Statistical Analysis Plan

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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
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Glossary of Abbreviations

Abbreviation	Definition
AE	Adverse event
AP	acute pyelonephritis
ATC	Anatomical Therapeutic Chemical Classification
BMI	Body Mass Index
CE	clinically evaluable
CFU	colony forming unit
CI	confidence interval
CN	clinically notable
CrCl	creatinine clearance
DMC	Data Monitoring Committee
DMID	Division of Microbiology and Infectious Diseases
eCRF	electronic case report form
EOT	end of treatment
FFU	final follow-up
ICF	informed consent form
ITT	intent-to-treat
iv	Intravenous(ly)
IxRS	Interactive Response System
LEV	levofloxacin
ME	microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
micro-ITT	microbiological intent to treat
mPSAQ	modified Patient Symptom Assessment Questionnaire
N	number of subjects
OMC	omadacycline
PK	pharmacokinetic
po	oral(ly)
PT	preferred term
PTE	Post Therapy Evaluation
QTc	QT, corrected

SAP	Statistical Analysis Plan
SD	standard deviation
SI	International System
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
UTI	urinary tract infection
WBC	white blood cell

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Paratek Pharma Protocol PTK0796-AP-17202 (A Randomized, Double-Blinded, Adaptive Phase 2 Study to Evaluate the Safety and Efficacy of intravenous (iv) or iv/po omadacycline and iv/po levofloxacin in the Treatment of Adults with Acute Pyelonephritis).

The reader of this SAP is encouraged to read the study protocol for details on the conduct of this study, the operational aspects of clinical assessments, and the timing for completing the participation of a patient in this study.

The SAP is intended to be in agreement with the protocol, especially with regards to the primary and all secondary endpoints and their respective analyses. However, the SAP may contain more details regarding these particular points of interest, or other types of analyses (e.g. other endpoints). When differences exist in descriptions or explanations provided in the study protocol and this SAP, the SAP prevails; the differences will be explained in the Clinical Study Report.

Methods of reporting of pharmacokinetic (PK) data are outside of scope of this SAP.

2 STUDY OBJECTIVES, ENDPOINTS, AND MEASURES

The primary objective of this study is to evaluate the efficacy of iv and iv to oral (iv/po) dosing regimens of omadacycline and levofloxacin in the treatment of adults with acute pyelonephritis (AP).

The efficacy endpoints include clinical response, microbiological response, and the composite of clinical and microbiological (overall) response, as measured by the number and percentage of subjects achieving success.

The efficacy outcomes are measured by the number and percentage of subjects with successes in the ITT, micro-ITT populations, and other populations of interest as appropriate.

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

Methods of reporting of PK data are outside of scope of this SAP.

3 STUDY DESIGN

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 (Table 1). 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. 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 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.

A study schedule of events is provided in Table 1 of the protocol.

For details regarding interim adaptive design refer to Section 3.4.

3.1 Sample Size Considerations

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 of the

composite endpoint 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.

The decisions affecting changes of randomization to treatment groups, hence affecting total sample size, will be based on the recommendation of the Data Monitoring Committee (DMC) at interim analyses in a blinded to study team manner based on safety, and tolerability of treatments. Details are documented in the Data Monitoring Committee Charter for Phase II Trial for PTK0796-AP-17202.

3.2 Data Monitoring Committee

A DMC will provide ongoing monitoring of data. The charter for the DMC will outline membership, all roles, responsibilities, and decision-making criteria.[1] 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.

3.3 Randomization and Blinding

Initially, subjects will be randomized 1:1:1:1:1 to one 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]
Group 1	omadacycline	200 mg iv	200 mg iv	200 mg iv
Group 2	omadacycline	200 mg iv	100 mg iv	100 mg iv
Group 3	omadacycline	200 mg iv	300 mg po or 100 mg iv	300 mg po or 100 mg iv
Group 4	omadacycline	200 mg iv	450 mg po or 100 mg iv	450 mg po or 100 mg iv
Group 5	levofloxacin	750 mg iv	750 mg po or 750 mg iv	750 mg po or 750 mg iv

iv = intravenous, po = per oral;
Note: dosing in all treatment groups is once-per-day:[a]The total duration of treatment for subjects is 7-10 days, up to 14 days of treatment for subjects with bacteremia.

All eligible subjects will be randomized via an Interactive Response System (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.

It is possible that not all treatment arms will be enrolling subjects at the same time. Arms may be dropped based on DMC recommendations. 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 on DMC recommendation and will be incorporated into the IxRS system.

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 electronic case report form (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.

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 and at the conclusion of the study.

3.4 Interim Analyses

This is an adaptive dose-response finding study.

Interim analyses will be conducted when data are available for approximately 40, 80 and 100 subjects in order for DMC to provide recommendation on the following:

- Omadacycline treatment group(s) that can be initiated or dropped from the trial
- Modification of the randomization ratios among the treatment groups
- Need for extension of the trial beyond 200 enrolled subjects to provide more precise estimates of the efficacy outcome

To protect the integrity of the clinical study, neither the actual randomization schedule nor the data from the data reviews will be made available to the Sponsor Study team or the Study Reporting team. Data for the unblinded data reviews by the DMC will only be released to the DMC, the independent reporting statistician, and the DMC Reporting team. For details refer to Data Monitoring Committee Charter for Phase II Trial for PTK0796-AP-17202.

Decisions on randomization re-allocation and/or dropping dose groups will be based primarily on safety and tolerability. Efficacy will only be considered for dose-reallocation if the DMC deems the response rates as too low to proceed with enrollment. Efficacy is not pre-planned with statistical decision criteria due to high variability in small sample sizes.

Based on the results of analyses during the interim reviews, the DMC may recommend continuation of enrollment above 200 subjects. The purpose of an increase in sample size, among other reasons, may be due to the need to provide more precise estimates of the efficacy outcome or for further exploration of safety and tolerability data.

3.5 Final Analyses and Reporting

All analyses identified in this SAP will be performed according to the study protocol, ie, after the end of study as defined in the study protocol.

This SAP and any corresponding amendments will be approved before database lock. The randomization codes will not be unblinded until this SAP has been approved and issued.

4 ANALYSIS POPULATIONS

The following subject analysis populations have been defined.

4.1 Intent-to-treat Population

The intent-to-treat (ITT) population will consist of all randomized subjects regardless of whether or not the subject received test article.

A subject is considered randomized when the IxRS provides the test article assignment by providing the kit number (i.e., completes a randomization transaction). Subjects in this population will be summarized according to randomized test article assignment.

4.2 Safety Population

The Safety population will consist of all randomized subjects who receive any amount of test article. All safety analyses will be conducted in this population; subjects will be summarized according to actual test article received.

4.3 Microbiological ITT Population

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 unit (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.

Rules for Sponsor's determination of qualifying pathogens is described in the Pathogen and CE.

4.4 Clinically Evaluable Population

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

Inclusion into the CE populations will be determined programmatically based on the data on the eCRF and a manual review by the Sponsor as necessary prior to unblinding. Details on allocation to each CE population are described in the Pathogen and CE.

