with an uninformative Bayesian prior distribution.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABSSSI	acute bacterial skin and skin structure infections
AC	alveolar cells
AE	adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALT	alanine aminotransferase (SGPT)
AP	acute pyelonephritis
AST	aspartate aminotransferase (SGOT)
AUC	area under the concentration time curve
β-hCG	serum β-human chorionic gonadotropin
BP	Blood pressure
CABP	community-acquired bacterial pneumonia
CD4	cluster of differentiation 4
CE	clinically evaluable
CFR	Code of Federal Regulations
CFU	colony forming units
CI	confidence interval
CrCl	creatinine clearance
CRF	case report form
CSA	clinical study agreement
CSR	Clinical Study Report
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
ELF	epithelial lining fluid
EOT	end of treatment
ESBL	extended spectrum beta-lactamase
GCP	Good Clinical Practice

HIV	Human Immunodeficiency Virus
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
iv	intravenous
IxRS	interactive voice/web response system
ME	microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
micro-ITT	microbiological intent-to-treat
OTC	over-the-counter
PI	Principal Investigator
PK	pharmacokinetics
po	Per Oral
mPSAQ	Modified Patient Symptom Assessment Questionnaire
PT	preferred term
PTE	Post Therapy Evaluation
q24h	every 24 hours
q12h	every 12 hours
REB	Research Ethics Board
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOC	system organ class
TEAE	treatment-emergent adverse event
TFL	tables, figures, and listings

ULN	Upper Limit of Normal
US	United States
UTI	urinary tract infection
WBC	White Blood Cell (Count)

1 DISCLOSURE STATEMENT

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2 CONTACTS

2.1 Emergency Contacts

Name/Title: [redacted]

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Phone (after business hours):
E-mail (not for emergencies):
Address:

Name/Title: [redacted]

Phone (during business hours):
Phone (after business hours):

E-mail (not for emergencies): [redacted]
Address:

Name/Title: [redacted]

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2.2 Additional Contacts

SAE contact information:
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3 INTRODUCTION

3.1 Acute Pyelonephritis

Acute pyelonephritis (AP), or upper UTI, is a common infection featuring fever, chills, , flank pain, costovertebral angle tenderness, and nausea or vomiting.[1] Nearly all cases of AP are caused by the ascension of uropathogens from the urinary bladder to the kidney; a minority of cases are caused by the hematogenous route.[1] The incidence of AP is highest among young women, followed by infants and the elderly population.[1] The annual rates of AP among ambulatory women and men are approximately 12–13 and 2–3 cases per 10,000, respectively.[2] Although the mortality associated with AP is relatively low, UTIs including AP account for approximately 5% to 7% of all cases of severe sepsis.[3,4]

Acute pyelonephritis is caused predominantly by members of the *Enterobacteriaceae*; for example, *E. coli* causes approximately 80% of cases of AP in women and 70% of cases in men.[2] Although rates of antibacterial resistance against various antimicrobial classes is increasing among *E. coli* strains causing AP (eg, > 10%-20% resistance to trimethoprim sulfamethoxazole), the rate of fluoroquinolone resistance remains relatively low in the United States (US) (eg, ciprofloxacin resistance increased from 0.2% of *E. coli* isolates to 1.5% of isolates between 1997 and 2001).[2] However, recent global data suggests that fluoroquinolone resistance in complicated UTI may be as high as 35% to 50% in some countries, underlying the urgent medical need for new antibacterial agents for these infections.[5]

3.2 Omadacycline

The investigational product, omadacycline (formerly named PTK 0796), is the first member of the aminomethylcycline class of antibiotics, which are semi synthetic derivatives of the tetracycline class. As a class, the tetracyclines have been in use for approximately 70 years. They are well-tolerated, and have proven effective in the treatment of a variety of bacterial infections. Omadacycline is being developed for clinical use by both intravenous (iv) and per oral (po) administration. The targeted indications include community-acquired bacterial pneumonia (CABP), acute bacterial skin and skin structure infections (ABSSSI), uncomplicated UTI and AP.

Omadacycline has been evaluated in two global Phase 3 studies, one comparing the safety and efficacy of iv and/or po omadacycline to iv and/or po linezolid in the treatment of adult subjects with ABSSSI (PTK0796-ABSI-1108; PTK0796-ABSI-16301). In addition, a global Phase 3 study has been conducted to evaluate the safety and efficacy of iv and po omadacycline compared to iv and po moxifloxacin in the treatment of adult subjects with CABP (PTK0796-CABP-1200). In all three studies, omadacycline was well-tolerated and demonstrated non-inferiority to its respective comparator.

The drug is active against strains expressing both mechanisms of tetracycline resistance, namely efflux and ribosomal protection.[6] Omadacycline has *in vitro* activity against the most common AP uropathogens including *E. coli.* Resistance to other antibiotics does not affect omadacycline activity. Omadacycline is not affected by tetracycline-resistance, presence of

extended spectrum beta-lactamase (ESBL), or other common resistance mechanisms. Omadacycline is active against the Enterobacteriaceae with a significant proportion of isolates having a minimum inhibitory concentration (MIC) < 2.0 µg/ml. The MICs for at least 90% of the isolates tested (MIC_{90}) for omadacycline 2 µg/mL for *E. coli*, regardless of ESBL status.[6]

Study PTK0796-UUTI-15103 was a randomized (1:1:1), open-label, parallel-designed Phase 1b study evaluating 3 dosing regimens of omadacycline in 31 female adults with cystitis. During the treatment period, serial blood and urine samples were collected for safety, microbiological, and pharmacokinetic (PK) analyses of omadacycline. In this study, the PK of omadacycline in women with cystitis was found to be similar to the PK in healthy subjects. At steady-state, 10% to 13% of a po omadacycline dose is excreted in the urine, resulting in high urine concentrations. With the treatment regimens studied, observed urine concentrations of omadacycline compared favorably with MIC values for common UTI pathogens, and a high percentage of subjects achieved clinical success and favorable microbiological responses. There was a higher than expected incidence of nausea and vomiting, which contrasts with the notably lower rates of nausea and vomiting observed in other omadacycline studies using comparable dosing regimens and active controls. The reason(s) for the increased incidences in nausea and vomiting are difficult to ascertain given the open-label study design, small sample size, and lack of prior experience with omadacycline in the UTI study population.

This study is intended to evaluate the efficacy and safety of iv/po omadacycline as compared to iv/po levofloxacin in the treatment of adult subjects with AP. This data will be important to determine the potential utility of omadacycline for the treatment of UTI and will help in selection of dosing regimens that may be used in future UTI studies.

It is expected that the dosing regimens evaluated in this study will provide urine concentrations of omadacycline that will exceed the MIC_{90} for the common AP pathogens (see dose selection discussion in Section 7.4).

Please refer to the current version of the Investigator's Brochure for additional information on omadacycline.[7]

4 STUDY OBJECTIVES

4.1 Primary Objective

The primary objective of this study is:

To evaluate the efficacy of intravenous (iv) and iv to oral (iv/po) dosing regimens of omadacycline and levofloxacin in the treatment of adults with AP.

4.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the safety of omadacycline in the treatment of adults with AP.
- To evaluate the PK of omadacycline in adults with AP.

5 INVESTIGATIONAL PLAN

5.1 Overall Study Description

This is a randomized, double-blinded, adaptive designed Phase 2 study evaluating once-daily iv or iv/po dosing regimens of omadacycline compared to one once-daily dosing regimen of iv/po levofloxacin in the treatment of adults with AP. The planned length of subject participation in the study is up to 30 days which includes a total duration of study therapy for 7 to 10 days (iv only or iv and oral combined). Subjects with bacteremia confirmed from local blood culture drawn at screening can receive up to 14 days of treatment.

The study will consist of 3 protocol-defined phases: Screening, double-blind treatment and follow-up. All Screening evaluations should be completed within the 24 hours prior to randomization. Subjects who meet inclusion criteria, and do not meet exclusion criteria will be randomly assigned to iv or iv/po omadacycline dosing regimens or a regimen of iv/po levofloxacin (see Table 1 and Table 2). Subjects should receive their first dose of test article at the site within 4 hours after randomization. Iv and oral treatment will be double-blinded and oral treatment will be double-dummy (see Table 2). Please refer to Section 9 of the protocol for further details on study phases and required assessments/procedures per phase.

During the study treatment period, blood samples will be collected for safety analysis and for PK analysis of omadacycline. Blood will also be drawn during each subject's Screening evaluation for microbiologic culture; repeat samples will be taken during subsequent visits if bacteremia is identified during Screening. Urine samples will be collected during the study period for safety, PK analysis, and microbiological analysis. Safety assessments will include monitoring of adverse events (AEs), concomitant medications, clinical laboratory test results, vital sign measurements, pregnancy testing and physical examination findings.

Subject visits occur on Days 1 to 7. If treatment extends beyond 7 days, subject visits may occur on Days 8 to 10. If treatment extends beyond 10 days for subjects with bacteremia based on screening culture, visits will occur on Days 11 to 13. An end of treatment (EOT) visit will be conducted on the day of or within 2 days following the last dose of test article. Subjects will return to the study site for a Post Therapy Evaluation (PTE) on Day 21 (± 2 days). A Final Follow-up visit (Final Follow-up) will be conducted on Day 28 (± 2 days) following the first dose of test article. The Final Follow-up assessment may be conducted via telephone contact or by another interactive technology for subjects who were considered to be clinical successes and had no AEs or clinically significant laboratory or electrocardiogram (ECG) abnormalities noted at or after the PTE visit. Otherwise, this assessment is to be performed with an in-person study visit. During the Follow up call/visit, if the subject reports symptoms of potential recurrence, additional procedures will be performed. See Appendix 1 for the full schedule of events.

5.1.1 Adaptive Design

This is an adaptive dose-response finding study. Initially, allocation to treatment arms will be equal between treatment arms. During the course of the study, Bayesian analysis will be used to adaptively allocate new subjects to one of the treatment arms, conditional on the

availability of primary efficacy endpoint data (overall response comprised of clinical and microbiologic response). When there is sufficient information available about the dose-response, results from the Bayesian analysis will be reviewed by a Data Monitoring Committee (DMC) to determine if enrollment in any omadacycline treatment group(s) should be initiated, stopped, or modified. Modifications to omadacycline treatment groups may also be based on safety and tolerability. It is possible that not all treatment arms will be enrolling subjects at the same time. Arms may be dropped based on the Bayesian analysis or initiated based on the Bayesian analysis of the ongoing treatment arms. There will always be at least one omadacycline arm and one levofloxacin arm open. Modifications to the total number of subjects enrolled may also be based on the evaluability rate for the microbiological intent-to-treat (micro-ITT) population.

Bayesian analyses will be conducted after efficacy data (overall response at PTE) are available for approximately 40, 80 and 100 subjects in the micro-ITT population in order to:

- Determine omadacycline treatment group(s) that can be initiated or dropped from the trial, or
- Modify the randomization ratios among the treatment groups to improve the precision of the selected dose groups comparison of overall success to that of the levofloxacin group.

Additional analyses may be carried out for the same purposes. Response criteria are targeted towards estimating the probability that the overall success rate (proportion of subjects) for each omadacycline treatment group is within 10% of that of the levofloxacin group. If at the interim analyses, that probability falls below 30% for a particular treatment group, recruitment for that treatment group may be stopped or curtailed. If that probability exceeds 70% for a particular treatment group, recruitment for that treatment group may be stopped or increased to improve the precision of the estimate. Concurrent bacteremia are higher among adults >65 years of age.[11] After approximately 100 subjects have been enrolled, the inclusion of females >65 years of age may be allowed based on review of interim analysis.

5.2 Rationale for Study Design

Omadacycline is the first member of the aminomethylcycline class of antibiotics, which are semi-synthetic derivatives of the tetracycline class. Omadacycline has *in vitro* activity against the most common bacterial pathogens associated with AP. Omadacycline has been shown to have a sufficient fraction of the administered dose excreted by the kidneys and is present as active drug in the urine. The safety, efficacy and pharmacokinetics (PK) of omadacycline have not been evaluated in adults with acute pyelonephritis.

5.3 Rationale for Control Group

According to contemporary guidelines for management of AP by the Infectious Diseases Society of America and European Society for Microbiology and Infectious Diseases, once-daily fluoroquinolone therapy—including levofloxacin 750 mg—is an appropriate empiric antibacterial regimen for AP where the prevalence of fluoroquinolones resistance of community uropathogens is not known to exceed 10%.[8] In regions with low levels of

fluoroquinolone resistance among outpatient uncomplicated pyelonephritis isolates (eg, in most areas of the US), the fluoroquinolones are the preferred antimicrobial class for oral therapy for acute uncomplicated pyelonephritis.[8] Recent studies support the use of relatively short courses of levofloxacin therapy (ie, 5-7 days) versus the traditional 14-day regimen for mild to moderate AP.[9] This was further demonstrated in a contemporary complicated UTI trial in which ceftolozane-tazobactam was compared to levofloxacin 750 mg every 24 hours (q24h) for 7 days; approximately 82% of subjects enrolled in this trial were diagnosed with AP.[10] Both treatment regimens were associated with high and similar overall outcomes (clinical cures and microbiological eradication rates) at the test-of-cure visit among subjects with AP (79.0% vs 73.2%, treatment difference 5.8% [95% confidence interval (CI): -0.7, 12.3%]), supporting the durable efficacy of fluoroquinolone therapy in AP.

