Clinical Trial Protocol: PTK0796-UUTI-17201

Study Title:	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
Study Number:	PTK0796-UUTI-17201
Study Phase:	2
Product Name:	Omadacycline (PTK 0796)
IND Number:	75,928 73,431
Indication:	Uncomplicated Urinary Tract Infection (Cystitis)
Investigators:	Multicenter
Sponsor:	Paratek Pharma, LLC A wholly-owned subsidiary of Paratek Pharmaceuticals, Inc. 75 Park Plaza, 4th Floor Boston, MA 02116 1000 First Ave Suite 200 King of Prussia, PA 19406
Sponsor Contact:	Tel: +1 617-275-0040
Medical Monitor:	[redacted]

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SYNOPSIS

Sponsor:
Paratek Pharma, LLC
A wholly-owned subsidiary of Paratek Pharmaceuticals, Inc.

Name of Finished Product:
Omadacycline oral tablet, 150 mg

Name of Active Ingredient:
Omadacycline

Study Title:
A Randomized, Double-Blinded, Adaptive Phase 2 Study to Evaluate the Safety and Efficacy of Oral Omadacycline and Oral Nitrofurantoin in the treatment of Female Adults with Cystitis

Study Number:
PTK0796-UUTI-17201

Study Phase: 2

Study Rationale:
Omadacycline is the first member of the aminomethylcycline class of antibiotics, which are semisynthetic derivatives of the tetracycline class. Omadacycline- has in vitro activity against the most common bacterial pathogens associated with cystitis. Omadacycline has been shown to have a significant fraction of the administered dose excreted by the kidneys and is present as active drug in the urine. The safety, efficacy and pharmacokinetics (PK) of omadacycline have been evaluated in a limited number of adults with cystitis.

Primary Objective:
To evaluate the efficacy of omadacycline and nitrofurantoin in the treatment of female adults with cystitis.

Secondary Objectives:
- 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.

Study Design:
This is a randomized, double-blinded, adaptive designed Phase 2 study evaluating 4 dosing regimens of omadacycline compared to nitrofurantoin 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.

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 be randomized to the following 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*

Dosing double-blind, double-dummy design:

Dosing		Group 1	Group 2	Group 3	Group 4	Group 5	Dosing Condition
		omadacycline	omadacycline	omadacycline	omadacycline	nitrofurantoin	
Day 1	Dose 1	Two 150 mg omadacycline tablets, one placebo tablet resembling omadacycline	Three 150 mg omadacycline tablets	Three 150 mg omadacycline tablets	Three 150 mg omadacycline tablets	Three placebo tablets resembling omadacycline	2 hours after light meal[a]
		One placebo capsule resembling nitrofurantoin	One placebo capsule resembling nitrofurantoin	One placebo capsule resembling nitrofurantoin	One placebo capsule resembling nitrofurantoin	One 100 mg nitrofurantoin capsule	
	Dose 2[b]	Two 150 mg omadacycline tablets, one placebo tablet resembling omadacycline	Three 150 mg omadacycline tablets	Three 150 mg omadacycline tablets	Three 150 mg omadacycline tablets	Three placebo tablets resembling omadacycline	2 hours after light meal[a]
		One placebo capsule resembling nitrofurantoin	One placebo capsule resembling nitrofurantoin	One placebo capsule resembling nitrofurantoin	One placebo capsule resembling nitrofurantoin	One 100 mg nitrofurantoin capsule	
Days 2-7	Dose 3 and odd doses	Two 150 mg omadacycline tablets, one placebo tablet resembling omadacycline	Two 150 mg omadacycline tablets, one placebo tablet resembling omadacycline	Three 150 mg omadacycline tablets	Three 150 mg omadacycline tablets	Three placebo tablets resembling omadacycline	Fasting[c]
		One placebo capsule resembling nitrofurantoin	One placebo capsule resembling nitrofurantoin	One placebo capsule resembling nitrofurantoin	One placebo capsule resembling nitrofurantoin	One 100 mg nitrofurantoin capsule	
	Dose 4 and even doses	Three placebo tablets resembling omadacycline	Three placebo tablets resembling omadacycline	Three placebo tablets resembling omadacycline	Three 150 mg omadacycline tablets	Three placebo tablets resembling omadacycline	2 hours after light meal[d]
		One placebo capsule resembling nitrofurantoin	One placebo capsule resembling nitrofurantoin	One placebo capsule resembling nitrofurantoin	One placebo capsule resembling nitrofurantoin	One 100 mg nitrofurantoin capsule	

Day is defined as the 24-hour period, not calendar day. All subjects will be dosed twice daily, ~12 hours apart, except where noted.

[a] Doses 1 & 2 of the omadacycline tablets or placebo tablets resembling omadacycline and nitrofurantoin or placebo capsules resembling nitrofurantoin should be taken approximately 2 hours after a light meal on Day 1. After dosing, no food for 2 hours and no dairy products, antacids or multivitamins containing multivalent cations (eg, aluminum, magnesium, calcium, bismuth, iron, or zinc) for 4 hours.

[b] Dose 2 can be taken a minimum of 8 hours and up to 12 hours after Dose 1. Dose 3 should be taken a minimum of 8 hours after Dose 2.

[c] Beginning with Dose 3, all consecutive odd numbered doses of the omadacycline tablets and placebo tablets resembling omadacycline 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 for 2 hours, no dairy products, antacids or multivitamins containing multivalent cations (eg, aluminum, magnesium, calcium, bismuth, iron, or zinc) for 4 hours.

[d] Beginning with Dose 4, all even numbered doses should be taken approximately 2 hours after a light meal.

During the study treatment period, blood samples will be collected for safety analysis and for PK analysis of omadacycline. 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.

Subjects will return to the clinical 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 the 2 days following the last dose of test article. Subjects will return to the study site for a Post Therapy Evaluation (PTE) on Day 14 (+/- 2 days) after the subject's first dose of test article. A Final Follow-up assessment will be conducted within 30 to 37 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 are not having any symptoms and had no AEs or clinically significant laboratory 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.

Rationale for Omadacycline Dose Regimen Selection:

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

- While the driver of efficacy for omadacycline in UTI is not known, a pragmatic assumption was made that maximizing the time of urine concentration above pathogen MIC (ideally, throughout the dosing interval) would be desirable.
- In PTK0796-UUTI-15103, omadacycline dosed as 300 mg po every 12 hours (q12h) on Day 1 followed by 300 mg po daily for 5 days and 450 mg po q12h on Day 1 followed by 450 mg po daily for 5 days both demonstrated high urinary concentrations on Day 1 and Day 5. For the 300 mg dosing group, over the 24 hour dosing period, mean urinary concentrations ranged from 14 to 20 µg/mL on Day 1 and 17 to 30 µg/mL on Day 5. For the 450 mg dosing group, over the 24 hour dosing period, mean urinary concentrations ranged from 11 to 25 µg/mL on Day 1 and 30 to 48 µg/mL on Day 5.
- In PTK0796-UUTI-15103, both the 300 mg and 450 mg omadacycline treatment groups had nausea reported in 60% of subjects. Vomiting occurred in 40% and 20% of the 300 mg and 450 mg treatment groups, respectively. In the recently completed PTK0796-ABSI-16301 study which compared omadacycline 450 mg po every 24 hours (q24h) for 2 doses followed by 300 mg po q24h for a total of 7 to 14 days to linezolid 600 mg po every 12 hours for a total of 7 to 14 days, nausea and vomiting rates of 30.2% and 16.8% were observed. In both studies, most events of nausea and vomiting occurred early in the treatment associated with the loading doses of omadacycline.
- The effect of a light meal administered approximately 1.5 hours before dosing was evaluated using the free base formulation of omadacycline and resulted in approximately 20% decrease in exposure. In the recently completed study

PTK0796-DDI-17106, the effect of a light meal administered approximately 1.5 hours before dosing with the same formulation of omadacycline used in the pivotal Phase 3 studies was evaluated. The results demonstrated an approximately 19% to 25% reduction in exposure when a light meal was administered 1.5 hours before dosing.

- The Sponsor has decided to add an omadacycline treatment group dosed at 450 mg twice daily for 7 days. The rationale for the change includes:
  1) Since the driver of efficacy is unknown and the mean renal excretion of a 300 mg oral dose is 14.4%, a regimen that maximizes the tolerated dose of omadacycline may provide additional information on the dose necessary for clinical and microbiologic success in uUTI and allow comparison to the daily dosed omadacycline treatment groups.
  2) The proposed dosing of 450mg twice daily for 7 days will provide approximately 2x or greater the amount of omadacycline that is excreted into the urine compared to the daily omadacycline treatment groups.
  3) Blinded review of the first 145 subjects reveals good tolerability. Nausea has occurred in approximately 10% of all subjects with only a single subject (0.7%) reporting vomiting. There has been only one treatment discontinuation due to adverse events of nausea and/or vomiting reported. Therefore, even if all cases of nausea and vomiting were in a single omadacycline treatment group, nausea and vomiting appears lower than observed in PTK0796-UUTI-15103 study.
  4) Dose-limiting transaminase increases were seen in Phase 1 studies at 600mg IV which is higher than the exposure at 450mg PO twice daily.
  5) Increases in heart rate following omadacycline are Cmax associated. Cmax concentrations with the 450mg PO dose (1077 ng/mL) at steady state are approximately one-half the Cmax concentration with the 100mg IV dose (2120 ng/mL) suggesting that heart rate increases above 12-17 bpm observed with 100-200mg IV doses in healthy patients is unlikely following 450mg twice daily dosing.

