STATISTICAL ANALYSIS PLAN

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GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
BID	twice daily
BMI	Body Mass Index
CE	clinically evaluable
CE-EOT	clinically evaluable at the end of treatment
CE-FFU	clinically evaluable at the final follow-up
CE-PTE	clinically evaluable at the post-therapy evaluation
CFU	colony forming unit
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
ITT	Intent-to-treat
IxRS	Interactive Response System
ME	microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
ME-EOT	microbiologically evaluable at the end of treatment
ME-PTE	microbiologically evaluable at the post therapy evaluation
Mg	milligram
MIC	minimum inhibitory concentration
micro-ITT	microbiological intent to treat
micro-m1ITT	modified microbiological intent to treat 1
micro-m2ITT	modified microbiological intent to treat 2
OMC	omadacycline
po	orally
PT	preferred term
PTE	post therapy evaluation
q12h	every 12 hours
q24h	every 24 hours
QTc	QT, corrected
SAP	Statistical Analysis Plan
SD	standard deviation
SI	International System of Units
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
UTI	urinary tract infection

Abbreviation	Definition
UTISA	UTI Symptoms Assessment
WBC	white blood cell

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Paratek Pharma Protocol PTK0796-UUTI-17201 (A Randomized, Double-Blinded, Adaptive Phase 2 Study to Evaluate the Safety and Efficacy of Oral Omadacycline and Oral Nitrofurantoin in the Treatment of Female Adults with Cystitis).

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 (eg, 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 data and details pertaining to interim analyses within the scope of Data Monitoring Committee (DMC) 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 omadacycline and nitrofurantoin in the treatment of female adults with cystitis.

The primary efficacy endpoint is investigator's assessment of clinical response at Post Therapy Evaluation (PTE) in the intent-to-treat (ITT) population, as measured by the number of subjects in each treatment group. The primary efficacy outcome is the percentage of subjects with an overall clinical success at the PTE Assessment in the ITT population. For further details refer to Section 7.1.1.2 (PTE Visit Clinical Response Assessment) and Section 7.2 (Primary Efficacy Endpoint Analysis).

The secondary objectives of this study are:

- To evaluate the safety of omadacycline in the treatment of female adults with cystitis.
- To evaluate the clinical and microbiologic response according to the identified causative pathogen.
- To evaluate the pharmacokinetics of omadacycline in female adults with cystitis.

The secondary safety endpoints include adverse events (AEs), vital signs, clinically notable events, and laboratory assessments, as measured by number and percentage for discrete data, and changes from baseline for continuous data. Exposure to study medication, compliance, and protocol deviations will also be evaluated. All subjects from safety analyses set are included in these assessments. For further details refer to Section 8.

3 STUDY DESIGN

This is a randomized, double-blinded, adaptive designed Phase 2 study evaluating 3 dosing regimens of once-daily omadacycline and 1 dosing regimen of twice-daily omadacycline compared to nitrofurantoin twice daily in the treatment of female adults with cystitis. The planned length of subject participation in the study is up to 37 days, which includes a total duration of study therapy for 7 days. Approximately 225 subjects will participate in this study at up to 25 sites within the United States.

The study will consist of 3 protocol-defined phases: screening, double-blind treatment and follow-up.

Following a Screening period of up to 24 hours, eligible subjects will be randomly assigned to receive one of 3 dosing regimens of once-daily omadacycline treatment, 1 dosing regimen of twice-daily omadacycline, or a twice-daily regimen of nitrofurantoin. Treatment will be double-blinded and double-dummy.

Subjects will return to the clinic site for visits on Day 1, Day 3, Day 5, and for an End of Treatment (EOT)/Day 7 visit on the day of or within 2 days following the last dose. Subjects will also return to the study site for a PTE on Day 14 (± 2 days) after the subject's first dose of test article. A Final Follow-up (FFU) assessment will be conducted within 30 to 37 days following the first dose of test article.

A study schedule of events is provided in tabular form in the protocol (Appendix 1: Schedule of Events).

This is an adaptive dose-response finding study. During the course of the study, a 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 (investigator assessment of clinical response at PTE). When there is sufficient information available about the dose-response, results from the Bayesian analysis will be reviewed by DMC to determine if enrollment in any Omadacycline treatment arms should be stopped or modified. Modifications to Omadacycline dosing regimens/treatment arms may also be based on safety and tolerability.