5.4 Approximate Duration of Subject Participation

Subjects will participate in the study for up to 30 days. Following Screening, eligible subjects will be randomly assigned to receive 7 to 10 days of iv/po treatment of either omadacycline or levofloxacin. Subjects with bacteremia confirmed from local blood culture drawn at screening can receive up to 14 days of treatment. Subjects will return to the site for an EOT visit on the day of or within 2 days following the last dose of test article. Subjects will return to the study site for a PTE on Day 21 (± 2 days). A final follow-up assessment will be conducted Day 28 (± 2 days) following the first dose of test article.

5.5 Approximate Duration of Study

The study is expected to be clinically complete in approximately 12 months.

5.6 Approximate Number of Subjects

Approximately 200 subjects will participate in this study at up to 35 sites.

6 STUDY POPULATION SELECTION

Each subject must participate in the informed consent process and sign and date an IRB/IEC/ REB approved informed consent form (ICF) before any procedures specified in this protocol are performed.

6.1 Study Population

Approximately 200 subjects will be enrolled at approximately 35 sites. Initially, subjects will be randomized (1:1:1:1:1) to 1 of 5 treatment groups. Enrollment of a total of approximately 200 subjects is planned to achieve at least 150 evaluable subjects. If required, to improve the precision of the interim or projected final analysis estimates of overall response, enrollment may be increased above the approximate 200 subjects.

6.2 Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled in this study:

Main Criteria for Inclusion:

1. Written and signed informed consent must be obtained before any assessment is performed.
2. a. Females age 18-65 years.
   b. Females age 18 years or older.

   Inclusion 2a will be followed for first 100 subjects enrolled. Following an interim analysis, see adaptive design section for additional information, inclusion 2b may be allowed. An administrative memo will be issued to sites to formally notify them if/when Inclusion 2b will be followed. No subjects >65 years may be enrolled until an administrative memo is received and acknowledged by the investigator.
3. Clinical signs and symptoms of acute uncomplicated pyelonephritis with onset or worsening within 96 hours prior to randomization. Clinical signs and symptoms are defined as:
   - Flank pain or costovertebral angle tenderness on physical examination plus at least one of the following:
     - Chills or rigors or warmth associated with fever (oral, tympanic, rectal or core temperature > 38°C [> 100.4°F], which must be observed and documented by a health care provider), or
     - Nausea or Vomiting
4. A clean-catch midstream urine sample with dipstick analysis positive (at least ++) for leukocyte esterase or pyuria (white blood cell [WBC] count > 10/µL in unspun urine or ≥ 10 per high power field in spun urine sediment).
5. Female subjects must have a negative pregnancy test at Screening, and agree to comply with using an acceptable form of birth control (eg, abstinence, oral contraceptive, intrauterine device [IUD], barrier contraception [condom], tubal ligation, hysterectomy, bilateral oophorectomy, postmenopausal or vasectomized partner) from Screening through PTE.

6. Ability to communicate well with the investigator, to understand and comply with the requirements of the study.

6.3 Exclusion Criteria

Patients who meet any of the following exclusion criteria will be excluded from the study:

Main Criteria for Exclusion:

1. Pregnant or nursing (breastfeeding) women.
2. Receipt of any dose of a potentially therapeutic antibacterial agent (with potential activity against uropathogens in the urinary tract) from 72 hours prior to randomization until the first dose of test article. [NOTE: Subjects who developed the current pyelonephritis while receiving prophylactic antibacterial therapy (for any reason) may be eligible if all prophylactic antibacterials are stopped (no further dosing after randomization) and approved by the study medical monitor.]
3. Anticipated need for systemic antibacterial therapy other than test article (for treatment or prophylaxis) during the study period.
4. Infection at baseline that in the Investigator's judgment would require more than 10 days of antibacterial therapy (subjects determined to have bacteremia based on blood cultures collected at screening can be treated for up to 14 days).
5. Symptoms of AP present longer than 7 days prior to randomization.
6. Confirmed or suspected AP caused by a pathogen that is resistant to tetracyclines or fluoroquinolones, including infection caused by fungi (eg, Candida spp.) or mycobacteria (eg, urogenital tuberculosis).
7. Known or suspected rapidly-progressing or life-threatening illness including septic shock. Septic shock can be identified using the clinical criteria of hypotension requiring vasopressor therapy to maintain mean arterial blood pressure of 65mmHg or greater and having a serum lactate level greater than 2 mmol/L after adequate fluid resuscitation.
8. Use of an indwelling urinary catheter, nephrostomy tubes or other indwelling urinary tract device within the 30 days prior to randomization.
9. Confirmed or suspected urinary retention (≥ 100 mL of residual urine after voiding) from any cause, including neurogenic bladder or obstruction.
10. History of surgically modified or abnormal urinary tract anatomy (eg, bladder diverticula or redundant urine collection system).
11. Confirmed or suspected complete or partial obstruction of the urinary tract, or obstructive uropathy that is scheduled to be medically or surgically relieved during the study therapy period (eg, renal calculi, urethral or ureteral stricture).
12. Confirmed or suspected renal disease or condition that, in the opinion of the investigator, may confound the assessment of efficacy, including but not limited to the following:
    - Perinephric or intrarenal abscess
    - Emphysematous pyelonephritis
    - Chronic pyelonephritis, including xanthogranulomatous pyelonephritis
    - Polycystic kidney disease
    - Renal carcinoma

13. History of renal transplant or a surgically created intestinal conduit for urinary diversion.
14. Suspected or confirmed non-renal source of infection (eg, prostatitis, epididymitis, orchitis, endocarditis, osteomyelitis, abscess, meningitis, pneumonia).
15. Confirmed or suspected vaginitis or sexually transmitted infection or lower UTI (ie, cystitis) without symptoms/signs of acute pyelonephritis.
16. Has any of the following at Screening:
    - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 × Upper Limit of Normal (ULN)
    - total bilirubin > 1.5 × ULN
    - suspected or confirmed clinical evidence of end-stage liver disease (eg, ascites, hepatic encephalopathy)
17. History of unstable cardiac disease (eg, unstable angina, myocardial infarction, acute congestive heart failure, unstable cardiac arrhythmia, etc.) within the 3 months prior to randomization.
18. Significant immunological disease determined by any of the following:
    - Current or anticipated neutropenia defined as less than 500 neutrophils/mm^3
    - Known infection with Human Immunodeficiency Virus (HIV) and a cluster of differentiation 4 (CD4) count that is unknown or documented to be less than 200 cells/mm^3 within the last year, or other Acquired Immune Deficiency Syndrome (AIDS)-defining illness as determined by the investigator.
19. Receipt of cancer chemotherapy, radiotherapy, or potent, non-corticosteroid immunosuppressant drugs (eg, cyclosporine, azathioprine, tacrolimus, immune-modulating monoclonal antibody therapy, etc.) within the 3 months prior to randomization, or the receipt of systemic corticosteroids equivalent to or greater than 40 mg of prednisone per day (see equivalent corticosteroid doses in Appendix 2) or 40 mg of prednisone per day for more than 14 days in the 30 days prior to randomization.
20. History of hypersensitivity or allergic reaction (eg, anaphylaxis, urticaria, other significant reaction) to any tetracycline (eg, minocycline, doxycycline or tigecycline) or fluoroquinolone (eg, levofloxacin, ciprofloxacin, moxifloxacin) antibiotic.
21. Inability to swallow 6 tablets in succession.
22. History of pseudotumor cerebri, or prior (within 2 weeks prior to randomization) or planned concomitant use of isotretinoin.
23. History of systemic lupus erythematosus or lupus-like syndrome.
24. Has current evidence of pancreatitis.
25. History of myasthenia gravis.
26. Screening calculated creatinine clearance (CrCl) < 50 mL/minute, using the Cockcroft-Gault equation (see equation in Appendix 2), requires any form of dialysis (eg, hemodialysis, peritoneal dialysis, or continuous veno-venous hemofiltration), or other evidence of severe renal disease.
27. History of tendinitis, tendon rupture, arthralgia, myalgia, peripheral neuropathy, or central nervous system effects (eg, hallucinations, anxiety, depression, insomnia, severe headaches, and confusion). *
28. Has a QT interval > 500 msec, or known long QT syndrome. *
29. Current use of antiarrhythmic agents of Class IA (eg, quinidine, procainamide) or Class III (eg, amiodarone, sotalol). *

30. Use of other investigational drugs within 5 half-lives or 30 days prior to randomization, whichever is longer.
31. Has previously been treated with omadacycline or previously enrolled in this study.
32. Unable or unwilling, in the opinion of the investigator, to comply with the protocol requirements, or has any concomitant condition or planned medical intervention that, in the opinion of the investigator, is likely to interfere with evaluation of the response of the infection under study, determination of AEs, or completion of the expected course of treatment.

* Exclusions required due to fluoroquinolone comparator

6.4 Screen Failures

Subjects who sign the ICF but withdraw or are withdrawn from the study before random assignment to double-blind treatment are defined as screen failures. All screen failures should be recorded on the subject master list. Limited information including reason for screen failure will be recorded on the electronic case report form (eCRF) or interactive voice/web response system (IxRS) system for screen failures. Screen failure subjects may be re-screened at the discretion of the investigator and in consultation with the medical monitor as needed. A subject who discontinues participation or is withdrawn before receiving a treatment assignment, and who is re-screened at a later time will be assigned a new subject number and recorded as re-screened

7 STUDY TREATMENT(S)

7.1 Treatments Administered

Test articles will be supplied by Paratek Pharma, Inc (the sponsor). Test articles will be labeled according to regulations.

The test articles should be administered only to subjects who have provided informed consent and who meet all of the inclusion criteria and none of the exclusion criteria. Once the test article has been assigned to a subject, it must not be reassigned to another subject.

Following a Screening period of up to 24 hours, eligible subjects will be randomly assigned to receive iv or iv/po dosing regimens of omadacycline treatment or an iv/po regimen of levofloxacin. Intravenous treatment will be double-blind and oral treatment will be double-blind and double-dummy.

7.2 Identity of the Investigational Product: Omadacycline

Intravenous Formulation (Omadacycline)

Name	Omadacycline
Excipients	Tosylate acid counter ion, sucrose, hydrochloric acid and sodium hydroxide to adjust the pH
How supplied	Sterile, lyophilized powder for reconstitution packaged in a clear, glass vial with a rubber stopper and aluminum overseal. The labeled content of the vial is 100 mg of omadacycline base. There is a 4% overfill to allow for the extraction of a 100 mg dose.
Storage	Store at 25˚C (77˚F). Excursions permitted to 15°C to 30°C (59-86˚F)
Preparation and handling	To prepare the 100 mg dose, add 5 mL of the reconstituted solution (the content of one 100 mg vial) to the infusion container 150 mL Normal Saline (NS). To prepare the 200 mg dose, add 10 mL of the reconstituted solution (the contents of two 100 mg vials) to the infusion container of 150 mL NS. The prepared infusion solution should be used within 8 hours or stored at up to 24 hours at 2°C to 8°C (36°F to 46°F). **Please refer to the Pharmacy Manual for additional information.**
Administration	Please reference Table 2 in Section 7.6.6.1

Oral Formulation (Omadacycline)

Name	Omadacycline Tablet, 150 mg
Excipients	Lactose monohydrate, microcrystalline cellulose, sodium stearyl fumarate, crospovidone, colloidal silicone dioxide, sodium bisulfite, polyvinyl alcohol, titanium dioxide, talc, glycerol monocaprylocaprate, sodium lauryl sulfate, iron oxide yellow
How supplied	High-Density Polyethylene (HDPE) bottles with induction seal, child resistant closure and desiccant
Storage	Store at 25˚C (77˚F). Excursions permitted to 15°C-30°C (59-86˚F) (Per Pharmacy Manual)
Preparation and handling	No special requirements
Administration	Please reference Table 2 in Section 7.6.6.1

7.3 Comparator Test Article: Levofloxacin

Intravenous Formulation (Levofloxacin)

Name	Levofloxacin
Excipients	Sodium chloride, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment), and water for injection
How supplied	Levofloxacin 5 mg/ml in saline. Single-Use premixed solution in container for intravenous infusion.
Storage	Store at 25˚C (77 ˚F) or below. Do not freeze or refrigerate
Preparation and handling	Transfer 150 mL of solution into an evacuated container. **Please refer to Pharmacy Manual for additional information**.
Administration	Please reference Table 2 in Section 7.6.6.1

Oral Formulation (Levofloxacin)

Name	Levofloxacin Tablet, 250 mg
Excipients	Over encapsulated in DB0, Swedish Orange capsule shell with microcrystalline cellulose backfill.
How supplied	High-Density Polyethylene (HDPE) bottles with induction seal, child resistant closure and desiccant
Storage	Store at 25˚C (77 ˚F). Excursions permitted to 15°C-30°C (59-86˚F) (In Pharmacy Manual)
Preparation and handling	No special requirements
Administration	Please reference Table 2 in Section 7.6.6.1

7.4 Dose Selection Rationale

The dosing regimen of omadacycline selected for this study is based on the nonclinical and clinical experience to date, including *in vitro* antibacterial activity, PK characteristics, clinical efficacy in prior studies, and the overall safety and tolerability profile. Key considerations in dose selection are summarized below:

- In PTK0796-SDES-0501, the PK of omadacycline iv were linear over the entire dose range (25 mg to 600 mg) as assessed by area under the concentration time curve (AUC). Therefore, the loading dose given on Day 1 in the pivotal Phase 3 trials, 100 mg iv every 12 hours (q12h), is from an exposure perspective comparable to the 200 mg iv loading dose on Day 1 to be utilized in this study.
- In PTK0796-MDES-0601, 200 mg iv for seven days was safe and well tolerated. Alanine aminotransferase was reported as increased in 26% of subjects however the post-baseline change was approximately 30 IU/L on the last day of infusion. A heart rate model demonstrated that the post-baseline increase in heart rate for a 200 mg dose could be minimized to 15 beats per minute with infusion over 60 minutes.
- In PTK0796-UUTI-15103, omadacycline dosed as 200 mg iv on Day 1 followed by 300 mg po daily for 5 days, 300 mg po q12h on Day 1 followed by 300 mg po daily for 5 days and 450 mg po q12h on Day 1 followed by 450 mg po daily for 5 days demonstrated high urinary concentration on Day 1 and Day 5. For the 200 mg iv load followed by 300 mg daily dosing group, mean urinary concentrations ranged from 22 to 65 μg/mL on Day 1 and 21 to 42 μg/mL on Day 5. For the 300 mg dosing group, mean urinary concentrations ranged from 14 to 20 μg/mL on Day 1 and 17 to 30 μg/mL on Day 5. For the 450 mg dosing group, mean urinary concentrations ranged from 11 to 25 μg/mL on Day 1 and 30 to 48 μg/mL on Day 5.