Since patient count may differ depending on timepoint, CE populations will be defined by milestone visit (CE-EOT, CE-PTE and CE-FFU). To be included in the populations, subjects must meet all criteria defined below:

1. Qualifying infection:
   Inclusion Criterion #2: Females age 18 years or older

Inclusion Criterion #3: Clinical signs and symptoms of acute uncomplicated pyelonephritis with onset or worsening within 96 hours prior to randomization.

Inclusion Criterion #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).

2. Assessment of Outcome for CE population:

Subjects must meet all of the following to be included in the CE populations:

- Subject did not meet one of the exclusion criteria 6 through 15 of the protocol (Baseline event exclusion)
- Received the randomized test article and was at least 80% compliant with the dosing regimen (Compliance to test article intake).
- Study personnel involved in the assessment of efficacy remained blinded to study treatment, unless a treatment limiting AE occurred which required emergency unblinding.

  In addition, for each endpoint the following needs to be satisfied, as appropriate:

  a. For the CE-EOT population:

     i. Completed the investigator's assessment of clinical response (i.e., was not deemed an indeterminate outcome) at the EOT visit, and

     ii. The EOT visit occurred on the day of, or within ± 2 days, following the last dose of test article (3 days window).

  b. For the CE-PTE population:

     i. The Overall Clinical Response (based on the investigator's assessment) at the PTE Visit is not Indeterminate (see Table 5).

     ii. The PTE Visit occurred Day 21 (± 2 days), unless the subject was considered to be a Clinical Failure based on the investigator's assessment at the EOT visit.

  c. For the CE-FFU population:

     i. The overall Clinical Response (based on the investigator's assessment) at the Final Follow-up (FFU) Visit is not Indeterminate.

     ii. The FFU Visit occurred on Day 28 (± 2 days) from the first dose of test article), unless the subject was considered to be a Clinical Failure based on the investigator's assessment at the PTE visit.

3. Other Evaluability Criteria

   a. Prior Antibiotic Therapy

   Exclusion Criterion #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.] Subjects who meet exclusion criteria #5 will be excluded from the CE populations.

b. Concomitant Antibiotic Therapy

Subjects who receive any systemic concomitant antibiotic therapy from the start of administration of the first dose of test article through the EOT visit (CE-EOT population), PTE visit (CE-PTE population) or FFU visit (CE-FFU population) that is potentially effective against the baseline pathogen, will be excluded from the CE population. If no pathogen is isolated and the systemic concomitant antibiotic is effective against Gram-negative uropathogens, the subject will be excluded from the respective CE population. Subjects who are a clinical failure on the particular visit and received non-study antibiotics for insufficient therapeutic effect of the test article, will not be excluded from the CE populations. Subjects who receive a systemic concomitant antibiotic that is not potentially effective against the baseline pathogen will be included in the CE populations.

c. Evaluable Success and Failure

Evaluable success: The subject received at least 3 doses of active test article and the investigator classifies the subject as a clinical success at the EOT visit (CE EOT population) or the overall clinical response (based on the investigator's assessment) at the PTE visit (CE-PTE population) or the overall clinical response (based on the investigator's assessment) at the FFU visit (CE-FFU population) is clinical success/cure.

Evaluable failure: The subject received at least 2 doses of active test article and the investigator classifies the subject as a clinical failure at the EOT visit (CE EOT population) or the overall clinical response (based on the investigator's assessment) at the PTE Visit (CE-PTE population) or the overall clinical response (based on the investigator's assessment) at the FFU visit (CE-FFU population) is clinical failure/relapse.

4.5 Microbiologically Evaluable Populations

The microbiologically evaluable (ME) population will include subjects in the CE and micro-ITT populations who have both 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).

Since patient count may differ depending on timepoint, ME populations will be defined by milestone visit (ME-EOT and ME-PTE).

The ME populations consist of subjects in the micro-ITT population and the CE-EOT and CE-PTE populations, respectively who also have:

- A clean-catch urine specimen at the EOT and PTE visits, and
- Interpretable urine culture results at the EOT and PTE visits.

Subjects with an unfavorable microbiological outcome at EOT will be included in the ME-PTE population, regardless of whether they provide a urine culture at the PTE visit.

An interpretable post-baseline urine culture is one that has a clearly identified pathogen or one where the baseline pathogen(s) can be excluded (i.e., there is no growth of the baseline pathogen). A urine culture is considered uninterpretable if more than two bacterial isolates are identified, unless any of the following is observed:

- There is $<10^4$ CFU/mL of the baseline pathogen(s), indicating eradication.
- There is $\geq 10^4$ CFU/mL of the baseline pathogen(s), indicating persistence

At any visit after Screening, a pathogen the same species as the Baseline pathogen with a CFU count of $\geq 1 \times 10^4$ CFU/mL should be considered a persisting pathogen.

At any visit after Screening, any culture with a CFU count of $< 10^4$ CFU/mL should be considered a negative culture.

5 OVERALL STATISTICAL CONSIDERATIONS

5.1 General

All analyses will use SAS version 9.4 or higher. Results will be reported by treatment group, unless otherwise specified.

Unless otherwise stated, listings corresponding to all summaries will be provided. Generally, listings will be provided for all randomized patients, however sometimes they may be limited to a smaller set depending on parameter (e.g. compliance to a test article will be limited to safety population).

Unless otherwise noted, categorical variables will be summarized using counts and percentages. Percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places and percentages will not be displayed for zero counts.

Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum and maximum.

5.2 Definitions

In Table 2 general definitions are provided used in the statistical analysis.

Table 2 General Definitions

Variable	Definition
Baseline	Unless otherwise stated, baseline is defined as the value closest to but prior to the initiation of test article administration.
Change from baseline	Change from baseline will be defined as the post-baseline value minus the baseline value (on a subject level). Change from baseline will only be calculated for subjects who have both baseline and at least one post-baseline value for any parameter.
Duration Variables	Duration variables will be calculated using the general formula: Duration (days) = End date - Start date + 1 If applicable, where time is collected: Duration (hh:mm) = End datetime - Start datetime
Calculated Creatinine Clearance (mL /min), Cockcroft-Gault equation	$\frac{(140 - \text{age [yrs]}) * \text{weight [kg]} * Z}{\text{Creatinine [mg/dL]} * 72}$ Z = 0.85 for Female subjects
Body Mass Index (BMI)	BMI = Weight (kg) / Height $(m)^2$

5.3 Missing Data and Data Imputation Methods

Missing data will be handled as outlined below

1. Adverse Events and Safety Data:

- All missing and partial dates for AEs will be queried for a value. If no value can be obtained, substitutions will be made as detailed in Section 8.4. These substitutions will be used in calculations; however, the actual value recorded on the eCRF will be used in all listings.
- If the time of the first dose of test article is missing, it will be imputed with time of randomization + 1 minute. If time is missing for other doses it will be imputed with time of previous dose + 12 h.
- An AE is considered treatment emergent if the AE start date and time is on or after the start date and time of the first dose of test article.
- If time of the AE is missing and it occurred on the same date as the first dose of test article, the AE will be defined as treatment emergent. If the start date of the AE is partial or missing and it cannot be determined if the AE occurred prior to or after the first dose of test article, the AE should be defined as treatment emergent. Appendix 4 Adverse Event Start/Stop Date Imputation provides imputation for partial or missing date information. For AE listings, all dates and times will be displayed as reported on the Case Report Forms.
- If no value can be obtained for all other times for events and assessments occurring after randomization, the time will not be imputed but will remain missing.
- The severity and causality assessment for AEs cannot be missing. Missing data will be queried for a value. The highest severity and most related causality should be used if query is missing. If query will return missing, then the highest severity and most related causality will be used for the purpose of summaries.
- If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table (e.g., a character string is reported for a parameter of the numerical type), a coded value must be appropriately determined and used in the statistical analyses. A value that is in the lower limit of the normal range will be calculated as 99.99% of the value if it is reported as "<" (e.g. <5 will be converted to 5*0.99=4.9995). A value that is in the upper limit of the normal range will be converted to 100.01% if it is reported as ">" (e.g.>7 will be converted to 7*1.001=7.007). However, the actual values as reported in the database will be presented in data listings.
- Prior and Concomitant Medication start date imputation will be imputed according to table in Appendix 4 Concomitant Medication Start Date Imputation.