3.1 Sample Size Considerations

Enrollment of a total of approximately 225 subjects is planned. The Bayesian posterior probability that the clinical success rate at the PTE Visit is within 0.10 of that of the nitrofurantoin group will be estimated for each omadacycline dose group. The target probability is 0.80. If the true underlying clinical success rates for the nitrofurantoin and omadacycline dose groups are 0.82, then the sample size of N = 50 per treatment has approximately 79% power/probability to yield the target probability (N = 53 per treatment for 80% power).

The sample size may be increased for a particular omadacycline dose group by changing the randomization ratio and/or dropping a dose group to achieve improved power/probability of achieving the target probability that clinical success rates for a dose group is within 0.10 of that of the nitrofurantoin group. If required to improve the precision of the interim or projected final

analyses estimates of response rates or posterior probabilities, sample size may be increased to a maximum sample size of 300 patients.

The decisions affecting changes of randomization to treatment groups, hence affecting total sample size, will be based on the recommendation of the DMC at interim analyses in an unblinded manner. Statistical details relevant to pre-defined decision rules for the DMC are documented in the DMC SAP[1].

3.2 Randomization and Blinding

Approximately 225 female subjects will be enrolled at up to 25 sites. Subjects will be randomized (1:1:1:1:1) to five treatment groups (see Table 1).

Table 1 Description of Treatment groups

Group	Test Article	Study Day 1	Study Days 2-7*
1	omadacycline	300 mg po q12h, fed	300 mg po q24h
2	omadacycline	450 mg po q12h, fed	300 mg po q24h
3	omadacycline	450 mg po q12h, fed	450 mg po q24h
4	omadacycline	450 mg po q12h, fed	450 mg po q12h
5	nitrofurantoin	100 mg po q12h, fed	100 mg po q12h

q12h= every 12 hours, q24h= every 24 hours
*Odd doses on Study Days 2-7 should be taken in a fasted state. Even doses on Study Days 2-7 will be administered approximately 2 hours following a light meal

The site delegate will contact the Interactive Response System (IxRS) after confirming that the subject fulfills all the inclusion criteria and 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 and centrally balanced as defined in the IxRS specifications. 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.

3.3 Data Monitoring Committee

A DMC will provide ongoing monitoring of data in an unblinded manner. The charter for the DMC will outline membership, roles, and responsibilities. This will include a detailed description of the manner in which security and blinding of the data for the study blinded management team will be maintained, in addition to the procedures that ensure the independence and objectivity of the DMC's activities. The purpose of DMC is to monitor safety, tolerability, and to provide efficacy decisions based on the Interim Analyses as described in Section 3.4, for further details please refer to DMC Charter.

3.4 Interim Analyses

This is an adaptive dose-response finding study. Bayesian efficacy analyses will be conducted when data is available from 40, 80 and 100 subjects for the DMC to:

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

Detailed description of the analyses and decision rules related to efficacy are included in the DMC SAP.[1]

Interim analyses will be performed by an independent unblinded statistician. Results will be reviewed by the DMC in closed session. Of note, modifications to omadacycline dosing regimens/treatment arms may also be based on safety and tolerability. The DMC's decisions will be documented in meeting minutes.

PRA Health Sciences and Sponsor's study teams will remain blinded throughout the course of the study.

3.5 Final Analyses and Reporting

All analyses identified in this SAP will be performed 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

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 (ie, 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 in this population will be summarized according to actual test article received.

4.3 Microbiological Intent-to-Treat Population

The microbiological Intent-to-treat (micro-ITT) population will consist of subjects in the ITT population who have a study-qualifying pre-treatment Baseline urine culture with 1 or 2 uropathogens at $\geq 10^5$ colony forming unit (CFU)/mL.

If more than two bacterial isolates are identified, the culture will be considered contaminated. Rules for Sponsor's determination of qualifying pathogens are described in the Pathogen and CE Review Plan: PTK0796-uUTI-17201[2].

4.4 Clinically Evaluable Population

The clinically evaluable (CE) population will consist of all ITT subjects who received test article, have a qualifying infection, an assessment of outcome, and meet all other evaluability criteria as described below.

Inclusion into the CE populations will be determined programmatically based on the data on the electronic case report form (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 Review Plan: PTK0796-uUTI-17201[2].

