Statistical Analysis Plan
(SAP)

A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Safety and Efficacy of Intravenous Sulbactam-ETX2514 in the Treatment of Hospitalized Adults With Complicated Urinary Tract Infections, Including Acute Pyelonephritis

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SAP APPROVAL FORM

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
A. baumannii	*Acinetobacter baumannii*
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AP	Acute pyelonephritis
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve
BMI	Body mass index
CE	Clinically Evaluable
CFU	Colony-forming units
CI	Confidence interval
cUTI	Complicated urinary tract infection
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
EOT	End of Treatment
ETX2514SUL	Sulbactam-ETX2514
FDA	Food and Drug Administration
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IV	Intravenous(ly)
LFU	Late Follow-up
LLN	Lower limit of normal
ME	Microbiologically Evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent-to-Treat
m-MITT	Microbiologically modified Intent-to-Treat
PCS	Potentially clinically significant
PK	Pharmacokinetics
PT	Preferred Term
q6h	Every 6 hours
QTcF	QT interval corrected using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System organ class
TEAE	Treatment-emergent adverse event
TOC	Test-of-Cure

Abbreviation	Definition
ULN	Upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) is created based on Protocol CS2514-2017-0003 (Version 1.0, August 01, 2017) and describes in detail the statistical methodology and the statistical analyses to be conducted for the above mentioned protocol.

2. STUDY OBJECTIVES

The primary objective of this study is to evaluate the safety profile of Sulbactam-ETX2514 (ETX2514SUL) versus placebo in patients with complicated urinary tract infection (cUTI), including acute pyelonephritis (AP).

The secondary objectives of this study are the following:

To evaluate the efficacy of ETX2514SUL in patients with cUTI, including AP, in the microbiologically modified Intent-to-Treat (m-MITT) Population;

To compare the clinical cure rate in the 2 treatment groups in the modified Intent-to-Treat (MITT), m-MITT, Clinically Evaluable (CE), and Microbiologically Evaluable (ME) Populations at the Test-of-Cure (TOC) Visit; and

To compare the microbiological eradication rate in the m-MITT and ME Populations at the TOC Visit.

[redacted]

3. STUDY DESIGN

3.1. General Study Design and Plan

This study is a double-blind, randomized, placebo-controlled study to evaluate the safety and efficacy of intravenous (IV) ETX2514SUL in patients with cUTIs who are otherwise relatively healthy. Patients providing informed consent and meeting all study eligibility criteria will be enrolled in the study and have a pre-treatment urine and blood sample obtained and submitted to the local laboratory. Approximately 80 patients will be randomized 2:1 to receive either 1 g ETX2514/1 g sulbactam IV or matching placebo every 6 hours (q6h). All patients will receive background therapy with 500 mg IV imipenem/cilastatin q6h. Randomization will be stratified by baseline diagnosis (symptomatic cUTI versus AP). At least 30% of patients will have a diagnosis of AP at study entry.

Receipt of any long-acting, potentially-effective systemic antibiotic with activity against Gram-negative uropathogens for more than 24 hours within the 72-hour window prior to randomization is prohibited. However, patients who have received a single dose of a short-acting systemic antibiotic up to 24 hours prior to randomization may be randomized up to a maximum of 25% of the study enrollment. A short-acting antibiotic is defined as having a dosage frequency of more than once daily (eg, every 12 hours or more frequently).

Any organism isolated from the blood or urine cultures will be identified by genus and species by the local laboratory. Urine organisms will be cultured and quantified at the local laboratory, and

susceptibility of the organism(s) may be performed per local laboratory standards. All baseline urine organisms that grow $\geq 10^5$ colony-forming units (CFU)/mL and not deemed to be a contaminant, as detailed in the Microbiology Procedures Manual, are to be sent from the local laboratory to the central laboratory. Potential pathogens that grow in both the urine and blood will also be sent to the central laboratory prior to randomization.

For post-baseline urine cultures, only those potential pathogens that grow at $\geq 10^3$ CFU/mL and deemed not to be contaminants will be sent to the central laboratory.