  Therefore based on the pharmacokinetic, clinical, and safety data, the 450mg twice daily dose will increase urinary concentration, may provide additional clinical and microbiologic benefit while maintaining the safety profile observed with daily dosing.

In order to minimize the effect of food on exposure and to potentially minimize the impact of nausea and vomiting during the omadacycline loading dose, omadacycline will be dosed twice on Day 1 with each dose administered 2 hours following a light meal, and all even numbered doses will be administered approximately 2 hours following a light meal.Given the urinary concentrations observed in PTK0796-UUTI-15103 and the expected impact of a light meal, urinary concentrations should remain above the typical omadacycline MIC_{90} of 2 µg/mL for *Escherichia coli*, the most common uropathogen in uncomplicated cystitis.

Study Population:

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.

Adaptive design:

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 a 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.

Bayesian analyses will be conducted after efficacy data (investigator assessment of clinical response at PTE) are available for approximately 40, 80, and 100 subjects in order to:

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

Additional analyses may be carried out for the same two purposes. Response criteria are targeted toward estimating the probability that the clinical success rate (proportion of subjects) for each dose group is within 10% of that of the nitrofurantoin group. If at the analyses, that probability falls below 30% for a particular dose group, recruitment for that dose group may be stopped or curtailed. If that probability exceeds 80% for a particular dose group, recruitment for that dose group may be increased to improve the precision of the estimate.

Main Criteria for Inclusion:

1. Written and signed informed consent must be obtained before any assessment is performed
2. Females age 18 years or older
3. Onset of TWO or more of the following clinical signs and symptoms of cystitis within 96 hours prior to randomization:
   - Dysuria
   - Frequency
   - Urgency
   - Suprapubic pain

   NOTE: symptoms should be continuing at the time of randomization
4. A clean-catch midstream urine sample with pyuria (white blood cell [WBC] count >10/µL in unspun urine or ≥10 per high power field in spun urine) or dipstick analysis positive (at least ++) for leukocyte esterase. Urine sample must also be sent for microbiologic culture prior to randomization.
5. Must have a negative pregnancy test at Screening, and agree to comply with using an acceptable form of birth control (eg, abstinence, oral contraceptive, intrauterine device [IUD], barrier contraception [condom], tubal ligation, hysterectomy, bilateral oophorectomy, postmenopausal or vasectomized partner) from Screening through PTE
6. Ability to swallow 4 tablets/capsules in succession
7. Ability to communicate well with the investigator, to understand and comply with the requirements of the study

Main Criteria for Exclusion:

1. Males
2. Pregnant or nursing (breastfeeding) women
3. *Criterion no longer applicable as per Protocol Amendment #1*
4. *Criterion no longer applicable as per Protocol Amendment #1*
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 the current cystitis 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.]
6. Anticipated need for systemic antibacterial therapy other than test article (for treatment or prophylaxis) during the study period
7. Has a suspected upper UTI (eg, fever [≥ 38°C, ≥ 100.4°F], chills, rigors, flank pain, or costovertebral angle tenderness)
8. Symptoms/signs suggestive of vaginitis or sexually transmitted infection (eg, vaginal discharge or vaginal irritation)
9. Known prior UTI caused by *Pseudomonas aeruginosa* or *Proteus* spp., or suspected current infection with *P. aeruginosa* or *Proteus* spp. or nitrofurantoin-resistant pathogen
10. Has a confirmed or suspected complicated UTI, defined as:
    - Use of an indwelling urinary catheter, nephrostomy tubes or other indwelling urinary tract device within the 30 days prior to randomization or scheduled to be used during

the study period

- Known urinary retention (≥100 mL of residual urine after voiding) within the 30 days prior to randomization
- History of surgically modified or abnormal urinary tract anatomy (eg, bladder diverticula or redundant urine collection system)
- Complete or partial obstruction of the urinary tract, or obstructive uropathy that is scheduled to be medically or surgically relieved during the study therapy period
- History of renal transplant or a surgically created intestinal conduit for urinary diversion
- Suspected or confirmed renal calculi, stricture, primary renal disease (eg, polycystic renal disease), neurogenic bladder, or other anatomical or functional abnormalities predisposing to UTI
- Had an overnight stay in the hospital within the past 6 months

11. Screening calculated creatinine clearance (CrCl) < 60 mL/minute, using the Cockcroft-Gault equation (see equation in Appendix 2), requires any form of dialysis (eg, hemodialysis, peritoneal dialysis), or other evidence of severe renal disease
12. Has any of the following at Screening:
    - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 × Upper Limit of Normal (ULN)
    - total bilirubin > 1.5 × ULN
    - suspected or confirmed clinical evidence of end-stage liver disease (eg, ascites, hepatic encephalopathy)
13. History of having experienced unstable cardiac disease (eg, unstable angina, myocardial infarction, acute congestive heart failure, unstable cardiac arrhythmia, etc.) within the 3 months prior to randomization
14. Significant immunological disease determined by any of the following:
    - Current or anticipated neutropenia defined as less than 500 neutrophils/mm^3
    - Known infection with Human Immunodeficiency Virus (HIV) and a cluster of differentiation 4 (CD4) count that is unknown or documented to be less than 200 cells/mm^3 within the last year, or other Acquired Immune Deficiency Syndrome (AIDS)-defining illness as determined by the investigator
15. Receipt of 40 mg of prednisone per day (or equivalent) or receipt of 40 mg of prednisone per day (or equivalent) for more than 14 days in the 30 days prior to randomization
16. History of hypersensitivity or allergic reaction (eg, anaphylaxis, urticaria, other significant reaction) to any tetracycline (eg, minocycline, doxycycline or tigecycline) or nitrofurans (nitrofurantoin)
17. History of pseudotumor cerebri, or prior (within 2 weeks prior to randomization) or planned concomitant use of isotretinoin
18. History of systemic lupus erythematosus or lupus-like syndrome
19. Has current evidence of pancreatitis
20. History of known glucose-6-phosphate dehydrogenase deficiency or hemolytic anemia
21. History of adverse reaction to nitrofurantoin (eg, lung or liver reaction or peripheral neuropathy) after use of nitrofurantoin or other nitrofurans in the past

22. Need for concurrent use of uricosuric drugs (eg, probenecid, colchicine, sulfinpyrazone)
23. Use of other investigational drugs within 5 half-lives or 30 days prior to randomization, whichever is longer
24. Has previously been treated with omadacycline or previously enrolled in this study
25. Unable or unwilling, in the opinion of the investigator, to comply with the protocol requirements, or has any concomitant condition or planned medical intervention that, in the opinion of the investigator, is likely to interfere with evaluation of the response of the infection under study, determination of AEs, or completion of the expected course of treatment.

Test Article; Dose; and Mode of Administration:

Group 1: Omadacycline 300 mg po q12h x 1 day followed by 300 mg po q24h
Group 2: Omadacycline 450 mg po q12h x 1 day followed by 300 mg po q24h
Group 3: Omadacycline 450 mg po q12h x 1 day followed by 450 mg po q24h
Group 4: Omadacycline 450 mg po q12h
Group 5: Nitrofurantoin 100 mg po q12h

Duration of Treatment:

The total duration of therapy for all subjects will be 7 days.

Pharmacokinetic Assessments

- Blood Collection (plasma);
- Urine Collection

Safety Assessments:

- Physical examinations;
- Vital signs (body weight, body temperature, blood pressure [BP], heart rate);
- Laboratory tests (Hematology, serum chemistry, urinalysis);
- AEs and Serious Adverse Events (SAEs);
- AEs of Interest (nausea and vomiting);
- Concomitant medications;
- Pregnancy assessments.

Efficacy Assessments:

- Investigator's assessment of clinical response. Clinical success is defined as resolution of signs and symptoms of the infection to the extent that further antibacterial therapy is not necessary;
- Microbiological assessment of the infection;
- Subject assessment of UTI signs and symptoms severity (via the UTI Symptoms Assessment [UTISA] questionnaire).

Statistical Methods:

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 dosing 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 provided in the statistical analysis plan (SAP). Subjects will be randomized (1:1:1:1:1) to five treatment groups.

The following subject analysis populations have been defined:

- Intent-to-treat (ITT): all randomized subjects.
- Safety: all randomized subjects who receive any amount of test article.
- The microbiological ITT (micro-ITT) population will consist of subjects in the ITT population who have a study-qualifying pre-treatment positive Baseline urine culture with 1 or 2 uropathogens at $\geq 10^5$ Colony Forming Units (CFU)/mL. (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.
- 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 detailed in the SAP.
- 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.