- The driver of efficacy for omadacycline in urinary tract infection (UTI) is not known, however the extensive tissue distribution of omadacycline suggests that plasma levels may not be the best predictor of efficacy for every indication. Extensive tissue distribution is likely essential for the eradication of susceptible bacteria in the intracellular compartment of peripheral tissues. In the BAL-15104 study examining lung tissue concentrations following iv administration of 100 mg omadacycline in healthy subjects, at steady-state, the concentration of omadacycline was 25.79-fold higher in alveolar cells (AC, 302.46 h·μg/mL) than in plasma, and 1.47-fold higher in epithelial lining fluid (ELF, 17.23 h·μg/mL) than in plasma.

- A pragmatic assumption was made in the recently completed Phase 1 study of uncomplicated UTI (PTK0796-UUTI-15103) that maximizing the time of omadacycline concentration in urine above the pathogen MIC (ideally, throughout the dosing interval) would be desirable. In addition, the omadacycline concentrations in urine determined in the phase 1 study demonstrated that the urine concentrations were above the *E. coli* MIC_{90} of 2 μg/mL. It is appropriate to determine the optimal iv and oral dose for AP to achieve clinical success similar to a standard comparator. Therefore, both the standard 100 mg iv dose as well as the higher 200 mg iv dose will be explored. Oral doses of 300

mg and 450 mg will be explored as was done in PTK0796-UUTI-15103 and is being explored for the uncomplicated UTI (acute cystitis) in PTK0796-UUTI-17201.

7.5 Description of Treatments

Subjects will be randomized to 1 of the following 5 treatment groups:

Table 1. Description of Treatment Groups

Group	Test Article	Study Day 1	Study Days 2 to 7	Study Days 8 to 10[a]
1	omadacycline	200 mg iv	200 mg iv	200 mg iv
2	omadacycline	200 mg iv	100 mg iv	100 mg iv
3	omadacycline	200 mg iv	300 mg po or 100 mg iv	300 mg po or 100 mg iv
4	omadacycline	200 mg iv	450 mg po or 100 mg iv	450 mg po or 100 mg iv
5	levofloxacin	750 mg iv	750 mg po or 750 mg iv	750 mg po or 750 mg iv

Dosing in all treatment groups is once-per-day.
All iv doses will be administered as continuous infusions over 90 minutes.
All oral doses will be taken in a fasted state (no food, antacids or multivitamins containing multivalent cations [eg, aluminum, magnesium, calcium, bismuth, iron, or zinc] or drink except water for at least 6 hours prior to dosing; after dosing, no food for 2 hours, no dairy products, antacids or multivitamins containing multivalent cations for 4 hours).
iv = intravenous, po = per oral.
[a] The total duration of treatment for subjects is 7-10 days, up to 14 days of treatment for subjects with bacteremia.

It is possible that not all treatment arms will be enrolling subjects at the same time. Arms may be dropped based on the Bayesian analysis or initiated based on the Bayesian analysis of the ongoing treatment arms. There will always be at least one omadacycline arm and the levofloxacin arm open.

7.6 Test Article Administration

7.6.1 Intravenous Treatment Phase

The iv treatment phase (minimum 1 day, 1 dose) will follow a double-blind design for omadacycline and levofloxacin. Infusions of both test articles will be administered continuously over approximately 90 minutes. All infusion start and stop times are to be recorded in the source documents and on the eCRF. Because the color of the test article and placebo infusions are different, all infusion bags and iv tubing will be covered with materials provided by the sponsor (as described in the Pharmacy Manual) so that subjects and blinded study personnel will not know the identity of the test article being administered. Subjects in each study arm will receive the same infusion volumes with the same blinded administration instructions. All iv infusions will be administered by qualified blinded personnel. However, unblinded personnel may administer the iv infusions provided they will not be performing

any efficacy assessments. If gravity administration is not the standard of care then an infusion pump may be used. If an infusion pump is used then an unblinded administrator will be required.

7.6.2 Selection and Timing of iv Dose for Each Subject

To facilitate study enrollment at all times of the day and permit subjects to be "shifted" to a more practical dosing schedule consistent with hospital schedules, provision is made for limited adjustment of the dosing interval. Specifically, infusion times may be adjusted up to ± 2 hours per infusion interval until the desired administration schedule is achieved.

Once the desired start of infusion time is determined, subsequent infusions should be "anchored" to that time. That is, thereafter, the start of infusion should be within ± 1 hour of the specified target infusion time.

7.6.3 Management While on iv Test Article

While the subject is receiving iv therapy, the investigator will assess the subject daily and choose one of the following outcomes based on the overall clinical response of the subject:

- Continue iv test article
- Assess for po test article using the protocol defined criteria (after a minimum of 1 days [1 doses] of iv therapy), see Section 7.6.5. Note, the first po dose should be administered in the morning, 12 to 24 hours after the last dose of iv test article.
- Discontinue test article – this decision will prompt the EOT evaluation (even if the subject does not complete the minimum of 7 days of dosing)

Subjects who meet the criteria and are switched to po test article administration will continue to receive iv infusions throughout their treatment phase in order to maintain the blind. Subjects randomized to an IV only treatment group will continue to receive active IV treatment and placebo po treatment. Subjects randomized to an IV/PO treatment group will receive placebo IV and active po treatment. At all times during the study the decision to continue iv, switch to po, or discontinue test article is made based on the clinical judgment of the investigator. Each daily decision is to be recorded on source documents and the information transferred to eCRFs by blinded study site personnel.

7.6.4 Investigator's Decision to Continue or Discontinue Treatment

At all times during the study the decision to continue iv, switch to po, or discontinue test article is made based on the clinical judgment of the investigator. The investigator may use the culture and susceptibility results from the local microbiology laboratory to help guide therapy; however, decisions to continue or discontinue test article should be based on clinical response rather than susceptibility results (as omadacycline susceptibility testing is not available at the local site). If the AP is caused by a microorganism that is not susceptible to levofloxacin *in vitro,* the decision to continue or discontinue study treatment should be based on the subject's clinical course and the investigator's clinical judgment. These cases should be discussed with the Medical Monitor. The rationale for this decision should be recorded in source documents.

7.6.5 Investigator's Decision to Switch from iv to po Treatment

Initially, all randomized subjects will receive at least 1 day of iv antibacterial therapy. Beginning on the day 2 visit, the subject may be eligible to switch from iv to po therapy.

Switch from active iv to active po study drug therapy is optional, and will occur based on treatment group assigned. Upon decision to switch, subjects randomized to iv only groups will begin to receive placebo po in addition to their active iv test article. Those in an iv/po group will begin to receive active po test article and placebo iv infusions. The decision should be made by the investigator based on by the investigator based on evaluation of the criteria below. Criteria will be confirmed and documented in source documents:

- Afebrile for ≥ 24 hours (highest daily oral, tympanic, rectal, or core temperature < 37.8ºC [100.0ºF]) without the use of anti-pyretics,
- Improvement or resolution of the signs and symptoms of the index AP,
- Ability to tolerate and ingest oral therapy (eg, no nausea, vomiting), and
- For subjects with baseline bacteremia, follow-up blood cultures must be negative.

Subjects who are switched to po test article administration will continue to receive iv infusions in order to maintain the blind. Switch to po will not be permitted until after the subject has completed at least the first day of iv treatment (after 1 dose). The date and time the investigator confirmed the criteria for the subject's eligibility for po treatment were met and made the decision to switch to po treatment will be recorded on source documents and the information transferred to eCRFs by study site personnel.

7.6.6 Oral Treatment Phase

When switching from iv to po test article the recommended interval between doses will be maintained. The first po dose, for both omadacycline and levofloxacin treatment arms, should be given in the morning 12 to 24 hours after the last dose of iv test article.

The po treatment phase will employ a double-blind, double-dummy design using omadacycline placebo comparator tablets of matching size and shape to active omadacycline tablets and matching over-encapsulated placebo and active levofloxacin tablets.

To maintain investigator and subject blinding, subjects in both arms will receive both tablets and over-encapsulated tablets during each dose. Subjects in groups 1 and 2 will receive placebo omadacycline tablets and placebo over encapsulated levofloxacin tablets. Subjects in groups 3, 4 and 5 will also continue to receive iv placebo infusions to maintain the blind.

The po treatment will be administered by study staff during visit assessments.

All doses of oral test article should be taken with water.

All oral doses should be taken in a fasted state. Fasting is defined as no food, antacids or multivitamins containing multivalent cations (eg, aluminum, magnesium, calcium, bismuth, iron, or zinc) or drink except water for at least 6 hours before dosing. After dosing, no food is permitted for 2 hours as well as no dairy products, antacids or multivitamins containing multivalent cations (eg, aluminum, magnesium, calcium, bismuth, iron, or zinc) for 4 hours.

7.6.6.1 Management While on Oral Test Article

While the subject is receiving po therapy, the investigator will assess the subject daily and choose one of the following outcomes based on the overall clinical response of the subject:

- Continue po test article
- Discontinue test article – this decision will prompt the EOT evaluation (even if the subject does not complete the minimum of 7 days of dosing)

At all times during the study the decision to continue or discontinue test article is made based on the clinical judgment of the investigator. Each daily decision is to be recorded on source documents and the information transferred to eCRFs by blinded study site personnel.

Table 2. Dosing Blinded iv and Oral Double-Blind, Double-Dummy Design

Dosing		Group 1 omadacycline	Group 2 omadacycline	Group 3 omadacycline	Group 4 omadacycline	Group 5 Levofloxacin
Day 1		omadacycline 200 mg iv in 150 mL NS	omadacycline 200 mg iv in 150 mL NS	omadacycline 200 mg iv in 150 mL NS	omadacycline 200 mg iv in 150 mL NS	levofloxacin 750 mg iv in 150 mL saline
Days2 to 7-10[a, b, c]	**continue iv**	omadacycline 200 mg iv in 150 mL NS	omadacycline 100 mg iv in 150 mL NS	omadacycline 100 mg iv in 150 mL NS	omadacycline 100 mg iv in 150 mL NS	levofloxacin 750 mg iv in 150 mL saline
	switch to po[b]	omadacycline 200 mg iv in 150 mL NS **and** three placebo tablets resembling omadacycline **and** three over-encapsulated placebo tablets resembling levofloxacin	omadacycline 100 mg iv in 150 mL NS **and** three placebo tablets resembling omadacycline **and** three over-encapsulated placebo tablets resembling levofloxacin	150 mL NS **and** two 150 mg omadacycline tablets, one placebo tablet resembling omadacycline, **and** three over-encapsulated placebo tablets resembling levofloxacin	150 mL NS **and** three 150 mg omadacycline tablets **and** three over-encapsulated placebo tablets resembling levofloxacin	150 mL NS **and** three placebo tablets resembling omadacycline **and** three over-encapsulated 250 mg levofloxacin tablets

Dosing in all treatment groups is once-per-day.
All iv doses will be administered as continuous infusions over 90 minutes.
All oral doses will be taken in a fasted state (no food, antacids or multivitamins containing multivalent cations [eg, aluminum, magnesium, calcium, bismuth, iron, or zinc] or drink except water for at least 6 hours prior to dosing; after dosing, no food for 2 hours, no dairy products, antacids or multivitamins containing multivalent cations for 4 hours).
iv = intravenous, NS = normal saline, po = per oral.
[a] The total duration of treatment is 7-10 days, Subjects with bacteremia can continue treatment for up to 14 days.
[b] Starting on Day 2, per investigator's discretion, subjects may be switched to oral dosing per oral switch criteria.
[c] All therapy may be discontinued after the seventh day of treatment, when the infection is considered clinically cured (based on normalization of the clinical signs and symptoms of infection and the investigator's clinical assessment that continued systemic antibacterial therapy is no longer needed).

7.7 Dose Adjustments and Interruptions of Test Article

No dose adjustments or planned interruptions of test article will be permitted during this study.