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 CE populations, subjects must meet all criteria defined below:

1. Qualifying infection:
    - Exclusion Criterion #2, 3, and 4; Note: for subjects randomized after amendment 1 or later exclusions 3 and 4 are not applicable.
2. Assessment of outcome for CE population:

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

    - Subject did not meet any of the exclusion criteria 1 and 7 through 10 in 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 that 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 (ie, was not deemed an indeterminate outcome) at the EOT visit

ii. The EOT visit occurred on the day of, or within +2 days following the last dose of test article (3-day 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 on Day 14 (± 2 days) after the subject's first dose of test article, 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 (Sustained) Clinical Response (based on the investigator's assessment) at the FFU Visit is not Indeterminate (see Table 6)

ii. The FFU Visit/Call occurred 30 to 37 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 #5: 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 current cystitis while receiving prophylactic antibacterial therapy may be eligible if all prophylactic antibacterials are stopped]. 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 that is potentially effective against the baseline pathogen 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) will be excluded from the CE populations. 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 assuming they meet all other CE criteria. 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 4 doses of active test article (omadacycline groups 1, 2, and 3) at least 6 doses of active test article (nitrofurantoin and omadacycline group 4) 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) is Clinical Success.

Evaluable failure: The subject received at least 3 doses of active test article (omadacycline groups 1, 2, and 3) or at least 4 doses of active test article (nitrofurantoin and omadacycline group 4) 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) is Clinical Failure.

4.5 Microbiologically Evaluable Populations

The microbiologically evaluable (ME) population will include subjects in the CE population who have a study-qualifying pre-treatment Baseline urine culture with 1 or 2 uropathogens at $\geq 10^5$ CFU/mL.

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.

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), for further details refer to Pathogen and CE Review Plan: PTK0796-uUTI-17201[2].

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

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.

4.6 Additional Populations

For the purpose of sensitivity analyses described in Section 7.5.1, the following modified micro-ITT populations are defined.

The modified microbiological ITT 1 (micro-m1ITT) population will consist of subjects in the ITT population who have a study-qualifying pre-treatment Baseline urine culture with 1 or 2 uropathogens at $\geq 10^4$ CFU/mL.

The modified microbiological ITT 2 (micro-m2ITT) population will consist of subjects in the ITT population who have a study-qualifying pre-treatment Baseline urine culture with 1 or 2 uropathogens $\geq 10^3$ CFU/mL.

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 noted, categorical variables will be summarized using counts and percentages. Percentages will be rounded to one decimal place except for 100%, which will be displayed without any decimal places. In addition, 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.

5.1.1 Definitions

In Table 2 the general definitions provided are 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)	$BMI = \text{Weight (kg)} / \text{Height (m)}^2$

5.1.2 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 (Adverse Events). 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. Table 3 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.

Table 3 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.

- 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 (eg, 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 or lower limit of normal range (eg will be calculated as 99.99% of the value if it is reported as "<" (eg <5 will be converted to 5*0.99=4.9995). The upper normal range of a value will be converted to 100.01% if it is reported as ">" (eg >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 will be denoted "indeterminate" unless otherwise stated.
- 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.
- UTISA data for bothersome score will be imputed with score of 0 for each question for which severity is answered "Did not have".
- Missing UTISA responses at baseline will be imputed with Day 1 responses.

5.1.3 Visit Windows

For efficacy outcomes, the data collected at the EOT, PTE and FFU visits, regardless of when these occur will be utilized in the analysis of the ITT and micro-ITT populations. 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 4). Thus, if a subject has a visit outside the scheduled visit window, for example, a PTE Visit occurred 20 days after the subject's last day of therapy, 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, 14 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.

Table 4 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- 6	As entered in the eCRF* for these visits
EOT	Day 7	Within 2 days following the last dose of test article
PTE	Day 14	14 ± 2 days after the subject's first dose of test article
Final Follow-up (FU)	Day 30 to 37	30 to 37 days after the start of the first dose 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. *Days 2, 4, 6 are completed at home.

5.1.4 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 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 (defined as 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, 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 for ITT, micro-ITT, CE-PTE, and ME-PTE.

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 for ITT, micro-ITT, CE-PTE, and ME-PTE populations. 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 and will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT).

