Clinical Trial Protocol: IT-004-401

Study Title:	A prospective, Phase 4, open label, multi-center study of the clinical and microbiologic efficacy of ciprofloxacin for the treatment of uncomplicated urinary tract infections in adult women.
Study Number:	IT-004-401
Study Phase:	Phase 4
Product Name:	Ciprofloxacin
Indication:	Uncomplicated urinary tract infection
Investigators:	Multicenter
Sponsor:	Iterum Therapeutics US Limited
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	Date
Original FINAL Protocol	September 29, 2017

Confidentiality Statement

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SYNOPSIS

Sponsor:

Iterum Therapeutics US Limited

Name of Finished Product:

Ciprofloxacin

Study Title:

A prospective, Phase 4, open label, multi-center study of the clinical and microbiologic efficacy of ciprofloxacin for the treatment of uncomplicated urinary tract infections in adult women.

Study Number:

IT-004-401

Study Phase: Phase 4

Primary Objective(s):

To evaluate the clinical and microbiologic response of patients with a uUTI treated with ciprofloxacin.

Secondary Objective(s):

To evaluate the validity of specific tests found on the urine dipstick as a screening tool to identify symptomatic patients with a positive urine culture, defined as growth of $\geq 10^5$ CFU/mL of a uropathogen at baseline.

Study Design:

This prospective, Phase 4, open label, multi-center study documents the clinical and microbiologic response of adult women patients with uUTI treated empirically with ciprofloxacin. Approximately 250 adult women with uUTI will receive oral ciprofloxacin 250 mg twice daily for 3 days.

The primary outcome measure for efficacy evaluation will be the overall response on Day 12 (+/- 1 day). For the primary efficacy evaluation, these percentages will be based on a microbiologic-modified intent to treat population (m-MITT). The m-

MITT population will be comprised of all patients who received at least one dose of ciprofloxacin and had $\geq 10^5$ CFU/mL of a baseline pathogen isolated from a urine culture specimen taken at baseline, prior to initiation of ciprofloxacin therapy.

Study Population:

A total of approximately 250 patients are planned.

Inclusion Criteria:

1. Female patients ≥18 years of age with more than 24 hours of urinary symptoms attributable to a UTI
2. Two of the following signs and symptoms of uUTI: urinary frequency, urinary urgency, pain or burning on micturition, suprapubic pain, gross hematuria
3. A mid-stream urine specimen collected for the purpose of diagnosing a UTI with:
    a. a dipstick analysis positive for nitrite **AND**
    b. a dipstick analysis positive for leukocyte esterase
4. Has given written informed consent to participate in the study prior to Screening/Baseline (D1)

Exclusion Criteria:

1. Presence of signs and symptoms suggestive of acute pyelonephritis defined as: fever (temperature > 38° Celsius), chills, costovertebral angle tenderness, flank pain, nausea and/or vomiting
2. Receipt of prior effective antibacterial drug therapy for uUTI for the presenting illness unless the recovered pathogen demonstrates resistance to the initial antibiotic and clinical symptoms persist

3. Concurrent use of non-study antibacterial drug therapy that would have a potential effect on outcome evaluations in patients with uUTI
4. Patients with ileal loops or urinary stoma
5. Patients with an indwelling urinary catheter in the previous 30 days
6. Patients with paraplegia
7. Patients who are likely to receive ongoing antibacterial drug prophylaxis after treatment of uUTI (e.g., patients with vesico-ureteral reflux)
8. Any history of trauma to the pelvis or urinary tract
9. Patient's urine culture results, if available at study entry, identify more than 2 microorganisms regardless of colony count or a potential fungal pathogen
10. Patient's urine culture results, if available at study entry, identifies causative uropathogen for the presenting illness to be resistant to ciprofloxacin
11. Patient has severe chronic kidney disease, or is receiving hemodialysis, or peritoneal dialysis or had a renal transplant
12. Patient is known to have severe neutropenia
13. Patient is known to be pregnant
14. Patients with uncontrolled diabetes mellitus
15. Patients with a known history of myasthenia gravis
16. Patients who require concomitant administration of tizanidine
17. Patients with a history of allergy to quinolones
18. Patient is considered unlikely to survive the study period or has a rapidly progressive or terminal illness, including septic shock, associated with a high risk of mortality

Test Product, Dose, and Mode of Administration:

Patients will receive ciprofloxacin 250 mg, to be taken by mouth twice daily for 3 days.

Formulation and Packaging:

The site Investigator or designee will provide the patient with either a pharmacy prescription or a supply for a 3 day (250 mg BID) course of generic ciprofloxacin for the treatment of their uUTI. The generic ciprofloxacin will be supplied by a local pharmacy, in the form of a filled prescription, that includes 6- 250 mg tablets of ciprofloxacin.

Preparation and Dispensing:

All generic ciprofloxacin will be prepared and provided to the patient via a prescribing pharmacy prescription, or, provided by the Investigator or designee.

Administration:

The patient will receive one 3-day treatment course of generic ciprofloxacin, with instructions to take one tablet or capsule of oral ciprofloxacin 250 mg twice daily beginning day 1 through 3 (+ 1 day).

In the event a patient's first dose is taken in the PM on Day 1, the patient will be expected to take an AM dose on Day 4 to receive the 6 doses of ciprofloxacin, and the EOT visit will occur on day 4 instead of day 3.

Safety Assessments

Safety will be assessed by means of collection of adverse events. Adverse events will be collected at every visit, beginning from the signing of Informed Consent.

Efficacy Assessments:

The assessment of clinical response includes a review of the following symptoms: urinary frequency, urinary urgency, pain or burning on micturition, suprapubic pain and gross hematuria.

Microbiologic response assessments will be made based on quantitative cultures performed on collected urine specimens.

Statistical Methods:

General Statistical Considerations:

Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minimums, and maximums for continuous variables will be provided. Comparisons will be made between response rates for patients with infection due to ciprofloxacin-susceptible and ciprofloxacin-non-susceptible isolates. Exploratory analyses may also be performed. Listings of individual patient's data will be produced.

Efficacy Analyses:

The study is designed to determine the clinical and microbiologic response of patients with a uUTI, due to ciprofloxacin-sensitive and ciprofloxacin-non-susceptible isolates, treated with ciprofloxacin for the outcome measure of overall response (combined clinical and microbiologic response) at Day 12 **(**+/- 1 day).

A patient will be defined as a responder if the following criteria are met:

- The patient is alive
- The patient has received no rescue therapy for uUTI
  - If an antibiotic active against the urinary tract pathogen is given for other reasons, then the patient will be considered indeterminate, and analyzed as a non-responder for uUTI
- The patient has resolution of the symptoms of uUTI present at trial entry and no new uUTI symptoms
- Urine culture taken on Day 12 (+/- 1 day) demonstrates $<10^3$ CFU/mL of the baseline uropathogen

All other patients will be considered non-responders. If data are unavailable to determine if the patient is a responder or non-responder, the patient will be considered an indeterminate response.

The number and percentage of responders, non-responders and indeterminates will be determined. Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minimums, and maximums for continuous variables will be provided. In addition to the randomized m-MITT population, additional analyses will be performed in the subset of patients with ciprofloxacin-susceptible organisms at baseline and in

those with ciprofloxacin-non-susceptible organisms at baseline. Exploratory analyses may also be performed. Listings of individual patient's data will be produced. A comprehensive Statistical Analysis Plan (SAP) will be finalized prior to the database lock.