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

The number and percentage of subjects with investigator's assessment of clinical response and a microbiological response will be presented at each time point measured by treatment group. Exact 95% confidence intervals will be determined for the point estimates of the clinical success rates and the microbiological success. A comparison of the clinical success rate at PTE between each omadacycline dose group and the nitrofurantoin group will be conducted using a beta distribution with an uninformative Bayesian prior distribution.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABSSSI	Acute Bacterial Skin and Skin Structure Infection
AE	Adverse Event
AIDS	Auto-Immune Deficency Syndrome
ALT	Alanine Aminotransferase (SGPT)
AST	Aspartate Aminotransferase (SGOT)
B hCG	Serum β-human chorionic gonadotropin
BP	Blood Pressure
CABP	Community-Aquired Bacterial Pneumonia
CD4	Cluster of Differentiation 4
CE	Clinically Evaluable
CFR	Code of Federal Regulations
CFU	Colony Formimg Units
CI	Confidence Interval
CrCl	Creatinine Clearance
CSA	Clincial Study Agreement
CSR	Clinical Study Report
DMC	Data Monitoring Committee
EBSL	Extended Spectrum Beta-Lactamase
eCRF	Electronic Case Report Form
EOT	End of Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference foron Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug

IRB	Institutional Review Board
ITT	Intent-to-Treat
iv	Intravenous
IxRS	Interactive Voice/Web Response System
ME	Microbiologically Evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
Micro-ITT	Microbiological modified Intent-to-Treat
NSAID	Nonsteroidal anti-inflammatory
OTC	Over the Counter
PI	Package Insert
PK	Pharmacokinetics
po	by mouth
PT	Preferred Term
PTE	Post Treatment Evaluation
q24h	Every 24 hours
q12h	Every 12 hours
REB	Research Ethics Board
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TFL	Tables, Figures and Listings
ULN	Upper Limit of Normal
US	United States
UTI	Urinary Tract Infection
UTISA	Urinary Tract Infection Symptoms Assessment
WBC	White Blood Cell (Count)

1 DISCLOSURE STATEMENT

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3 INTRODUCTION

3.1 Uncomplicated Urinary Tract Infection (UTI)

Uncomplicated Urinary tract infection (UTI) or acute cystitis is characterized by dysuria, frequency and urgency with pyuria, and bacteriuria in a person without underlying urologic or renal abnormalities. The burden of UTI is high in women; up to 60% of women have an episode during their lifetime.[1,2,3,4] Long-term morbidity is low; however, the 30% to 40% recurrence rate is significant.[1,2,5] Short-term morbidity has been described in female college students who experienced a mean of 6.1 symptomatic days and 2.4 days of restricted activity per episode.[1,3] Recieveing no treatment or an ineffective treatment for an uUTI increases the duration of symptoms and can be complicated by pyelonephritis in approximately 2.6% of women.[6,7]

Uncomplicated UTIs are predominately caused by *E. coli* (80% to 85%) and *Staphylococcus saprophyticus* (5% to 15%) with a small minority caused by *Klebsiella pneumoniae*, *Proteus mirabilis*, and other uropathogens.[1,6] Increasing rates of resistance among UTI pathogens to trimethoprim/sulfamethoxazole, beta-lactams and fluoroquinolones, as well as, a recent safety warning to previously recommended first-line antibiotics (fluoroquinolone Food and Drud Adminstration [FDA] safety alert and black box warnings) has necessitated reconsideration of antibiotic treatment recommendations.

Fosfomycin and nitrofurantoin are now considered first-line agents in the treatment of UTI. Resistance is generally low however emerging resistance has been observed in multi-drug resistant isolates. As a result, there is a need for new agents with efficacy against resistant uropathogens including extended-spectrum β-lactamase (ESBL) producing *E. coli*.[8]

3.2 Omadacycline

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

Omadacycline has been evaluated in a global Phase 3 study comparing the safety and efficacy of iv and po omadacycline to iv and po linezolid in the treatment of adult subjects with ABSSSI (PTK0796-ABSI-1108). In addition, a global Phase 3 study has been conducted to evaluate the safety and efficacy of iv and po omadacycline compared to iv and po moxifloxacin in the treatment of adult subjects with CABP (PTK0796-CABP-1200). The latest United States (US)-only Phase 3 study compared the safety of po only omadacycline to po only linezolid in the treatment of adult subjects with ABSSSI (PTK0796-ABSI-16301). In all three studies, omadacycline was well-tolerated and demonstrated non-inferiority to its respective comparator. Omadacycline (IV and PO) has recently been approved by US FDA for the treatment of adults with ABSSSI and CABP infections.

The drug is active against strains expressing both mechanisms of tetracycline resistance,namely efflux and ribosomal protection.[9] Omadacycline has in vitro activity against the most common uUTI uropathogens including *E. coli* and *S. saprophyticus.* Resistance to other antibiotics does not affect omadacycline activity. Omadacycline is not affected by tetracycline-resistance, presence of ESBL, or other common resistance mechanisms. Omadacycline is active against the Enterobacteriaceae with a significant proportion of isolates having an minimum inhibitory concentration (MIC) < 2.0 µg/ml. The minimum inhibitory concentrations for at least 90% of the common uUTI pathogens tested (MIC_{90}) for omadacycline are 0.5 µg/mL for *S. saprophyticus*, 2 µg/mL for ESBL-negative *E. coli*, and 2 µg/mL for ESBL-producing *E. coli*.[9]

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

This study is intended to evaluate the efficacy and safety of oral omadacycline as compared to oral nitrofurantoin in the treatment of adult female subjects with cystitis. These data will be important to determine the potential utility of omadacycline for the treatment of UTI and will help in selection of dosing regimens that may be used in future UTI studies.

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

Please refer to the current version of the Investigator's Brochure[10] for additional information on omadacycline.

4 STUDY OBJECTIVES

4.1 Primary Objective

The primary objective of this study is:

To evaluate the efficacy of omadacycline and nitrofurantoin in the treatment of female adults with cystitis.

4.2 Secondary Objectives

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.

5 INVESTIGATIONAL PLAN

5.1 Overall Study Description

This is a randomized, double-blinded, adaptive designed Phase 2 study evaluating 3 dosing regimens of once-daily omadacycline, 1 dosing regimen of twice-daily omadacycline compared to twice-daily nitrofurantoin 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.

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 1 of 3 oral omadacycline dosing regimens or a twice-daily regimen of oral nitrofurantoin (see Table 1 and Table 2). Subjects should receive their first dose of test article at the site within 4 hours after randomization. Treatment will be double-blinded and double-dummy (see Table 2). Please refer to Section 9 of the protocol for further details on study phases and required assessments/procedures per phase.

During the study treatment period, blood samples will be collected for safety analysis and for PK analysis of omadacycline. 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.

Subjects will return to the clinical 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 Post Therapy Evaluation (PTE) on Day 14 (+/- 2 days) after the subject's first dose of test article. A Final Follow-up assessment will be conducted within 30 to 37 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 are not having any symptoms and had no AEs or clinically significant laboratory abnormalities noted at or after the PTE visit. Otherwise, this assessment is to be performed with an in-person study visit. During the Follow-up call/visit if the subject reports symptoms of potential recurrence, additional procedures will be performed.

See Appendix 1 for the full Schedule of Events.

5.1.1 Adaptive Design

This is an adaptive dose-response finding study. Initially, subjects will be randomized (1:1:1:1:1) to five treatment groups. 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 a 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.
Bayesian analyses will be conducted after efficacy data (investigator assessment of clinical response at PTE) are available for approximately 40, 80, and 100 subjects in order to:

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

Additional analyses may be carried out for the same two purposes. Response criteria are targeted toward estimating the probability that the clinical success rate (proportion of subjects) for each omadacycline dose group is within 10% of that of the nitrofurantoin group. If at the analyses, that probability falls below 30% for a particular dose group, recruitment for that dose group may be stopped or curtailed. If that probability exceeds 80% for a particular omadacycline dose group, recruitment for that dose group may be increased to improve the precision of the estimate.

5.2 Rationale for Study Design

Omadacycline is the first member of the aminomethylcycline class of antibiotics, which are semisynthetic derivatives of the tetracycline class. Omadacycline- has in vitro activity against the most common bacterial pathogens associated with cystitis. Omadacycline has been shown to have a significant fraction of the administered dose excreted by the kidneys and is present as active drug in the urine. The safety, efficacy and pharmacokinetics (PK) of omadacycline have been evaluated in a limited number of adults with cystitis.

5.3 Rationale for Control Group

Nitrofurantoin (Macrobid) is approved in the US for the treatment of acute uncomplicated urinary tract infection (acute cystitis) at a dose of 100 mg administered orally every 12 hours (q12h) for 7 days.[11] It is recommended as a first line treatment by the Infectious Disease Society of America and the European Society of Microbiology and Infectious Diseases.[6] Clinical studies have demonstrated equivalent microbiologic eradication with other nitrofurantoin formulations (Macrodantin).[11] Equivalent early and late clinical efficacy and early bacterial cure with other commonly used first line therapies for uUTI including trimethoprim-sulfamethoxazole, fosfomycin, and ciprofloxacin have been demonstrated in four randomized clinical trials.[6] Resistance to nitrofurantoin is low and the therapy is generally well tolerated.[6] The most frequently reported AEs that are possibly or probably drug related include nausea, headache, and flatulence.[11]

5.4 Approximate Duration of Subject Participation

Subjects will participate in the study for up to 37 days. Following Screening, eligible subjects will be randomly assigned to receive 7 days of po treatment of either omadacycline or nitrofurantoin. Subjects will return to the site for an EOT visit within 2 days following the last dose of test article, and then again for a PTE visit on Day 14 (+/- 2 days) after the

subject's first dose of test article. A final follow-up assessment will be conducted within 30 to 37 days following the first dose of test article.