All blood organism(s) cultured at the local laboratory from blood samples (whether at baseline or post-baseline) and not deemed to be a contaminant per the Microbiology Procedures Manual will be sent to the central laboratory for confirmation of identification and susceptibility testing.

Day 1 is defined as the first day of study drug administration. The subsequent study days are defined by the number of calendar days thereafter. The duration of antibiotic treatment with study drug therapy will be 7 days (28 doses), with a prolongation of therapy up to 14 days if clinically indicated in patients with concurrent bacteremia.

All patients should receive at least 8 doses of IV study drug before the Investigator considers the patient to be a clinical failure and discontinues the patient from study drug therapy. No oral switch option is allowed. Patients who withdraw from study drug dosing should perform all End of Treatment (EOT) Visit procedures and should be followed through the Late Follow-up (LFU) Visit for safety assessments, even if they withdraw from dosing due to clinical failure.

Throughout the study, all patients will be monitored for signs and symptoms of cUTI or AP and the occurrence of adverse events. Laboratory data, including chemistry panels, complete blood counts, and samples for urine and blood cultures, as well as electrocardiograms (ECGs), will be collected from all patients at specified times throughout the study.

Sparse pharmacokinetic (PK) sampling (ie, a total of 5 samples per patient) will be performed to refine the population PK model. To maintain the blind, PK samples will be collected from both treatment groups. Samples obtained from the ETX2514SUL group will be analyzed using a validated assay by a central bioanalytical laboratory.

Patients will be enrolled in the study for approximately 21 days, with a maximum duration of study participation of 30 days. Screening procedures can be performed as standard of care within 48 hours prior to randomization on Day 1, with the exception of local laboratory serum creatinine determination, which must be obtained at the local laboratory within 24 hours of the first dose of study drug. The Treatment Period begins on Day 1, and study drug will be administered for 7 calendar days (or up to 14 days in patients with concurrent bacteremia). The EOT Visit will be completed on the final dosing day or the following day (allowing for a 1-day window to complete EOT procedures). The TOC Visit will be completed 7 days (±1 day) after the EOT for all patients. The LFU Visit will be completed 7 days (±2 days) after the TOC Visit for all patients.

3.2. Study Population

The population for this study is approximately 80 hospitalized adult patients with cUTI, including AP. At least 30% of patients will have a diagnosis of AP at study entry.

3.3. Randomization and Blinding

Qualifying patients will be randomized in a 2:1 ratio to receive 1 g ETX2514/1 g sulbactam or placebo via the Interactive Response Technology (IRT) system. All patients will receive 500 mg IV imipenem/cilastatin q6h.

Randomization will be stratified by baseline diagnosis (symptomatic cUTI versus AP). A manual will be provided that describes the IRT system and includes user instructions.

At least 30% of patients will have a diagnosis of AP at study entry.

Patients who have received a single dose of short-acting antibiotic (see Protocol Appendix C for a list of allowed and disallowed antibiotics) for cUTI or AP within 24 hours of randomization will comprise a maximum of approximately 25% of the study enrollment. Patients who have received any potentially therapeutic and long-acting antibiotic for more than 24 hours within the 72-hour window of the start of administration of the first dose of study drug will be excluded from the study.

A randomization notification will be sent to the unblinded pharmacist (or appropriately qualified unblinded designee) at the site. A blinded randomization notification will be sent to the appropriate blinded site personnel.

The Investigator, site personnel, Sponsor, and the Sponsor's designees involved in monitoring, data management, and other aspects of the study will be blinded to treatment assignment. An unblinded site monitor will be assigned to review unblinded pharmacy data and will follow documented procedures to ensure that the blind is maintained throughout the study.

3.4. Breaking the Blind

The Sponsor designee (eg, IRT vendor, etc.) will have a designated randomization administrator who will maintain the randomization codes in accordance with Standard Operating Procedures to ensure that the blind is properly maintained and that only Sponsor personnel who require knowledge of treatment assignments will be unblinded (eg, staff involved in maintaining the randomization codes or serious adverse events [SAEs] reporting).

Unblinding should only occur in the event of an emergency or adverse event for which it is necessary to know the study drug treatment to determine an appropriate course of therapy. If the patient's study drug must be unblinded, the Investigator or qualified designee should contact IRT, but not the site's unblinded pharmacist, for the study drug information. The IRT documentation indicating the blind break must be retained with the patient's source documentation in a way as to not unblind the treatment assignment to other site or Sponsor personnel.