7.8 Method of Assigning Patients to Treatment Groups

All eligible subjects will be randomized via an IxRS that assigns them to the treatment arm. The site delegate will contact the IxRS after confirming that the subject fulfills all the

inclusion criteria and has none of the exclusion criteria. The IxRS will assign a test article to the subject based on a computer-generated randomization schedule. The randomization will be a blocked randomization sequence as defined in the IxRS specifications and Statistical Analysis Plan (SAP). It is possible that not all treatment arms will be enrolling subjects at the same time. Arms may be dropped based on the Bayesian analysis or initiated based on the Bayesian analysis of the ongoing treatment arms. There will always be at least one omadacycline arm and the levofloxacin arm open. Subjects randomized into the study will be assigned the treatment corresponding to the next available number from the computer-generated randomization schedule. The subject is considered randomized when the IxRS provides the test article assignment, regardless of whether the subject actually receives any medication. As this is an adaptive design trial, any updates to the randomization schedule based upon the Bayesian analysis will be incorporated into the IxRS system.

7.8.1 Subject Numbering

Upon signing the informed consent, the subject will be assigned a unique subject number. Subjects who have been pre-screened, but who do not sign an ICF will not be assigned a subject number. A subject who discontinues participation or is withdrawn before receiving a treatment assignment, and who is re-screened at a later time will be assigned a new subject number and recorded as re-screened. Re-screening is at the discretion of the investigator and in consultation with the medical monitor. The investigator will maintain a subject master list to document every subject who has signed an ICF. A copy of this list should be retained in the investigator's study files.

7.9 Dispensing Test Article

Each study site will be supplied by the sponsor with the investigational product and comparator. The IxRS will instruct the pharmacist or designee as to the appropriate therapy, omadacycline or levofloxacin, to be administered. The unblinded site pharmacist or designee will prepare the test article as instructed. The unblinded pharmacist or designee will provide the blinded nurse administering the infusion with the appropriate solutions for each subject covered to conceal the identity of the test article using materials provided by the sponsor and labeled with blinded administration instructions. The po test article will be supplied to the sites in kits that contain active omadacycline tablets or matched placebo tablets, and active levofloxacin over-encapsulated tablets or matched placebo over-encapsulated tablets resembling levofloxacin. Oral test article supplies are completely blinded. Therefore, oral test article supplies can be transferred from the unblinded study personnel to blinded study personnel for storage, dispensation, and reconciliation. The study coordinator/staff will instruct the subject on the use of po test article. The procedures are detailed in the Pharmacy Manual.

7.10 Blinding

The investigator and sponsor will be blinded to treatment group assignments throughout the study. The sponsor designee (eg, study statistical team, IxRS vendor, etc.) will have a designated randomization administrator who will maintain the randomization codes in accordance with standard operating procedures to ensure the blind is properly maintained,

and that only sponsor personnel who require knowledge of treatment assignments will be unblinded (eg, staff involved in maintaining the randomization codes). The DMC will review safety data and the results from the Bayesian analysis of efficacy. Based on this analysis, modifications may be made to the omadacycline treatment groups.

The investigator and sponsor will be blinded to treatment arm assignments. The iv and po phases of the study will be double-blind.

Because the color of the iv test article infusions and placebo infusions differ, all infusion bags and iv tubing will be covered with materials provided by the sponsor so that subjects and blinded study personnel will not know the identity of the test article being administered. The infusion regimen will follow a blinded design with subjects in each study arm receiving the same infusion volumes with the same administration instructions. Blinded study personnel will administer the infusions and collect, review and enter data regarding the iv infusions (eg, start and stop times) into an eCRF. If gravity administration is not the standard of care then an infusion pump may be used. If an infusion pump is used then an unblinded administrator will be required. Personnel identified as unblinded administrators will not participate in any study procedures other than iv administration of test article and the collection, review and entry of iv related data (eg, start and stop times) into an eCRF.

During the po phase, a double-blind, double-dummy design will be used to ensure the blind is maintained. Subjects on the omadacycline arms may receive active omadacycline tablets and over-encapsulated levofloxacin placebo tablets. Subjects on the levofloxacin arm will receive omadacycline placebo tablets and over-encapsulated active levofloxacin tablets. Infusions will be administered concomitantly along with the po treatment to maintain the overall study blind.

The unblinded source documentation binder containing all descriptions of pharmacy preparations and infusions or distributions of test article and any unblinded subject randomization data should be stored separately, and under lock and key, separate from the documents containing blinded information.

Data that could potentially lead to unblinding will not be accessible to anyone other than the following site personnel:

- unblinded study pharmacist or designee
- unblinded study monitor
- unblinded administrator(s)

Unblinding is only to occur in the case of subject emergencies (see Section 7.11, below) and at the conclusion of the study.

7.11 Emergency Unblinding of Treatment Assignment

Emergency unblinding should only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, test article discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an

emergency condition. It is encouraged for the investigator, when contemplating unblinding, to contact the sponsor or sponsor's designated Medical Monitor or designee to confirm the need to unblind, prior to unblinding (see Section 2 for contact information). However, if required, the investigator can unblind without consulting the Medical Monitor.

Emergency code breaks are performed using the IxRS. When the investigator contacts the system to unblind a subject, he/she must provide the requested subject identifying information and confirm the necessity to unblind the subject. The investigator will then receive details of the drug treatment for the specified subject and a fax or e-mail confirming that the treatment assignment of the subject was unblinded. The system will automatically inform the sponsor's monitor for the site and the sponsor that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place at their site to allow access to the IxRS code break information in case of emergency. The investigator will inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable. The investigator will provide protocol number, test article name if available, subject number, and instructions for contacting the sponsor (or any entity to which it has delegated responsibility for emergency code breaks) to the subject in case emergency unblinding is required at a time when the investigator and backup are unavailable.

All steps outlined above will be followed, including contacting the Medical Monitor as soon as possible and not more than 24 hours afterwards. It will be the responsibility of all study personnel to ensure that, except for the above procedure, investigator blinding is maintained until after study completion.

7.12 Prior & Concomitant Therapy

Treatments that have been administered within the 7 days prior to the date of informed consent, or during the Screening phase, will be recorded in the eCRF. The investigator is to instruct the subject to notify the study site about any new medications he/she takes after the start of the test article. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject starts treatment with test article must be listed in the eCRF (see Section 9). In addition, for antibacterial agents and anti-emetics administered, the dose, unit, frequency and route must be entered in the eCRF.

7.13 Prohibited Therapy

- All investigational medications or devices used during the 30 days prior to Screening are prohibited.

All of the following therapies are excluded starting from the time of consent through EOT visit:

- Potentially therapeutic antibacterial agents (with potential activity against uropathogens responsible for AP) are prohibited for 72 hours prior to randomization through EOT, with

the exception of cases where a subject is deemed a clinical failure during the course of the study and requires treatment with an additional antibacterial agent

- Subjects will be instructed to avoid taking antacids and multivitamins containing multivalent cations (eg, aluminum, magnesium, calcium, bismuth, iron, or zinc) for 6 hours before and within 4 hours after oral doses

7.13.1 Concomitant Medications That May Interact with Levofloxacin

Use of antiarrhythmic agents of Class IA (eg, quinidine, procainamide) or Class III (eg, amiodarone, Sotalol) is prohibited from the time that informed consent is obtained through EOT.

7.14 Permitted Treatments

All other treatments not specified as prohibited are permitted during the study. Subjects requiring additional or alternative antibacterial therapy for their AP will be judged as Clinical Failures and test article will be discontinued. Further treatment for their infection is at the discretion of the investigator or the subject's health care provider and will be considered as a concomitant medication.

Subjects should be encouraged to contact site personnel before starting any new treatment.

For all treatments received by the subject during the study, relevant information must be recorded on the subject's eCRF.

7.15 Treatment Compliance

Intravenous and oral administration will be managed by study personnel. Compliance and any unresolved discrepancies will be documented in the source document and on the drug inventory record. The test article eCRF should reflect the reconciled dosing information provided by the subject charts.

7.16 Packaging and Labeling

The investigational test article, omadacycline and comparator, levofloxacin, will be packaged by the sponsor and supplied to the investigator. Please refer to the Pharmacy manual for additional information.

7.17 Storage and Accountability

Test article must be received at the study site by a designated person, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated staff have access. Upon receipt, the test article should be stored according to the instructions specified on the drug labels. Storage conditions must be adequately monitored and appropriate temperature logs maintained as source data.

The designated study personnel must maintain an accurate record of the shipment and dispensing of test articles in the study specific medication accountability ledger iv drug

accountability will be performed by unblinded personnel. Oral drug accountability can be performed by blinded or unblinded personnel.

7.18 Investigational Product Retention at Study Site

At the conclusion of the study, and as appropriate during the course of the study, with instruction from the sponsor, the designated study personnel will destroy on site as permitted by local site operating procedures, or return all unused test articles, packaging, and drug labels. Destruction/return of all test article will be documented and maintained in the site files.

8 STUDY PROCEDURES

Written, signed, and dated informed consent will be obtained before any study-related procedures have been performed. Upon signing the informed consent, the subject will then be assigned a study subject number. Adverse events must be recorded from the time the ICF is signed. Subjects who have been pre-screened on the telephone but who do not sign an ICF will not be assigned a subject number. The investigator will maintain a subject master list to document every subject who has signed an ICF. A copy of this list should be retained in the investigator's study files.

8.1 Informed Consent

The investigator will provide for the protection of the subjects by following all applicable regulations. These regulations are available upon request from the sponsor. The ICF must be reviewed by the sponsor and approved by the IRB/IEC/REB.

Before any procedures specified in the protocol are performed, a subject must:

- Be informed of all pertinent aspects of the study and all elements of informed consent
- Be given time to ask questions and time to consider the decision to participate
- Voluntarily agree to participate in the study
- Sign and date an IRB/IEC/REB approved ICF

8.2 Subject Demographics/Other Baseline Characteristics

Subject demographic and Baseline characteristic data to be collected on all subjects include: date of birth, gender, and race/ethnicity.

8.3 Medical History

The investigator will perform a comprehensive history at the Screening visit. Significant medical history (at any time) and any medical history within the past 6 months including ongoing medical conditions at the time of signing of the ICF will be recorded. In addition, subject history of prior UTI and AP will be captured. Where possible, diagnoses are to be recorded. Any event or change in the subject's condition or health status occurring after signing the ICF will be reported as an AE.

8.4 Physical Examination

At Screening, a full physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and vascular and neurological systems. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed.

Information for all physical examinations must be included in the source documentation at the study site. Significant and relevant findings that are present prior to the start of test

article must be included in the subject's eCRF. Relevant findings that are present prior to the start of test article must be included in the relevant medical history/current medical conditions screen on the subject's eCRF. Significant findings made after the start of test article which meet the definition of an AE must be recorded on the AE screen of the subject's eCRF.

8.5 Vital Signs

Vital signs include blood pressure (BP), heart rate, and body temperature.

- Blood pressure and heart rate should be measured within 30 min before, and approximately (± 15 minutes) 1 hour after and 3 hours after the completion of the first dose.

The subject's BP and heart rate should be captured after at least 5 minutes (+ 5 minutes) of rest while in a non-standing position (supine or semi-recumbent, head of bed from 0° to 90°). Subsequent vital sign measurements should be captured in the same non-standing position.

Systolic and diastolic BP will be measured using an automated calibrated device, with an appropriately sized cuff.

Heart rate will be measured using an automated calibrated device, when available. If not available, heart rate will be measured manually.

Temperature will be obtained using an electronic (rapid reading) device whenever possible.

8.6 Height and Weight

Height and body weight will be collected.

8.7 Clinical Laboratory Tests

Clinical laboratory tests to be performed include hematology (including coagulation), serum chemistry, urine or serum pregnancy assessments, and urinalysis. The Central Laboratory will be used for safety analysis of all specimens collected. Details on the collection tubes and containers, shipment of samples and reporting of results by the Central Laboratory are provided to investigators in the Central Laboratory Manual.

Because subject enrollment will not permit using Central Laboratory results to assess a subject's meeting inclusion/exclusion criteria, it is expected that local laboratory testing will be used in circumstances where this testing is needed to assess a subject's WBC count or differential, serum transaminase or bilirubin levels, serum creatinine or pregnancy testing.

The total volume of blood collected from each subject will be approximately 4 – 11 mL per visit, or approximately 44 mL (3 tablespoons) over the course of the study. In addition, a blood culture will be collected at Screening and repeated if positive. The preferred volume for each blood culture bottle is 10 mL. However, since these are analyzed locally, site staff should refer to their individual laboratory or manufacturers' recommendation.

8.7.1 Central Laboratory Parameters

Clinical laboratory tests will include the following:

Table 3. Clinical Laboratory Tests (Central)

Hematology: • Hematocrit (Hct) • Hemoglobin (Hgb) • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Mean corpuscular volume (MCV) • Platelet count • Red blood cell (RBC) count • White blood cell (WBC) count with differential Pregnancy (all female subjects): • Serum β-human chorionic gonadotropin (β-HCG)	Serum Chemistry: • Alkaline phosphatase (ALP) • Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Blood urea nitrogen (BUN) • Calcium (Ca) • Carbon dioxide (CO2) • Chloride (Cl) • Creatinine • Creatine phosphokinase (CK) • Gamma-glutamyl transpeptidase (GGT) • Lipase • Magnesium • Phosphorus (P) • Potassium (K) • Sodium (Na) • Total bilirubin

8.7.2 Local Laboratory Parameters

8.7.2.1 Pregnancy Assessments

All subjects will have a local urine or serum pregnancy test at the site at the Screening. Urine pregnancy test kits will be provided by the sponsor through the Central Laboratory. If a positive urine or serum pregnancy test result is obtained at the site during Screening, the subject is not to be randomized. A serum sample for serum β-human chorionic gonadotropin (β-hCG) testing will be collected at the Screening visit and sent to the Central Laboratory for confirmation of the local urine or serum pregnancy test results as well as at EOT. If a positive β-hCG result is reported by the Central Laboratory after a subject is enrolled, test article administration should be discontinued (see Section 8.17.6).