2. Efficacy Data

- Analysis of efficacy data will be based on the available data, unless otherwise stated.
- Missing data for clinical and microbiological outcomes is denoted "indeterminate", unless any of the below rules apply.
- Missing microbiological outcomes at EOT will be imputed by last day of test article intake.
- The Overall Clinical Response at PTE and FFU visits are derived based on the "worst case scenario" to accommodate for missing visit assessments and intercurrent events (eg rescue

medication at EOT visit). Similar imputations were applied to microbiological response endpoints. Details are described in Section 7.

- mPSAQ data for bothersome score will be imputed with score of 0 for each question for which severity is answered "Did not have".

5.4 Visit Windows

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. A tabular summary of the visit schedule is displayed in Table 3.

Table 3 Scheduled Study Visits

Study Visit	Study Day	Notes
Baseline	Day -1 or Day 1	Except where indicated, last measurement prior to the first dose of test article. Screening assessments are to be taken within 24 hours prior to randomization if no test article is taken, the date and time of randomization is used in place of randomization date.
On Treatment (note: analysis visit will be each Study Day)	Day 1 to Day 7 Day 8 to Day 14 (latest on treatment Day)	As entered in the eCRF for these visits
EOT	Not later than Day 16	Within 2 days following the last dose of test article
PTE	Day 21	On Day 21 (± 2 days) after the subject's first day of test article
Final Follow-up (FU)	Day 28	On Day 28 (± 2 days) after the subject's first day of test article

Study Day is calculated relative to the first dose of test article (Day 1); there is no Day 0 – the day prior to the first dose of test article is Day -1. If no test article is taken, study day is calculated relative to the date of randomization.

For efficacy outcomes, the data collected at the EOT, PTE and FFU visits, regardless of when these occur will be utilized in the analysis in the ITT and micro-ITT population. The CE and ME populations exclusions due to windowing are outlined in Sections 4.4 and 4.5.

For each safety outcome and UTISA data, analyses will utilize assessments occurring during the scheduled visit windows (provided in Table 3). Thus, if a subject has a visit outside the scheduled visit window, for example, a PTE Visit occurred 20 days after the subject's first investigational product dose, the assessment will not be summarized with the PTE Visit but will be considered an unscheduled assessment. If a subject does not have an assessment at a scheduled visit and an unscheduled assessment was taken within the window for the time point (for example, 21 days (± 2 days) after the subject's first day of therapy for PTE), these assessments will be summarized in the by time point analyses. If more than one measurement is

taken during the visit window, the value taken on the scheduled visit will be utilized or if no scheduled visit was done, the first (earliest) measurement in the visit window will be used. If more than one measurement is taken on the same day, the assessment closest to the start of the dose will be used for on treatment values and the last measurement on the day will be used for post-treatment values. For worst overall post-baseline analyses, all assessments including those obtained from unscheduled visits will be included.

5.5 Multiple comparison and multiplicity

No adjustment for multiplicity will be applied to any endpoints, thus any inferential statistics will be nominal.

6 POPULATION SUMMARIES

Unless otherwise stated, listings corresponding to all summaries in this section will be provided for all randomized subjects (ITT analysis population).

6.1 Subject Disposition

The number of subjects included in each of the analysis populations defined in this SAP and the reasons for exclusion will be summarized by treatment group. A listing will be provided to indicate each subject's inclusion/exclusion from the populations, and the reason for exclusion from a population will be presented.

A list of randomized subjects who did not meet all inclusion/exclusion criteria, and which criteria were not met will be presented.

The number and percentage of subjects completing the study (completing the EOT, PTE and FFU visits, as reported on CRF), as well as the completion status of EOT, PTE, and FFU visits will be presented. Reasons for not completing the study and for missing visits, as recorded on the eCRF, will be summarized (number and percentage) by treatment group for ITT, micro-ITT, CE and PTE populations.

The number and percentage of subjects completing and prematurely discontinuing test article and the reasons for discontinuation will be presented by treatment group. A listing of all subjects who prematurely discontinued from test article or who did not complete the study will be presented, along with the primary reason for discontinuation of test article or not completing the study.

The number of screen failures and reason for screen failure will be presented overall. For randomized subjects, a listing will be provided that indicates the date and time of randomization, randomization number, randomized treatment assignment, drug unit identifications, and corresponding drug codes.

6.2 Demographic and Baseline Characteristics

Demographic characteristics will be summarized in ITT, micro-ITT, CE-PTE, and ME-PTE populations analysis sets defined in this SAP. The summary table will include age, race, and ethnicity, along with baseline characteristics for height, weight, body mass index (BMI), number of prior urinary tract infections (UTIs) (lifetime), and renal function. Age will be summarized as a continuous variable and as categorical, based on the following groups: 18 to 45 years, > 45 to 65 years, > 65 years.

Renal function will be categorized as normal (creatinine clearance [CrCl] > 89 mL/min), mild renal impairment (CrCl > 60 to 89 mL/min), moderate renal impairment (CrCl 30 to 60 mL/min) and severe renal impairment (CrCl < 30 mL/min). Creatinine clearance will be calculated from the local laboratory data and will be determined from the Cockcroft-Gault equation, for female subjects:

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

Gender will not be included in the summary, as all subjects enrolled in this study will be female, per inclusion criteria.

General medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT).

Results of the Modified Patient Symptom Assessment Questionnaire (mPSAQ) will be summarized as the number and percentage of subjects responding to each item, including individual severity symptom scores, individual bothersome scores, and overall severity and bothersome score.

6.3 Baseline Microbiology

6.3.1 Urine

The microbiological assessment of the urine culture by the local laboratory will be summarized by treatment group for the ITT and micro-ITT populations.

The number of subjects with local urine culture performed, number of subjects with a clean catch sample, number of subjects with urine culture growth and number of isolates per subject where CFU count $\geq 10^5$ CFU/mL.

Each isolate identified will also be reported and will include the CFU counts as recorded on the CRF ($<10^3$ CFU/mL, $10^3 \leq$ and $<10^4$ CFU/mL, $10^4 \leq$ and $<10^5$ CFU/mL, and $\geq 10^5$ CFU/mL).

Test article received disk diffusion value (mm) to baseline pathogen will be provided for micro-ITT population.