If possible, the Investigator should attempt to contact the site monitor or the Medical Monitor prior to unblinding in order to get additional information about the study drug. If not possible, the Investigator should notify the site monitor or Medical Monitor as soon as possible of the unblinding without disclosing the treatment assignment of the unblinded patient. The Investigator must document the patient's identification, reason for breaking the blind, and the date and time for breaking the blind.

After the database is locked and the SAP is final, the study blind codes will be broken.

3.5. Study Assessments

Table 1 presents the schedule of procedures of the study.

Table 1. Schedule of Procedures

Procedure	Screening	Treatment							TOC	LFU
	-48 Hours to Day 1 [1]	Day 1	Day 2 [2]	Day 3 [2]	Day 4 [2]	Day 5 [2]	Day 6 [2]	Day 7 to Day 14/ EOT +1 Day [2]	7 Days Post-EOT ±1 Day [3]	7 Days Post-TOC ±2 Days [3]
Informed consent	X									
Inclusion/exclusion criteria	X									
Medical/surgical history	X [4]									
Prior/concomitant medications	X [5]		X	X	X	X	X	X	X	X
Demographics [6]	X									
Complete physical examination [7]	X			X		X		X [8]		
Limited physical examination [7]			X		X		X		X	X
Vital signs [9]	X	X	X	X	X	X	X	X	X	X
Assess clinical signs/symptoms	X		X	X	X	X	X	X	X	X
Assess clinical outcome [10]						X		X [11]	X [10]	X [10]
Randomization		X								
Pregnancy test [12]	X							X [13]		
Serum chemistry [14]	X	X		X		X		X [11]	X	X
Hematology [15]	X	X		X		X		X [11]	X	X
Urinalysis [16, 17]	X	X		X				X [11]	X	X
12-lead ECG	X [18,19]			X [18]						
Blood cultures	X		X [20]	X [20]	X [20]	X [20]	X [20]	X [20]	X [20]	X [20]
Urine cultures	X [21,22]					X [21]		X [21]	X [21]	X [21]
Administer study drug [23]		X	X	X	X	X	X	X		
Administer imipenem/cilastatin [24]		X	X	X	X	X	X	X		
Assessment of adverse events [25]	X	X	X	X	X	X	X	X	X	X
PK samples		X [26]		X [26]						

1. Screening procedures may be performed up to 48 hours prior to the first dose of study drug. All Screening procedures must be completed prior to randomization and the first dose of study drug (Day 1). All Screening laboratories will be performed at the local laboratory and may have been collected as standard of care within 48 hours prior to randomization, with the exception of serum creatinine determination, which must be obtained at the local laboratory within 24 hours of the first dose of study drug.
2. Study procedures are only required on treatment days that the patient receives IV therapy. If EOT occurs before Day 14, study procedures are not required to be performed on subsequent days until the TOC Visit.
3. The TOC Visit must occur 7 days (±1 day) after the EOT Visit. The LFU Visit must occur 7 days (±2 days) following the TOC Visit. The LFU Visit should be performed as an in-office visit; however, if the patient is unable to attend the LFU Visit at the site, then the patient may be contacted by telephone call for follow-up assessment of concomitant medications, clinical signs and symptoms, and adverse events.
4. Obtain medical/surgical history, including urological history; record inactive conditions diagnosed within the previous 5 years, complete urological/renal history, and all active conditions.
5. Reasonable effort will be made to determine all relevant treatments (including all antibiotics, prescription and non-prescription medications, herbal medications, and vitamin supplements, supportive therapies, and non-pharmacologic treatments) received within 14 days before the first dose of study drug and during the study.
6. Demographic data will be collected, including sex, age, race, and ethnicity.
7. Complete physical examination includes weight (and height at Screening only). Limited physical examination does not include weight.