Results of the UTI Symptoms Assessment (UTISA) questionnaire will be as the number and percentage of subjects responding to each item, including individual severity scores, individual bothersome scores, and overall severity (ITT, micro-ITT, CE populations).

6.3 Baseline Microbiology

The microbiological assessment of the urine culture by the local laboratory will be summarized by treatment group for the ITT, micro-ITT, micro-m1ITT, and micro-m2ITT populations and will include as follows:

- The number of subjects with local urine culture performed
- The number of subjects with a clean catch sample
- The number of subjects with urine culture growth
- The 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 (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.
- 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 nitrofurantoin, 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.

6.4 Medical 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 ICF will be recorded.

In addition, subject history of prior UTI infection 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 Medical Dictionary for Regulatory Activities (MedDRA).

The incidence of medical history abnormalities will be summarized using descriptive statistics by system organ class (SOC) and preferred term. Patients are counted only once in each preferred term and SOC category. Summaries will be presented by treatment group and for all patients.

6.5 Prior and Concomitant 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. 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, 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 and antibiotic medications will also be provided 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 at least one minor protocol deviation will be summarized for the ITT, micro-ITT, and CE-PTE populations. The summaries of major deviations will also be presented by category.

6.7 Other Baseline Summaries

Abnormal laboratory results and abnormal vital signs at baseline will be reported. For further details refer to Section 8.5.

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. Only changes from Screening assessments will be recorded as AEs in the eCRFs. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed. Subject listings of all physical examination results by body system will be provided. Any changes from baseline will be recorded as AEs.

7 EFFICACY ENDPOINTS AND ANALYSES

7.1 Efficacy Endpoints

The efficacy endpoints are as follows:

	Endpoint	Visit	Population
Primary	Overall Investigator's assessment of clinical response	PTE	ITT
Secondary	Investigator's assessment of clinical response	EOT	ITT CE-EOT micro-ITT
	Overall Investigator's assessment of clinical response	PTE	CE-PTE micro-ITT
	Overall (Sustained) Investigator's assessment of clinical response	FFU	ITT CE-FFU micro-ITT
	Microbiologic response	EOT	micro-ITT ME-EOT
	Overall Microbiologic response	PTE	micro-ITT ME-PTE
Exploratory	UTISA	by timepoint	ITT, micro-ITT, CE-EOT, CE-PTE, CE-FFU
Sensitivity	[redacted]		

Note: Microbiological response is summarized both by patient and by pathogen

7.1.1 Investigator's assessment of clinical response

The primary efficacy endpoint is the investigator's assessment of clinical success at the PTE visit in the ITT population. Detailed definition is included in Section 7.1.1.2.

Additional efficacy endpoints are described below.

7.1.1.1 EOT Visit Clinical Response Assessment

At the EOT visit (on the day of or within 2 days following the last dose of test article) the investigator will determine whether the subject meets the criteria of 1 of the following clinical outcomes:

- **Clinical Success**: Sufficient resolution of signs and symptoms at the EOT visit such that no additional systemic 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 additional systemic antimicrobial therapy for the current infection is required.
- **Indeterminate:** EOT visit not completed, due to the subject being lost to follow-up or the subject withdrawing consent, or other specified reason.

7.1.1.2 PTE Visit Clinical Response Assessment

At the PTE visit (Day 14 (± 2) days after the subject's first dose of test article), the investigator will determine whether or not the subject meets the criteria of 1 of the following clinical outcomes:

- **Clinical Success**: Sufficient resolution of signs and symptoms at the PTE such that no additional systemic 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.
- **Indeterminate**: PTE visit not completed.

For the purpose of analysis, Overall Clinical Response at PTE is determined as follows (Table 5) from the investigator's assessments at the EOT and PTE Visits as per the CRF:

Table 5 Overall 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 Overall Clinical Response is derived 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:

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

7.1.1.3 FFU Visit Clinical Response Assessment

At the follow-up assessment (FFU), subjects will be re-evaluated by the Investigator for clinical response and will be reported for the micro-ITT and CE-FFU population by treatment group.

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

- **Clinical Success:** Sufficient resolution of signs and symptoms at the Final Follow-up visit such that no additional systemic 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 Final Follow-up visit such that use of additional systemic antimicrobial therapy for the current infection is required.

- **Indeterminate:** Final Follow-up visit not completed.