5.5 Approximate Duration of Study

The study is expected to be clinically complete in approximately 24 months.

5.6 Approximate Number of Subjects

Approximately 225 subjects will participate in this study at up to 25 sites.

6 STUDY POPULATION SELECTION

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

6.1 Study Population

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

6.2 Inclusion Criteria

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

Main Criteria for Inclusion:

1. Written and signed informed consent must be obtained before any assessment is performed
2. Females age 18 years or older
3. Onset of 2 or more of the following clinical signs and symptoms of cystitis within 96 hours prior to randomization:
   - Dysuria
   - Frequency
   - Urgency
   - Suprapubic pain

   NOTE: symptoms should be continuing at the time of randomization
4. A clean-catch midstream urine sample with pyuria (white blood cell [WBC] count > 10/μL in unspun urine or ≥ 10 per high power field in spun urine) or dipstick analysis positive (at least ++) for leukocyte esterase. Urine sample must be sent for microbiologic culture prior to randomization.
5. Must have a negative pregnancy test at Screening, and agree to comply with using an acceptable form of birth control (eg, abstinence, oral contraceptive, intrauterine device [IUD], barrier contraception [condom], tubal ligation, hysterectomy, bilateral oophorectomy, postmenopausal or vasectomized partner) from Screening through PTE
6. Ability to swallow 4 tablets/capsules in succession
7. Ability to communicate well with the investigator, to understand and comply with the requirements of the study

6.3 Exclusion Criteria

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

Main Criteria for Exclusion:

1. Males
2. Pregnant or nursing (breastfeeding) women
3. *Criterion no longer applicable as per Protocol Amendment #1*
4. *Criterion no longer applicable as per Protocol Amendment #1*
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 the current cystitis 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]
6. Anticipated need for systemic antibacterial therapy other than test article (for treatment or prophylaxis) during the study period
7. Has a suspected upper UTI (eg, fever [≥ 38°C, ≥ 100.4°F], chills, rigors, flank pain, or costovertebral angle tenderness)
8. Symptoms/signs suggestive of vaginitis or sexually transmitted infection (eg, vaginal discharge or vaginal irritation)
9. Known prior UTI caused by *P. aeruginosa or Proteus* spp., or suspected current infection with *P. aeruginosa* or *Proteus* spp. or nitrofurantoin-resistant pathogen
10. Has a confirmed or suspected complicated UTI, defined as:
    - Use of an indwelling urinary catheter, nephrostomy tubes or other indwelling urinary tract device within the 30 days prior to randomization or scheduled to be used during the study period
    - Known urinary retention (≥ 100 mL of residual urine after voiding) within the 30 days prior to randomization
    - History of surgically modified or abnormal urinary tract anatomy (eg, bladder diverticula or redundant urine collection system)
    - Complete or partial obstruction of the urinary tract, or obstructive uropathy that is scheduled to be medically or surgically relieved during the study therapy period
    - History of renal transplant or a surgically created intestinal conduit for urinary diversion
    - Suspected or confirmed renal calculi, stricture, primary renal disease (eg, polycystic renal disease), neurogenic bladder, or other anatomical or functional abnormalities predisposing to UTI
    - Had an overnight hospital stay within the past 6 months
11. Screening calculated creatinine clearance (CrCl) < 60 mL/minute, using the Cockcroft-Gault equation (see equation in Appendix 2), requires any form of dialysis (eg, hemodialysis, peritoneal dialysis), or other evidence of severe renal disease
12. Has any of the following at Screening:
    - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 × Upper Limit of Normal (ULN)
    - total bilirubin > 1.5 × ULN
    - suspected or confirmed clinical evidence of end-stage liver disease (eg, ascites, hepatic encephalopathy)

13. History of having experienced unstable cardiac disease (eg, unstable angina, myocardial infarction, acute congestive heart failure, unstable cardiac arrhythmia, etc.) within the 3 months prior to randomization
14. Significant immunological disease determined by any of the following:
    - Current or anticipated neutropenia defined as less than 500 neutrophils/mm^3
    - Known infection with Human Immunodeficiency Virus (HIV) and a cluster of differentiation 4 (CD4) count that is unknown or documented to be less than 200 cells/mm^3 within the last year, or other Acquired Immune Deficiency Syndrome (AIDS)-defining illness as determined by the investigator
15. Receipt of 40 mg of prednisone per day (or equivalent) or receipt of 40 mg of prednisone per day (or equivalent) for more than 14 days in the 30 days prior to randomization (see Appendix 2)
16. History of hypersensitivity or allergic reaction (eg, anaphylaxis, urticaria, other significant reaction) to any tetracycline (eg, minocycline, doxycycline or tigecycline) or nitrofurans (nitrofurantoin)
17. History of pseudotumor cerebri, or prior (within 2 weeks prior to randomization) or planned concomitant use of isotretinoin
18. History of systemic lupus erythematosus or lupus-like syndrome
19. Has current evidence of pancreatitis
20. History of known glucose-6-phosphate dehydrogenase deficiency or hemolytic anemia
21. History of adverse reaction to nitrofurantoin (eg, lung or liver reaction or peripheral neuropathy) after use of nitrofurantoin or other nitrofurans in the past
22. Need for concurrent use of uricosuric drugs (eg, probenecid, colchicine, sulfinpyrazone)
23. Use of other investigational drugs within 5 half-lives or 30 days prior to randomization, whichever is longer
24. Has previously been treated with omadacycline or previously enrolled in this study
25. Unable or unwilling, in the opinion of the investigator, to comply with the protocol requirements, or has any concomitant condition or planned medical intervention that, in the opinion of the investigator, is likely to interfere with evaluation of the response of the infection under study, determination of adverse events (AEs), or completion of the expected course of treatment

6.4 Screen Failures

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

7 STUDY TREATMENT(S)

7.1 Treatments Administered

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

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

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

7.2 Identity of the Investigational Product: Omadacycline

Oral Formulation

Name	**Omadacycline Tablet, 150 mg**
Excipients	Lactose monohydrate, microcrystalline cellulose, sodium stearyl fumarate, crospovidone, colloidal silicone dioxide, sodium bisulfite, polyvinyl alcohol, titanium dioxide, talc, glycerol monocaprylocaprate, sodium lauryl sulfate, iron oxide yellow
How supplied	High-Density Polyethylene (HDPE) bottles with induction seal, child resistant closure and desiccant
Storage	Do not store above 25°C (77°F). Protect from moisture
Preparation and handling	No special requirements
Administration	Please reference Table 2 in Section 7.6

7.3 Comparator Test Article: Nitrofurantoin

Oral Formulation

Name	**Macrobid 100 mg capsules (nitrofurantoin Monohydrate/macrocrystals)**
[redacted]	
How supplied	High-Density Polyethylene (HDPE) bottles with induction seal, child resistant closure and desiccant
Storage	Do not store above 25°C (77°F). Protect from moisture
Preparation and handling	No special requirements
Administration	Please reference Table 2 in Section 7.6

HDPE = High-Density Polyethylene; PVC = Polyvinyl Chloride; DBAA=Double-Blind size AA

The comparator drug, nitrofurantoin, is an antibacterial agent specific for urinary tract infections. It has an acceptable and well-defined safety profile. Nitrofurantoin is well-tolerated, can be administered orally, is well-concentrated in the urine and is shown to be effective against common uncomplicated UTI uropathogens including *E. coli* and *Staphylococcus saprophyticus*.

7.4 Dose Selection Rationale

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

- While the driver of efficacy for omadacycline in UTI is not known, a pragmatic assumption was made that maximizing the time of urine concentration above pathogen MIC (ideally, throughout the dosing interval) would be desirable.
- In PTK0796-UUTI-15103, omadacycline dosed as 300 mg po q12h on Day 1 followed by 300 mg po daily for 5 days and 450 mg po q12h on Day 1 followed by 450 mg po daily for 5 days both demonstrated high urinary concentrations on Day 1 and Day 5. For the 300 mg dosing group, over the 24-hour dosing period, mean urinary concentrations ranged from 14 to 20 µg/mL on Day 1 and 17 to 30 µg/mL on Day 5. For the 450 mg dosing group, over the 24-hour dosing period, mean urinary concentrations ranged from 11 to 25 µg/mL on Day 1 and 30 to 48 µg/mL on Day 5.
- In PTK0796-UUTI-15103, both the 300 mg and 450 mg omadacycline treatment groups had nausea reported in 60% of subjects. Vomiting occurred in 40% and 20% of the 300 mg and 450 mg treatment groups, respectively. In the recently completed PTK0796-ABSI-16301 study which compared omadacycline 450 mg po every 24 hours (q24h) for 2 doses followed by 300 mg po q24h for a total of 7 to 14 days to linezolid 600 mg po q12h for a total of 7 to 14 days, nausea and vomiting rates of 30.2% and 16.8% were observed. In both studies, most events of nausea and vomiting occurred early in the treatment associated with the loading doses of omadacycline.
- The effect of a light meal administered approximately 1.5 hours before dosing was evaluated using the free base formulation of omadacycline and resulted in approximately 20% decrease in exposure. In the recently completed study PTK0796-DDI-17106, the effect of a light meal administered approximately 1.5 hours before dosingwith the same formulation of omadacycline used in the pivotal Phase 3 studies was evaluated. The results demonstrated an approximately 19% to 25% reduction in exposure when a light meal was administered 1.5 hours before dosing.
- The Sponsor has decided to add an omadacycline treatment group dosed at 450 mg twice daily for 7 days. The rationale for the change includes:
    1) Since the driver of efficacy is unknown and the mean renal excretion of a 300 mg oral dose is 14.4%, a regimen that maximizes the tolerated dose of omadacycline may provide additional information on the dose necessary for

clinical and microbiologic success in uUTI and allow comparison to the daily dosed omadacycline treatment groups.

