Statistical Analysis Plan: 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 infections
Sponsor:	Iterum Therapeutics US Limited
Study Statistician:	Karthik Akinapelli
Study Clinician:	Steven I. Aronin, M.D.
Final SAP Date:	07/30/2019
Revised SAP Date:	*{date}*

SIGNATURE PAGE

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I have read this report and confirm that to the best of my knowledge it accurately describes the statistical analysis plan for the study.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
CE	Clinically evaluable
CFU	Colony forming unit
CRF	Case report form
CSR	Clinical study report
EOT	End of treatment
ESBL	Extended-spectrum bets-lactamase
ITT	Intent-to-treat
ME	Microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MG	Milligram
MIC	Minimal inhibitory concentration
MITT	Modified intent-to-treat
m-MITT	Micro-modified intent-to-treat
mL	Milliliter
SAE	serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
TOC	Test of cure
US	United States
uUTI	Uncomplicated urinary tract infection

1 INTRODUCTION

This document presents the Statistical Analysis Plan (SAP) for the IT-004-401, "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." This plan contains definitions of analysis populations, derived variables and statistical methods for the analysis of clinical and microbiologic efficacy. The statistical plan described is an "a priori" plan, and the analyses outlined here have not been conducted prior to the preparation of this plan.

This SAP summarizes the design and objectives of protocol IT-004-401 and provides details of the definitions of the outcome measures and statistical methodology that will be used to analyze the data from the study. Any deviation from the planned analysis will be documented in clinical study report (CSR).

2 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.

3 STUDY OBJECTIVES

3.1 Primary Objective

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

3.2 Secondary Objective

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.

4 DEFINITION OF ANALYSIS POPULATION

The definition of analysis populations included in this study are below.

4.1 Intent-to-Treat (ITT) Population

All enrolled patients regardless of whether or not they received ciprofloxacin.

4.2 Modified Intent-to-Treat (MITT) Population

All patients in ITT population who received at least a single dose of ciprofloxacin.

4.3 Safety Population

All patients in ITT population who received at least a single dose of ciprofloxacin.

4.4 Micro-MITT (m-MITT)

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.

4.5 Clinically Evaluable (CE)

Clinically evaluable is defined both at the end of treatment (EOT) and test of cure (TOC) visits.

- All patients who were included in the MITT population and meet the following criteria are clinically evaluable.
  a) Received a minimum of four doses of ciprofloxacin.
  b) Had no important protocol deviations that would affect the assessment of efficacy as indicated in the protocol deviation log (see section 7.9). These will be pointed out by clinical team and marked in the CE spreadsheet.
  c) Had a Clinical response assessment of clinical cure or clinical failure (and not indeterminate) at the EOT or TOC visits (within Protocol visit window), respectively.

     Note: Since the PSAQ does not contain a date completed, the date if lab culture will be used.
  d) 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).

     Note: This rule will be applied through the manual review of CE spreadsheet by the sponsor.

4.6 Microbiologically Evaluable (ME)

All patients included in both the m-mITT and CE populations at the EOT visit (ME-EOT), and at the TOC visit (ME-TOC) and meet the following criteria are microbiologically

evaluable:

a) Have an appropriately collected urine culture specimen and interpretable urine culture result at the EOT and TOC visits, respectively.

b) Had a microbiologic assessment of eradication or persistence (and not indeterminate) at the EOT or TOC visits, respectively.

4.7 Determination of Inclusion in Analysis Populations

Inclusion into the ITT, MITT, m-MITT and Safety populations will be determined programmatically from the electronic case report form (e-CRF) data. Inclusion into the CE populations will be determined programmatically from the e-CRF data and through a manual review conducted by the sponsor. The sponsor will review both clinical and microbiological data for determination of criteria used to assess inclusion in the CE populations and for determination of baseline and post-baseline pathogens. The sponsor will review the data concurrent with the conduct of the study. Inclusion into the ME populations will be determined programmatically.