The number and percentage of patients with a microbiologic success at the Day 12 (+/-1 day) visit will be determined. The validity of the urine dipstick as a screening tool to identify patients with a positive urine culture will be evaluated by calculating the percentage of patients with both a positive nitrite test and a positive test for pyuria on dipstick/urinalysis, who have $\geq 10^5$ CFU/ml of a uropathogen isolated from urine culture. Safety analyses will be conducted in all patients who receive any amount of ciprofloxacin. Safety will be assessed through summaries of AEs.

Date of Original Approved Protocol: September 29, 2017

Date of Most Recent Protocol Amendment (if applicable): March 27, 2018

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC_{0-24}	Area under the curve from zero to 24 hours
βhCG	Beta Human Chorionic Gonadotropin
BUN	Blood Urea Nitrogen
C_{max}	Maximum concentration
CA	Community-acquired
CBC	Complete Blood Count
CE	Clinically Evaluable
CI	Confidence Interval
CLSI	Clinical and Laboratory Standards Institute
CrCl	Creatinine Clearance
CRF	Case Report Form
CTA	Clinical Trial Application
ECG	Electrocardiogram
E.coli	*Escherichia coli*

EIU	Exposure in Utero
EOT	End of Treatment Visit
ESBL	Extended Spectrum Beta-lactamase
FDA	Food and Drug Administration
FSH	Follicle-stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl Transpeptidase
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
HPF	High Power Field
hs-CRP	High-sensitivity C-reactive Protein
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IRB/IEC	Institutional Review Board /Independent Ethics Committee
ITT	Intent-to-Treat
IUD	Intrauterine Device
IV	Intravenous
IWRS	Interactive Web Randomization System

LDH	Lactate Dehydrogenase
LTFU	Lost to Follow-Up
ME	Microbiologically Evaluable
MIC	Minimal Inhibitory Concentration
MITT	Modified ITT (MITT)
mMITT	Micro-MITT (mMITT)
NI	Non-inferior
PK	Pharmacokinetic
PK/PD	Pharmacokinetic / Pharmacodynamic
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TOC	Test of Cure
T_{max}	Time to maximum concentration
uUTI	Uncomplicated urinary tract infection
WBC	White Blood Cell

1 INTRODUCTION

1.1 Indication

Ciprofloxacin is being studied for the treatment of the following indications:

- Uncomplicated urinary tract infections

1.2 Background and Rationale

1.2.1 Rationale for Study

ß-lactam antimicrobials are widely recognized for their efficacy and low toxicity and form the cornerstone of therapy for the treatment of infections caused by gram-positive and gram-negative bacteria. However, extensive use of ß-lactams during the past 50 years has resulted in the development of microbial resistance to these agents among clinically important bacteria. This resistance commonly takes the form of ß-lactamase production, development of porins or alterations in penicillin-binding proteins (PBPs). Such mechanisms have reduced the clinical utility of frequently prescribed ß-lactams such as amoxicillin, amoxicillin plus clavulanate (a ß-lactamase inhibitor), and cephalosporins. For *Escherichia coli*, ampicillin resistance has risen to ≥50% in high-risk populations, and resistance to third generation cephalosporins is now being seen in certain areas. Furthermore, the prevalence of infections caused by extended-spectrum β-lactamase (ESBL) producing Enterobacteriaceae has been increasing worldwide. An analysis of data reported from 2011 to 2014 to the National Healthcare Safety Network performed by the Centers for Disease Control in March 2016 revealed that the proportion of *E. coli* resistant to extended-spectrum cephalosporins causing hospital-acquired infection was 13.4% nationally, with rates as high as 24% reported in some Northeastern, Southern and Western states. The same analysis also demonstrated that over a third of *E. coli* isolates in 2014 were resistant to fluoroquinolones. Data reported by the European Antimicrobial Resistance Surveillance Network (EARS-NET) in Europe demonstrate that the prevalence of fluoroquinolone resistant *E. coli* and *E. coli* resistant to third-generation cephalosporins is > 25% and *E. coli* resistant to third generation cephalosporins, aminoglycosides and fluoroquinolones has increased to >10% in some southern and eastern European countries. Oral antibiotic treatment options are extremely limited for patients with these infections, resulting in lengthy hospital stays to facilitate administration of intravenous antibiotics, even for those with uncomplicated infections. The currently available oral antibiotics with activity against ESBL

producing organisms include nitrofurantoin, fosfomycin, fluoroquinolones and trimethoprim-sulfamethoxazole. Nitrofurantoin and fosfomycin are only approved for the treatment of uncomplicated urinary tract infections in the United States, have rising rates of resistance and are associated with inferior efficacy [Munoz-Davila 2014; Schito 2009]. Resistance to trimethoprim-sulfamethoxazole is uniformly above 20% in the US. Increasing prevalence of resistance to fluoroquinolones and their propensity to cause collateral damage resulted in relegation of fluoroquinolones to second-line therapy by the Infectious Disease Society of America (IDSA) for UTI [Gupta 2011]. Even with these limitations, almost two-thirds of patients with a uUTI receive therapy with a fluoroquinolone antibiotic. Furthermore, there is a percentage of uUTI patients treated with a fluoroquinolone who respond to therapy despite predicted failure based upon the results of in vitro susceptibility testing. The reason for this is likely multifactorial, including PK/PD relationships (i.e., concentration and duration of drug at the site of infection) and host factors. The proportion of patients with infection due to fluoroquinolone resistant pathogens who have clinical or bacteriological response to fluoroquinolone therapy has not been well studied, and most studies which have evaluated this issue have done so as part of a secondary analysis of a UTI treatment trial.

1.2.2 Dose Rationale

Ciprofloxacin

The recommended dose of ciprofloxacin for the treatment of uncomplicated UTI is 250 mg twice daily by mouth for 3 days, per the Ciprofloxacin USPI and Ciprofloxacin SmPC.

2 STUDY OBJECTIVES

2.1 Objectives

The primary objective of this study is to evaluate the clinical and microbiologic response of patients with a uUTI treated with ciprofloxacin.

The secondary objective of this study is to evaluate the validity of specific tests found on the urine dipstick as a screening tool to identify symptomatic patients with a positive urine culture, defined as growth of $\geq 10^5$ CFU/mL of a uropathogen at baseline.

3 STUDY DESIGN

This prospective, Phase 4, open label, multi-center study documents the clinical and microbiologic response of adult women patients with uUTI treated empirically with ciprofloxacin. Since UTIs in males are classified as complicated, males will not be included in this study. Approximately 250 adult women with uUTI will receive oral ciprofloxacin 250 mg twice daily for 3 days.

The primary outcome measure for efficacy evaluation will be the overall response on Day 12 (+/- 1 day). For the primary efficacy evaluation, these percentages will be based on a microbiologic-modified intent to treat population (m-MITT). The m-MITT population will be comprised of all patients who received at least one dose of ciprofloxacin and had $\geq 10^5$ CFU/mL of a baseline pathogen isolated from a urine culture specimen taken at baseline, prior to initiation of ciprofloxacin therapy.

See Appendix 1, Schedule of Activities Table.

3.1 Investigational Study Medications

Patients who present with uUTI symptoms, have a urine dipstick analysis positive for both leukocyte esterase AND nitrite who meet all of the inclusion and none of the exclusion criteria, and who agree to participate in the study, will be treated for their uUTI with ciprofloxacin.