All of the below reports will be provided for micro-ITT and ME populations.

- The number and percentage of subjects with a positive urine culture by pathogenic organism will be provided for the micro-ITT and ME populations.
- The number and percentage of subjects with a Gram-positive organism (aerobes and anaerobes) and with a Gram-negative organism (aerobes and anaerobes) will be presented by genus and species.
- The number and percentage for minimum inhibitory concentration (MIC) data will be provided as:
  - The MIC distribution to omadacycline and levofloxacin, across treatment groups
  - The MIC distribution to the test article received, by treatment group
  - MIC summary statistics (ie, range, MIC_{50}, and MIC_{90}) to the test article received. The MIC range will be provided for all baseline pathogens. The MIC_{50} and MIC_{90} will be

provided only for those pathogens isolated at least 10 times in a treatment group. MIC_{50} and MIC_{90} values are defined as the lowest concentration of the antibiotic at which 50% and 90% of the isolates were inhibited.

- MIC summary statistics (ie, range, MIC_{50}, and MIC_{90}) to the test article received for each pathogen at baseline.

A listing will be provided that includes for each subject all baseline and post-baseline isolates identified by Genus and species from the local and central urine culture including the CFU count and whether or not the isolate is a pathogen.

6.3.2 Blood

Blood culture samples are taken at screening and as required during treatment. If bacteria are isolated from baseline blood cultures, repeated blood cultures will be collected. If subsequent blood cultures were also positive, repeated blood cultures as necessary were taken until negative blood cultures were obtained.

The pathogenic organisms identified from the baseline blood culture will be presented by genus and species.

The number and percentage of subjects with a positive blood culture by pathogenic organism will be provided for the micro-ITT and ME populations. The number and percentage of subjects with a Gram-positive organism (aerobes and anaerobes) and with a Gram-negative organism (aerobes and anaerobes) will be presented by genus and species.

A listing will be provided that includes all baseline and post-baseline isolates obtained from the blood.

Similar tables providing the MIC data for the pathogens identified from the baseline blood cultures will be provided for the micro-ITT and ME populations as described for the urine cultures in Section 6.3.1 above.

6.4 General Medical History, AP, and UTI History

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 informed consent form (ICF) will be recorded.

In addition, subject history of prior UTI infection and AP will be captured, where possible, diagnoses are to be recorded. Of note, any event or change in the subject's condition or health status occurring after signing the ICF will be reported as an AE. All medical history will be coded using the MedDRA.

The incidence of medical history abnormalities will be summarized using descriptive statistics by SOC and PT. Patients are counted only once in each PT and SOC category. Summaries will be presented by treatment group and for all patients.

6.5 Prior Medications

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.

If a medication is taken prior to the first dose of test article or if their start date is unknown, then it will be summarized as a prior medication. Medications are considered concomitant if taken on or after the first dose of test article, or if their stop date is unknown or marked as continuing. Thus, in cases where a medication starts prior to the first dose, and continues throughout the treatment period, the medication will be summarized as both prior and concomitant.

Summary of prior antiemetic medication will also be provided for the ITT population.

Summaries of prior antibiotic use will be summarized for ITT and micro-ITT populations.

6.6 Protocol Deviations

Deviations will be reviewed in a blinded manner by the sponsor and categorized into general categories (eg. inclusion/exclusion criteria). The sponsor will also categorize the protocol deviations as major and minor. Review of deviations will be conducted and finalized prior to unblinding the database.

A major deviation is defined as one that potentially affects the efficacy and/or safety analyses.

The number and percentage of subjects with at least one major protocol deviation or with at least one minor protocol deviation will be summarized for the ITT and micro-ITT population. The summaries of major deviations will also be presented by category.

A listing of all protocol deviations will be provided.

6.7 Other Baseline Summaries

Abnormal laboratory results and abnormal vital signs at baseline will be reported.

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.

Significant and relevant findings that are present prior to the start of test article must be included in the subject's eCRF. Relevant findings (except for signs and symptoms related to the index AP) 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.

Subject listings of all physical examination results by body system will be provided.

7 EFFICACY ENDPOINTS AND ANALYSES

7.1 Efficacy Endpoints

In this phase 2 study all efficacy endpoints are exploratory and are analyzed as per Table 4 below.

Table 4 Efficacy Endpoints

Endpoint	Visit	Population
(Overall) Investigator's assessment of clinical response	PTE/EOT/FFU	ITT micro-ITT CE, ME
(Overall) Microbiologic response	PTE/EOT	micro-ITT ME
[redacted]		
Modified Patient Symptom Assessment Questionnaire (mPSAQ)	By visit/day	ITT, micro-ITT, CE-EOT, CE-PTE
[redacted]		

7.1.1 Investigator's assessment of clinical response

7.1.1.1 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.

7.1.1.2 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 occurred at or before the PTE visit.
- **Indeterminate**: PTE visit not completed.

Overall Clinical Response at PTE (based on the investigator's assessment) is determined as follows (Table 5) from the investigator's assessments at the EOT and PTE Visits:

Table 5 Investigator's Assessment of Clinical Response at PTE Visit

EOT Visit	PTE Visit	Overall Clinical Response at PTE Visit
Success	Success	Success
Success	Failure	Failure
Success	Indeterminate	Indeterminate
Failure	Success	Failure
Failure	Failure	Failure
Failure	Indeterminate	Failure
Indeterminate	Success	Indeterminate
Indeterminate	Failure	Failure
Indeterminate	Indeterminate	Indeterminate

EOT = end of treatment; PTE = post-therapy evaluation.

The derived Overall Investigator's Clinical Response is based on the "worst case scenario" to accommodate for missing visit assessment and intercurrent events (eg rescue medication at EOT visit). For the ITT and micro-ITT populations, the proportion of subjects with a Clinical Success is defined using the following formula (missing information at the PTE visit will be counted as Indeterminate):

$$\frac{\textit{\# of subjects with Clinical Success}}{\textit{(\# of subjects with Clinical Success + \# of subjects with Clinical Failure + \# of subjects with Indeterminate response)}}$$

By definition, subjects in the CE-PTE population cannot have an Indeterminate response. Thus, for the CE population, the proportion of subjects with a Clinical Success is defined using the following formula:

$$\frac{\#\text{ of subjects with Clinical Success}}{(\#\text{ of subjects with Clinical Success} + \#\text{ of subjects with Clinical Failure})}$$

7.1.1.3 Investigator's Assessment of Clinical Response at FFU

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 or failure at PTE visit.
- **Indeterminate:** Final Follow-up visit not completed. If FFU visit assessment is not within the visit window the EOT response is defined as indeterminate.

Overall Response (based on the investigator's assessment) is determined as defined in Table 6.