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

Table 6 Overall 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	Success	(Sustained) Clinical Cure
Success	Failure	Clinical Failure
Success	Indeterminate	Indeterminate
Failure	Success	Clinical Failure
Failure	Failure	Clinical Failure
Failure	Indeterminate	Clinical Failure
Indeterminate	Success	Indeterminate
Indeterminate	Failure	Clinical Failure
Indeterminate	Indeterminate	Indeterminate

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 cystitis. Baseline pathogens and post-baseline pathogens will be identified for each patient programmatically with a 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 Review Plan: PTK0796-uUTI-17201[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 (by definition subjects in the ME population cannot have an indeterminate response).

Pathogen microbiological outcome categories are: eradication, persistence, and indeterminate and these are defined in Table 7. Favorable microbiological outcomes include eradication. Unfavorable microbiological outcomes include persistence or indeterminate.

Table 7 Pathogen Microbiological Outcome Categories at EOT and PTE

Category	Criteria	Interpretation
Eradication	Urine specimen shows absence of the original baseline pathogen or the baseline pathogen grew at $<10^4$ CFU/mL at visit.	Favorable
Persistence	Urine culture shows continued presence (defined as $\geq 10^4$ CFU/mL) of the original baseline pathogen(s) at visit.	Unfavorable
Indeterminate	Urine specimen was not available to culture (or the culture result was not interpretable).	Unfavorable

*for PTE visit use Overall Clinical Response at PTE

Per-subject microbiological responses will be based on per-pathogen outcomes. To have an overall per subject favorable microbiologic response, the outcome for each baseline pathogen must be favorable. If the outcome for any baseline pathogen is unfavorable, the subject will be considered to have an unfavorable per-subject microbiologic response. Subjects with an indeterminate response for all baseline pathogens will be considered to have an indeterminate per-subject microbiologic response. Subjects with at least one indeterminate response for a baseline pathogen when all other baseline pathogens have a favorable response will be considered to have an indeterminate per-subject microbiologic response.

Table 8 Per-Subject Microbiologic Response

Condition	Microbiologic Response at Visit	Per-Subject Microbiologic Response at Visit
All per-pathogen microbiological responses at visit	Favorable (Eradication)	Favorable
Any per-pathogen microbiological response at visit	Unfavorable (Persistence)	Unfavorable
All per-pathogen microbiological responses at visit	Indeterminate	Indeterminate
At least one per-pathogen microbiological response at visit when other responses are Favorable (Eradication)	Indeterminate	Indeterminate

Per-pathogen and per-subject overall microbiological responses at PTE are determined as follows (Table 9) from the per-pathogen and per-subject microbiological responses at the EOT and PTE Visits:

Table 9 Microbiologic Response at PTE

Microbiologic Response at EOT Visit	Microbiologic Response at PTE Visit	Overall Microbiologic Response at PTE
Favorable	Favorable	Favorable
Favorable	Unfavorable	Unfavorable
Favorable	Indeterminate	Indeterminate
Unfavorable	Favorable	Unfavorable
Unfavorable	Unfavorable	Unfavorable
Unfavorable	Indeterminate	Unfavorable
Indeterminate	Favorable	Indeterminate
Indeterminate	Unfavorable	Unfavorable
Indeterminate	Indeterminate	Indeterminate

Favorable is defined as the eradication of the baseline pathogen.
Unfavorable is defined as the persistence of a baseline pathogen
EOT = end of treatment; PTE = post-therapy evaluation.

7.1.2.3 Other microbiological endpoints

[redacted]

7.1.3 UTI Signs and Symptoms Assessment

Subject assessment of UTI signs and symptoms severity will be collected at Screening, and daily through EOT (including self-completion by subject at home on Days 2, 4 and 6), at PTE and at FFU via the UTISA questionnaire.

The UTISA is a subject completed, 14-item questionnaire that assesses the levels of 'severity' and 'bothersomeness' for each of the seven most frequently reported symptoms and signs of UTI:

- Frequency
- Urgency
- Pain/burning on urination
- Incomplete voiding
- Pain in pelvic area
- Low back pain

- Blood in 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 7 items for the severity of signs and symptoms scores and total scores for the 7 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 21. The total score 0 is indicating the least severity of signs and symptoms and a total score of 21 is indicating the worst severity. For bothersomeness, the total score 0 is indicating the least bothersome score and a total score of 21 is indicating the most bothersome score.