8.7.2.2 Urine Culture and Dipstick Tests

A clean-catch midstream urine sample should be collected, analyzed by urine dipstick test for leukocyte esterase, and optionally sent to the local laboratory for microscopic examination. If sent for microscopic evaluation, the sample should be analyzed for pyuria (WBC count > 10/μL in unspun urine or ≥ 10 per high power field in spun urine). Results will be recorded on the eCRF.

The sample will also be used for quantitative urine culture by appropriate methods using a calibrated loop that would identify bacteria at a lower limit of 1.0×10^3 colony forming units

(CFU)/mL. A Baseline culture must grow at least 1 and no more than 2 bacterial isolates at ≥ 1.0×10^5 CFU/mL each. If more than two bacterial isolates are identified, the culture will be considered contaminated. In general, at any visit, bacteria identified at 1.0×10^5 CFU/mL or greater should be considered a bacterial pathogen (probability of true pathogen is greater than probability of contamination). At any visit after Screening, a pathogen of the same species as the Baseline pathogen with a CFU count of $\geq 1 \times 10^4$ CFU/mL and should be considered a persisting pathogen and should be sent to the central laboratory. At any visit after Screening, any culture with a CFU count of $< 10^4$ CFU/mL should be considered a microbiologic cure.

Culture results are to include identification of all pathogens to the level of genus and species. *In vitro* antimicrobial susceptibility testing of the isolates to antimicrobial drugs that may be used to treat AP can be performed locally using a standard method chosen by the laboratory.

All bacterial isolates that grow ≥ 10^3 CFU/mL (whether at Baseline or post-Baseline) identified by the local laboratory from urine culture will be submitted to the Central Laboratory for verification of genus and species and for standardized MIC testing performed for omadacycline, levofloxacin and a panel of other antibiotics. In the event that local laboratory genus and species identification are not consistent with Central Laboratory results, a back-up isolate should be sent to the Central Laboratory.

Details concerning cultures and shipment to the Central Laboratory will be provided in a Clinical Microbiology Laboratory Manual.

The investigator may use the culture and susceptibility results from the local microbiology laboratory to help guide therapy; however, decisions to continue or discontinue test article should be based on clinical response rather than susceptibility results (as omadacycline susceptibility testing is not available at the local site). The decision to continue or discontinue study treatment should be based on the subject's clinical course and the investigator's clinical judgment. The rationale for this decision should be recorded in source documents.

8.7.2.3 Blood Cultures

Two sets of blood cultures (1 set = 1 aerobic bottle + 1 anaerobic bottle) should be collected within the 24 hours prior to the first dose of test article. Each set of blood cultures should be collected by direct venipuncture from independent body sites at least 15 minutes apart. If bacteria are isolated from baseline blood cultures, repeat blood cultures should be collected on the day that the positive blood culture is detected. If subsequent blood cultures are also positive, repeat the blood cultures as necessary until negative blood cultures are obtained. Blood culture isolates should be sent to the Central Laboratory.

8.8 Efficacy Assessments

8.8.1 Investigator's Assessment of Clinical Response

8.8.1.1 Investigator's Assessment of Clinical Response at EOT

The investigator will determine whether or not the subject meets the criteria of 1 of the following clinical outcomes:

- Clinical Success: The complete resolution or significant improvement of the baseline signs and symptoms of AP at the EOT visit such that no additional antimicrobial therapy is required for the current infection.
- Clinical Failure: No apparent response to therapy or persistence of signs and symptoms of infection at the EOT visit such that use of alternative or additional systemic antimicrobial therapy for the current infection is required or death prior to the EOT visit.
- Indeterminate: EOT visit not completed.

8.8.1.2 Investigator's Assessment of Clinical Response at PTE

For subjects who were determined to be a clinical success or indeterminate at the EOT visit, the investigator will determine whether or not the subject meets the criteria of 1 of the following clinical outcomes:

- Clinical Success: The complete resolution or significant improvement of the baseline signs and symptoms of AP symptoms at the PTE such that no additional antimicrobial therapy is required for the current infection.
- Clinical Failure: No apparent response to therapy or persistence of signs and symptoms of infection or reappearance of signs and symptoms at or before the PTE visit such that use of additional systemic antimicrobial therapy for the current infection is required or death at or before the PTE visit.
- Indeterminate: PTE visit not completed.

8.8.1.3 Investigator's Assessment of Clinical Response at Final Follow-up

For subjects that were determined to be a clinical success at the PTE visit, the investigator will determine whether or not the subject meets the criteria of 1 of the following clinical outcomes:

- Clinical Cure: The complete resolution or significant improvement of the baseline signs and symptoms of AP at FFU visit such that no additional antimicrobial therapy is required for the current infection.
- Relapse: The reappearance of signs and symptoms at or before the FFU Visit such that use of alternative or additional systemic antimicrobial therapy for the current infection.
- Clinical Failure: Death between the PTE and Final Follow-up.
- Indeterminate: Final Follow-up visit not completed.

8.9 Microbiologic Response

Microbiologic outcome at EOT and PTE will be programmatically determined for each pathogen isolated at baseline. Per-pathogen microbiologic response categories are eradication, persistence and indeterminate.

Category	Criteria
Eradication	The demonstration that the baseline bacterial pathogen is reduced to $< 10^4$ CFU/mL on urine culture and negative on repeat blood culture (if positive at baseline)
Persistence	The urine culture taken at the study visit grows $\geq 10^4$ CFU/mL of the baseline pathogen identified at study entry and/or a positive blood culture at the study visit demonstrates the same baseline pathogen. Pathogens that are a persistence at EOT will be considered a persistence at PTE.
Indeterminate	No follow-up urine culture is available, or the follow-up urine culture cannot be interpreted for any reason. For a baseline blood pathogen, no follow-up blood culture is available.

CFU = colony forming units, EOT = end of treatment, PTE = post therapy evaluation.

An overall per-subject microbiologic response at EOT and PTE will be programmatically determined for each subject based on the individual outcomes for each baseline pathogen. For a subject to have a microbiologic response of success, the outcome for each baseline pathogen must be eradicated. If the outcome for any pathogen is persistence, the subject will be considered to have a microbiologic response of failure. Subjects with a persistence at EOT will be considered a persistence at PTE.

Category	Criteria
Success	The outcome of all baseline pathogens must be eradication at the specified visit (EOT or PTE)
Failure	The outcome of at least 1 baseline pathogen is persistence. Subjects with a persistence at EOT will be considered a persistence at PTE.
Indeterminate	The outcome of at least 1 baseline pathogen is indeterminate and there is no outcome of persistence for any baseline pathogen

EOT = end of treatment, PTE = post therapy evaluation.

8.10 Modified Patient Symptom Assessment Questionnaire

The subject will report the severity of their pyelonephritis symptoms and how bothersome they are with the Modified Patient Symptom Assessment Questionnaire (mPSAQ). The questionnaire will be completed during each study visit. The subject will rate the severity and how bothersome each symptom on a 4-point scale (no symptom, mild, moderate, severe and not at all, a little, moderately, a lot) and the results will be recorded in the eCRF. The investigator must review the subject's responses and record any AEs as appropriate. See Appendix 3 for the mPSAQ.

8.11 Pharmacokinetic Assessments

Instructions will be provided to sites with detailed information on sample collection, handling, and shipment requirements. All samples will be given a unique identifier. The exact clock time of dosing, date and time of last food intake, as well as actual sample collection date and time will be entered on the eCRF.

8.11.1 PK Blood Collection and Processing

Blood samples will be collected and analyzed for omadacycline concentration at the following times:

- Just prior to the dose on Day 3 and just prior to last dose of test article;
- 2 to 3 hours after dose on Day 3 and 2 to 3 hours after last dose of test article.

8.11.2 PK Urine Collection and Processing

Urine will be collected, the volume recorded, and analyzed for omadacycline concentration at the following times:

- Day 3 to 4: pooled total urine from 0 to 24 hours after the Day 3 dose;
- Day 6 to 7: pooled total urine from 0 to 24 hours after the Day 6 dose

Omadacycline urine concentration data will be used to determine the 24-hr average urinary concentration and amount of drug excreted in the urine in a dosing interval at steady-state.

8.11.3 Storing and Shipping of PK Samples

After all PK samples from a single subject have been collected and frozen at - 20°C or colder, the primary samples from each time point can be batched together and carefully packaged and shipped frozen at - 20°C or colder to the central laboratory designated by the sponsor. Samples are to be shipped with sufficient dry ice to remain frozen during overnight transit. For each subject and time point, the remaining stored aliquots will be retained on site at - 20°C or colder until released or requested by the sponsor.

8.12 Adverse Events

An AE is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observations occurring in a person given a test article or in a clinical study. The event does not need to be causally related to the test article or clinical study. An AE includes, but is not limited to, the following:

- Any clinically significant worsening of a preexisting condition.
- An AE occurring from overdose of a test article, whether accidental or intentional. Overdose is a dose greater than that specified in the protocol.
- An AE occurring from abuse (eg, use for nonclinical reasons) of a test article
- An AE that has been associated with the discontinuation of the use of a test article

8.13 Serious Adverse Events

A serious adverse event (SAE) is an AE that:

- Results in death
- Is life-threatening (see below)
- Requires hospitalization or prolongation of an existing hospitalization (see below)
- Results in a persistent or significant disability or incapacity (see below)
- Results in a congenital anomaly or birth defect
- Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent any one (1) of the outcomes listed above in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Life-threatening refers to immediate risk of death as the event occurred per the reporter. A life-threatening experience does not include an experience, had it occurred in a more severe form, might have caused death, but as it actually occurred, did not create an immediate risk of death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

Hospitalization is official admission to a hospital. Hospitalization or prolongation of a hospitalization constitutes criteria for an AE to be serious; however, it is not in itself considered an SAE. In absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported as an SAE by the participating investigator. This is the case in the following situations:

- The hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol
- The hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (eg, stent removal after surgery). This should be recorded in the study file.
- A hospitalization for a preexisting condition that has not worsened

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

If there is any doubt about whether the information constitutes an SAE, the information is treated as an SAE.

8.14 Other Reportable Information

Certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes:

- Pregnancy exposure to a test article: If a pregnancy is confirmed, use of the test article must be discontinued immediately. Information about pregnancy exposure includes the entire course of pregnancy and delivery, and perinatal and neonatal outcomes, even if there are no abnormal findings. Both maternal and paternal exposures are considered other reportable information. For exposure involving the female partner of a male subject, the necessary information must be collected from the subject, while respecting the confidentiality of the partner.
- Lactation exposure to a test article with or without an AE
- Overdose of a test article as specified in this protocol with or without an AE
- Inadvertent or accidental exposure to a test article with or without an AE

8.15 Overdose

Any administration of omadacycline of greater than 1350 mg within a 24-hour period will be an overdose, regardless of whether the overdose is intentional or accidental, it is a reportable event and the sponsor must be notified within 1 business day. Any administration of greater than 750 mg of levofloxacin in a single administration will be an overdose. In the event that a study subject takes an overdose of test article, the investigator may obtain the subject's treatment assignment by contacting the IxRS. Interactive Response System will also provide a confirmation report of the drug assignment to site personnel. The site personnel will retain this confirmation report. In the case of a potential overdose, the subject should maintain a high level of fluid intake to promote urinary excretion (as recommended in the levofloxacin USPI).

The physician managing the overdose may order any test he/she thinks is necessary to manage the subject properly.

8.16 Medication Errors

Medication errors are the result of administration or consumption of the wrong product, by the wrong subject, at the wrong time, and/or by the wrong administration route, due to human error.

Medication errors include, but are not limited to, the following:

- The administration and/or consumption of test article that has not been assigned to the subject
- Administration of expired test article

All AEs and SAEs must be handled as specified in this protocol whether or not they are associated with a medication error. A medication error associated with an SAE (including overdose, inadvertent exposure, and/or accidental exposure) will be reported with the SAE on

the SAE Report Form. All other medication errors will be reported by e-mailing the Clinical Test Article Error Incident Report Form as indicated in the Emergency Contacts (see Section 2).

8.17 Recording and Reporting

A subject's AEs and SAEs will be recorded and reported from the signing of the ICF to the time of the Final Follow-up assessment. The investigator must instruct the subject to report AEs and SAEs during this time period. Reports of death within 30 days after the last contact with the subject will be reported to the sponsor and additional information relative to the cause of death will be sought and documented.

All AEs and SAEs must be recorded on source documents. All AEs and SAEs for subjects who receive a treatment assignment will be recorded in the eCRFs.

The investigator must follow-up as medically necessary on all AEs and SAEs until the events have subsided, the condition has returned to Baseline, or in case of permanent impairment, until the condition stabilizes.