Table 6 Investigator's Assessment of Clinical Response at FFU Visit

Overall Clinical Response at PTE Visit	Clinical Response at FFU Visit	Overall Clinical Response at FFU Visit
Success	Clinical Cure	Clinical Success
Success	Clinical Failure	Clinical Failure
Success	Indeterminate	Indeterminate
Success	Relapse	Relapse
Failure	Clinical Cure	Clinical Failure
Failure	Clinical Failure	Clinical Failure
Failure	Indeterminate	Clinical Failure
Failure	Relapse	Clinical Failure
Indeterminate	Clinical Cure	Indeterminate
Indeterminate	Clinical Failure	Clinical Failure
Indeterminate	Indeterminate	Indeterminate
Indeterminate	Relapse	Relapse

PTE = post-therapy evaluation; FFU = Final Follow-up

7.1.2 Microbiologic Response

Per-pathogen and per-subject microbiologic response will be programmatically determined at the EOT and PTE Visits in the micro-ITT and ME populations (by definition subjects in the ME population cannot have an indeterminate response).

Microbiological response will be derived using electronically transferred microbiology data from the central laboratory (or local laboratory if central data are not available).

Overall per-pathogen microbiological response at PTE is determined as follows (Table 7) from the per-pathogen microbiological responses at the EOT and PTE Visits.

7.1.2.1 Pathogen Determination

A pathogen is defined as bacteria implicated as causative in a subject's AP. Baseline pathogens and post-baseline pathogens will be identified for each patient programmatically with manual review and confirmation. Sponsor determination review will be performed in a blinded manner by Sponsor's internal microbiology review committee. Details are documented in the Pathogen and CE[2].

7.1.2.2 Microbiologic Response

Per-pathogen microbiological response will be programmatically determined at the EOT and PTE Visits in the micro-ITT and ME populations (subjects in the ME population cannot have an indeterminate response).

Pathogen microbiological outcome categories are: eradication, persistence, and indeterminate and these are defined in the following table (Table 7).

Table 7 Per-Pathogen Microbiologic Response at EOT and PTE

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 demonstrate persistence at EOT will be considered as 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.

Per-subject microbiological responses will be based on per-pathogen outcomes (see Table 8). 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. A persistent baseline pathogen at EOT will be considered persistence at PTE.

Table 8 Per-Subject Microbiologic Response at EOT and 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 determination at EOT will be considered to have 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

7.1.2.3 Other microbiological endpoints

[redacted]

[redacted]

[redacted]

[redacted]

7.1.4 Modified Patient Symptom Assessment Questionnaire

The subject will report the severity of their pyelonephritis symptoms and how bothersome they are with the 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 had to review the subject's responses and record any AEs as appropriate.

The mPSAQ is a self-administered, 6-item questionnaire that assesses the levels of 'severity' and 'bothersomeness' for each of the seven most frequently reported symptoms and signs of pyelonephritis symptoms:

Lower back pain or flank pain

Chills, rigors or warmth

Pain or uncomfortable pressure in the lower abdomen/pelvic area

Pain or burning when passing urine

Frequency of urination or going to the toilet very often

Urgency of urination or a strong and uncontrollable urge to pass urine

Each item has a Likert-type response scale, the 'severity' item response options being 'did not have', 'mild', 'moderate', 'severe', scored 0–3; and the bothersomeness item response options being 'not at all', 'a little', 'moderately', 'a lot', scored 0–3.

Total scores of the 6 items for the symptom severity scores and total scores for the 6 items related to the bothersomeness will be calculated for each subject and visit. The total scores for severity and bothersomeness will be between 0 and 18. The total score 0 is indicating the least severity of symptoms and a total score of 18 is indicating the worst symptom severity. For bothersomeness, the total score 0 is indicating the least bothersome score and a total score of 18 is indicating the most bothersome score.

For calculating the individual subject score by visit for both sub-scales the scores of non-missing item scores are summed up and divided by the number of non-missing items and then multiplied by 6. If less than 4 items are answered for each sub-scale, the total score is set to 'missing' for the sub-scale of the subject.

Total scores of the 6 items (Item 1 to 6) for the severity of symptoms scores and total scores for the 6 items related to the bothersomeness (Item 7 to 12) will be calculated.

7.2 Efficacy Endpoint Analysis

The efficacy endpoints include clinical response, microbiological response, and the composite of clinical and microbiological (overall) response, as measured by the number and percentage of subjects achieving success. The efficacy outcomes are measured by the number and percentage of subjects with successes in the ITT, micro-ITT populations, and other populations (CE and ME) as appropriate.

7.2.1 Investigator's Assessment of Clinical Success

The number and percentage of subjects with clinical success, failure, and indeterminate response as per investigator's assessment at the PTE visit in the ITT population will be determined by treatment group. Difference in success rates between levofloxacin and each omadacycline group will be provided. Point estimates will be provided together with the corresponding 95% confidence interval.

In addition, 95% credible intervals will be provided for the difference in success rates using the modeling as follows. Assuming the likelihood for number of responders to have binomial distribution [$Y_i \sim Bin(n_i, p_i)$] and non-informative beta priors [$p_i \sim \text{Beta}(0.5, 0.5)$]. The posterior probability of non-inferiority will be computed as $P(p_{OMC} - p_L > -0.1 \mid \text{data})$ for assessment.

Reason for investigator assessment of clinical failure and indeterminant at EOT, and for overall assessment at PTE and FFU visits will be tabulated for ITT, micro-ITT, and CE populations.

The analysis as described above will be repeated for EOT and FFU visits and provided also for CE and ME populations, as appropriate.

Overall clinical success at the PTE and EOT visits will be presented by pathogen and by pathogen and MIC for the micro-ITT and ME populations.

The analyses as described above will be repeated for pooled groups 2-4.

7.2.2 Microbiological Response Analysis

7.2.2.1 Per-Subject Microbiological Analysis

The per-subject microbiological (overall) response at the EOT and PTE Visits in the micro-ITT, ME-EOT and ME-PTE populations will be determined to support the clinical findings.

The number and percentage of subjects classified with a favorable (eradication and presumed eradication) and unfavorable (persistence, presumed persistence, and indeterminate) microbiological response (by definition, indeterminates are excluded from the ME population) will be tabulated for both treatment groups. Exact 95% CIs will be determined for the point estimates of the favorable microbiologic outcome rates in each treatment group.

Concordance of microbiological outcome with clinical outcome at EOT and PTE visits for micro-ITT and ME populations will be provided.

[redacted]

7.2.4 Sensitivity Analyses

[redacted]

7.2.5 Modified Patient Symptom Assessment Questionnaire

Results of the mPSAQ questionnaire will be summarized in all populations.

Shifts from baseline will be summarized separately for symptom scores and bothersome scores at each post-Baseline assessment, daily up to EOT, PTE and at Final Follow-up.

Scores for symptoms and bothersomeness will be summarized by time point using descriptive statistics, for both the actual values and the change from baseline.

8 SAFETY ENDPOINTS AND ANALYSES

8.1 General

The safety population will be used for all safety analyses and safety summaries will be presented by treatment group.

8.2 Duration of Exposure to Test Article and Compliance

Exposure summary by treatment group and separately by route of administration (iv, po) will be presented for the Safety and micro-ITT populations.

The distribution of subjects by the total number of days on therapy (0, 1, 2-3, 4-6, 7-10, 11-14, and > 14 days), the number of days on iv infusion and the number of days of oral test article will be presented.

A summary of the number of days of iv therapy prior to oral switch defined as 24-hour periods (ie, time to oral switch), the day of oral switch, and the criteria for iv to oral switch will be presented by treatment group. For the Safety population, the summary of test article exposure will be based on the actual treatment received whereas for all other analysis sets, the summary will be based on the randomized treatment.