The ciprofloxacin, or a pharmacy prescription for ciprofloxacin, will be provided to the patient by the enrolling study site.
Patients will be asked to take one 250 mg tablet or capsule twice daily (day 1 to 3 + 1 day) for 3 days. In the event a patient's first dose is taken in the PM on Day 1, the patient will be expected to take an AM dose on Day 4 to complete the 6 doses of ciprofloxacin, and the EOT visit will occur on day 4 instead of day 3.

3.2 Adjunctive Systemic Antibiotics

None allowed

3.3 Additional, Non-Study Therapy Antibiotics

Concurrent use of non-study antibacterial drug therapy is permitted only if the therapy would not have a potential effect on outcome evaluations in patients with uUTI.

4 STUDY POPULATION SELECTION

Female patients who present with uUTI and who have a urine dipstick positive for both leukocyte esterase AND nitrite, and who meet all of the inclusion and none of the exclusion criteria will be eligible for participation in this study.

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a particular patient is suitable for enrollment under this protocol.

4.1 Inclusion Criteria

1. Female patients ≥18 years of age with more than 24 hours of urinary symptoms attributable to a UTI
2. Two of the following signs and symptoms of uUTI: urinary frequency, urinary urgency, pain or burning on micturition, suprapubic pain, gross hematuria
3. A mid-stream urine specimen collected for the purpose of diagnosing a UTI with:
    a. a dipstick analysis positive for nitrite **AND**
    b. a dipstick analysis positive for leukocyte esterase
4. Has given written informed consent to participate in the study prior to Screening/Baseline (D1).

4.2 Exclusion Criteria

1. Presence of signs and symptoms suggestive of acute pyelonephritis: fever (temperature > 38°Celsius), chills, costovertebral angle tenderness, flank pain, nausea and/or vomiting
2. Receipt of prior effective antibacterial drug therapy for uUTI for the presenting illness unless the recovered pathogen demonstrates resistance to initial antibiotic and clinical symptoms persist
3. Concurrent use of non-study antibacterial drug therapy that would have a potential effect on outcome evaluations in patients with uUTI
4. Patients with ileal loops or urinary stoma
5. Patients with an indwelling urinary catheter in the previous 30 days
6. Patients with paraplegia
7. Patients who are likely to receive ongoing antibacterial drug prophylaxis after treatment of uUTI (e.g., patients with vesico-ureteral reflux)
8. Any history of trauma to the pelvis or urinary tract
9. Patient's urine culture results, if available at study entry, identify more than 2 microorganisms regardless of colony count or patient has a potential fungal pathogen
10. Patient’s urine culture results, if available at study entry, identifies the causative uropathogen for the presenting illness to be resistant to ciprofloxacin
11. Patient has severe chronic kidney disease, or is receiving hemodialysis or peritoneal dialysis or had a renal transplant
12. Patient is known to have severe neutropenia

13. Patient is known to be pregnant
14. Patients with uncontrolled diabetes mellitus
15. Patients with a known history of myasthenia gravis
16. Patients who require concomitant administration of tizanidine
17. Patients with a history of allergy to quinolones
18. Patient is considered unlikely to survive the study period or has a rapidly progressive or terminal illness including septic shock which is associated with a high risk of mortality

4.3 Enrollment Criteria

Patients will be enrolled into the study to receive ciprofloxacin provided they have satisfied all patient selection criteria.

4.4 Women of Child-Bearing Potential

If the patient is a woman of childbearing potential, she and any male partner are required to simultaneously use 2 effective contraceptive methods, from the following list of 5:

1. A barrier (condoms, diaphragm or cervical cap) with spermicide;
2. A second, different barrier method (condoms, diaphragm or cervical cap);
3. Oral or similar contraceptive, which includes, but is not limited to: injectable, implanted, or patch hormone therapy, and intrauterine device (IUD) at least 7 days prior to baseline;
4. Documented surgical sterilization at least 4 weeks prior to baseline;
5. Partner vasectomy at least 6 months prior to baseline.

She and any male partner must agree to continue all of these contraceptive methods until the TOC Visit. Within these limits, the specific forms of contraception employed are left to the discretion of the patient, and/or the principal investigator, and/or the patient's physician.

Women of childbearing potential include those that meet one of the following criteria:

- Females who are <45 years of age and have not had a documented hysterectomy, tubal ligation and/or bilateral oophorectomy
- Females who are ≥45 years of age and have not been amenorrheic for at least 1 year

5 STUDY TREATMENTS

5.1 Allocation to Treatment

This is a non-randomized, open label, multi-center study of oral ciprofloxacin in the treatment of uUTI. Approximately 250 female patients with uUTI will be administered oral ciprofloxacin twice daily for 3 days. Patients who withdraw prior to initial dose, will be replaced to ensure all 250 patients have received at least a single-dose of ciprofloxacin.

A patient will be eligible for the study once it has been determined that she meets all inclusion criteria and has none of the exclusion criteria.

5.2 Drug Supplies

5.2.1 Formulation and Packaging

The site Investigator or designee will provide the patient with a pharmacy prescription or a supply for a 3 day (250 mg BID) course of generic ciprofloxacin for the treatment of their uUTI.

5.2.2 Preparation and Dispensing

The patient will receive one 3-day treatment course of generic ciprofloxacin, with instructions to take one tablet or capsule of oral ciprofloxacin 250 mg twice daily beginning day 1 through 3 (+ 1 day).

In the event a patient's first dose is taken in the PM on Day 1, the patient will be expected to take an AM dose on Day 4 to receive the 6 doses of ciprofloxacin, and the EOT visit will occur on day 4 instead of day 3.

5.2.3 Compliance

All patients should be informed that compliance with taking all oral medication
as instructed is imperative. A site designee will phone the patient or the pharmacy on Day 1 to ensure that the prescription of ciprofloxacin was picked up and the first dose was taken. This phone call should be documented in the patient's source and include the date and estimated time the patient took the initial dose.

Patients will receive a dosing diary on Day 1 and asked to record the dosing administration for the duration of the treatment period.

The total amount of oral dosing completed during the treatment period will be documented in the CRF.

5.3 Drug Storage and Drug Accountability

Drug should be stored by the patient according to the guidance provided by the site or pharmacy. For drug accountability, the site will provide the patient with a diary to collect daily ingestion of ciprofloxacin. The patient should return the diary to the clinic along with the prescription bottle/container after completion of their ciprofloxacin course of treatment. Site staff will keep diary in source and record in the CRF.

5.4 Medication(s), Adjunctive Therapy and Non-drug Therapy

5.4.1 Concomitant Medications

Any medication taken by the patient, other than ciprofloxacin, is considered a concomitant medication. Any concomitant medication which is administered from Screening through the TOC Visit must be recorded in the patient's source record.

Any concomitant medication which is an antibiotic, administered for the treatment of the primary uUTI, should also be recorded in the CRF. No other concomitant medications need to be recorded in the CRF.

At each visit, the Investigator or site designee will obtain information on any therapeutic interventions (e.g., drug and non-drug therapy, surgery, etc.) provided. The use of any investigational drug is prohibited and patients may not participate in any other studies involving other marketed products concomitantly while in this study.

The use of other (non-antibacterial) medications should be limited to those essential for the care of the patient. All medications required by the patient to manage underlying illnesses, other than the infection under study, and any drugs that may be required for emergency treatments must be recorded in the source document.

The bioavailability of ciprofloxacin is significantly reduced when co-administered with magnesium or aluminum containing antacids. As a result, co-administration of these antacids with ciprofloxacin is not permitted.