5 DEFINITION OF OUTCOME MEASURES

5.1 Primary Efficacy Outcome Measure

The primary efficacy outcome is overall response assessed on Day 12 (+/- 1 day) in the m-MITT using the definitions listed below.

A patient will be programmatically defined as a responder based on the following:

- 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);
- The patient has resolution of the symptoms of uUTI present at trial entry and no new uUTI symptoms, on Day 12 (+/- 1 day);
- Urine culture taken on Day 12 (+/- 1 day) demonstrates $<10^3$ CFU/mL of the baseline uropathogen;

A patient will be defined as a non-responder if at least one of the following criteria is met:

- The patient has died;
- The patient has received 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 no resolution or worsening of the symptoms of uUTI present at trial entry and/or with new uUTI symptoms;
- Urine culture taken demonstrates $\geq 10^3$ CFU/mL of the baseline uropathogen;

All other patients will be considered indeterminate, including those with missing data needed to determine if the patient is a responder or non-responder. For example, if either urine culture or uUTI symptoms are not completed, the patient will be considered an indeterminate.

For the ITT and m-MITT populations, the proportion of ITT or m-MITT patients with a responder is defined using the following formula:

$$\frac{\text{Number of responders}}{\text{Number of responders + Number of non-responders + Number of indeterminates}}$$

By definition, patients in the CE and ME populations must have sufficient information for determination of efficacy response. Thus, the proportion of CE and ME patients is defined using the following formula:

$$\frac{\text{Number of responders}}{\text{Number of responders + Number of non-responders}}$$

5.1.1 Additional Analysis of the Primary Efficacy Outcome Measure

In addition to the primary efficacy outcome measure, following sensitivity analyses will be performed on Day 12 (+/- 1 day) in the m-MITT population,

- Sensitivity Analysis 1: Will follow the same definition of primary outcome measure defined in section 5.1 except, urgency is excluded and considering all other symptoms (in Appendix 2) are resolved and no new uUTI symptoms.
- Sensitivity Analysis 2: Will follow the same definition of primary outcome measure defined in section 5.1 except, frequency is excluded and considering all other symptoms (in Appendix 2) are resolved and no new uUTI symptoms.
- Sensitivity Analysis 3: Will follow the same definition of primary outcome measure defined in section 5.1 except, improvement of symptoms (instead of resolution, in Appendix 2) from baseline and no worse than mild from baseline and no new uUTI symptoms are considered.
- Sensitivity Analysis 4: Will follow the same definition of primary outcome measure defined in section 5.1 except, improvement of symptoms (instead of resolution, in Appendix 2) from baseline and no new uUTI symptoms are considered.
- Sensitivity Analysis 5: Will follow the same definition of primary outcome measure defined in section 5.1 except, urgency and frequency are improved and no worse than mild from baseline and all other symptoms (in Appendix 2) are resolved and no new uUTI symptoms are considered.
- Sensitivity Analysis 6: Will follow the same definition of primary outcome measure defined in section 5.1 except, investigator response will be used instead of symptoms filled in by patient (from patient dairy).

5.2 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 $\geq 10^5$ CFU/mL of a uropathogen will be evaluated.

5.3 Additional Efficacy Outcomes Measures

- Microbiologic response

Microbiologic response is assessed on Day 3 or 4 (+1 day) EOT and Day 12 (+/- 1 day) TOC in the ITT, m-MITT, CE-EOT, CE-TOC, ME-EOT and ME-TOC populations.

Microbiological response	**Definition**
Eradication	A urine culture taken at baseline and compared with the culture from the Day 3 (+1 day) (EOT) visit or Day 12 (+/- 1 day) (TOC) visit showed that the urine culture obtained at the relevant visit demonstrated $<10^3$ CFU/mL of the original uropathogen.
Persistence	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.