8. A complete physical examination is required on Day 7 and at the EOT Visit only. A limited physical examination should be performed on Day 8 to Day 14 if the patient has received blinded study drug.
9. Vital signs include blood pressure, heart rate, and respiratory rate.
10. If a patient is a clinical failure at EOT, the patient is automatically considered a failure at the TOC and LFU Visits, and the assessment of clinical response by the Investigator should be listed as "failure at EOT."
11. Day 7 and EOT Visit only.
12. A highly sensitive urine or serum pregnancy test will be performed at Screening, before the first dose of study drug, and at EOT for women of childbearing potential. If Screening occurs within 48 hours of randomization, study procedures performed at Screening do not need to be repeated.
13. EOT Visit only.
14. See Protocol Appendix B for a full list of clinical laboratory analytes.
15. Hematology includes complete blood count (with red blood cell count, total white blood cell count with differential counts, platelet count, hemoglobin, and hematocrit). See Protocol Appendix B for a full list of clinical laboratory analytes.
16. Urinalysis includes urine dipstick analysis for leukocytes, nitrites, or a catalase test of the urine specimen, microscopic evaluation, specific gravity, and pH. See Protocol Appendix B for a full list of clinical laboratory analytes.
17. Urine sample should be collected by clean-catch midstream or other appropriate method that minimizes risk of bacterial contamination.
18. The 12-lead ECG will be performed at baseline at Screening and repeated as close as possible to the end of the infusion of study drug administration on the day on which post-dose PK samples are drawn (Day 3, Day 4, or Day 5). The day on which the post-dose PK samples are drawn is at the discretion of the Investigator. All 12-lead ECGs will be performed after the patient has been in a supine position for at least 10 minutes.
19. Consult the Medical Monitor and local cardiologist in cases of clinically significant abnormal findings (eg, a QTcF >480 msec).
20. If baseline blood cultures were positive, repeat blood cultures should be obtained daily until negative or if the patient is a treatment failure.
21. An adequate clean-catch urine specimen for culture (or other appropriate method to collect a urine culture that minimizes risk of bacterial contamination) should be obtained at the specified time points. At any point in the study if a patient fails while on therapy, a urine specimen should be obtained.
22. A repeat urine sample for culture must be obtained prior to the start of study drug treatment for any patient enrolled in the study who has received a single dose of a short-acting antibiotic in the 24 hours prior to randomization or for patients who failed preceding antimicrobial therapy. This sample should be taken as close to randomization as possible (within 2 hours prior to randomization, if possible).
23. Study drug should be administered q6h for a minimum of 7 days (28 doses), as described in the protocol.
24. All patients will be administered imipenem/cilastatin q6h.
25. Adverse events should be captured as described in the protocol.
26. PK samples will be collected immediately prior to the first dose of study drug on Day 1 and post-dose of any study drug infusion on Day 4 (±1 day) at the end of the infusion when the infusion pump is turned off, 0.5 hours after the end of the infusion, 2 hours after the end of the infusion, and 3 hours after the end of the infusion (prior to the start of the next infusion).

ECG = electrocardiogram; EOT = End of Treatment; IV = intravenous; LFU = Late Follow-up; PK = pharmacokinetics; q6h = every 6 hours; QTcF = QT interval corrected using Fridericia's formula; TOC = Test-of-Cure.

4. SAMPLE SIZE DETERMINATION

Overall, the study is anticipated to randomize approximately 80 patients in a 2:1 ratio to receive ETX2514SUL or placebo. No formal power calculations have been performed for this study. The sample size is based on practical considerations.

5. STUDY ASSESSMENT

5.1.1. Assessment of Clinical Signs and Symptoms

Clinical signs and symptoms will be assessed at Screening, daily during IV treatment beginning on Day 2, at the EOT Visit, at the TOC Visit, and at the LFU Visit. When possible, the same study personnel should complete the assessments at approximately the same time each day. Maximum daily temperature (defined as the maximum temperature reported on a single calendar day) will be recorded. Body temperature may be taken per the site's preferred method and will be recorded in the appropriate eCRF. The same method of measuring a patient's body temperature should be used throughout the study.

The following signs and symptoms will be assigned a classification of absent, mild, moderate, or severe:

- Urinary frequency,
- Urinary urgency,
- Dysuria,
- Nausea,
- Vomiting,
- Abdominal pain,
- Suprapubic pain or discomfort,
- Flank pain, and
- Costo-vertebral angle tenderness.