Adverse events should be based on the signs or symptoms detected during the physical examination and on clinical evaluation of the subject. In addition to the information obtained from those sources, the subject should be asked the following nonspecific question: "How have you been feeling since your last visit?" Whenever possible, AEs should be reported as a diagnosis rather than individual signs and symptoms. If a definitive diagnosis is not possible, the individual signs and symptoms should be recorded using standard medical terminology.

If an AE requires a surgical or diagnostic procedure, the illness leading to the procedure should be recorded as the AE, not the procedure itself.

Death should be recorded in the eCRF as an outcome of an AE. Any unanticipated risks to the subjects must be reported promptly to the IRB/IEC/REB.

8.17.1 Serious Adverse Event Reporting

All SAEs and follow-up information must be reported within 1 business day or 24 hours as required by local regulations by emailing a completed SAE Report to the email address below.

Serious Adverse Event (SAE) contact information:
E-Mail: [redacted]

8.17.2 Assessment of Relatedness

The investigator will assess causality (ie, whether there is a reasonable possibility that test article caused the event) for all AEs and SAEs. The relationship will be characterized using the following classification:

- Not related: This relationship suggests that there is no association between test article and the reported event. The event can be explained by other factors such as an underlying medical condition, concomitant therapy, or accident, and no plausible temporal or biologic relationship exists between test article and the event.
- Related: This relationship suggests that a definite causal relationship exists between test article administration and the AE, or there is a reasonable possibility that the event was caused by the study medication, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

Adverse events and SAEs also will be assessed for their potential relationship to the protocol. A protocol-related AE is one that is not related to the test article, but is considered by the investigator or the medical monitor (or designee) to be related to the research conditions, ie, related to the fact that a subject is participating in the study. For example, a protocol-related AE may be an untoward event related to a medical procedure required by the protocol.

8.17.3 Assessment of Severity

The severity (or intensity) of an AE will be classified using the following criteria:

- Mild: These events are usually transient, require minimal or no treatment, and do not interfere with the subject's daily activities.
- Moderate: These events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with normal functioning but pose no significant or permanent risk of harm.
- Severe: These events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Changes in the severity of an AE should be documented as a new event to allow an assessment of the duration of the event at each level of intensity to be performed.

8.17.4 Laboratory Findings

Protocol-defined safety laboratory test results will be analyzed as part of specific laboratory safety analyses. Additional laboratory test results at other time points may be available to the investigator as part of standard clinical practice. Throughout the study, laboratory-related abnormalities should be recorded as AEs only if considered clinically significant, outside the range of expected values given the subject's Baseline assessments and clinical course, and not known to be part of another AE diagnosis.

8.17.5 Worsening or Progression of Disease Under Study

Worsening or progression of the qualifying pyelonephritis should be recorded as a clinical failure (as part of the efficacy assessment), rather than an AE, unless the worsening/progression also meets the criteria for a serious AE (in which case the event also should be reported as an SAE). In contrast, any new or secondary infections that the

investigator considers to be distinct from the qualifying pyelonephritis should be reported as AEs in all cases, whether non-serious or serious.

8.17.6 Pregnancies

To ensure subject safety, each pregnancy in a subject on test article must be reported to the sponsor within 1 business day of learning of its occurrence. Test article should be discontinued immediately and the pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the sponsor. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the test article of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8.18 Concomitant Medication Assessments

The investigator should instruct the subject to notify the study site about any new medications they take after the start of the test article.

All prescription medications, over-the-counter (OTC) drugs, and recreational drugs taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant Medications/Non-Drug Therapies page of the eCRF. Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation dates, and the reason for therapy.

8.19 Subject Discontinuation or Withdrawal

Reasons why a subject may discontinue or be withdrawn from the study include, but are not limited to, AE, lost to follow up, withdrawal by subject, physician decision, death, and other (specify reason eg, subject non-compliance or study termination by the sponsor). Subjects may voluntarily withdraw from the study for any reason at any time. Subjects are considered withdrawn from the study if they state an intention to withdraw, or fail to return for visits, or become lost to follow up for any other reason. If premature withdrawal from the study occurs for any reason, the investigator should determine the primary reason for a subject's premature withdrawal from the study and record this information on the eCRF.

Subjects who discontinue study treatment should not be considered withdrawn from the study (unless the subject withdraws informed consent). The date and primary reason for discontinuation of study treatment should be recorded. Subjects who discontinue study treatment prematurely should complete the EOT visit, PTE visit and Final Follow-up Assessment, if possible (see Schedule of Events - Appendix 1). The site should also collect subject safety information through the Final Follow-up assessment.

Site personnel should also contact the IxRS to register the subject's discontinuation from test article.

For subjects who are lost to follow up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, eg, dates of telephone calls, registered letters, etc.

9 STUDY ACTIVITIES

The full assessment schedule is presented in the Schedule of Events (see Appendix 1). Subjects should be seen for all visits on the designated day.

9.1 Screening Phase

The Screening visit should be completed within a 24-hour period prior to randomization. The Screening procedures will be used to establish subject eligibility and Baseline characteristics for each subject. Following the signing of an ICF, the site staff will collect/perform the following:

- mPSAQ
- Demographics
- Medical history
- Physical examination
- Vital signs: body weight & height, body temperature, BP, heart rate
- 12-lead ECG (to confirm eligibility)
- Review of inclusion/exclusion criteria
- Laboratory tests (blood):
  - Blood culture
  - Hematology (includes coagulation)
  - Serum Chemistry
  - Serum pregnancy test
- Laboratory tests (urine):
  - Urinalysis via dipstick with optional microscopic exam
  - Urine culture
  - Urine pregnancy test
- Concomitant medications (past 7 days)
- AEs since the signing of the ICF

9.2 Double-Blind Treatment Phase

The double-blind treatment period is 7 to 10 days in duration. Subjects with bacteremia confirmed from local blood culture drawn at screening can receive up to 14 days of treatment. Subjects who meet all of the inclusion criteria and none of the exclusion criteria may be randomized.

9.2.1 Day 1 Visit Procedures

The following assessments will be performed:

- Review of inclusion/exclusion criteria
- Randomization
- Concomitant medications
- Vital signs: body temperature, BP, heart rate
- AEs
- Laboratory tests (blood)
- Blood culture (as required if bacteremia was confirmed at Screening and has not resolved)
- Dispensation and Administration of test article

9.2.2 Day 2 Visit Procedures

The following assessments will be performed:

- mPSAQ
- Concomitant medications
- Laboratory tests (urine):
  Urinalysis via dipstick with optional microscopic exam
  Urine culture
- Laboratory tests (blood):
  Blood culture (as required if bacteremia was confirmed at Screening and has not resolved)
- Vital signs: body temperature
- AEs
- Administration and accountability of test article
- Assessment for po switch

9.2.3 Day 3 Visit Procedures

The following assessments will be performed:

- mPSAQ
- Concomitant medications
- Laboratory tests (urine):
  Urinalysis via dipstick with optional microscopic exam
  Urine culture
- Laboratory tests (blood):
  Hematology (includes coagulation)
  Chemistry
  Blood culture (as required if bacteremia was confirmed at Screening and has not resolved)

- Vital signs: body temperature, BP, heart rate
- AEs
- PK blood collection
- PK urine collection
- Administration and accountability of test article
- Assessment for po switch

9.2.4 Day 4 Visit Procedures

The following assessments will be performed:

- mPSAQ
- Concomitant medications
- Laboratory tests (urine):
- Urinalysis via dipstick with optional microscopic exam
- Urine culture
- Laboratory tests (blood):
- Blood culture (as required if bacteremia was confirmed at Screening and has not resolved)
- Vital signs: body temperature
- AEs
- Administration and accountability of test article
- Assessment for po switch

9.2.5 Day 5 Visit Procedures

The following assessments will be performed:

- mPSAQ
- Concomitant medications
- Laboratory tests (urine):
- Urinalysis via dipstick with optional microscopic exam
- Urine culture
- Laboratory tests (blood):
- Blood culture (as required if bacteremia was confirmed at Screening and has not resolved)
- Vital signs: body temperature
- AEs
- Administration and accountability of test article

- Assessment for po switch

9.2.6 Day 6 Visit Procedures

The following assessments will be performed:

- mPSAQ
- Concomitant medications
- Laboratory tests (urine):
- Urinalysis via dipstick with optional microscopic exam
- Urine culture
- Laboratory tests (blood):
- Blood culture (if bacteremia is positively identified during Screening)
- PK urine collection
- Vital signs: body temperature
- AEs
- Administration and accountability of test article
- Assessment for po switch

9.2.7 Day 7 Visit Procedures

Beginning on Day 7, subjects are eligible to have their test article discontinued at the discretion of the investigator (see Section 8.8.1.1). If the investigator determines that the subject does not need further antibacterial therapy on Day 7, the EOT evaluation may be performed the day of or within 2 days of the last dose of test article.

The following assessments will be performed:

- mPSAQ
- Concomitant medications
- Laboratory tests (urine):
- Urinalysis via dipstick with optional microscopic exam
- Urine culture
- Laboratory tests (blood):
- Blood culture (if bacteremia is positively identified during Screening)
- Vital signs: body temperature, BP, heart rate
- AEs
- Assessment for po switch
- Investigator's decision to continue or discontinue test article
- Administration and accountability of test article

9.2.8 Day 8, 9 Visit Procedures

Day 8 and 9 visits will only be performed if the EOT visit does not coincide with the day of the last dose. The following assessments will be performed only if the subject is still receiving test article:

- mPSAQ
- Concomitant medications
- Laboratory tests (urine):
- Urinalysis via dipstick with optional microscopic exam
- Urine culture
- Laboratory tests (blood):
- Blood culture (if bacteremia is positively identified during Screening)
- Vital signs: body temperature
- AEs
- Assessment for po switch
- Investigator's decision to continue or discontinue test article
- Administration and accountability of test article

9.2.9 Day 10 Visit Procedures

Day 10 visit will only be performed if the EOT visit does not coincide with the day of the last dose. The following assessments will be performed only if the subject is still receiving test article:

- mPSAQ
- Concomitant medications
- Laboratory tests (urine):
- Urinalysis via dipstick with optional microscopic exam
- Urine culture
- Laboratory tests (blood):
- Blood culture (if bacteremia is positively identified during Screening)
- Vital signs: body temperature, BP, heart rate
- AEs
- Assessment for po switch
- Investigator's decision to continue or discontinue test article
- Administration and accountability of test article

9.2.10 Day 11, 12, 13 Visit Procedures

Day 11, 12, and 13 visits will only be performed for subjects with bacteremia whose treatment duration is extended beyond 10 days and if the EOT visit does not coincide with the day of the last dose.

The following assessments will be performed only if the subject is still receiving test article:

- mPSAQ
- Concomitant medications
- Laboratory tests (urine):
- Urinalysis via dipstick with optional microscopic exam
- Urine culture
- Laboratory tests (blood):
- Blood culture (if bacteremia is positively identified during Screening)
- Vital signs: body temperature
- AEs
- Assessment for po switch
- Investigator's decision to continue or discontinue test article
- Administration and accountability of test article

9.3 EOT Visit Procedures

The EOT evaluation should be conducted on the day of or within the 2 days following the last dose of test article. If the subject voluntarily withdraws or is discontinued from her dosing regimen, these procedures should be performed on that day:

- mPSAQ
- Concomitant medications
- Physical examination
- Laboratory tests (urine):
- Urinalysis via dipstick with optional microscopic exam
- Urine culture
- Laboratory tests (blood):
- Hematology (includes coagulation)
- Chemistry
- PK Blood Collection
- Serum pregnancy test
- Blood culture (if bacteremia is positively identified during Screening)
- Vital signs: body weight, body temperature, BP, heart rate

- AEs
- Investigator's assessment of clinical response
- Accountability of test article

9.4 Follow-up Phase

9.4.1 Post-Treatment Evaluation Visit (Day 21) Procedures

The PTE visit should be conducted on Day 21 (± 2 days). This evaluation should also be conducted for any prematurely withdrawn subject. The following assessments will be performed at the PTE visit:

- mPSAQ
- Concomitant medications
- Physical examination
- Laboratory tests (urine):
- Urinalysis via dipstick with optional microscopic exam
- Urine culture
- Laboratory tests (blood):
- Hematology (includes coagulation)
- Chemistry
- Serum pregnancy test
- Vital signs: body weight, body temperature, BP, heart rate
- AEs
- Investigator's assessment of clinical response

9.4.2 Final Follow-up

The Final Follow-up assessment should be conducted on Day 28 (± 2 days) after the subject's first dose of test article. This evaluation should also be conducted for any prematurely withdrawn subject with the exception of subjects who withdraw consent. The Final Follow-up assessment may be conducted via telephone contact or by another interactive technology for subjects who are not having any symptoms and had no AEs or clinically significant laboratory or ECG abnormalities noted at or after the PTE visit. Otherwise, the visit must be conducted in person.

The standard procedures for final follow-up call/visit are as follows:

- mPSAQ
- Concomitant medications
- AEs
- Investigator's assessment of clinical response

If during the final follow-up visit or call the subject reports symptoms of potential recurrence, the following additional procedures will be performed in clinic:

- Laboratory tests (urine):
  Urinalysis via dipstick with optional microscopic exam
  Urine culture
- Vital signs: body temperature, BP, heart rate

10 STUDY SUSPENSION, TERMINATION, AND COMPLETION

10.1 Study Completion and Post-Study Test Article

A subject will have successfully completed the study after the planned test article regimen has been administered, and all assessments and visits have been performed up through the final follow-up assessment (Final Follow-up). The study will be completed when the last subject has either discontinued or completed the Final Follow-up assessment.