6) The proposed dosing of 450mg twice daily for 7 days will provide approximately 2x or greater the amount of omadacycline that is excreted into the urine compared to the daily omadacycline treatment groups.
7) Blinded review of the first 145 subjects reveals good tolerability. Nausea has occurred in approximately 10% of all subjects with only a single subject (0.7%) reporting vomiting. There has been only one treatment discontinuation due to adverse events of nausea and/or vomiting reported. Therefore, even if all cases of nausea and vomiting were in a single omadacycline treatment group, nausea and vomiting appears lower than observed in PTK0796-UUTI-15103 study.
8) Dose-limiting transaminase increases were seen in Phase 1 studies at 600mg IV which is higher than the exposure at 450mg PO twice daily.
9) Increases in heart rate following omadacycline are Cmax associated. Cmax concentrations with the 450mg PO dose (1077 ng/mL) at steady state are approximately one-half the Cmax concentration with the 100mg IV dose (2120 ng/mL) suggesting that heart rate increases above 12-17 bpm observed with 100-200mg IV doses in healthy patients is unlikely following 450mg twice daily dosing.

Therefore based on the pharmacokinetic, clinical, and safety data, the 450mg twice daily dose will increase urinary concentration, may provide additional clinical and microbiologic benefit while maintaining the safety profile observed with daily dosing.

In order to minimize the effect of food on exposure and to potentially minimize the impact of nausea and vomiting during the omadacycline loading dose, omadacycline will be dosed twice on Day 1 with each dose administered approximately 2 hours following a light meal. In addition, all even numbered doses will also be administered approximately 2 hours following a light meal. Given the urinary concentrations observed in PTK0796-UUTI-15103 and the expected impact of a light meal, urinary concentrations should remain above the typical omadacycline MIC_{90} of 2 μg/mL for *E.coli*, the most common uropathogen in uncomplicated cystitis.

7.5 Description of Treatments

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

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*

7.6 Test Article Administration – Fed and Fasting State

All doses of test article should be taken with water. There are fed and fasting requirements for test article administration of the odd numbered doses due to effects of food on oral omadacycline (see Table 2).

Doses 1 & 2 of the omadacycline tablets or placebo tablets resembling omadacycline and nitrofurantoin or placebo capsules resembling nitrofurantoin should be taken approximately 2 hours after a light meal on Day 1 (24-hour period after randomization). In addition, all even numbered doses beginning with Dose 4 will also be administered approximately 2 hours following a light meal. A light meal is defined in general as a meal of < 300 calories (ie, tea or non-calcium fortified orange juice and toast) with no calcium containing products. 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.

Beginning with Dose 3, all consecutive odd numbered doses of the omadacycline tablets and placebo tablets resembling omadacycline 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.

Table 2. Dosing: Double-Blind, Double-Dummy Design

Dosing		Group 1	Group 2	Group 3	Group 4	Group 5	Dosing Condition
		omadacycline	omadacycline	omadacycline	omadacycline	nitrofurantoin	
Day 1	Dose 1	Two 150 mg omadacycline tablets, one placebo tablet resembling omadacycline	Three 150 mg omadacycline tablets	Three 150 mg omadacycline tablets	Three 150 mg omadacycline tablets	Three placebo tablets resembling omadacycline	2 hours after light meal[a]
		One placebo capsule resembling nitrofurantoin	One placebo capsule resembling nitrofurantoin	One placebo capsule resembling nitrofurantoin	One placebo capsule resembling nitrofurantoin	One 100 mg nitrofurantoin capsule	
	Dose 2[b]	Two 150 mg omadacycline tablets, one placebo tablet resembling omadacycline	Three 150 mg omadacycline tablets	Three 150 mg omadacycline tablets	Three 150 mg omadacycline tablets	Three placebo tablets resembling omadacycline	2 hours after light meal[a]
		One placebo capsule resembling nitrofurantoin	One placebo capsule resembling nitrofurantoin	One placebo capsule resembling nitrofurantoin	One placebo capsule resembling nitrofurantoin	One 100 mg nitrofurantoin capsule	
Days 2-7	Dose 3 and odd doses	Two 150 mg omadacycline tablets, one placebo tablet resembling omadacycline	Two 150 mg omadacycline tablets, one placebo tablet resembling omadacycline	Three 150 mg omadacycline tablets	Three 150 mg omadacycline tablets	Three placebo tablets resembling omadacycline	Fasting[c]
		One placebo capsule resembling nitrofurantoin	One placebo capsule resembling nitrofurantoin	One placebo capsule resembling nitrofurantoin	One placebo capsule resembling nitrofurantoin	One 100 mg nitrofurantoin capsule	
	Dose 4 and even doses	Three placebo tablets resembling omadacycline	Three placebo tablets resembling omadacycline	Three placebo tablets resembling omadacycline	Three 150 mg omadacycline tablets	Three placebo tablets resembling omadacycline	2 hours after light meal[d]
		One placebo capsule resembling nitrofurantoin	One placebo capsule resembling nitrofurantoin	One placebo capsule resembling nitrofurantoin	One placebo capsule resembling nitrofurantoin	One 100 mg nitrofurantoin capsule	

Day is defined as the 24-hour period, not calendar day. All subjects will be dosed twice daily, ~12 hours apart, except where noted.

[a] Doses 1 & 2 of the omadacycline tablets or placebo tablets resembling omadacycline and nitrofurantoin or placebo capsules resembling nitrofurantoin should be taken approximately 2 hours after a light meal on Day 1. After dosing, no food for 2 hours and no dairy products, antacids or multivitamins containing multivalent cations (eg, aluminum, magnesium, calcium, bismuth, iron, or zinc) for 4 hours.

[b] Dose 2 can be taken a minimum of 8 hours and up to 12 hours after Dose 1. Dose 3 should be taken a minimum of 8 hours after Dose 2.

[c] Beginning with Dose 3, all consecutive odd numbered doses of the omadacycline tablets and placebo tablets resembling omadacycline 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 for 2 hours, no dairy products, antacids or multivitamins containing multivalent cations (eg, aluminum, magnesium, calcium, bismuth, iron, or zinc) for 4 hours.

[d] Beginning with Dose 4, all even numbered doses should be taken approximately 2 hours after a light meal.

7.7 Dose Adjustments and Interruptions of Test Article

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

7.8 Method of Assigning Patients to Treatment Groups

Initially, all eligible subjects will be randomized via an IxRS that assigns them to 1 of the 5 treatment arms (in a 1:1:1:1:1 ratio). The site delegate will contact the IxRS (via phone or web) 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 as defined in the IxRS specifications and Statistical Analysis Plan (SAP). Subjects randomized into the study will be assigned the treatment corresponding to the next available number from the computer-generated randomization schedule. The subject is considered randomized when the IxRS provides the test article assignment, regardless of whether the subject actually receives any medication. As this is an adaptive design trial, any updates to the randomization schedule based upon the Bayesian analysis will be incorporated into the IxRS system.

7.8.1 Subject Numbering

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

7.9 Dispensing Test Article

Each study site will be supplied by the sponsor with the investigational product and comparator. Test articles will be supplied to the sites in kits that contain active omadacycline tablets or matched placebo tablets, and active nitrofurantoin over-encapsulated capsules or matched placebo over-encapsulated capsules. Oral test article supplies are completely blinded and blinded study personnel can conduct storage, dispensation, and reconciliation. The IxRS will assign the test article kit to be given to the subject. The study coordinator/staff will instruct the subject on the use of po test article.

7.10 Blinding

The investigator and sponsor will be blinded to treatment group assignments throughout the study. The sponsor designee (eg, study statistical team, IxRS vendor, etc.) will have a designated randomization administrator who will maintain the randomization codes in accordance with standard operating procedures to ensure the blind is properly maintained, and that only sponsor personnel who require knowledge of treatment assignments will be unblinded (eg, staff involved in maintaining the randomization codes). The DMC will review safety data and the results from the Bayesian analysis of efficacy based on masked (treatments groups 1 to 4) treatment assignments. Based on this analysis, modifications may be made to the omadacycline treatment groups.