Treatment compliance is defined as the number of iv doses (including partial doses, active and placebo) and oral

$$\%\ Compliance = 100\% * \frac{number\ of\ doses\ actually\ received}{number\ of\ doses\ expected\ to\ received}$$

The number of dosed expected to be received by the patient will be calculated over the time period defined by the first infusion date and the last dose date.

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.

Number of subjects and percentage with a compliance ≥80% will be presented. A summary of compliance to oral test article intake with the pre and post-dose fasting requirements will also be provided for subjects switching to oral administration. The percent fasting compliance will be determined based on the total doses taken for days the subjects were on po medication. The percentage of subjects who were < 50%, 50% to < 80%, and 80% to 100% compliance with the pre-dose and post-dose fasting requirements met will be summarized.

8.3 Concomitant Medications

Medications will be coded by WHODRUG Anatomical Therapeutic Chemical Classification (ATC) level 3 and generic medication name. Treatments that have been administered within 7 days prior to the date of informed consent until the end of study are recorded in the eCRF.

Medications are considered concomitant if taken on or after the first dose of test article, or if their stop date is unknown or marked as continuing. Thus, in cases where a medication starts prior to the first dose, and continues throughout the treatment period, the medication will be summarized as both prior and concomitant. Subjects will be counted only once for an ATC class and generic medication name.

All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject starts treatment with test article will be listed.

8.4 Adverse Events

Adverse events (AEs) will be recorded and reported from signing of the ICF to the end of study. AEs will be coded using the MedDRA to the SOC and PT levels.

A treatment-emergent AE is defined as any AE that newly appeared or worsened in severity on or after the initiation of test article. An AE is considered treatment emergent if the AE start date and time is on or after the start date and time of the first dose of test article.

Summary tables will be provided for all treatment-emergent adverse events (TEAEs).

An overall summary of AEs will include the number of subjects who experienced at least one AE of the following categories: any AE, any TEAE, any drug-related TEAE, any severe TEAE, any serious TEAE, any drug-related serious adverse event, any serious TEAE leading to death, any TEAE leading to premature discontinuation of test article and any TEAE leading to premature discontinuation from study, and any serious TEAE leading to premature discontinuation of test article.

The number and percentage of subjects reporting a TEAE in each treatment group will be tabulated by SOC and PT. The incidence of serious TEAEs, TEAEs judged to be related to test article, TEAE leading to premature discontinuation of test article and from study will be summarized by SOC and PT. Additionally, a summary by SOC, PT, and severity (mild, moderate, and severe) will be provided. For all analyses of TEAEs, if the same AE (based on PT) is reported for the same subject more than once, the AE is counted only once for that PT and at the highest severity and strongest relationship to test article.

For the two omadacycline dose groups and the levofloxacin treatment group with the possibility to switch from iv to oral test article AEs will be summarized by incidence of subjects with events starting during iv treatment and events starting after the switch to oral treatment and combined for the total treatment group. This summary will be presented by SOC and PTs.

In addition, all AEs (including non-TEAEs), serious TEAEs, and TEAEs leading to discontinuation of test article will be provided in listings by treatment group, study site, subject, verbatim term, MedDRA SOC and PT, start and end date, seriousness flag, severity, relationship to test article, relationship to study protocol, action taken with test article, non-test article action taken and outcome.

For subjects with a TEAE of nausea or vomiting (based on the MedDRA PT), the total number of nausea and vomiting events, descriptive statistics of the study day of first onset of these events, and descriptive statistics for the duration (in days) of events, will be presented by treatment group.

Listings of hospitalizations will be provided.

8.5 Clinical Laboratory Results

Clinical laboratory safety assessments include hematology (including coagulation), serum chemistry, and urinalysis.

Clinical laboratory parameters include those listed in the Appendix 1 Clinical Laboratory Tests (Central) and Local Urinalysis.

Baseline is defined as the central lab value closest to and prior to the first dose of test article. If no central lab value is available prior to the first dose of study drug, the local lab value that is closest to and prior to the first dose of study drug will be used as baseline. For by visit analyses, central lab values will be used unless no central lab value was obtained in the visit window. In this case, local lab values will be used for the by visit analyses. All lab values (central and local) are used for determination of the overall worst post-baseline value.

Laboratory data will be summarized by timepoint and for the overall worst post-baseline value using descriptive statistics (based on International System [SI] units) for the actual results and change from baseline for hematology and serum chemistry assessments.

Descriptive statistics (based on SI units) for chemistry, hematology and coagulation values and the change from baseline will be summarized by treatment group at each time point, and for the overall worst value post-baseline (which includes unscheduled visits).

Appendix 2 Directionality of Worst Laboratory Parameters provides the directionality of the worst values for each laboratory parameter.

Clinically notable laboratory values will be determined based on the Appendix 3 Modified Division of Microbiology and Infectious Diseases Adult Toxicity Table(DMID) criteria.

Shift tables will be presented to show the number of subjects with a laboratory value with a grade of 0, 1, 2, 3 or 4 at baseline versus the value at each visit. Number and percentage of subjects with at least a 2-grade increase from baseline (based on DMID criteria) will be summarized by treatment arm. Percentages for each laboratory test will be based on the number of subjects with a baseline and post-baseline evaluation of the specific laboratory test. A listing

will be provided for subjects who have at least a 2-grade increase from baseline in a given laboratory test.

The number and percentage (based on the number of subjects with a normal level at baseline) of subjects in each treatment group with an elevated transaminase level (> 3 × upper limit of normal [ULN], > 5×ULN, and > 10 × ULN), an elevated bilirubin level (> 1.5 × ULN and > 2 × ULN) will be presented by study visit. A listing of subjects who meet the laboratory criteria for Hy's law at the same visit will also be provided. The laboratory criteria for Hy's law is defined as 1) ALT or AST> 3 × ULN, ALP ≤ 2.0 × ULN, and total bilirubin > 1.5 ULN and 2) ALT or AST> 3 × ULN, ALP ≤ 2.0 × ULN, and total bilirubin > 2 × ULN.

Tabulated results of urine dipstick tests for leukocyte esterase and nitrates will be summarized by treatment group across visits and will include descriptive statistics for the microscopic evaluations for white blood cells.

Subject listings of all laboratory data (local and central laboratory data) collected during the study will be provided, including calculated CrCl (using the Cockcroft-Gault equation). Laboratory values outside normal limits will be identified in the subject data listings with flags for low (L) and high (H) as will laboratory values that meet the clinically notable (CN) thresholds.

8.6 Vital Signs

Vital signs will include blood pressure (diastolic and systolic) and heart rate and will be collected at Screening, Days 1, Day 3, Day 7, Day 10 and at EOT, PTE and FFU visits. On Day 1, blood pressure and heart rate is recorded within 30 min before, and 1 hour (± 15 minutes) after and 3 hours (± 15 minutes) after the completion of the first dose.

Body temperature is recorded at all visits.

Additionally, height will be collected at the Screening visit, and body weight will be collected at the Screening, EOT and FFU visits.