No long-term follow-up of subjects is planned, with the exception of pregnancies, as described in Section 8.17.6, and SAEs described in Section 8.17.1.

Sites will be notified by either the Sponsor or IxRS to stop enrollment when the desired number of treated subjects have been enrolled. Subjects already consented, but not yet randomized will be allowed to continue Screening procedures.

Upon study completion, the investigator will provide the sponsor, IRB/IEC/REB, and regulatory agency with final reports and summaries as required by regulations. The investigator must submit a written report to the sponsor and the IRB/IEC/REB within 3 months after the completion or termination of the study.

10.2 Study Suspension or Termination

The sponsor may suspend or terminate the study or part of the study at any time for any reason. Should this be necessary, subjects should be seen as soon as possible and treated as described in Section 9.3 for prematurely withdrawn subjects. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing IRBs and/or Ethics Committees (ECs) of the early termination of the study.

If the investigator suspends or prematurely terminates their participation in the study, the investigator will promptly inform the sponsor and the IRB/IEC/REB and provide them with a detailed written explanation. Subjects should be seen as soon as possible and treated as described in Section 9.3 for prematurely withdrawn subjects. The investigator will also return all test articles, containers, and other study materials to the sponsor.

11 QUALITY CONTROL AND ASSURANCE

The sponsor performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any subjects in this study, sponsor personnel and the investigator review the protocol, the Investigator's Brochure, the case report forms (CRFs) and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the sponsor monitors the conduct of the study by visiting the site and by contacting the site by telephone and e-mail. During these site visits, information recorded in the CRFs is verified against source documents.

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

All analyses of data for this study will comply with International Council on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH-E9) and the sponsor's guidance documents and standards. Statistical analyses will be performed using Statistical Analysis Software (SAS®).

A SAP incorporating the sections below and with mock tables, figures, and listings (TFL) shells will be prepared, approved and finalized by the sponsor prior to database lock. This plan will define populations for analysis, outline all data handling conventions, and specify statistical methods to be used for analysis of safety and efficacy. Analyses of PK endpoints will be described in a separate analysis plan.

Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviation, medians, minimums, and maximums for continuous variables will be provided. Exploratory analyses may also be performed. Listings of individual subject's data will be produced.

All eCRFs must be completed, entered and source data verified; all safety and microbiology laboratory results must have been reported; all AEs must have been fully characterized (eg, relationship to test article determined) and coded; and all queries must have been resolved prior to database lock and unblinding. Determination of inclusion in the analysis populations, characterization of protocol deviations as major/minor and final approval of the SAP will also be completed prior to database lock.

12.2 Determination of Sample Size

Enrollment of approximately 200 subjects is planned to achieve at least 150 subjects in the micro-ITT population. The Bayesian posterior probability that the overall success rate at the PTE Visit is within 0.10 of that of the levofloxacin group will be estimated for each omadacycline treatment group. The target probability is 0.70. If the true underlying overall success rates for the levofloxacin and omadacycline treatment groups are 0.69, then the sample size of N = 30 per treatment group has approximately 65% power/probability to yield the target probability (N = 80 per treatment group for 80% power). If the true underlying overall success rates for the levofloxacin and omadacycline treatment groups are 0.78, then the sample size of N = 30 per treatment group has approximately 68% power/probability to yield the target probability (N = 64 per treatment group for 80% power). The sample size may be increased for a particular omadacycline treatment group by changing the randomization ratio and/or dropping a treatment group to have improved power/probability of achieving the target probability that overall success rates for a treatment group is within 0.10 of that of the levofloxacin group. If required to improve the precision of the interim or projected final analyses estimates of overall success rates or posterior probabilities, the sample size may be increased to a maximum sample size provided in the SAP.

12.3 Analysis Populations

The following subject analysis populations have been defined:

- Intent-to-treat (ITT): all randomized subjects.
- Safety: all randomized subjects who receive any amount of test article.

- The micro-ITT population will consist of subjects in the ITT population who have an appropriately collected pretreatment baseline urine culture with at least 1 uropathogen at $\geq 10^5$ CFU/mL and not more than 2 bacterial isolates at any count. If more than 2 bacterial isolates are identified, the culture will be considered contaminated regardless of colony count, unless 1 of the isolates that grows in the urine at $\geq 10^5$ CFU/mL is also isolated from a blood culture at the same visit.

- The clinically evaluable (CE) population will consist of all ITT subjects who received test article, have acute uncomplicated pyelonephritis, an assessment of outcome, and meet all other evaluability criteria detailed in the SAP.

- The microbiologically evaluable (ME) population will include subjects in the CE and micro-ITT populations who have an appropriately collected post-baseline urine sample and an interpretable post-baseline urine sample. An interpretable post-baseline urine culture is one that has a clearly identified pathogen or one where the baseline pathogen(s) can be excluded (ie, there is no growth of the baseline pathogen).

12.4 Demographics and Baseline Characteristics

Demographics (including age, ethnicity and race) and baseline characteristics will be summarized in the ITT and micro-ITT populations by treatment group. Baseline microbiology will be summarized in the micro-ITT population by treatment group. Descriptive statistics of the duration of test article treatment will be provided by treatment group. The number and percentage of subjects who prematurely discontinued test article and the reason for discontinuation and the number and percentage of subjects prematurely discontinuing the study and the primary reason for discontinuation will be presented by treatment group.

12.5 Primary Endpoint(s)

12.5.1 Efficacy Endpoint

The primary efficacy outcome is overall response at the PTE Visit in the micro-ITT population, which is a composite of per-subject microbiologic response and investigator's assessment of clinical response as follows:

Category	Criteria
Success:	A subject who is deemed a clinical success AND a microbiologic success
Failure:	A subject who is deemed a clinical failure OR a microbiologic failure
Indeterminate:	Insufficient data are available to determine if the subject is an overall success or failure

The number and percentage of subjects with overall success, overall failure and indeterminate response at the PTE Visit in the micro-ITT population will be determined by treatment group. Exact 95% CIs will be determined for the point estimates of the overall success rates in each treatment group.

A comparison of the overall success rate at the PTE Visit between each omadacycline treatment group and the levofloxacin treatment group will be conducted using a beta distribution with an uninformative Bayesian prior distribution.

12.6 Secondary Endpoint(s)

12.6.1 Safety Endpoint(s)

All safety analyses will utilize the Safety population. Summary tables will be provided for all treatment-emergent adverse events (TEAEs). A TEAE is defined as an AE with a start date and time on or after the first dose of test article. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by presenting the number and percentage of subjects having each TEAE for each treatment group by system organ class (SOC) and preferred term (PT), by SOC, PT and severity, and by SOC, PT and relationship to test article. Additional tabulations will provide summaries by SOC and PT of subjects experiencing SAEs and TEAEs leading to discontinuation of test article.

The following variables will be analyzed descriptively by treatment group in the Safety population:

- Vital signs (systolic and diastolic BP, heart rate, body temperature), including change from Baseline by visit and time point measured
- Clinically notable vital signs (meeting predefined criteria as specified in the SAP) by visit and time point measured
- Laboratory parameters, including change from Baseline by visit and overall worst post-baseline
- Clinically notable laboratory parameters (meeting predefined criteria as specified in the SAP) by visit and overall worst post-baseline

12.6.2 Efficacy Endpoint(s)

The number and percentage of subjects with an overall response of success, failure and indeterminate at the EOT (micro-ITT and ME populations) and PTE Visits (ME population, by definition subjects in the ME population cannot have an indeterminate response) will be

determined by treatment group. Exact 95% CIs will be determined for the point estimates of the overall success rates in each treatment group.

The number and percentage of subjects with an Investigator's assessment of clinical success, clinical failure and indeterminate response at the EOT, PTE and Final Follow-up Visits (ITT, micro-ITT, CE and ME populations; by definition subjects in the CE and ME populations cannot have an indeterminate response) will be determined by treatment group. Exact 95% CIs will be determined for the point estimates of the clinical success rates in each treatment group.

The number and percentage of subjects with a per-subject microbiologic response of success, failure and indeterminate response at the EOT and PTE Visits (micro-ITT and ME populations; by definition subjects in the ME population cannot have an indeterminate response) will be determined by treatment group. Exact 95% CIs will be determined for the point estimates of the microbiologic success rates in each treatment group.

Overall success, clinical success and per-pathogen microbiologic eradication at the PTE visit will be presented by pathogen and by pathogen and MIC for the micro-ITT and ME populations.

12.7 Interim Analysis

This is an adaptive dose-response finding study. Initially, allocation to treatment arms will be equal between treatment arms. During the course of the study, Bayesian analysis will be used to adaptively allocate new subjects to one of the treatment arms, conditional on the availability of primary efficacy endpoint data (overall response comprised of clinical and microbiologic response). When there is sufficient information available about the dose-response, results from the Bayesian analysis will be reviewed by a DMC to determine if enrollment in any omadacycline treatment group(s) should be initiated, stopped, or modified. Modifications to omadacycline treatment groups may also be based on safety and tolerability. It is possible that not all treatment arms will be enrolling subjects at the same time. Arms may be dropped based on the Bayesian analysis or initiated based on the Bayesian analysis of the ongoing treatment arms. There will always be at least one omadacycline arm and the levofloxacin arm open.

Modifications to the total number of subjects enrolled may also be based on the evaluability rate for the micro-ITT population.

Bayesian analyses will be conducted after efficacy data (overall response at PTE) are available for approximately 40, 80 and 100 subjects in the micro-ITT population in order to:

- Determine omadacycline treatment group(s) that can be initiated or dropped from the trial, or
- Modify the randomization ratios among the treatment groups to improve the precision of the selected dose groups comparison of overall success to that of the levofloxacin group

Additional analyses may be carried out for the same purposes. Response criteria are targeted towards estimating the probability that the overall success rate (proportion of subjects) for each omadacycline treatment group is within 10% of that of the levofloxacin group. If at the interim analyses, that probability falls below 30% for a particular treatment group, recruitment for that treatment group may be stopped or curtailed. If that probability exceeds 70% for a particular treatment group, recruitment for that treatment group may be stopped or increased to improve the precision of the estimate.

Concurrent bacteremia are higher among adults >65 years of age.[11] After approximately 100 subjects have been enrolled, the inclusion of females >65 years of age may be allowed based on review of interim analysis.

12.8 Data Monitoring Committee

A DMC will provide ongoing monitoring of data. The charter for the DMC will clearly outline membership, all roles, responsibilities, and decision-making criteria. This will include a detailed description of the manner in which security and blinding of the data for the study management team will be maintained, in addition to the procedures that ensure the independence and objectivity of the DMC's activities. As the DMC will be reviewing data for this study, it may require reports indicating treatment assignment to assist in clinical interpretation of its findings. Therefore, the DMC charter will provide a detailed explanation of the processes by which the DMC will obtain the information necessary for its operation that will not prejudice or create any potential source of bias in the conduct of the study.

13 ADMINISTRATIVE CONSIDERATIONS

13.1 Investigators and Study Administrative Structure

The investigator will permit study-related monitoring, audits, IRB/IEC/REB review, and regulatory inspections by providing direct access to source data and documents.

All information will be recorded on source documents. All required data will be recorded in the eCRFs.

If an investigator retires, relocates, or otherwise withdraws from conducting the study, the investigator must notify the sponsor to agree upon an acceptable storage solution. Regulatory agencies will be notified with the appropriate documentation.

An updated form 1572 will be filed with the sponsor for any changes in the study personnel reported in the current form 1572.

13.2 Institutional Review Board or Independent Ethics Committee Approval

The protocol and the proposed ICF must be reviewed and approved by a properly constituted IRB/IEC/REB before study start. A signed and dated statement that the protocol and ICF have been approved by the IRB/IEC/REB must be given to the sponsor before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to the sponsor, monitors, auditors, designated agents of the sponsor, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform the sponsor immediately that this request has been made.

13.3 Ethical Conduct of the Study

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC, US 21 Code of Federal Regulations (CFR), and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

13.4 Patient Information and Consent

The investigator will provide for the protection of the subjects by following all applicable regulations. These regulations are available upon request from the sponsor. The ICF must be reviewed by the sponsor and approved by the IRB/IEC/REB.

Before any procedures specified in the protocol are performed, a subject must:

- Be informed of all pertinent aspects of the study and all elements of informed consent;

- Be given time to ask questions and time to consider the decision to participate;
- Voluntarily agree to participate in the study;
- Sign and date an IRB/IEC/REB-approved ICF.

13.5 Direct Access, Data Handling, and Record Keeping

13.5.1 Investigator

The investigator will permit study-related monitoring, audits, IRB/IEC/REB review, and regulatory inspections by providing direct access to source data and documents.

All information will be recorded on source documents. All required data will be recorded in the eCRFs.

If an investigator retires, relocates, or otherwise withdraws from conducting the study, the investigator must notify the sponsor to agree upon an acceptable storage solution. Regulatory agencies will be notified with the appropriate documentation.

An updated form 1572 will be filed with the sponsor for any changes in the study personnel reported in the current form 1572.

13.5.2 Sponsor

The data is entered into an electronic database via eCRFs. The Sponsor Medical Monitor reviews the data for safety information. The data is reviewed for completeness and logical consistency. Automated validation checks identify missing data, out-of-range data, and other data inconsistencies. The central safety and microbiology data will be processed electronically. Requests for data clarification are forwarded to the investigative site for resolution.