The study will follow a double-dummy design. Subjects assigned to omadacycline will receive active omadacycline tablets and over-encapsulated nitrofurantoin placebo capsules. Subjects assigned to the nitrofurantoin arm will receive omadacycline placebo tablets and over-encapsulated active nitrofurantoin capsules.

Randomization data are kept strictly confidential until the time of database lock and unblinding at the end of the study.

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

7.11 Emergency Unblinding of Treatment Assignment

Emergency unblinding should only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, test article discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. It is encouraged for the investigator, when contemplating unblinding, to contact the sponsor or sponsor's designated Medical Monitor or designee to confirm the need to unblind, prior to unblinding (see Section 2 for contact information). However, if required, the investigator can unblind without consulting the Medical Monitor.

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

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

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

7.12 Prior & Concomitant Therapy

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

7.13 Prohibited Therapy

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

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

- Potentially therapeutic antibacterial agents (with potential activity against uropathogens responsible for UTI) are prohibited for 72 hours prior to randomization through EOT, with the exception of cases where a subject is deemed a clinical failure during the course of the study and requires treatment with an additional antibacterial agent
- Subjects will be instructed to avoid taking antacids and multivitamins containing multivalent cations (eg, aluminum, magnesium, calcium, bismuth, iron, or zinc) for 6 hours before and within 4 hours after doses 1, 2 and all subsequent odd numbered doses
- Non-steroidal anti-inflammatory drugs (NSAIDs) are prohibited
- Anti-spasmodic medications are prohibited
- Consumption of cranberry juice and/or cranberry pills and over-the-counter (OTC) D-mannose-containing products are also prohibited
- Any other treatments used to treat the symptoms of UTI

7.13.1 Concomitant Medications That May Interact with Nitrofurantoin

Use of uricosuric drugs (eg, probenecid, colchicine, sulfinpyrazone) are prohibited from the time of consent through EOT visit.

7.14 Permitted Treatments

All other treatments not specified as prohibited are permitted during the study. Subjects requiring additional or alternative antibacterial therapy for their cystitis will be judged as Clinical Failures and test article will be discontinued. Further treatment for their infection is

at the discretion of the investigator or the subject's health care provider and will be considered as a concomitant medication.

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

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

7.15 Treatment Compliance

Study personnel at the site should monitor po test article compliance at each study visit by comparing the returned test article with the dosing information reported by the subject. Compliance and any unresolved discrepancies will be documented in the source document and on the drug inventory record. The test article eCRF should reflect the reconciled dosing information provided by the subject.

7.16 Packaging and Labeling

The investigational test article, omadacycline, will be packaged by the sponsor and supplied to the investigator. This includes: omadacycline 150-mg oral tablets and matching placebo.

The comparator test article, nitrofurantoin, will be packaged by the sponsor and supplied to the investigator. This includes: nitrofurantoin 100-mg oral capsules and matching placebo.

7.17 Storage and Accountability

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

The designated study personnel must maintain an accurate record of the shipment and dispensing of test articles in the study specific medication accountability ledger. Test article supplies are completely blinded. Subjects will be asked to return all unused test article and packaging at each visit and at the end of the study, last study visit or at the time of test article discontinuation. Monitoring of oral medication accountability will be performed by the field monitor during site visits and at the completion of the study.

7.18 Investigational Product Retention at Study Site

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

8 STUDY PROCEDURES

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

8.1 Informed Consent

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

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

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

8.2 Subject Demographics/Other Baseline Characteristics

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

8.3 Medical History

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

8.4 Physical Examination

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

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

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

8.5 Vital Signs

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

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

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

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

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

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

8.6 Clinical Laboratory Tests

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

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

The total volume of blood collected from each subject will be approximately 4 – 14 mL per visit, or approximately 48 mL (3 tablespoons) over the course of the study.

8.6.1 Central Laboratory Parameters

Clinical laboratory tests will include the following:

Table 3. Clinical Laboratory Tests (Central)

Hematology:
Hematocrit (Hct)
- Hemoglobin (Hgb)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Mean corpuscular volume (MCV)
- Platelet count
- Red blood cell (RBC) count
- White blood cell (WBC) count with differential

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

8.6.2 Local Laboratory Parameters

8.6.2.1 Pregnancy Assessments

All subjects will have a local urine or serum pregnancy test at the site at the Screening and PTE visits. Urine pregnancy test kits will be provided by the sponsor through the Central Laboratory. If a positive urine or serum pregnancy test result is obtained at the site during Screening, the subject is not to be randomized. A serum sample for Serum β-human chorionic gonadotropin (β-hCG) testing will be collected at the Screening visit and sent to the Central Laboratory for confirmation of the local urine or serum pregnancy test results as well as at EOT. If a positive β-hCG result is reported by the Central Laboratory after a subject is enrolled, test article administration should be discontinued (see Section 8.15.6).

8.6.2.2 Urine Culture and Dipstick Tests

A clean-catch midstream urine sample should be collected and immediately sent to the local microbiology laboratory for microscopic examination and culture. The sample should be analyzed for pyuria microscopically (WBC count greater than 10/μL in unspun urine or greater than or equal to 10 per high power field in spun urine) or by urine dipstick test for leukocyte esterase. Results will be recorded on the eCRF.

Quantitative urine culture by appropriate methods should be performed using a calibrated loop that would identify bacteria at a lower limit of 1.0×10^3 colony forming units (CFU)/mL. A study-qualifying pretreatment Baseline culture must grow at least 1 and no more than 2 bacterial isolates at $\geq 1.0 \times 10^5$ CFU/mL each. If more than two bacterial isolates are identified, the culture will be considered contaminated. In general, at any visit, bacteria identified at 1.0×10^5 CFU/mL or greater should be considered a bacterial pathogen (probability of true pathogen is greater than probability of contamination). At any visit after Screening, a pathogen 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.

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

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

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

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

8.7 Efficacy assessments

8.7.1 Investigator's Assessment of Clinical Response

8.7.1.1 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: 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.

8.7.1.2 Investigator's Assessment of Clinical Response at PTE

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.

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

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.

8.8 Subject Assessment of UTI Signs and Symptoms Severity

The subject will record her assessment of UTI signs and symptoms severity using the UTI Symptoms Assessment questionnaire (UTISA). The UTISA is a 14-item instrument asking about the severity and bothersomeness of seven key uUTI symptoms, and applies a 4-point scale: No Symptoms, Mild, Moderate, Severe.

The investigator must review subject's responses to the questionnaire and record any AEs as appropriate (please refer to section 8.15.5).

8.9 Pharmacokinetic Assessments

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

8.9.1 PK Blood Collection and Processing

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

- Day 1: 2 hours after the first odd-numbered dose
- Day 5: During study visit

8.9.2 PK Urine Collection and Processing

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

- Day 3: During study visit
- Day 5: During study visit

8.9.3 Storing and Shipping of PK Samples

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

8.10 Adverse Events

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

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

8.11 Serious Adverse Events

A Serious Adverse Event (SAE) is an AE that:

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

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

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

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

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

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

8.12 Other Reportable Information

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

- Pregnancy exposure to a test article: If a pregnancy is confirmed, use of the test article must be discontinued immediately. Information about pregnancy exposure includes the entire course of pregnancy and delivery, and perinatal and neonatal outcomes, even if there are no abnormal findings.
- Lactation exposure to a test article with or without an AE
- Overdose of a test article as specified in this protocol with or without an AE
- Inadvertent or accidental exposure to a test article with or without an AE

8.13 Overdose

Any administration of omadacycline of greater than 1350 mg within a 24-hour period will be an overdose, regardless of whether the overdose is intentional or accidental, it is a reportable event and the sponsor must be notified within 1 business day. Any administration of greater than 300 mg of nitrofurantoin within a 24-hour period will be an overdose. In the event that a study subject takes an overdose of test article, the investigator may obtain the subject's treatment assignment by contacting the IxRS. Interactive Response System will also provide a confirmation report of the drug assignment to site personnel. The site personnel will retain this confirmation report. In the case of a potential overdose, the subject should maintain a high level of fluid intake to promote urinary excretion (as recommended in the nitrofurantoin USPI[11]).

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

8.14 Medication Errors

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

Medication errors include, but are not limited to, the following:
- The administration and/or consumption of test article that has not been assigned to the subject
- Administration of expired test article

All AEs and SAEs must be handled as specified in this protocol whether or not they are associated with a medication error. A medication error associated with an SAE (including overdose, inadvertent exposure, and/or accidental exposure) will be reported with the SAE on the SAE Report Form. All other medication errors will be reported by e-mailing the Clinical Test Article Error Incident Report Form as indicated in the Emergency Contacts (see Section 2).

8.15 Recording and Reporting

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

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

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

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

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

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

8.15.1 Serious Adverse Event Reporting

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

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

8.15.2 Assessment of Relatedness

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

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

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

8.15.3 Assessment of Severity

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

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

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

8.15.4 Laboratory Findings

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

8.15.5 Worsening or Progression of Disease Under Study

Worsening or progression of the qualifying UTI should be recorded as a clinical failure (as part of the efficacy assessment), rather than an AE, unless the worsening/progression also meets the criteria for a serious AE (in which case the event also should be reported as an SAE). In contrast, any new or secondary infections that the investigator considers to be distinct from the qualifying UTI should be reported as AEs in all cases, whether non-serious or serious.