- Clinical response:

Clinical response (done programmatically) will use the definitions below to document response at Day 3 or Day 4 (+ 1 day) (EOT), Day 12 (+/- 1 day) (TOC) and Day 21 in the ITT, m-MITT, CE-EOT, CE-TOC, ME-EOT and ME-TOC populations.

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 or Day 21 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 and received rescue antibiotics
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 Day 3 or Day 12 or Day 21, respectively, where uUTI was clearly noncontributory

In addition to the clinical response above, following sensitivity analyses will be performed on Day 12 (+/- 1 day) in the m-MITT population,

- Sensitivity Analysis 1: Will follow the same definition of clinical response defined in section 5.3 except, urgency is excluded and considering all other symptoms are resolved and no new uUTI symptoms.
- Sensitivity Analysis 2: Will follow the same definition of clinical response defined in section 5.3 except, frequency is excluded and considering all other symptoms are resolved and no new uUTI symptoms.
- Sensitivity Analysis 3: Will follow the same definition of clinical response defined in section 5.3 except, improvement of symptoms (instead of resolution) from baseline and no worse than mild from baseline and no new uUTI symptoms are considered.
- Sensitivity Analysis 4: Will follow the same definition of clinical response defined in section 5.3 except, improvement of symptoms (instead of resolution) from baseline and no new uUTI symptoms are considered.
- Sensitivity Analysis 5: Will follow the same definition of clinical response defined in section 5.3 except, urgency and frequency are improved and no worse than mild from baseline and all other symptoms are resolved and no new uUTI symptoms are considered.

- Investigator response:

Investigator-determined response will use the definitions below to document response at Day 3 or Day 4 (+ 1 day) (EOT) and Day 12 (+/- 1 day) (TOC) in the ITT, m-MITT, CE-EOT, CE-TOC, ME-EOT and ME-TOC populations.

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 Day 3 or Day 12, respectively, where uUTI was clearly noncontributory

- Patient Symptom Assessment Questionnaire (filled out by patient) at Day 3 or Day 4 (+ 1 day) (EOT) and Day 12 (+/- 1 day) (TOC) in the ITT, m-MITT, CE-EOT, CE-TOC, ME-EOT and ME-TOC populations
- Overall response at Day 3 or Day 4 (+ 1 day) (EOT) in the ITT, m-MITT, CE-EOT and ME-EOT populations
- Overall response at Day 12 (+/- 1 day) (TOC) in the ITT, CE-TOC and ME-TOC population (m-MITT is used with the primary endpoint)
- Overall response, microbiologic response, clinical response and investigator response at the EOT and TOC visits by baseline pathogen (key pathogens) in the m-MITT and ME populations
- Overall response, microbiologic response and clinical response at the EOT and TOC visits by baseline ESBL in the m-MITT and ME populations
- Distribution of pathogens by culture concentration at EOT and TOC in the m-MITT, ME-EOT and ME-TOC populations

5.4 Safety Outcome Measures

The safety parameters include adverse events (AEs). No additional laboratory testing will be performed beyond routine urine testing for uUTI. AEs will be coded using the Medical Dictionary of Regulatory Activities (MedDRA) Version 21.0 to the System Organ Class and Preferred Term levels.

6 STATISTICAL METHODS

6.1 Sample Size

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 a total of 250 patients

will receive at least a single-dose of ciprofloxacin.

6.2 Randomization

No randomization performed. Approximately 250 female patients with uUTI will be administered oral ciprofloxacin twice daily for 3 days.

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.

6.3 Visit Windows for Efficacy Analysis

No analysis will be performed for any unscheduled visits.