Dosing with food does not affect the overall absorption of ciprofloxacin.

5.4.2 Concomitant Antibacterial Medications

Concomitant systemic antibacterials are prohibited during the study, up to the TOC visit, unless it has been determined that the antibacterial would not have a potential effect on outcome evaluations in patients with uUTI.

5.4.3 Non-drug Adjunctive Therapy

None allowed

6 STUDY PROCEDURES

6.1 Screening (Day 1)

If a patient is presenting with uUTI symptoms and has a positive dipstick for leukocyte esterase AND nitrite, and all other Inclusion and no Exclusion criteria are met then the Investigator (or an appropriate delegate at the Investigator site) will obtain written informed consent from each patient prior to the initiation of any study related activities.

The following procedures will be performed prior to ciprofloxacin administration:

- Demographics and medical history
- Temperature reading
- Collect Height and Weight
- Collect urine for dipstick analysis. If done at an outside institution, then repeat testing.
- Review previous drug and non-drug treatments (defined as within the past 30 days) and concomitant drug treatments
- Adverse events occurring after signing of ICF
- Administer and collect patient assessment questionnaire from patient (Appendix 3)

6.2 Treatment Period

6.2.1 Baseline (Day 1)

The following activities will be completed:

- Collect urine for urinalysis, and urine culture and sensitivity

- Issue prescription of generic ciprofloxacin
- Check and document compliance with study medication (phone call)
- Distribute patient dosing diary

6.2.2 End Of Treatment (EOT) Day 3 or 4 (+1 day)

- Collect urine for culture and sensitivity
- Review concomitant medications
- Check and document compliance with study medication
- Collect patient dosing diary
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?
- Administer and collect patient assessment questionnaire from patient (Appendix 3)
- Investigator-Determined Assessment of Clinical Response (Section 7.2.3)

6.3 Follow-up Period

6.3.1 Test of Cure (TOC) Day 12 (+/- 1 day)

- Collect urine for culture and sensitivity
- Review concomitant medications
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as “How do you feel?
- Administer and collect patient assessment questionnaire from patient (Appendix 3)
- Investigator-Determined Assessment of Clinical Response (Section 7.2.3)

6.3.2 Post Test of Cure (TOC) Day 21 (+/- 3 days)

Call patient to assess for resolution of uUTI symptoms

6.4 Patient Withdrawal from Treatment or Study

Patients may withdraw from the study or ciprofloxacin at any time at their own request, or they may be withdrawn at any time at the discretion of the Investigator or Iterum Therapeutics for safety, behavioral, or administrative reasons.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible. If the patient withdraws or is withdrawn from ciprofloxacin treatment, the Investigator should inquire about the reason for withdrawal, request the patient to return for all protocol-specified assessments, if possible, and follow-up with the patient regarding any unresolved AEs through the TOC.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further study-specific evaluations should be performed, and no additional data should be collected. Iterum Therapeutics may retain and continue to use any data collected before such withdrawal of consent.

7 ASSESSMENTS

7.1 Safety

7.1.1 Clinical Laboratory Assays

No additional laboratory testing will be performed beyond routine urine testing for uUTI.

7.2 Efficacy

7.2.1 Overall Response

Overall Response is assessed on Day 12 (+/- 1 day) TOC using the definitions listed below:

A patient will be defined as a responder if the following criteria are met (programmatically, based on the data on the CRF):

- The patient is alive
- The patient has received no rescue therapy for uUTI
    - If an antibiotic active against the urinary tract pathogen is given for other reasons, then the patient will be considered indeterminate, and analyzed as a non-responder for uUTI
- The patient has resolution of the symptoms of uUTI present at trial entry and no new uUTI symptoms
- Urine culture taken on Day 12 (+/- 1 day) demonstrates $<10^3$ CFU/mL of the baseline uropathogen

All other patients will be considered non-responders**.** If data are unavailable to determine if the patient is a responder or non-responder, the patient will be considered as having an indeterminate response.

7.2.2 Microbiologic

Microbiologic Response is assessed on Day 3 or 4 (+1 day) EOT and Day 12 (+/- 1 day) TOC using the definitions listed below:

Microbiological response	Definition
Eradication	A urine culture taken at baseline and compared with the culture from the EOT visit or TOC visit showed that the urine culture obtained at the relevant visit demonstrated $<10^3$ CFU/mL of the original uropathogen.
Persistence	A uropathogen present at baseline grew at $\geq 10^3$ CFU/mL at the time-point of analysis, i.e. EOT or TOC.
Indeterminate	Patient was lost to follow-up or an assessment was not undertaken such that no urine culture was obtained (or culture results could not be interpreted for any reason) at either the EOT or the TOC visit.

7.2.3 Investigator-Determined Clinical Response

Investigators will use the definitions below to document clinical response at Day 3 or 4 (+ 1 day) (EOT) and Day 12 (+/- 1 day) (TOC):

Clinical response	Definition
Clinical cure	All pre-therapy signs and symptoms of the index infection had resolved such that no additional antibiotics were required
Clinical failure	Patients who met any one of the criteria below were considered as failure: Death related to uUTI prior to Day 3 or Day 12 respectively No apparent response to treatment; persistence or progression of most or all pre-therapy signs and symptoms or use of additional antibiotics for the current infection Patient previously met criteria for failure

Clinical response	Definition
Indeterminate	Study data were not available for evaluation of efficacy for any reason, including: Patient lost to follow-up or assessment not undertaken such that a determination of clinical response could not be made at either the EOT or TOC visit Death prior to EOT visit or Day 12, respectively, where uUTI was clearly noncontributory

7.2.4 Other Assessments

Patients will score their symptoms and record them on a Patient Symptom Assessment Questionnaire (Appendix 3).

8 ADVERSE EVENT REPORTING

8.1 Adverse Events

All observed or volunteered AEs, regardless of suspected causal relationship, will be reported as described in the following sections.

For all AEs, the Investigator must pursue and obtain adequate information both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious AE (SAE) requiring immediate notification to Iterum Therapeutics. For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE. The Investigator is required to assess causality. All AEs will be followed-up by the Investigator until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator, and Iterum concurs with that assessment.

8.2 Reporting Period

Adverse events will be collected from the time that the patient provides informed consent through TOC.

For SAEs, the reporting period to Iterum Therapeutics begins from the time that the patient signed informed consent, which may be prior to the patient's participation in the study, i.e., prior to undergoing any study-related procedure through the TOC. Any SAE occurring any time after the reporting period must be promptly reported if a causal relationship to investigational product is suspected

All AEs should be recorded on the CRF if they occur from the time the patient provides informed consent through TOC.

8.3 Definition of an AE

An AE is any untoward medical occurrence in a clinical investigation patient administered a product or medical device, unless the event is captured in the study endpoint, as defined below; the event need not necessarily have a causal relationship with the treatment or usage.

An event would be considered as adequately captured in the study endpoint if it is accurately and fully represented by a protocol-defined reason for clinical failure (other than mortality) or relapse. Such an event should not be reported as an adverse event unless it is a serious adverse event as defined in this protocol.

Events represented by the study endpoints include all of the following:

- Symptoms of uUTI have not resolved from Baseline to such an extent that new antibiotics are not needed for the infection under study
- Development of new uUTI symptoms not present at Baseline
- Follow up urine cultures do not reveal eradication of causative uropathogen

Except for circumstances as defined above, examples of AEs include but are not limited to:

- Clinically significant symptoms and signs;
- Hypersensitivity;
- Progression/worsening of underlying disease.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug abuse;
- Drug misuse;
- Drug interactions;
- Drug dependency;
- Exposure during Pregnancy.