8.15.6 Pregnancies

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

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

8.16 Concomitant Medication Assessments

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

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

8.17 Subject Discontinuation or Withdrawal

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

Subjects who discontinue study treatment should not be considered withdrawn from the study (unless the subject withdraws informed consent). The date and primary reason for

discontinuation of study treatment should be recorded. Subjects who discontinue study treatment prematurely should complete the EOT visit, PTE visit and Final Follow-up Assessment, if possible (see Schedule of Events - Appendix 1). The site should also collect subject safety information through the Final Follow-up assessment.

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

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

9 STUDY ACTIVITIES

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

9.1 Screening Phase

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

- Demographics
- Medical history
- Physical examination
- Vital signs: body weight & height, body temperature, blood pressure, heart rate
- Review of inclusion/exclusion criteria
- Laboratory tests (blood):
  - hematology (includes coagulation)
  - chemistry
  - serum pregnancy test
- Laboratory tests (urine):
  - Urinalysis via dipstick with optional microscopic exam_
  - Urine culture
  - Urine pregnancy test
- Concomitant medications (past 7 days)
- AEs since the signing of the ICF
  Subject assessment of UTI signs and symptoms severity (UTISA questionnaire)

9.2 Double-Blind Treatment Phase (Day 1, Day 3 and Day 5 In-Office Visits)

The double-blind treatment period is 7 days in duration. Subjects who meet all of the inclusion criteria and none of the exclusion criteria may be randomized.

9.2.1 Day 1 Visit Procedures

The following assessments will be performed:

- Review of inclusion/exclusion criteria
- Randomization
- Concomitant medications
- Vital signs: body temperature, blood pressure, heart rate
- AEs
- Dispensation and Administration of test article (2 hours after light meal)
- PK blood collection (2 hours after first odd numbered dose of test article)
- Subject assessment of UTI signs and symptoms severity (UTISA questionnaire)

9.2.2 Day 3 Visit Procedures

The following assessments will be performed:

- Subject assessment of UTI signs and symptoms severity (UTISA questionnaire)
- Concomitant medications
- Laboratory tests (urine):
  - Urinalysis via dipstick with optional microscopic exam
  - Urine culture
- Vital signs: body temperature, blood pressure, heart rate
- AEs
- PK urine collection
- Administration and accountability of test article

9.2.3 Day 5 Visit Procedures

The following assessments will be performed:

- Subject assessment of UTI signs and symptoms severity (UTISA questionnaire)
- Concomitant medications
- Laboratory tests (urine):
  - Urinalysis via dipstick with optional microscopic exam
  - Urine culture
- Vital signs: body temperature, blood pressure, heart rate
- AEs
- PK blood collection
- PK urine collection
- Administration and accountability of test article

9.3 Double-Blind Treatment Phase (Day 2, Day 4 and Day 6 At-Home Requirements)

- Administration of test article
- Subject assessment of UTI signs and symptoms severity (UTISA questionnaire)

9.4 End of Treatment/Day 7 Visit Procedures

The End of Treatment (EOT)/Day 7 evaluation should be conducted on the day of or within the 2 days following the last dose of test article. If the subject voluntarily withdraws or is discontinued from her dosing regimen, these procedures should be performed on that day:

- Subject assessment of UTI signs and symptoms severity (UTISA questionnaire)
- Concomitant medications
- Physical Examination
- Vital signs: body weight, body temperature, blood pressure, heart rate
- Laboratory tests (blood):

  - hematology (includes coagulation)
  - chemistry
  - serum pregnancy test
- Laboratory tests (urine):
  - Urinalysis via dipstick with optional microscopic exam
  - Urine culture
- AEs
- Investigator's assessment of clinical response
- Accountability of test article

9.5 Follow-up Phase

9.5.1 Post-Treatment Evaluation (PTE) Visit

The PTE visit should be conducted on Day 14 (+/- 2 days) after the subject's first dose of test article. This evaluation should also be conducted for any prematurely withdrawn subject. The following assessments will be performed at the PTE visit:

- Subject assessment of UTI signs and symptoms severity (UTISA questionnaire)
- Physical examination
- Concomitant medications
- Laboratory tests (urine):
  - Urinalysis via dipstick with optional microscopic exam
  - Urine culture
- Vital signs: body temperature, blood pressure, heart rate
- Laboratory tests (blood):
  - hematology (includes coagulation) *
  - chemistry *
  - serum pregnancy test

    *Note: hematology & chemistry will be performed only if clinically significant abnormalities were noted at EOT
- AEs
- Investigator's assessment of clinical response

9.5.2 Final Follow-up

The Final Follow-up assessment should be conducted 30 to 37 days following the subject's first dose of test article. This evaluation should also be conducted for any prematurely withdrawn subject with the exception of subjects who withdraw consent. The Final Follow-up assessment may be conducted via telephone contact or by another interactive technology for subjects who are not having any symptoms and had no AEs or clinically significant laboratory abnormalities noted at or after the PTE visit. Otherwise, the visit must be conducted in person.

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

- Subject assessment of UTI signs and symptoms severity (UTISA questionnaire)
- Concomitant medications
- AEs
- Investigator's assessment of clinical response

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

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

10 STUDY SUSPENSION, TERMINATION, AND COMPLETION

10.1 Study Completion and Post-Study Test Article

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

No long-term follow-up of subjects is planned, with the exception of pregnancies, as described in Section 8.15.6, and SAEs described in Section 8.15.1.

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

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

10.2 Study Suspension or Termination

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

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

11 QUALITY CONTROL AND ASSURANCE

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

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

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

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

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

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

12.2 Determination of Sample Size

Enrollment of 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 pertreatment 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 provided in the SAP.

12.3 Analysis Populations

The following subject analysis populations have been defined:

- Intent-to-treat (ITT): all randomized subjects.

- Safety: all randomized subjects who receive any amount of test article.
- The microbiological ITT (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 $\geq 10^5$ CFU/mL.
- 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 detailed in the SAP
- 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.

12.4 Demographics and Baseline Characteristics

Demographics (including age, ethnicity and race) and Baseline characteristics will be summarized in the ITT population by treatment group.

Descriptive statistics of the duration of test article treatment will be provided by treatment group. The number and percentage of subjects who prematurely discontinued test article and the reason for discontinuation and the number and percentage of subjects prematurely discontinuing the study and the primary reason for discontinuation will be presented by treatment group.

12.5 Primary Endpoint(s)

12.5.1 Efficacy Endpoint

The primary efficacy endpoint is the Investigator's assessment of clinical success at PTE in the ITT population. The number and percentage of subjects with an Investigator's assessment of clinical success, clinical failure and indeterminate response at the PTE visit will be determined by treatment group in the ITT population. Exact 95% confidence intervals will be determined for the point estimates of the clinical success rates in each treatment group.

A comparison of the clinical success rate at the PTE Visit between each omadacycline dose group and the nitrofurantoin group will be conducted using a beta distribution with an uninformative Bayesian prior distribution. Additional analyses on the primary efficacy endpoint will be performed using Bayesian modeling. Details are described in SAP.

12.6 Secondary Endpoint(s)

12.6.1 Safety Endpoint(s)

All safety analyses will utilize the Safety population. Summary tables will be provided for all treatment-emergent adverse events (TEAEs). A TEAE is defined as an AE with a start date and time on or after the first dose of test article. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by presenting the number and percentage of subjects having each TEAE for each treatment group by system

organ class (SOC) and preferred term (PT), by SOC, PT and severity, and by SOC, PT and relationship to test article. Additional tabulations will provide summaries by SOC and PT of subjects experiencing SAEs and TEAEs judged to be related to test article.

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

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

12.6.2 Efficacy Endpoint(s)

The number and percentage of subjects with an Investigator's assessment of clinical success, clinical failure and indeterminate response at the EOT Visit (ITT and CE populations; by definition subjects in the CE population cannot have an indeterminate response) and PTE visit (CE and micro-ITT population) 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.

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

12.7 Interim Analysis

This is an adaptive dose-response finding study. Bayesian analysis will be conducted when primary efficacy endpoint data (investigator assessment of clinical response at PTE) is available from 40, 80 and 100 subjects in order to:

- Determine if omadacycline dose group(s) that 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.

Additional analyses may be carried out for these same two purposes. Response criteria are targeted toward estimating the probability that the clinical success rate (proportion of subjects) for each dose group is within 10% of that of the nitrofurantoin group. If at the specified analysis time point, that probability falls below 30% for a particular omadacycline dose group, recruitment for that omadacycline dose group may be stopped or curtailed by changing the randomization ratio. If that probability exceeds 80% for a particular

omadacycline dose group, recruitment for that dose group may be increased by changing the randomization ratio to improve the precision of the estimate.

Results from the Bayesian analysis will be reviewed by a 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. A DMC charter describing the composition of the DMC, roles and responsibilities, and statistical parameters will be developed and finalized prior to the first data review.