Visit	Window
Baseline	Day -1 or 1, defined as period prior to the administration of the first dose of study drug
Day 3 or Day 4 (EOT)	+1 day
Day 12 (TOC)	± 1 days
Day 21	± 3 days

6.4 Handling of Culture Data from Central and Local Laboratory

Culture data from both central lab (IHMA) and local lab at Baseline (no post-baseline for central lab) will be handled as outlined below:

- All the culture results from central and local labs are merged by subject id.
- Final pathogen, susceptibility (to Ciprofloxacin) and extended-spectrum beta-lactamases (ESBL) status at baseline will be determined in the following order as follows,
    1. For all uropathogen (Appendix 3) central records with concentration of $\geq 10^5$ CFU/mL then central lab pathogen, susceptibility and ESBL (ceftriaxone > 1 as positive) status is considered as final results.
    2. For all other central lab records with concentration $< 10^5$ CFU/mL or contaminated sample or 'no growth', if their local lab records have a uropathogen with concentration of $\geq 10^5$ CFU/mL then local pathogen, susceptibility and ESBL status is considered as final results.
    3. If both statement 1 and statement 2 do not apply, then central results are considered as final results.

6.5 Handling of Missing Data

Missing data will be handled as outlined below:

- All missing and partial dates for events and assessments occurring after start of enrollment or for medications received after start of enrollment will be queried for a value. If no value can be obtained, substitutions will be made as follows:
  - For start dates, missing months and days will be defined by "01", as long as this occurs on or after the first dose of study drug. If the algorithm produces a date prior to the first dose of study drug, the date of the first dose of study drug will be used for the partial date. For stop dates, missing months will be defined as "12" and days will be defined by the last day of the respective month. These substitutions will be used in calculations; however, the actual value recorded on the e-CRF will be used for all listings.
- The intensity and causality assessment for an AE cannot be missing. Missing data will be queried for a value. If no value can be obtained, worst possible scenario will be considered. For example, missing intensity will be considered as 'severe' and missing causality will be considered as 'treatment related'.

For efficacy response, missing data will be handled as follows:

- For any outcome measure,
  - Patients will be defined as an indeterminate at any outcome measure (overall or clinical or microbiological) if any data needed to determine the outcome of a patient is missing. For example, if the assessment of the symptoms was not completed at EOT, for any reason, the patient will be considered an indeterminate response. By definition, patients with an indeterminate response are included in the denominator for analyses in the ITT and m-mITT populations, and are considered failures.
- For the Investigator's assessment of clinical response at EOT and TOC
  - Patients will be considered an indeterminate response if data are not available for the evaluation of efficacy at EOT and TOC for any reason.
- Except as specifically noted for preplanned imputation analyses, missing values for other individual data points (not described above) will remain as missing. Missing values will not be imputed and only observed values will be used in data analyses and presentations.
- Where individual data points are missing, categorical data will be summarized based on reduced denominators (i.e., only patients with available data will be included in the denominators).

6.6 Comments on Statistical Analysis

The following general comments apply to all statistical analyses and data presentations:

- Summaries will include frequency and percentages for categorical data; frequency and median for ordinal data; and number, mean, standard deviation, and median, minimum and maximum for continuous data.
- Duration variables will be calculated using the general formula: (end date - start date) +1 for end dates after first dose and (end date - start date) for end dates before first dose.
- If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table (e.g., a character string is reported for a parameter of the numerical type),

a coded value must be appropriately determined and used in the statistical analyses. In general, a value or lower and upper limit of normal range such as '<10' or '≤ 5' will be treated as '10' or '5' respectively, and a value such as '>100' will be treated as '100'. However, the actual values as reported in the database will be presented in data listings.

- Individual patient listings of all data represented on the eCRFs will be provided to facilitate the investigation of tabulated values and to allow for the clinical review of all efficacy and safety parameters.
- Version 9.4 of SAS® statistical software package will be used to provide all summaries, listings, graphs, and statistical analyses.

7 STATISTICAL ANALYSES

7.1 Patient Disposition

The number of patients included in each of the study populations (i.e.: ITT, Safety, MITT, m-MITT, CE-EOT, CE-TOC, ME-EOT and ME-TOC) will be summarized by ciprofloxacin-susceptible, ciprofloxacin-non-susceptible, other (Includes patients with no pathogen or contaminated urine sample at baseline) and total (includes all patients). A listing will be provided that details each patient's inclusion in and exclusion from each analysis population and the reasons the patient is excluded from the population(s).