8.4 Abnormal Test Findings

No additional laboratory testing will be performed beyond urine testing for uUTI.

8.5 SAEs

An SAE or serious adverse drug reaction is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly/birth defect;
- Is assessed as being a medically important event based on medical and scientific judgment. Such medically important events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient and may require medical or surgical intervention to prevent one of the above outcomes. 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 inpatient hospitalization, or the development of drug dependency or drug abuse.

8.6 Hospitalization

Adverse events associated with hospitalization are considered serious. Admission also includes transfer within the hospital (e.g., from the psychiatric wing to a medical floor).

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (e.g., caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room evaluation;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (e.g., for work-up of persistent pre-treatment laboratory abnormality);
- Social admission (e.g., patient has no place to sleep);
- Administrative admission (e.g., for yearly physical exam);
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery). Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as an AE. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy should be recorded as treatment of the AE.

8.7 Severity Assessment

The Investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

- MILD: Does not interfere with the patient's usual function.
- MODERATE: Interferes to some extent with the patient's usual function.
- SEVERE: Interferes significantly with the patient's usual function.

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

8.8 Causality Assessment

The Investigator's assessment of causality must be provided for all AEs (serious and non-serious); the Investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the ciprofloxacin caused or contributed to an AE. If the Investigator does not know whether or not ciprofloxacin caused the event, then the event will be handled as "related to ciprofloxacin" for reporting purposes, as defined by Iterum Therapeutics (see Section 8.12 on Reporting Requirements). If the Investigator's causality assessment is "unknown but not related to ciprofloxacin", this should be clearly documented on study records. Specifically, the Investigator will choose whether the AE is unrelated, unlikely related, possibly related or probably related to ciprofloxacin.

In addition, if the Investigator determines an SAE is associated with study procedures, the Investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

The Investigator will assess causality of the event in relation to ciprofloxacin based on the following defined criteria:

- UNRELATED: No relationship between the event and medicinal product
- UNLIKELY: Event with a time to drug intake that makes a relationship improbable (but not impossible); Disease or other drugs provide plausible explanations
- POSSIBLY: Event with reasonable time relationship to drug intake; Could also be explained by disease or other drugs; Information on drug withdrawal may be lacking or unclear
- PROBABLY: Event with reasonable time relationship to drug intake; Unlikely to be attributed to disease or other drugs; Response to withdrawal clinically reasonable; Re-challenge not required

8.9 Exposure during Pregnancy

Ciprofloxacin is Pregnancy Category C, indicating that there are no adequate and well-controlled studies of ciprofloxacin in pregnant women. Ciprofloxacin should not be used during pregnancy unless the potential benefit justifies the potential risk to both fetus and mother. An expert review of published data on experiences with ciprofloxacin use during pregnancy by TERIS–the Teratogen Information System–concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk, but the data are insufficient to state that there is no risk.

If any study patient becomes or is found to be pregnant during the study, patient's treatment with ciprofloxacin, the investigator must complete a Med Watch Form FDA 3500 and submit it by email to Iterum Therapeutics. The decision to continue ciprofloxacin, stop ciprofloxacin, or switch to an alternative agent will be left to the discretion of the Investigator.

Follow-up is conducted to obtain pregnancy outcome information on all Pregnancy reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination (i.e., induced abortion) and then notify Iterum of the outcome.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth or neonatal death]), Iterum Therapeutics will submit the Med Watch Form FDA 3500 to the FDA and to the manufacturer of ciprofloxacin.

8.10 Discontinuation from Ciprofloxacin Due to AEs (See also Patient Withdrawal, Section 6.4)

Discontinuation from ciprofloxacin due to an AE should be distinguished from discontinuation due to insufficient response, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a patient discontinues ciprofloxacin due to an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.11 Eliciting AE Information

The Investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient from informed consent through the TOC. In addition, each study patient will be questioned about the occurrence of any AEs.

8.12 Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for an SAE. If an SAE occurs that is considered by the Investigator or Iterum Therapeutics to be at least possibly related to ciprofloxacin, the Investigator must complete a Med Watch Form FDA 3500 and submit it by email to Iterum Therapeutics who will then submit the Med Watch Form FDA 3500 to the FDA and to the manufacturer of ciprofloxacin.

8.12.1 SAE Reporting Requirements

If an SAE or exposure during pregnancy occurs, Iterum Therapeutics is to be notified within 24 hours of awareness of the event by the Investigator on a Med Watch Form FDA 3500. If the SAE is fatal or life-threatening, notification to Iterum must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of Pregnancy cases.

In the rare instance that the Investigator does not become aware of the occurrence of an SAE immediately (e.g., if an outpatient study patient initially seeks treatment elsewhere), the Investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

For all SAEs and pregnancies, the Investigator is obligated to pursue and provide information to Iterum Therapeutics in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by Iterum Therapeutics to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the Med Watch Form FDA 3500. In general, this information may include hospital discharge summary, laboratory test and X-ray results. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible by email to Iterum Therapeutics. The information should be reported on a Med Watch Form FDA 3500 and sent to Iterum Therapeutics.

8.12.2 Non-SAE Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. Please note that while all AEs are reported on the AE page of the CRF, there is an additional form used for collection of SAE information, as described in Section 8.12.1, which is not the same as the AE CRF. When the same data are collected, the two forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. Serious adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information. The information on the AE CRF and the SAE form must be the same and will be reconciled at defined periods throughout the study to ensure that they do.

8.12.3 Sponsor Reporting Requirements to Regulatory Authorities

Adverse event reporting, including reporting of suspected serious unexpected adverse reactions, will be carried out in accordance with applicable local regulations. Death and life-threatening Suspected Unexpected Serious Adverse Reactions (SUSARs) are subject to expedited reporting within a 7 calendar day (life-threatening and fatal) or 15 calendar day (all other SUSARs) timeframe.

9 DATA ANALYSIS/STATISTICAL METHODS

9.1 Sample Size Determination

The study is designed to determine the clinical and microbiologic efficacy of ciprofloxacin for adult female patients with uUTI, due to either a ciprofloxacin susceptible or non-susceptible organism. Two-hundred fifty (250) symptomatic patients will be enrolled with the expectation that there will be no screen failures. Of the 250 enrolled patients, we expect 50 will not have a positive urine culture for $\geq 10^5$ CFU/mL of a uropathogen at baseline. Of the 250 enrolled patients, we expect 40 will have a uUTI due to a ciprofloxacin non-susceptible organism.

Patients who withdraw prior to initial dose, will be replaced to ensure all 250 patients have received at least a single-dose of ciprofloxacin.

9.2 Definition of Analysis Populations

1. **Intent-to-Treat (ITT)**: all randomized patients regardless of whether or not the patient received ciprofloxacin
2. **Modified ITT (MITT)**: randomized patients who received at least a single-dose of ciprofloxacin
3. **Safety**: randomized patients who received any amount of ciprofloxacin

4. **Micro-MITT (mMITT)**: All MITT patients with a positive study entry urine culture defined as $\geq 10^5$ CFU/mL of a uropathogen and no more than 2 species of microorganisms identified in the study entry urine culture, regardless of colony count.