13.6 Protocol Adherence

13.6.1 Violations/Deviations

Investigators will agree to apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact the sponsor or its agents to request approval of a prospective protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the sponsor and approved by the IRB/IEC/REB, it cannot be implemented. All significant protocol deviations will be recorded and reported in the Clinical Study Report (CSR).

13.6.2 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the sponsor, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for subject safety may be implemented

prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the sponsor should be notified of this action and the IRB/IEC/REB at the study site should be informed within 10 working days.

13.7 Subject Injury

In general, subject to specific provisions in the clinical study agreement (CSA), if a subject is injured as a direct result of a test article, the sponsor will pay for reasonable and necessary medical treatment for the injury, to the extent that such expenses are not covered by the subject's medical insurance, a government program, or other responsible third party. If laws or regulations of the locality in which the study is taking place require additional payment of expenses, the sponsor shall comply with such laws or regulations. Where applicable, the sponsor has taken specific national insurance.

13.8 Pre-Study Documentation

The investigator must provide the sponsor with the following documents before enrolling any subjects:

- Completed and signed form 1572 or equivalent
- All applicable country-specific regulatory forms
- Current signed and dated curricula vitae for the investigator, sub-investigators, and other individuals having significant investigator responsibility who are listed on the form 1572 or equivalent, or the clinical study information form
- Copy of the IRB/IEC/REB approval letter for the protocol and informed consent. All advertising, recruitment, and other written information provided to the subject must be approved by the IRB/IEC/REB. Written assurance of continuing approval (at least annually) as well as a copy of the annual progress report submitted to the IRB/IEC/REB must also be provided to the sponsor.
- Copy of the IRB/IEC/REB-approved informed consent document to be used
- Where applicable, a list of the IRB/IEC/REB members and their qualifications, and a description of the committee's working procedure
- Copy of the protocol sign-off page signed by the investigator
- Fully executed CSA
- Where applicable, a financial disclosure form
- A written document containing the name, location, certification number, and date of certification of the laboratories to be used for laboratory assays and those of other facilities conducting tests. This document should be returned along with the statement of investigator form. The sponsor must be notified if the laboratory is changed or if any additional laboratory is to be used.

- List of normal laboratory values and units of measure for all laboratory tests required by the protocol. This is required for each laboratory to be used during the study. The sponsor must be notified if normal values or units of measurement change.

13.9 Retention of Data

The investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including but not limited to those defined by GCP as essential, for the longer of: (a) 2 years after the last marketing authorization for the investigational test article has been approved or the sponsor has discontinued its research with respect to such investigational test article or (b) such longer period as required by applicable global regulatory requirements. At the end of such period, the investigator shall notify the sponsor in writing of its intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

13.10 Publication and Disclosure Policy

The sponsor assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report, the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

Upon completion of the study, the investigator may publish the results in recognized (refereed) scientific journals subject to the provisions of the CSA. Unless otherwise specified in the CSA, the following process shall occur:

The institution and Principal Investigator (PI) shall not publish or present data from an individual study center until the complete multi-center study has been presented in full or for 2 years after the termination of the multi-center study, whichever occurs first. Subsequent publications must refer to the multi-center findings. Thereafter, if the PI expects to participate in the publication of data generated from this site, the institution and PI shall submit reports, abstracts, manuscripts, and/or other presentation materials to the sponsor for review before submission for publication or presentation. The sponsor shall have 60 days to respond with any requested revisions, including, without limitation, the deletion of confidential information. The PI shall act in good faith upon requested revisions, except that the PI shall delete any confidential information from such proposed publication. The PI shall delay submission of such publication or presentation materials for up to an additional 90 days in order to have a patent application(s) filed.

14 REFERENCE LIST

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Appendix 1 Schedule of Events

Study Phase	Screening[a]	Treatment Phase											Follow-up Phase	
Evaluation		Day 1[b]	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7[c]	Day 8, 9	Day 10[c]	Day 11, 12, 13	EOT[d]	PTE[t] Day 21	Final Follow-up[u] Day 28
								Only performed if EOT visit does not coincide with day of last dose OR treatment extends beyond 7 days					
Signed Informed Consent[e]	X													
Modified Patient symptom assessment questionnaire (mPSAQ) [f]	X		X----------									X	X	X
Demographics	X													
Medical History	X													
Prior & Concomitant Medications[g]	X	X----------										X		
Clean-catch, midstream urine sample for:														
Dipstick for leukocyte esterase and nitrites[h] with optional urinalysis for WBC counts	X		X	X	X	X	X	X	X	X	X	X	X	X[u]
Urine culture[h]	X		X	X	X	X	X	X	X	X	X	X	X	X[u]
Physical examination[i]	X											X	X	
Vital signs														
Body weight and height[v]	X											X	X	
Body temperature	X	X	X	X	X	X	X	X	X	X	X	X	X	X[u]
Blood pressure	X	X[j]		X				X		X		X	X	X[u]
Heart rate	X	X[j]		X				X		X		X	X	X[u]
12-lead ECG[k]	X													
Hematology and coagulation	X			X								X	X	
Serum chemistry	X			X								X	X	
Local urine or serum pregnancy test[l]	X													
Central serum pregnancy test[m]	X											X	X	
Blood culture[n]	X	As Required[n]												
Adverse Events[o]	X	X----------										X		

Study Phase	Screening[a]	Treatment Phase											Follow-up Phase	
Evaluation		Day 1[b]	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7[c]	Day 8, 9	Day 10[c]	Day 11, 12, 13	EOT[d]	PTE[t] Day 21	Final Follow-up[u] Day 28
								Only performed if EOT visit does not coincide with day of last dose OR treatment extends beyond 7 days						
Review of Inclusion and Exclusion criteria - Randomization (if Eligible)	X	X												
Test Article Administration and accountability[p]		X	X	X	X	X	X	X	X	X	X	X		
PK blood collection[r]				X				X[r]						
PK urine collection				X			X							
Assessment for po switch[q]			X	X	X	X	X	X	X	X	X			
Assessment of need to continue therapy								X	X	X	X			
Investigator's Assessment of Clinical Response												X	X	X

AE = adverse event, BP = blood pressure, CFU = colony forming unit, ECG = electrocardiogram, eCRF = electronic case report form, EOT = end of treatment, ICF = informed consent form, PK = pharmacokinetics, PTE = post-therapy evaluation, SAE = serious adverse event, UTI = urinary tract infection, WBC = white blood cell.

[a] Following the signing of an ICF, all screening evaluations should be completed within the 24 hours prior to randomization. The blood culture sample collection should be completed within 24 hours prior to the first dose of test article.

[b] Study Day 1 is the first day of test article administration.

[c] A Day 7 and 10 visits should be conducted for subjects with treatment extending beyond 7 or 10 days, unless this visit coincides with the EOT visit.

[d] To be conducted on the day of or within the 2 days following the last dose of test article. This evaluation should also be conducted for any prematurely withdrawn subject on the day treatment ends.

[e] Written and signed ICF must be obtained before any study-related assessment is performed.

[f] Subject assessment of symptoms severity will be collected daily through EOT, at PTE and at Final Follow-up.

[g] Treatments that have been administered within the 7 days prior to the date of signing the ICF or during the Screening phase will be recorded in the eCRF. All medications and significant non-drug therapies administered after the first dose of test article must be recorded in the eCRF.

[h] A clean-catch, midstream urine sample should be collected and immediately sent to the local microbiology laboratory for microscopic evaluation and culture. Quantitative urine culture by appropriate methods should be performed using a calibrated loop that would identify bacteria at a lower limit of 10^3 CFU/mL. WBC counts should be measured by microscopy from spun or unspun urine or dipstick analysis for leukocyte esterase and nitrites.

[i] A full physical examination will be completed at Screening, thereafter only changes from screening assessments should be recorded as AEs in the eCRFs.

[j] BP and heart rate should be measured within 30 min before, and approximately (± 15 minutes) 1 hour after and 3 hours after the completion of the doses on Day 1.

[k] A 12-lead ECG should be performed at Screening to confirm eligibility.

[l] All women will have a local urine or serum pregnancy test at Screening which results will be used to confirm eligibility.

[m] All women will have blood collected for a serum β-hCG pregnancy test at the Central Laboratory at the Screening, EOT and PTE visits.

Study Phase	Screening[a]	Treatment Phase											Follow-up Phase	
Evaluation		Day 1[b]	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7[c]	Day 8, 9	Day 10[c]	Day 11, 12, 13	EOT[d]	PTE[t] Day 21	Final Follow-up[u] Day 28
								Only performed if EOT visit does not coincide with day of last dose OR treatment extends beyond 7 days					

n If bacteria are isolated from baseline blood cultures, repeat blood cultures should be collected. If subsequent blood cultures are also positive, repeat the blood cultures as necessary until negative blood cultures are obtained.

o A subject's AEs and SAEs will be recorded and reported from signing of the ICF to the Final Follow-up assessment.

p Subjects should receive their first dose of test article within 4 hours after randomization. The total duration of test article therapy (iv plus po) for all subjects will be 7-10 days. The pharmacist or designee will be unblinded to prepare appropriate iv doses of the IxRS identified test article. An unblinded field monitor will perform drug accountability and review the pharmacist's records.

q Oral test article may be dispensed and reconciled by blinded or unblinded personnel. All oral doses should be taken in a fasted state (no food, antacids or multivitamins containing multivalent cations [eg, aluminum, magnesium, calcium, bismuth, iron, or zinc] or drink except water for at least 6 hours before dosing). Following oral doses, no food should be consumed for 2 hours and no dairy products, antacids or multivitamins containing multivalent cations should be consumed for 4 hours. For sites in which outpatient administration has been approved, subjects will be asked to return all unused po test article and packaging at each visit. and the EOT visit subjects will return any remaining unused po test article and site staff will perform accountability.

r PK blood collection will occur just prior to and 2-3 hours after doses on Day 3 and last day of test article. On days of PK collection, the date and time of last food intake prior to dosing will be collected.

s Starting on Day 2, subjects may be switched to po medication based on clinical stability and investigator discretion.

t A PTE will occur on Day 21 (± 2 days) for all subjects.

u The Final Follow-up may be performed via phone call. The visit should be in person if potential recurrence is known, so the procedures to be completed. If they are not known and the subject mentions it during the call, the subject must be asked to come to the clinic as soon as possible for an in person visit where the procedures will be conducted.

v Height should be collected only at screening.

Appendix 2 Equations and Conversion Factors

1. Cockcroft-Gault equation to calculate creatinine clearance (CrCl) (relevant to Exclusion criterion number 26):

$$\frac{(140\text{-age [yrs]}) * \text{weight (kg)} * (Z)}{\text{Cr (mg/dL)} * 72} \qquad Z = 0.85, \text{ if Female}$$

2. Corticosteroid conversions (relevant to Exclusion criterion number 19):

The following have equivalent glucocorticoid activity[a]	
Hydrocortisone	160 mg
Prednisone	**40 mg**
Prednisolone	40 mg
Methylprednisolone	32 mg
Triamcinolone	32 mg
Dexamethasone	6 mg

[a] Axelrod L. Glucocorticoid therapy. In: Jameson JL & De Groot LJ, eds. Endocrinology. 6th ed. Philadelphia, PA: Saunders; 2010:1840.

Appendix 3 Modified Patient Symptom Assessment Questionnaire (mPSAQ)

Pyelonephritis Symptoms	**Symptom Assessment** Please indicate whether you have had the symptom in the past 24 hours?	**Bothersome Assessment** If you have experienced the symptom in the past 24 hours, please indicate how bothersome they were?
Lower back pain or flank pain	No symptom Mild Moderate Severe	Not at all A little Moderately A lot
Chills, rigors or warmth	No symptom Mild Moderate Severe	Not at all A little Moderately A lot
Pain or uncomfortable pressure in the lower abdomen/pelvic area	No symptom Mild Moderate Severe	Not at all A little Moderately A lot
Pain or burning when passing urine	No symptom Mild Moderate Severe	Not at all A little Moderately A lot
Frequency of urination or going to the toilet very often	No symptom Mild Moderate Severe	Not at all A little Moderately A lot

Urgency of urination or a strong and uncontrollable urge to pass urine	No symptom Mild Moderate Severe	Not at all A little Moderately A lot

Appendix 4 Sponsor Signature

Study Title: A Randomized, Double-Blinded, Adaptive Phase 2 Study to Evaluate the Safety and Efficacy of IV or IV/PO Omadacycline and IV/PO Levofloxacin in the Treatment of Adults with Acute Pyelonephritis

Study Number: PTK0796-AP-17202

Final Date: 26 March 2018

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed: [redacted] Date: [redacted]

[redacted]

Paratek Pharmaceuticals, Inc

Appendix 5 Investigator's Signature

Study Title: A Randomized, Double-Blinded, Adaptive Phase 2 Study to Evaluate the Safety and Efficacy of IV or IV/PO Omadacycline and IV/PO Levofloxacin in the Treatment of Adults with Acute Pyelonephritis

Study Number: PTK0796-AP-17202

Final Date: 26 March 2018

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed:_____ Date:_____

Investigator Name:_____

Investigator Title:_____

Investigator Affiliation:_____

Investigator Address:_____

Investigator Phone Number:_____