12.8 Data Monitoring Committee

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

13 ADMINISTRATIVE CONSIDERATIONS

13.1 Investigators and Study Administrative Structure

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

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

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

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

13.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

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

13.3 Ethical Conduct of the Study

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

13.4 Patient Information and Consent

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

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

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

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

13.5 Direct Access, Data Handling, and Record Keeping

13.5.1 Investigator

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

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

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

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

13.5.2 Sponsor

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

13.6 Protocol Adherence

13.6.1 Violations/Deviations

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

13.6.2 Protocol Amendments

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

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

13.7 Subject Injury

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

13.8 Pre-Study Documentation

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

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

13.9 Retention of Data

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

13.10 Publication and Disclosure Policy

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

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

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

14 REFERENCE LIST

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11 Macrobid, US Package Insert.

Appendix 1 Schedule of Events

Study Phase	**Screening[a]**	**Treatment Phase**				**Follow-up Phase**	
Evaluation		**Day 1[b]**	**Day 3**	**Day 5**	**EOT[c]**	**PTE[r]**	**Final Follow-up[s]**
Signed Informed Consent[d]	X						
Subject assessment of UTI symptoms[e]	X	X----------X				X	X
Demographics	X						
Medical History	X						
Prior & Concomitant Medications[f]	X	X----------X					
Clean-catch, midstream urine sample:							
Urine dipstick for nitrites and leukocyte esterase (or microscopic evaluation for white blood cells)[g]	X		X	X	X	X	X[t]
Urine culture[h]	X		X	X	X	X	X[t]
Physical examination[i]	X				X	X	
Vital signs:							
Body weight (in kg)	X				X		
Body temperature	X	X	X	X	X	X	X[t]
Blood pressure	X	X[j]	X	X	X	X	X[t]
Heart rate	X	X[j]	X	X	X	X	X[t]
Hematology[k]	X				X	X[u]	
Serum chemistry	X				X	X[u]	
Local urine or serum pregnancy test[l]	X					X	
Central serum pregnancy test[m]	X				X		
Adverse Events[n]	X	X----------X					
Review of Inclusion and Exclusion Criteria	X	X					
Randomization (if eligible)		X					
Test Article							
Test Article Dispensation		X					
Test Article Administration – 2 hours after light meal[o,p]		X					
Test Article Administration[o]			X----------X				
Test Article Accountability[o]			X	X	X		
PK blood collection[q]		X		X			
PK urine collection			X	X			
Investigator's Assessment of Clinical Response					X	X	X

Study Phase	Screening[a]	Treatment Phase				Follow-up Phase	
Evaluation		**Day 1[b]**	**Day 3**	**Day 5**	**EOT[c]**	**PTE[r]**	**Final Follow-up[s]**

AE = adverse event; β-hCG = β-human chorionic gonadotropin; BP = blood pressure; CFU = colony forming unit; eCRF = electronic case report form; EOT = end of treatment; ICF = informed consent form; PK = pharmacokinetics; PTE = post therapy evaluation; SAE = serious adverse event; UTI = urinary tract infection; UTISA= urinary tract infection system assessment; WBC = white blood cell.

[a] Following the signing of an ICF, all Screening evaluations should be completed within the 24 hours prior to randomization.

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

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

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

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

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

[g] A clean-catch, midstream urine sample should be collected and immediately sent to the local microbiology laboratory for microscopic evaluation and culture. Quantitative urine culture by appropriate methods should be performed using a calibrated loop that would identify bacteria at a lower limit of 10^3 CFU/mL. White blood cell counts should be measured by microscopy from spun or unspun urine or dipstick analysis for leukocyte esterase and nitrites. The statement "or microscopic evaluation for white blood cells" refers to the alternative method to assess for the presence of pyuria (inclusion #4), but the dipstick assessment is required regardless of how inclusion is assessed.

[h] Urine isolates that grow $\geq 10^3$ CFU/mL (whether at Baseline or post-Baseline) and are not deemed to be a contaminant as detailed in the Micro Manual, are to be sent from the local lab to the Central Lab for further analysis.

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

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

[k] Hematology includes coagulation.

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

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

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

[o] Subjects should receive their first dose of test article within 4 hours after randomization in the office with a light meal. All other doses can be administered by subject at home. Beginning with Dose 3, all consecutive odd numbered doses of the omadacycline tablets and placebo tablets resembling omadacycline should be taken in a fasted state. Beginning with Dose 4, all even numbered doses should be taken approximately 2 hours after a light meal. The total duration of po test article therapy for all subjects will be 7 days. At the EOT visit, subjects will return any remaining unused po test article and site staff will perform accountability.

[p] Dose 2 can be taken a minimum of 8 hours and up to 12 hours after Dose 1. Dose 3 should be taken a minimum of 8 hours after Dose 2.

[q] PK blood collection to occur on Day 1 (2 hours after first dose of test article) and Day 5.

[r] A PTE will occur on Day 14 (+/- 2 days) after the subject's first dose of test article.

[s] A Final Follow-up will occur 30 to 37 days following the first dose of test article. The Final Follow-up may be performed via phone call or another interactive technology.

[t] During the Follow-up call/visit if the subject reports symptoms of potential recurrence, additional procedures will be performed.

[u] Hematology and serum chemistry will be repeated if any clinically significant abnormalities are noted at the EOT visit.

Appendix 2 Equations and Conversion Factors

1. Cockcroft-Gault equation to calculate creatinine clearance (CrCl) (relevant to Exclusion criterion number 11):

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

2. Corticosteroid conversions (relevant to Exclusion criterion number 15):

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

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

Appendix 3 Sponsor Signature

Study Title:	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
Study Number:	PTK0796-UUTI-17201
Protocol Amendment #2 Final Date:	18 February 2019

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

Signed:_____ Date:_____

[redacted]
Paratek Pharma, LLC

Appendix 4 Investigator's Signature

Study Title:	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
Study Number:	PTK0796-UUTI-17201
Protocol Amendment #2 Final Date:	18 February 2019

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

Signed:_____ Date:_____

Investigator Name:_____

Investigator Title:_____

Investigator Affiliation:_____

Investigator Address:_____

Investigator Phone Number:_____

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

SUMMARY OF CHANGES

Product Name: Omadacycline (PTK 0796)

Study Number: PTK0796-UUTI-17201

Date and Version: Version 3, 18 February 2019

Change	Rationale for Change
Addition of 450mg BID omadacycline treatment arm, to be dosed approximately 2 hours after a light meal.	Based on the pharmacokinetic, clinical, and safety data, the 450mg twice daily dose will increase urinary concentration, may provide additional clinical and microbiologic benefit while maintaining the safety profile observed with daily dosing. Refer to the protocol for additional/detailed rationale supporting this change.
Increased sample size to approximately 225 subjects (previously approximately 200 subjects).	The approximate total enrollment will increase to accommodate the addition of the 450mg BID treatment arm. The initial goal was to enroll at least n=53 subjects per arm for final analysis. Sample size may be increased for a particular omadacycline dose group, based on recommendations from DMC to change randomization ratio and/or drop 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.
Addition of statement regarding omadacycline approved uses	Omadacycline has recently been FDA-approved for CABP & ABSSSI (since original version of protocol was written)
Increased the approximate duration of the study to 24 months	Due to enrollment progressing slower than originally projected and the addition of 25 subjects to overall sample size
Indicated that additional analyses on the primary efficacy endpoint will be performed using Bayesian modeling.	An additional sensitivity analysis will be conducted on the efficacy endpoints to ensure improved interpretation and precision of estimates of efficacy analysis for dose selection.

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

SUMMARY OF CHANGES

Product Name: Omadacycline (PTK 0796)

Study Number: PTK0796-UUTI-17201

Date and Version: Version 2, 29 October 2018

Protocol Section	Change
Synopsis	Reference to ECG removed as this is not a required study procedure and was included in error
Synopsis & Exclusion Criteria	Exclusion criterion #4 removed (in alignment with current FDA UUTI guidance) & marked as *not applicable*
Synopsis & Exclusion Criteria	Inclusion criteria #3 timepoint for onset of symptoms related to randomization clarified & Exclusion criterion #3 removed/marked as *not applicable*
Synopsis & Exclusion Criteria	Exclusion criteria #7 temperature parameters for fever slightly modified to align with current UUTI FDA Guidance
Synopsis & Exclusion Criteria	Exclusion criteria #10 updated to specify for a '*confirmed or suspected* complicated UTI'
Study Procedures & Schedule of Assessments	Clarified timing of Day 1/Dose 1 PK collection
Efficacy Assessments	New section 8.7.1.3 added to collect Investigators Assessment of Clinical Response at Final Follow-up visit (*per previously issued protocol clarification letter)*
Concomitant Medication Assessments	updated title of eCRF page
Adaptive Design, Interim Analysis, Statistical Methods	probability % updated
Other Reportable Information	Removed references to paternal/male subject reporting as this is N/A for this study
UTISA	added reference to section 8.15.5 which discusses handling of worsening of disease under study and AE reporting
Multiple	Several section hyperlinks corrected
Schedule of Assessments	Typos corrected & footnotes G & U clarified