5. **Clinically evaluable:**

1) Clinically evaluable (CE) at the EOT and TOC visits population:

a) Received a minimum number of days of ciprofloxacin (to be defined in the Statistical Analysis Plan [SAP])

b) Had no important protocol deviations that would affect the assessment of efficacy (to be defined in the SAP)

c) Had an outcome assessment of clinical cure or failure (and not indeterminate) at the EOT, or TOC visits (i.e., within the protocol allowed visit window), respectively.

d) Had not received prior antibiotic before the initiation of study therapy for this infection unless the recovered pathogen demonstrates resistance to initial antibiotic and clinical symptoms persist

e) Did not receive any antibiotic therapy with potential activity against any of the baseline uropathogens collected at screening between the time of the baseline culture and the EOT or TOC culture, respectively. This excludes the protocol defined study therapy and patients who were considered clinical failures and required additional antibiotic therapy. Patients with a coinfection with a gram-positive uropathogen resistant to ciprofloxacin are allowed to receive agents with narrow spectrum gram-positive coverage (i.e., such as linezolid or vancomycin)

f) Had a study entry urine culture obtained before ciprofloxacin administration

2) Microbiologically evaluable (ME): all patients included in both the micro-mITT and CE populations at the (ME-EOT), and at the TOC visit (ME-TOC) and have an appropriately collected urine culture specimen and interpretable urine culture result at the EOT, and TOC visits, respectively.

9.3 General Statistical Considerations

Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minimums, and maximums for continuous variables will be provided. Comparisons will be made between response rates for patients with infection due to ciprofloxacin-susceptible and ciprofloxacin-non-susceptible isolates. Exploratory analyses may also be performed. Listings of individual patient's data will be produced. A comprehensive Statistical Analysis Plan (SAP) will be finalized prior to final database lock.

9.4 Patient Characteristics

Enrollment, protocol deviations, discontinuations from the ciprofloxacin and withdrawal from the study will be summarized. Demographics (age, race, sex), medical and surgical history, baseline assessment of the symptoms of uUTI, microbiological assessment of the urine, and ciprofloxacin administration will also be summarized.

9.5 Efficacy Analysis

9.5.1 Analysis of Primary Outcome Measure

The primary outcome is overall response (clinical plus microbiologic) at the Day 12 (+/- 1 day) visit in the m-MITT population. The number and percentage of responders, non-responders and indeterminates will be determined.

9.5.1.1 Additional Analyses of the Primary Efficacy Outcome

In addition to the overall response rate, response rates for patients infected by ciprofloxacin susceptible and non-susceptible organism will be evaluated.

9.5.2 Analysis of Secondary Efficacy Outcome Measure

All symptomatic subjects enrolled in the study will have a positive urine dipstick for both leukocyte esterase and nitrite. The number and percentage of subjects who go on to have a positive baseline urine culture for >100,000 CFU/mL of a uropathogen will be evaluated.

9.5.3 Analysis of Additional Efficacy Outcome Measures

The number and percentage of subjects treated with ciprofloxacin with an overall response of responder, non-responder, and indeterminate (by definition subjects with an indeterminate response are excluded the ME population) at the TOC visit will be presented for the m-MITT and ME-TOC populations.

Investigator determined clinical response (clinical cure, failure and indeterminate) at the Day 3 or 4 (+ 1 day) (EOT) and TOC Visits will be presented for the m-MITT, CE, and ME populations. The number and percentage of subjects with a microbiologic response of eradication, persistence, persistence with increasing MIC, and indeterminate (by definition subjects with an indeterminate response are excluded from the ME populations) will be presented for the following time points and analysis populations:

- Day 3 or 4 (+ 1 day) (EOT) in the m-MITT and ME-EOT populations
- Day 12 in the m-MITT and ME-Day12 populations

Overall response and microbiologic eradication at the EOT and TOC visits by baseline pathogen (key pathogens) will be summarized in the m-MITT and ME populations.

9.6 Safety Analyses

Safety will be assessed through summaries of AEs. All safety analyses will be based on the Safety population.

Summary tables of treatment-emergent AEs (TEAEs) will be provided. A TEAE is any AE that newly appeared, increased in frequency, or worsened in severity following initiation of ciprofloxacin. The incidence of TEAEs will be tabulated by system organ

class and preferred term, and by severity and relationship to treatment. Tables of TEAEs leading to ciprofloxacin discontinuation, withdrawal from the study or an SAE will be provided. AEs occurring prior to the first dose of ciprofloxacin (AEs are recorded from the time of informed consent) will be provided in a listing.

9.7 Handling of Missing Data

Details of the handling of missing data will be provided in the SAP. For the primary and secondary efficacy analyses, if any data field needed to determine overall response (primary) and microbiological response (secondary) is missing at the Day 12 (primary) visit, the patient will be considered an indeterminate response. By definition, patients with an indeterminate response are included in the denominator in the m-MITT population and thus, are analyzed in the same manner as non-responders and persistence. Additional sensitivity analyses for handling missing data will be detailed in the SAP. By definition, patients with missing data are excluded from the CE populations.

10 QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Iterum or its agent will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The Investigator and institution will allow Iterum monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the institutional review board (IRB)/independent ethics committee (IEC), and/or to quality assurance audits performed by Iterum, or companies working with or on behalf of Iterum, and/or to inspection by appropriate regulatory authorities.

It is important that the Investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11 DATA HANDLING AND RECORD KEEPING

11.1 Case Report Forms / Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Iterum and should not be made available in any form to third parties, except for authorized representatives of Iterum or appropriate regulatory authorities, without written permission from Iterum.

The Investigator has ultimate responsibility for the accuracy, authenticity, and timely collection and reporting of all clinical, safety, laboratory data entered on the CRFs and any other data collection forms. The CRFs must be signed by the Investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs and source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the Investigator's site as well as at Iterum and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2 Record Retention

To enable evaluations and/or audits from regulatory authorities or Iterum, the Investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, SAE forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone call reports). The records should be retained by the Investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Iterum should be prospectively notified. The study records must be transferred to a designee acceptable to Iterum, such as another Investigator, another institution, or to Iterum. The Investigator must obtain Iterum's written permission before disposing of any records, even if retention requirements have been met.

12 ETHICS

12.1 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the Investigator to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, e.g., recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Iterum or its agent

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the Investigator must notify the IRB/IEC and Iterum in writing immediately after the implementation.

12.2 Ethical Conduct of the Study

The study will be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Patients, adopted by the General Assembly of the World Medical Association (2013).

In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonisation (ICH) guideline on Good Clinical Practice (GCP), and applicable local regulatory requirements and laws.

12.3 Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Iterum will maintain high standards of confidentiality and protection of patient personal data.

The informed consent form must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Iterum before use.

The Investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The Investigator, or a person designated by the Investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The Investigator will retain the original of each patient's signed consent form.

Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable Competent Authority in any area of the World, or if the Investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Iterum should be informed immediately.

In addition, the Investigator will inform Iterum immediately of any urgent safety measures taken by the Investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the Investigator becomes aware of.

13 DEFINITION OF END OF STUDY

13.1 End of Study in Participating Countries

End of Study in all participating countries is defined as the TOC Visit.

14 SPONSOR STUDY TERMINATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Iterum.

If a study is prematurely terminated, Iterum will promptly notify the Investigator and the Investigator must also inform the IRB/IEC. After notification, the Investigator must contact all participating patients and the hospital pharmacy (if applicable) within 90 days. Investigator must also inform the IRB/IEC. As directed by Iterum, all study materials must be collected and all CRFs completed to the greatest extent possible.