The bothersomeness questions are only answered if the subject reported presence of the sign/symptom, otherwise this answer is omitted by design.

For calculating the individual total subject score by timepoint 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 7. 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.

Frequency of subjects with resolution of all symptoms, without occurrence of new symptoms (in comparison to baseline), and no worsening of baseline symptoms will be provided by timepoint.

7.2 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint is investigator's assessment of clinical response at PTE in the ITT population, as measured by the number of subjects in each treatment group.

The primary efficacy outcome is the percentage of subjects with an overall clinical success at the PTE Assessment in the ITT population. Each omadacycline treatment group will be compared to nitrofurantoin group for non-inferiority (pairwise). This non-inferiority test will be based on the lower limit of the 2-sided exact 95% confidence interval (CI).

The null and alternative hypotheses are as follows for overall clinical success:

$$H_0 : p_1 - p_2 \leq -\Delta \text{ and } H_1 : p_1 - p_2 > -\Delta,$$

where p_1 is the primary efficacy success rate in each of the omadacycline treatment group, p_2 is the primary efficacy success rate of nitrofurantoin group, and Δ is the non-inferiority margin of 10%. No multiplicity adjustment will be used to account for multiple doses being compared to levofloxacin.

To test the null hypothesis, a 2-sided 95% CI for the observed difference in primary outcome rates (omadacycline group minus nitrofurantoin group) will be calculated. If the lower limit of the 95% CI for the difference exceeds –10%, then the null hypothesis will be rejected and the non-inferiority of omadacycline to nitrofurantoin will be declared for that dose.

The number and percentage of subjects in each treatment group defined as an overall clinical success, failure and indeterminate (subjects with missing data or who are lost to follow-up) will be tabulated, as will the overall category combining failure and indeterminate.

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 [$p_i \sim$ Beta(0.5, 0.5)]. The posterior probability of non-inferiority will be computed as $P(p_{OMC} - p_N > -0.1 \mid \text{data})$ for assessment.

Additional sensitivity analyses are described in Section 7.5.2.

7.3 Secondary Efficacy Endpoint Analysis

7.3.1 Investigator's Assessment of Clinical Success

The number and percentage of subjects with an (overall) investigator's assessment of clinical success, clinical failure and indeterminate response at the EOT, PTE, and FFU visits (ITT, micro-ITT, and CE populations; by definition subjects in the CE population cannot have an indeterminate response) will be determined by treatment group. Exact 95% confidence intervals will be determined for the point estimates of the clinical success rates in each treatment group and for difference from nitrofurantoin (omadacycline - nitrofurantoin).

Reasons for investigator assessment of clinical failure and indeterminate at EOT and for overall assessment at PTE and FFU visits will be tabulated.

7.3.2 Per-Subject Microbiological Response

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 unfavorable (persistence and indeterminate) microbiological response (by definition, indeterminates are excluded from the ME population) will be tabulated for both treatment groups. Exact 95% confidence intervals will be determined for the point estimates of the favorable microbiologic outcome rates in each treatment group and for difference from nitrofurantoin (omadacycline - nitrofurantoin).

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

[redacted]

7.4 Exploratory Analyses

7.4.1 UTI signs and symptoms assessment

Results of the UTISA questionnaire will be summarized in the ITT, micro-ITT, and CE populations. Summaries will be based on the available data; no imputations will be applied to missing values.

Shifts from Baseline will be summarized separately for severity scores and bothersome scores at each post-Baseline assessment, daily up to EOT (including self-completion by subject at home on Days 2, 4 and 6), PTE and at FFU.

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

Frequency of subjects with resolution of all clinical UTI symptoms, subjects with no worsening symptoms, and subjects with the absence of new UTI symptoms will be presented.

7.5 Efficacy Sensitivity Analysis

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8 SAFETY ANALYSES

8.1 General

The safety population will be used for all safety analyses and safety summaries will be presented by treatment group unless otherwise stated. All tables will have a corresponding listing including all patients randomized.

8.2 Duration of Exposure to Test Article and Compliance

Exposure summary by treatment group will be presented for the safety, micro-ITT, and CE-PTE populations.