5.1.2. Clinical Outcome

Based on the assessment of signs and symptoms, the Investigator will choose 1 of the following clinical outcomes at the Day 5, EOT, and TOC Visits:

Clinical cure: complete resolution or significant improvement of signs and symptoms of cUTI or AP that were present at baseline and no new symptoms, such that no further antimicrobial therapy is warranted.

Clinical failure: symptoms of cUTI or AP present at study entry have not significantly improved or completely resolved, or new symptoms of cUTI or AP have developed and require the initiation of a non-study antibacterial drug therapy, or death.

Clinical indeterminate: insufficient data are available to determine if the patient is a cure or failure.

Based on the assessment of signs and symptoms, the Investigator will choose 1 of the following clinical outcomes at the LFU Visit:

Sustained clinical cure: met criteria for clinical cure at the TOC Visit and the LFU Visit.

Relapse: clinical cure at the TOC Visit but signs and symptoms of cUTI or AP are present at the LFU Visit.

Clinical failure: clinical failure at the TOC Visit carried forward to the LFU Visit or death between the TOC Visit and LFU Visit.

Clinical indeterminate: insufficient data are available to determine if the patient is a sustained clinical cure or clinical relapse.

Note: if a patient is a clinical failure at EOT, the patient is automatically considered a failure at the TOC and LFU Visits, and an assessment of clinical response by the Investigator will be listed as "failure at EOT."

5.1.3. Microbiologic Assessments

Urine culture samples will be obtained at Screening or Day 1, Day 5, Day 7, the EOT Visit, the TOC Visit, the LFU Visit, and any time the patient is deemed to have failed while on therapy. In patients with concurrent bacteremia who receive blinded study drug on Day 8 to Day 14, urine culture samples will be obtained daily. Urine cultures will be performed by the local laboratory. Additionally, a urinalysis including urine dipstick analysis for leukocytes, nitrites, or a catalase test of the urine specimen, microscopic evaluation, specific gravity, and pH will be performed at Screening, Day 1, Day 3, Day 7, the EOT Visit, the TOC Visit, and the LFU Visit. Screening urinalysis will be performed by the local laboratory; all other urinalysis samples will be sent to the central laboratory.

A urine sample taken to support diagnosis or to treat a medical condition within 48 hours prior to the first dose of study drug can be used for baseline microbiologic assessments if the organism(s) cultured were obtained and stored for shipment to the designated central laboratory. Otherwise, a repeat urine sample for baseline microbiologic assessments is required.

A repeat urine sample for culture must be obtained prior to the start of study drug treatment for any patient enrolled in the study who has received a single dose of a short-acting antibiotic in the 24 hours prior to randomization or for patients who failed preceding antimicrobial therapy. This sample should be taken as close to randomization as possible (within 2 hours prior to randomization, if possible).

Urine culture samples must be obtained through 1 of the following methods that minimizes the risk of bacterial contamination:

- Clean-catch mid-stream,
- Newly-inserted Foley catheter (bag specimens are not permitted),
- Bladder needle aspiration, or
- Ureter aspiration.

Baseline urine cultures must grow 1 or 2 bacterial organisms, each at $\geq 10^5$ CFU/mL. If a patient grows ≥3 organisms in the urine, the urine culture will be considered contaminated unless ≥1 of the organisms also grows in a concurrently obtained blood culture.

Two sets of blood culture samples must be obtained from 2 separate venipuncture sites at Screening. Each set is collected from a separate venipuncture and consists of 1 aerobic and 1 anaerobic blood culture bottle. Each set of blood cultures should be collected by direct venipuncture from independent sites approximately 15 to 30 minutes apart. If baseline blood cultures are positive and not considered contaminated, repeat blood cultures should be obtained daily until negative or if the patient is a treatment failure. To avoid unnecessary blood draws, the Investigator may wait until the result of the prior blood culture is known before performing the next blood culture.

The local laboratory will culture each sample for organism identification, quantification (urine only), and susceptibility testing. Any organism isolated from the blood or urine will be identified by genus and species by the local laboratory. Potential pathogen(s) cultured at the local laboratory from urine or blood samples will be sent to a designated central laboratory for confirmation of identification and susceptibility testing results.