15 PUBLICATION OF STUDY RESULTS

Publication of study results is discussed in the Clinical Study Agreement.

15.1 Communication of Results by Iterum

Iterum fulfills its commitment to publicly disclose the results of studies through registration and posting of the results of this study on clinicaltrials.gov.

If posting of study results to clinicaltrials.gov jeopardizes a planned publication of the study results, a Pending Full Publication notice is substituted for the synopsis until the study results publication has been issued or 2 years have elapsed, whichever occurs first.

15.2 Publications by Investigators

Iterum has no objection to publication by the Investigator of any information collected or generated by the Investigator, however, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, the Investigator will provide Iterum an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

The Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Iterum at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The Investigator will, on request, remove any previously undisclosed Confidential Information (other than the study results themselves) before disclosure.

If the study is part of a multi-center study, the Investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the Investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Iterum and the Institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

16 REFERENCE LIST

Munoz-Davila MJ. Role of old antibiotics in the era of antibiotic resistance. Antibiotics 2014; 3:39-48.

Schito GC, Naber KG, Botto H et al. The ARESC study: an international survey on the antimicrobial resistance of pathogens involved in uncomplicated urinary tract infections. International Journal of Antimicrobial Agents 34 (2009) 407–413.

Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011;52:e103-e120.

Semeniuk H & Church D. Evaluation of the leukocyte esterase and nitrite urine dipstick screening tests for detection of bacteriuria in women with suspected uncomplicated urinary tract infections. Journal of Clinical Microbiology, September 1999; 3051-3052.

Friedman J, Polifka J. Teratogenic effects of drugs: a resource for clinicians (TERIS). Baltimore, Maryland: Johns Hopkins University Press, 2000:149-195.

Appendix 1 Schedule of Activities

	SCREENING PERIOD	TREATMENT PERIOD		FOLLOW-UP PERIOD	
Protocol Activity	**Screening (D1)**	**Baseline (D1)**	**EOT[1] (D3 or D4) (+ 1 day)**	**TOC (D12) (+/- 1 day)**	**Post TOC (D21) (+/- 3 days)**
Informed Consent	X				
Medical History and Demographics	X				
Temperature	X				
Height and Weight	X				
Urine dipstick	X				
Urinalysis		X			
Urine Culture and Sensitivity		X	X	X	
Previous Drug and Non-Drug Treatments	X				
Concomitant Medications	X		X	X	
Treatment[1]		X (for 3 days)			
Treatment Compliance Check[2]		X[2]	X		
Patient Dosing Diary		Distribute	Collect		
Adverse Events	X		X	X	

Patient Symptom Assessment Questionnaire	X		X	X	
Investigator-Determined Clinical Response Evaluation			X	X	
Post TOC Telephone Contact					X

[1]In the event that the first dose of ciprofloxacin is taken in the morning on Day 1, the EOT visit will be on day 3 (+1 day). In the event that the first dose of ciprofloxacin is taken in the evening on Day 1, the EOT visit will be on day 4 (+1 day).

[2]Site personnel will call the patient and/or dispensing pharmacy on Day 1 (+1 day) to confirm patient is in receipt of medication.

Appendix 2 Microbiology

Method of Collection of Urine Specimens:

To obtain a clean catch sample of urine from a female patient, a thorough cleansing of the periurethral area is essential before specimen collection. Wash the area with a disinfectant and make all efforts to avoid any contact until urination is complete.

All patients should void the first part of the specimen into the toilet, then collect the remainder of the specimen in a sterile container.

Culture and Susceptibility testing

All gram-negative pathogens will be tested locally for antimicrobial susceptibility, as appropriate.

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Appendix 3 Patient Symptom Assessment Questionnaire (PSAQ)

INSTRUCTIONS: Do you have any of the following symptoms due to your current UTI? If yes, indicate severity by checking Mild, Moderate or Severe. If you do not have a symptom, or if a symptom is present but related to another known condition, then check No Symptom.

CHECK ONLY ONE RESPONSE PER QUESTION. REFER TO PAGE 2 FOR GUIDANCE SPECIFIC TO QUESTIONS 2 AND 4.

		Severity (check one)				***Complete the below on DAY 12 if you still have symptoms.***
		Mild	Moderate	Severe	No symptom/ Resolved *or returned to the same condition as before you had a UTI*	***Question: What is the impact of your remaining symptom(s) on your daily activities (i.e., how bothersome are the symptoms)?***
1	Gross hematuria (visible blood in your urine)	☐	☐	☐	☐	☐ Not at all ☐ Not significantly bothersome ☐ Moderately bothersome ☐ Severely bothersome
2	Pain (uncomfortable pressure) in the lower abdomen/pelvic area*	☐	☐	☐	☐	☐ Not at all ☐ Not significantly bothersome ☐ Moderately bothersome ☐ Severely bothersome
3	Burning (dysuria) when passing urine	☐	☐	☐	☐	☐ Not at all ☐ Not significantly bothersome ☐ Moderately bothersome ☐ Severely bothersome
4	Frequency, urgency of urination or going to the toilet very often**	☐	☐	☐	☐	☐ Not at all ☐ Not significantly bothersome ☐ Moderately bothersome ☐ Severely bothersome

ADDITIONAL GUIDANCE FOR QUESTIONS 2 AND 4

* Pain (uncomfortable pressure) in the lower abdomen/pelvic area	• Choose "No symptom" if no significant pain or back to before you had a UTI • Choose "Mild" if occasional pain, but usually overlooked • Choose "Moderate" if considerable pain, but tolerable • Choose "Severe" if severe pain requiring treatment
**For frequency/urgency of urination	• Choose "No symptom" if you can hold your urine for more than two hours during the daytime, or you can hold your urine as long as you could before you had a UTI • Choose "Mild" if more frequent than normal, but can hold your urine for 1-2 hours • Choose "Moderate" if considerably more frequent than normal, i.e., cannot hold urine for 1 hour • Choose "Severe" if very frequent, i.e. cannot even hold your urine for 30 minutes

Source: Adapted from Wagenlehner et al, Ceftazidime-avibactam versus doripenem for the treatment of complicated urinary tract infections including acute pyelonephritis: RECAPTURE, a phase 3 randomized trial program. CID 2016:63; 754-762.

Appendix 4 Ciprofloxacin Tablets – USPI

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CIPRO safely and effectively. See full prescribing information for CIPRO.

CIPRO® (ciprofloxacin hydrochloride) tablet, for oral use
CIPRO® (ciprofloxacin hydrochloride), for oral suspension
Initial U.S. Approval: 1987

WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND EXACERBATION OF MYASTHENIA GRAVIS

See full prescribing information for complete boxed warning.