Duration of exposure to test article (days) for the individual subject is the number of days subject received test article (last day of study test article – first day of test article + 1). Duration of treatment (days) will be summarized using descriptive statistics. The distribution of subjects by the total number of days on test article (1-3, 4-5, 6-7, and > 7 days) will be presented.

The degree of test article compliance will be determined by presenting the number of tablets taken as a percentage of the number required by the protocol.

$$\%Compliance = 100\% * \frac{Actual\ number\ of\ tablets\ taken}{Expected\ \#of\ tablets}$$

The last dose date is the last day the subject is expected to receive test article based on the length of therapy determined by the investigator or the actual last date the subject took test article, if s/he prematurely discontinued test article. For subjects who complete the study, the last dose day used in the denominator calculation will be the last expected dosing day. For early termination subjects, the last day of study drug used in the denominator calculation will be the last expected dosing day before termination day. A subject is expected to receive a total of 38 tablets during the treatment phase for subjects enrolled at the time preceding protocol amendment 2, and 56 tablets with amendment 2. For detail on dosing schedules refer to Table 2 of the study protocol.

Descriptive statistics for treatment and fasting compliance will be presented by treatment group and by protocol version at which a subject entered the study.

Number of subjects and percentage with a compliance ≥80% will be presented. A summary of compliance with the pre- and post-dose fasting requirements will also be provided. The percent fasting compliance will be determined based on the total doses taken where fasting is required. 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 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.

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.

Of note, summary of prior antiemetic and antibiotic medications will also be provided as described in Section 6.5 (Prior and Concomitant Medications).

8.4 Adverse Events

Adverse events (AEs) will be recorded and reported from signing of the inform consent form to the end of study. AEs will be coded using the MedDRA to the system organ class (SOC) and preferred term (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, any TEAE leading to premature discontinuation of test article and 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.

In addition, all 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, descriptive statistics for the duration (in days) of events, and number of subjects who required anti-emetic medication will be presented by treatment group.

Listings of all AEs for treated (by treatment group) and not treated subjects will be provided indicating day relative to the first intake of the test article intake to differentiate between TEAEs and pre-therapy AEs.

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).

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 modified Division of Microbiology and Infectious Diseases (DMID) criteria in Appendix 3 Modified Division of Microbiology and Infectious Diseases Adult Toxicity Table.

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 WBCs.

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), heart rate, and body temperature, and will be collected at Screening, Days 1, 3, 5, and EOT, as well as at the PTE. During the Follow-up call/visit vital signs are collected if the subject reports symptoms of potential recurrence and clinic visit is required.

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

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

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	High (CH)	≥ 105	Increase of ≥ 15 mmHg

Table 11 Criteria for Clinically Notable Vital Signs

Vital Sign Parameter	Flag	Criterion Value	Change from Baseline
(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. It is expected for pregnancy counts to be small and thus narratives will be provided in the CSR.

9 CHANGES FROM PROTOCOL

Not applicable.

10 REFERENCES

1. Statistical Analysis Plan for Data Monitoring Committee Meetings: Bayesian Design for Phase II Trial for PTK0796-UUTI-17201
2. Pathogen and CE Review Plan: PTK0796-uUTI-17201

APPENDIX 1 CLINICAL LABORATORY TESTS (CENTRAL)

Table 12 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

Coagulation:

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

Pregnancy (all subjects):

- Serum β-human chorionic gonadotropin (β-HCG)

Urinalysis:

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

Serum Chemistry:

- Albumin (ALB)
- Alkaline phosphatase (ALP)
- Alanine aminotransferase (ALT)
- Amylase
- Aspartate aminotransferase (AST)
- Blood urea nitrogen (BUN)
- Calcium (Ca)
- Carbon dioxide (CO2)
- Chloride (Cl)
- Creatinine
- Creatine phosphokinase (CK)
- Gamma-glutamyl transpeptidase (GGT)
- Glucose
- Lactate dehydrogenase (LDH)
- Lipase
- Magnesium
- Phosphorus (P)
- Potassium (K)
- Sodium (Na)
- Total bilirubin
- Total protein
- Uric acid

APPENDIX 2 DIRECTIONALITY OF WORST LABORATORY PARAMETERS

Laboratory Test	Parameter	Worst Value
Hematology	Hematocrit	Lowest value
	Hemoglobin	Lowest 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 (eg, 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 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

Prior and 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.

Document Approvals

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