Blood pressure (systolic and diastolic) and heart rate will be summarized by time point and treatment group and for the minimum and maximum post-baseline values using descriptive statistics, for both the actual values and the change from baseline. Temperature will be summarized by descriptive statistics including change from baseline) by time point

Figures (line graphs) of observed values for heart rate, systolic and diastolic blood pressure over time will also be provided by treatment group.

Post-baseline vital signs will be defined as CN if they meet 1) the criterion value at the given visit, or 2) meet both the criterion value and the change from baseline criterion listed in Table 11. The incidence of CN vital signs will be summarized by time point and treatment group and will be listed and flagged in by-subject listings. An overall post-baseline incidence of CN values for each vital sign parameter, will also be summarized. A separate listing will be provided of subjects with values for a vital sign noted as CN.

Table 11 Criteria for Clinically Notable Vital Signs

Vital Sign Parameter	Flag	Criterion Value	Change from Baseline
Systolic Blood Pressure (mmHg)	High (CH)	≥ 180	Increase of ≥ 20 mmHg
	Low (CL)	≤ 90	Decrease of ≥ 20 mmHg
Diastolic Blood Pressure (mmHg)	High (CH)	≥ 105	Increase of ≥ 15 mmHg
	Low (CL)	≤ 50	Decrease of ≥ 15 mmHg
Heart Rate (bpm)	High (CH)	≥ 120	Increase of ≥ 15 bpm
	Low (CL)	≤ 50	Decrease of ≥ 15 bpm

8.7 Pregnancies

Results of local (urine or serum) and central (serum) pregnancy tests will be listed for all subjects enrolled in the study by treatment group. As it's expected for pregnancy counts to be small narratives will be provided in CSR.

9 CHANGES FROM PROTOCOL

Table 12 outlines protocol deviations together with justification for change.

Table 12 Protocol Deviations and Justification for Change

	Protocol wording:	SAP language	Justification:
Micro-ITT pop primary	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	Bayesian analyses will be conducted after efficacy data (overall response at PTE) are available for approximately 40, 80 and 100 subjects in the ITT population	Dose re-allocation criteria at the interims is not based on efficacy. Review is based on the safety and tolerability of the enrolled subjects (ITT).
Interim analyses for efficacy	Protocol sections: 5.1.1, 7.5, 7.8, 7.10, 12.2, 12.5.1, and 12.7	Protocol states that Bayesian analysis will be utilized in Interim Analysis decisions to alter sample size, randomization allocation, and/or stopping arm for efficacy or futility.	Due to low probability of success of dose differentiation with 40, 80, and 100 subjects efficacy stopping rules were not defined, see Table X2 DMC recommendations at Interim Analyses will be based on safety and tolerability. See Table 13 for details.
Presentation of Efficacy Endpoints	Protocol classifies efficacy endpoints as primary and secondary.	All efficacy endpoints of the study will be considered exploratory and are presented in this as in order of clinical importance.	In accordance with Administrative Memo dated 5/20/2019 all efficacy endpoints of the study will be considered exploratory to understand the performance of omadacycline in the treatment of acute pyelonephritis and to inform dose selection for a potential Phase 3 program.

Table 13 Probability of Successful Non-Inferiority Differentiation of OMC Groups and LEV and Type 1 Error at Interim Analyses

Null hypothesized rates for OMC and LEV are 75%, Alternative hypothesizes rates OMC=65% LEV=75% Non-inferiority margin is assumed 10%			
# of subjects/group	**Type I error when OMC rate is 62.5% and LEV=75%**	**Probability of success**	**Type I error**
10	4.4%	12.1%	4.4%
20	3.0%	12.1%	3.0%
30	2.8%	15.6%	2.8%
40	2.8%	18.9%	2.8%

OMC – omadacycline, LEV - levofloxacin

Table 14 illustrates probabilities of discontinuation at the analysis when data from 200 subjects is available for evaluation for various response rate scenarios.

Power column indicates power of successful detecting non-inferiority at 10% of OMC versus LEV with additional enrollment of 50 subjects per arm beyond total of 200.

Table 14 Probabilities of Discontinuation

Additional enrollment 50/arm subjects enrolled						
levofloxacin	**OMC High dose**	**Pooled Groups 2-4**	**Probability of any OMC group discontinuation at 200 subject analysis**	**Pooled Groups 2-4**	**OMC High dose**	**Power***
0.75	0.75	0.75	0.0154	0.88074	0.10388	0.5695
0.75	0.75	0.625	0.1003	0.16462	0.73509	0.4377
0.75	0.625	0.625	0.7025	0.16567	0.13181	0.0298

The calculations were based on frequentist approach

*Non-inferiority is based on lower limit of 95% confidence interval for difference in success rate to exceed -10%

OMC – omadacycline LEV - levofloxacin

10 REFERENCES

1. Data Monitoring Committee Charter for Phase II Trial for PTK0796-AP-17202
2. Pathogen and CE Review Plan: PTK0796-AP-17202

APPENDIX 1 CLINICAL LABORATORY TESTS (CENTRAL) AND LOCAL URINALYSIS

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
- Coagulation (Ratio of prothrombin time (PT) and international normalized ratio (INR))

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

Urinalysis (Local Lab):

- Bilirubin
- Glucose
- Ketones
- Leukocyte esterase
- Microscopic examination of sediment with WBC count
- Nitrites
- Occult blood
- potential of hydrogen (pH)
- Protein
- Specific gravity
- Urobilinogen

APPENDIX 2 DIRECTIONALITY OF WORST LABORATORY PARAMETERS

Laboratory Test	Parameter	Worst Value
Hematology	Hematocrit	Lowest value
	Hemoglobin	Lowest value

Laboratory Test	Parameter	Worst Value
	Red blood cell count	Lowest value
	Mean cell hemoglobin	Lowest value
	Mean cell hemoglobin concentration	Lowest value
	Mean cell volume	Lowest value
	White blood cell count	Lowest value
	Platelets	Lowest value
	Neutrophils	Lowest value
	Lymphocytes	Lowest value
	Monocytes	Lowest value
	Eosinophils	Highest value
	Basophils	Lowest value
Chemistry	Albumin	Lowest value
	Alkaline phosphatase	Highest value
	Alanine aminotransferase ALT/SGPT)	Highest value
	Amylase	Highest value
	Aspartate aminotransferase (AST/SGOT)	Highest value
	Urea	Highest value
	Bicarbonate	Lowest value
	Calcium	Both highest value and lowest value
	Cholesterol	Highest value
	Chloride	Both highest value and lowest value
	Creatinine	Highest value
	Creatine kinase (CK)	Highest value
	Gamma-glutamyl transpeptidase (GGT)	Highest value
	Blood glucose	Both highest value and lowest value
	Lactate dehydrogenase (LDH)	Highest value
	Lipase	Highest value
	Magnesium	Both highest value and lowest value
	Phosphate	Both highest value and lowest value
	Potassium	Both highest value and lowest value
	Sodium	Both highest value and lowest value
	Total bilirubin	Highest value
	Total protein	Lowest value
	Uric acid	Highest value
Coagulation	International normalized ratio (INR)	Highest value

APPENDIX 3 MODIFIED DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES ADULT TOXICITY TABLE

The DMID Adult Toxicity Table (21-Nov-2007) was modified to exclude the clinical component of the toxicity grading because clinical signs and symptoms related to abnormal laboratory values are not collected in this study. In addition, Grade 0 was added to the table so that shifts from normal could be analyzed. The grades for several parameters including enzymes were modified to ensure that any possible numeric value can be categorized appropriately (e.g., for creatinine, Grade 3 is defined as ">1.5-3.0×ULN" instead of "1.6-3.0×ULN").