- The frequency and percentage of patients completing the study, prematurely discontinuing from the study will be presented for the ITT, MITT, m-MITT, CE-EOT, CE-TOC, ME-EOT and ME-TOC populations.
- Reasons for premature withdrawal from the study as recorded on the e-CRF will be summarized (frequency and percentage).
- A listing of all patients who prematurely withdrew from the study will be presented, and the primary reason for premature withdrawal from the study will be provided.
- A listing of death will be presented separately.

7.2 Demographics and Baseline Characteristics

Demographic data and baseline characteristics will be presented for the ITT, Safety, m-MITT, CE and ME populations. A table as well as a listing will present the patient demographics [e.g., age, height, weight, BMI and race] and baseline characteristics (height, weight, as a continuous variable). Age will be calculated from the date of birth to the date demographics were collected.

The UTI symptoms (gross hematuria, pain or uncomfortable pressure in the lower abdomen/pelvic area, pain or burning when passing urine, frequency of urination or going to the toilet very often, urgency of urination or a strong and uncomfortable urge to pass urine) will be summarized.

Pathogens at baseline will be summarized as well as a categorization by ESBL result. Patients with monomicrobial and polymicrobial will be summarized.

7.3 Baseline Microbiology

The bacterial pathogens identified from the baseline urine culture will be presented. In addition, the number and percentage of patients with mono-microbial and poly-microbial infections will be provided and also distribution of baseline pathogens by ESBL (positive/negative) and culture concentration will also be provided.

A listing will be provided that includes all baseline and post-baseline isolates obtained from specimens and whether or not the isolate is considered the pathogenic organism.

7.4 Prior and Concomitant Medications

All medications taken prior to the first dose of the study drug and through the TOC visit will be recorded on the source document. Concomitant antimicrobial medications will be summarized by WHODRUG (Version September 2014 or higher) ATC level 3 and generic medication name. Patients will be counted only once for an ATC class and generic medication name. Medications are considered concomitant if taken on or after the first dose of study drug, or if their stop date is unknown or marked as continuing.

The proportion of patients who 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, will be summarized.

A listing will be provided of all antibacterial medications taken within 30 days prior to the first dose of study drug.

7.5 Study Drug Exposure and 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.

Patients will receive a dosing diary on Day 1 and be 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 eCRF.

A dosing summary will be presented for the ITT, m-MITT, CE and ME populations. The distribution of patients by the number of active doses of study drug therapy will be presented.

7.6 Efficacy Analyses

There is only one treatment group, so hypothesis testing is not needed. Only descriptive statistics will be presented for each endpoint, which will mainly consist of frequency and percentage for each category of the endpoint.

The reasons for non-responder and indeterminate will be summarized for most endpoints.

7.7 Interim Analysis

N/A

7.8 Safety Analyses

Safety analysis will be conducted in the safety population. Safety parameters include adverse events.

Verbatim descriptions of AEs will be coded using Version 21.0 or higher of MedDRA. Summary tables will be provided for all treatment-emergent AEs (TEAEs). An AE is defined as 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. ATEAE is any AE that newly appeared, increased in frequency, or worsened in severity following initiation of ciprofloxacin. In addition, all AEs (including non-TEAEs), serious TEAEs, and TEAEs leading to study drug discontinuation will be provided in listings containing patient number, verbatim term, MedDRA system organ class and preferred terms, seriousness flag, intensity, relationship to study drug, action taken and outcome.

An overall summary of AEs will include number of patients who experienced at least one AE of the following categories: any AE, any TEAE, any drug-related TEAE defined as possibly or probably related to study drug, any serious TEAE, any drug- related SAE, any SAE leading to death, any TEAE leading to premature discontinuation of study drug, and any SAE leading to premature study drug discontinuation.