- **Fluoroquinolones, including CIPRO®, have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together (5.1), including:**
  - **Tendinitis and tendon rupture (5.2)**
  - **Peripheral neuropathy (5.3)**
  - **Central nervous system effects (5.4)**

  Discontinue CIPRO immediately and avoid the use of fluoroquinolones, including CIPRO, in patients who experience any of these serious adverse reactions (5.1)
- **Fluoroquinolones, including CIPRO, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid CIPRO in patients with known history of myasthenia gravis. (5.5)**
- **Because fluoroquinolones, including CIPRO, have been associated with serious adverse reactions (5.1-5.15), reserve CIPRO for use in patients who have no alternative treatment options for the following indications:**
  - **Acute exacerbation of chronic bronchitis (1.10)**
  - **Acute uncomplicated cystitis (1.11)**
  - **Acute sinusitis (1.12)**

---------- RECENT MAJOR CHANGES ----------

Boxed Warning M/2016 Indications and Usage (1.10, 1.11, 1.12) M/2016 Dosage and Administration, Dosage in Adults (2.1) M/2016 Warnings and Precautions (5.1) M/2016

---------- INDICATIONS AND USAGE ----------

CIPRO is a fluoroquinolone antibacterial indicated in adults (≥18 years of age) with the following infections caused by designated, susceptible bacteria and in pediatric patients where indicated: • Skin and Skin Structure Infections (1.1)

- Bone and Joint Infections (1.2)
- Complicated Intra-Abdominal Infections (1.3)
- Infectious Diarrhea (1.4)
- Typhoid Fever (Enteric Fever) (1.5)
- Uncomplicated Cervical and Urethral Gonorrhea (1.6)
- Inhalational Anthrax post-exposure in adult and pediatric patients (1.7)
- Plague in adult and pediatric patients (1.8)
- Chronic Bacterial Prostatitis (1.9)
- Lower Respiratory Tract Infections (1.10) ○ Acute Exacerbation of Chronic Bronchitis
- Urinary Tract Infections (1.11) ○ Urinary Tract Infections (UTI) ○ Acute Uncomplicated Cystitis

○ Complicated UTI and Pyelonephritis in Pediatric Patients • Acute Sinusitis (1.12)

Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CIPRO and other antibacterial drugs, CIPRO should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. (1.13)

---------- **DOSAGE AND ADMINISTRATION** ----------

Adult Dosage Guidelines			
Infection	**Dose**	**Frequency**	**Duration**
Skin and Skin Structure	500 -750 mg	every 12 hours	7 to 14 days

Adult Dosage Guidelines			
Infection	**Dose**	**Frequency**	**Duration**
Bone and Joint	500-750 mg	every 12 hours	4 to 8 weeks
Complicated IntraAbdominal	500 mg	every 12 hours	7 to 14 days
Infectious Diarrhea	500 mg	every 12 hours	5 to 7 days
Typhoid Fever	500 mg	every 12 hours	10 days
Uncomplicated Gonorrhea	250 mg	single dose	single dose
Inhalational anthrax (postexposure)	500 mg	every 12 hours	60 days

Plague	500–750 mg	every 12 hours	14 days
Chronic Bacterial Prostatitis	500 mg	every 12 hours	28 days
Lower Respiratory Tract	500 -750 mg	every 12 hours	7 to 14 days
Urinary Tract	250-500 mg	every 12 hours	7 to 14 days
Acute Uncomplicated Cystitis	250 mg	every 12 hours	3 days
Acute Sinusitis	500 mg	every 12 hours	10 days

- Adults with creatinine clearance 30–50 mL/min 250–500 mg q 12 h (2.3)
- Adults with creatinine clearance 5–29 mL/min 250–500 mg q 18 h (2.3)
- Patients on hemodialysis or peritoneal dialysis 250–500 mg q 24 h (after dialysis) (2.3)

Pediatric Oral Dosage Guidelines			
Infection	**Dose**	**Frequency**	**Duration**
Complicated UTI and Pyelonephritis (1 to 17 years of age)	10–20 mg/kg (maximum 750 mg per dose)	Every 12 hours	10–21 days
Inhalational Anthrax (Post-Exposure)	15 mg/kg (maximum 500 mg per dose)	Every 12 hours	60 days
Plague	15mg/kg (maximum 500 mg per dose)	Every 8 to 12 hours	10–21 days

---------- DOSAGE FORMS AND STRENGTHS ----------

- Tablets: 250 mg, 500 mg (3)
- Oral Suspension: 5% (250 mg/5 mL), 10% (500 mg/5 mL) (3)

---------- CONTRAINDICATIONS ----------

- Known hypersensitivity to CIPRO or other quinolones (4.1, 5.6, 5.7)
- Concomitant administration with tizanidine (4.2)

---------- WARNINGS AND PRECAUTIONS ----------

- Hypersensitivity and other serious reactions: Serious and sometimes fatal reactions (for example, anaphylactic reactions) may occur after the first or subsequent doses of CIPRO. Discontinue CIPRO at the first sign of skin rash, jaundice or any sign of hypersensitivity. (4.1, 5.6, 5.7)
- Hepatotoxicity: Discontinue immediately if signs and symptoms of hepatitis occur. (5.8)
- *Clostridium difficile*-associated diarrhea: Evaluate if colitis occurs. (5.10)

- QT Prolongation: Prolongation of the QT interval and isolated cases of torsade de pointes have been reported. Avoid use in patients with known prolongation, those with hypokalemia, and with other drugs that prolong the QT interval. (5.11, 7, 8.5)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions ≥1% were nausea, diarrhea, liver function tests abnormal, vomiting, and rash. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937 or FDA at 1-800FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

Interacting Drug	Interaction
Theophylline	Serious and fatal reactions. Avoid concomitant use. Monitor serum level (7)
Warfarin	Anticoagulant effect enhanced. Monitor prothrombin time, INR, and bleeding (7)
Antidiabetic agents	Hypoglycemia including fatal outcomes have been reported. Monitor blood glucose (7)
Phenytoin	Monitor phenytoin level (7)
Methotrexate	Monitor for methotrexate toxicity (7)
Cyclosporine	May increase serum creatinine. Monitor serum creatinine (7)
Multivalent cationcontaining products including antacids, metal cations or didanosine	Decreased CIPRO absorption. Take 2 hours before or 6 hours after CIPRO (7)

---------- USE IN SPECIFIC POPULATIONS ----------

See full prescribing information for use in pediatric and geriatric patients (8.4, 8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 7/2016

Appendix 5 Summary of Changes

This summary of changes provides an overview of substantive changes and additions made for protocol IT-004-401 amendments. In addition, minor editorial revisions have been made for consistency.

General

- All Pages: Header
  From: Amendment 01:08 November 2017
  To: Amendment 02:27 March 2018

Study Procedures

- Section 4, 4.1-3, 4.1-4: clarification of; study population requirement of positive for both leukocyte esterase and nitrite dipstick, mid-stream specimen for diagnosis, informed consent process
- Section 5.2-1, 5.2-3: removal of additional language that does not apply to this study, clarification of site to collect at least the day and time of patients first dose taken during treatment follow up.
- Section 6.1: updated language to align with revisions to Section 4.
- Section 6.3.2: added requirement for Post Test of Cure (TOC) Day 21 (+/- 3 days) follow up call
- Section 9.2-5: clarified outcome assessment language
- Appendix 1 Schedule of Activities: Post Test of Cure (TOC) Day 21 (+/- 3 days) follow up call added
- Appendix 2 Microbiology: removed reference to requirement of long term storage of specimen at local lab
- Appendix 3: Revised Patient Assessment Symptom Questionnaire

Appendix 6 Investigator's Signature

Study Title:	A prospective, Phase 4, open label, multi-center study of the clinical and microbiologic efficacy of ciprofloxacin for the treatment of uncomplicated urinary tract infections in adult women.
Study Number:	IT-004-401
Final Date:	March 27, 2018

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol. I understand the study protocol and will conduct the study according to the procedures therein and according to the principles of good clinical practice.

Name: _____

Signature: _____ **Date:** _____