For toxicity grades based on a multiple of the ULN, the normal range from the central laboratory will be applied.

For toxicity grades based on fixed values, the grades will be assigned regardless of the normal actual range values from the central laboratory. For example, a hemoglobin value of 10.0 gm/dL will be assigned a grade of 1 toxicity, even if the lower limit of normal from the laboratory was 9.8 gm/dL.

HEMATOLOGY

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin (gm/dL)	> 10.5	9.5-10.5	8.0-9.4	6.5-7.9	< 6.5
Absolute Neutrophil Count (count/mm^3)	> 1500	1000-1500	750-999	500-749	< 500
Platelets (count/mm^3)	≥ 100,000	75,000-99,999	50,000-74,999	20,000-49,999	< 20,000
WBCs (count/mm^3)	1000-10,999	11,000-12,999	13,000-14,999	15,000-30,000	> 30,000 or < 1,000

COAGULATION

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Prothrombin time (PT) (sec)	≤1 x ULN	1.01-1.25 x ULN	1.26-1.5 x ULN	1.51 - 3.0 x ULN	> 3 x ULN
International normalized ratio (INR)	Increased	≤ ULN	> 1 - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 x ULN

CHEMISTRY

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hyponatremia (mEq/L) (Na)	> 135	130-135	123-129	116-122	< 116
Hypernatremia (mEq/L) (Na)	< 146	146-150	151-157	158-165	> 165
Hypokalemia (mEq/L) (K)	> 3.4	3.0-3.4	2.5-2.9	2.0-2.4	< 2.0
Hyperkalemia (mEq/L) (K)	< 5.6	5.6-6.0	6.1-6.5	6.6-7.0	> 7.0
Hypoglycemia (mg/dL) (glucose)	≥ 65	55-64	40-54	30-39	< 30
Hyperglycemia (mg/dL) (nonfasting and regardless of prior history of diabetes)[1] (glucose)	< 116	116-160	161-250	251-500	> 500
Hypocalcemia (mg/dL) (corrected for albumin)[2] (Ca)	> 8.4	8.4-7.8	7.7-7.0	6.9-6.1	< 6.1
Hypercalcemia (mg/dL) (correct for albumin)[2] (Ca)	≤ 10.5	10.6-11.5	11.6-12.5	12.6-13.5	> 13.5
Hypomagnesemia (mEq/L) (Magnesium)	> 1.4	1.4- 1.2	1.1-0.9	0.8-0.6	< 0.6
Hypophosphatemia (mg/dL) (P)	≥ 2.5	2.0-2.4	1.5-1.9	1.0-1.4	< 1.0
Hyperbilirubinemia (total bilirubin)	< 1.1×ULN	1.1-1.5×ULN	> 1.5-2.5×ULN	> 2.5-5×ULN	> 5×ULN
Urea	< 1.25×ULN	1.25-2.5×ULN	> 2.5-5×ULN	> 5-10×ULN	>10×ULN
Hyperuricemia (uric acid) (mg/dL)	< 7.5	7.5–10.0	10.1–12.0	12.1–15.0	> 15.0
Creatinine	< 1.1×ULN	1.1-1.5×ULN	> 1.5-3.0×ULN	> 3.0-6×ULN	> 6×ULN

[1] The DMID toxicity table reports hyperglycemia detected in nonfasting specimens obtained from subjects with no prior diabetes.

[2] Calcium corrected for albumin = [0.8 x (normal albumin - subject's albumin)] + serum Ca level
Where normal albumin = 4 g/dl, albumin is in g/dL and calcium is in mg/dL

ENZYMES

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
AST (SGOT)	< 1.25×ULN	1.25-2.5×ULN	> 2.5-5×ULN	> 5-10×ULN	> 10×ULN
ALT (SGPT)	< 1.25×ULN	1.25-2.5×ULN	> 2.5-5×ULN	> 5-10×ULN	> 10×ULN
GGT	< 1.25×ULN	1.25-2.5×ULN	> 2.5-5×ULN	> 5-10×ULN	> 10×ULN
Alkaline Phosphatase	< 1.25×ULN	1.25-2.5×ULN	> 2.5-5×ULN	> 5-10×ULN	> 10×ULN
Amylase	< 1.1×ULN	1.1-1.5×ULN	> 1.5-2.0×ULN	> 2.0-5.0×ULN	> 5.0×ULN
Lipase	< 1.1×ULN	1.1-1.5×ULN	> 1.5-2.0×ULN	> 2.0-5.0×ULN	> 5.0×ULN

APPENDIX 4 CONCOMITANT MEDICATION START DATE IMPUTATION

Parameter	Type of Medication	Imputation
Start date for con meds	Non-Antibacterial	If it cannot be determined whether or not the start date of a medication (non-antibacterial) is prior to the first dose of study drug, it will be assumed that the medication was received prior to the first dose of study drug.
	Antibacterial	Missing start dates for antibacterials will be queried for a value. If it cannot be determined whether or not the start date of an antibacterial is prior to the first dose of study drug, it will be assumed that the medication was received prior to the first dose of study drug unless the indication notes that the medication was received after the first dose of study drug.
Stop date for con meds	Non-Antibacterial	If it cannot be determined whether or not the stop date of a medication (^{nonantibacterial}) is after the first dose of study drug, it will be assumed that the medication was received after the first dose of study drug
	Antibacterial	Missing stop dates for antibacterials will be queried for a value. If it cannot be determined whether or not the stop date of an antibacterial is after the first dose of study drug, it will be assumed that the medication was received after the first dose of study drug unless the indication notes that the medication was received prior to the first dose of study drug. If it cannot be determined whether the antibacterial was received prior to the assessment of Early Clinical Response, the EOT and/or the PTE Visit, the antibacterial will be assumed to have been received through the PTE Visit.

APPENDIX 4 ADVERSE EVENT START/STOP DATE IMPUTATION

Parameter	Missing	Additional Conditions	Imputation
Start date for AEs	D	M and Y same as M and Y of first dose of test article	Date of first dose of test article
		M and/or Y not same as date of first dose of test article	First day of month
	D and M	Y same as Y of first dose of test article	Date of first dose of test article
		Y prior to Y of first dose of test article but same as Y of screening date	Date of screening date
	D, M, Y	None - date completely missing	Date of first dose of test article
Stop date for AEs	D	M and Y same as M and Y of last dose of test article	Date of last dose of test article
		M and/or Y not same as date of last dose of test article	Use last day of month
	D and M	Y same as Y of last dose of test article	Date of last dose of test article
		Y not same as Y of last dose of test article	Use Dec 31
	D, M, Y	None - date completely missing	No imputation, but assume ongoing

D=day, M=month, Y=year

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month. Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.

In all cases, if it cannot be determined if the adverse event occurred prior to or after the first dose of test article, the adverse event should be defined as treatment emergent.

Document Approvals

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