The number and percentage of patients reporting a TEAE will be tabulated by system organ class and preferred term for all TEAEs and TEAEs through TOC. TEAEs through TOC will also be summarized separately by system organ class, preferred term, and intensity (mild, moderate, and severe); and by system organ class, preferred term, and relationship (unrelated or related to study drug). A table will provide all SAEs (through TOC) by system organ class and preferred term. For all analyses of TEAEs, if the same AE (based on preferred term) is reported for the same patient more than once, the AE is counted only once for that preferred term and at the highest intensity and strongest relationship to study drug.

Analysis of the distribution of the duration of each adverse event as well as an overall mean adverse event duration will be presented.

If an AE starts on the same day that dosing is initiated, and the start time of the AE is missing then the AE is considered TEAE.

7.9 Protocol Deviations

A listing of all protocol deviations will be provided. Deviations will also be reviewed by the Sponsor and categorized into general categories such as: inclusion/exclusion criteria, study drug administration, informed consent, visit schedule, test and procedures and other. Protocol deviations will be classified as major, minor or not a deviation. Also, protocol deviations that impact the analyses will be marked by the clinical team and will be excluded from the clinically evaluable population. The number of patients with at least one protocol deviation and the number of patients with at least one deviation in each category will be presented.

8 DIFFERENCES WITH ANALYSES SPECIFIED IN THE PROTOCOL

- The clinical evaluability rules in the protocol have been modified in the SAP (section 4.5). The prior antibiotic rule was dropped because it is an exclusion criterion in the protocol and applicable to all patients. The requirement that a study entry urine culture obtained before ciprofloxacin administration was dropped since the clinical evaluability rules should only be related to clinical data, not microbiological data.
- The primary efficacy outcome measure in the SAP (section 5.1) was further clarified by adding the rules for non-responder.
- Analyses were added to the SAP (section 5.3) for day 21 even though they weren't listed in the protocol.
- The rule, 'patient previously met criteria for failure', in the protocol for clinical response was modified in the SAP (section 5.3) to 'patient previously met criteria for failure and received rescue antibiotics' to specify the rule more precisely.

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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 - Patient Symptom Assessment Questionnaire (PSAQ)

UTI symptoms	Symptom assessment
Gross hematuria	No symptom
	Mild
	Moderate
	Severe
Pain or uncomfortable pressure in the lower abdomen/pelvic area	No symptom
	Mild
	Moderate
	Severe
Pain or burning when passing urine	No symptom
	Mild
	Moderate
	Severe
Frequency of urination or going to the toilet very often	No symptom
	Mild
	Moderate
	Severe
Urgency of urination or a strong and uncontrollable urge to pass urine	No symptom
	Mild
	Moderate
	Severe

New 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 3 - Organisms considered as Uropathogens

For the purpose of this study, the following organisms will always be considered a uropathogen when isolated from an acceptable urine culture specimen:

- Monomicrobial or polymicrobial infections caused by:
    - Enterobacteriaceae
    - Enterococci
    - *Pseudomonas aeruginosa*
    - *Staphylococcus. saprophyticus*

  The m-MITT population for this study will only include patients with UTIs caused by Enterobacteriaceae and/or *S. saprophyticus.*

- Even if the organism was isolated from an acceptable urine culture specimen, the following are never a pathogen:
    - *Corynebacterium spp.*
    - *S. epidermidis*
    - *S. aureus*
    - *Bacillus spp.*
    - *Diphtheroids*
    - *Micrococcus spp.*
    - *Lactobacillus spp.*
    - *Viridans Streptococci*
    - *Group B Streptococci*
    - *Gardnerella vaginalis*
    - *Neisseria gonorrhoeae*
    - *Yeasts*

All isolates not defined above will be assessed on a case-by-case basis via manual review by the Sponsor.