Only those baseline potential pathogens that grow in the urine at $\geq 10^5$ CFU/mL and deemed not to be contaminants will be sent to the central laboratory. Potential pathogens that grow in both the urine and blood will also be sent to the central laboratory prior to randomization.

For post-baseline urine cultures, only those potential pathogens that grow at $\geq 10^3$ CFU/mL and deemed not to be contaminants will be sent to the central laboratory.

5.1.4. Microbiologic Outcome

5.1.4.1. Per-Pathogen Microbiologic Outcome

Microbiologic outcome at Day 5, EOT, and TOC will be programmatically determined for each pathogen isolated at baseline. Per-pathogen microbiological response categories are eradication, persistence, and indeterminate defined as following:

Microbiologic eradication: the demonstration that the baseline bacterial pathogen(s) is reduced to $<10^4$ CFU/mL according to the Food and Drug Administration (FDA) criteria and $<10^3$ CFU/mL according to the European Medicines Agency (EMA) criteria on urine culture and negative on repeat blood culture (if positive at baseline).

Microbiologic persistence: the urine culture grows $\geq 10^4$ CFU/mL for the FDA ($\geq 10^3$ CFU/mL for the EMA) of any of the baseline pathogen(s) identified at study entry and/or a blood culture demonstrates the same baseline pathogen(s). Patients who are a persistence at EOT will be considered a persistence at TOC.

Microbiologic indeterminate: no follow-up urine culture is available, or the follow-up urine culture cannot be interpreted for any reason, or the follow-up urine culture is considered contaminated. For a baseline blood pathogen, no follow-up blood culture is available.

A per-pathogen microbiological outcome will be determined at the LFU visit. Per-pathogen microbiological outcome categories are sustained eradication, presumed sustained eradication,

continued persistence, recurrence, and indeterminate. A per-pathogen microbiologic outcome of persistence at TOC will be considered a continued persistence at LFU defined as following:

Sustained microbiologic eradication: microbiologic eradication at the TOC Visit and the LFU Visit.

Presumed sustained microbiologic eradication: no urine culture was done at LFU and patient meets clinical criteria for sustained clinical cure.

Microbiologic continued persistence: a per-pathogen microbiologic outcome of persistence at the TOC Visit will be considered a continued persistence.

Microbiologic recurrence: urine culture grows $\geq 10^4$ CFU/mL for the FDA ($\geq 10^3$ CFU/mL for the EMA) of any of the baseline pathogen(s) identified at study entry and/or a positive blood culture at any time after documented eradication at the TOC Visit up to and including the LFU Visit.

Microbiologic indeterminate: no follow-up urine culture is available, or the follow-up urine culture cannot be interpreted for any reason, or the follow-up urine culture is considered contaminated and the patient is not a sustained clinical cure.

5.1.4.2. Per-Patient Microbiologic Outcome

An overall per-patient microbiological response at Day 5, EOT, and TOC will be programmatically determined for each patient based on individual outcomes for each baseline pathogen. For a patient to have a microbiological response of eradication, the outcome for each baseline pathogen must be eradicated. If the outcome for any pathogen is persistence, the patient will be considered to have a microbiological response of persistence.

Microbiologic eradication: the outcome of all baseline pathogens must be eradication at the specified visit (Day 5, EOT or TOC).

Microbiologic persistence: the outcome of at least 1 baseline pathogen is persistence.

Microbiologic indeterminate: the outcome of at least 1 baseline pathogen is indeterminate and there is no outcome of persistence for any baseline pathogen.

An overall per-patient microbiological response at LFU will be determined for each patient and will be based on individual outcomes for each baseline pathogen. For a patient to have a microbiological response of sustained eradication, the outcome for each baseline pathogen must be sustained or presumed sustained eradication. If the outcome for any pathogen is recurrence, the patient will be considered to have an unfavorable microbiological response. A per-patient microbiologic outcome of persistence at TOC will be considered a per-patient continued persistence at LFU.

Sustained microbiologic eradication: the outcome of all baseline pathogens must be sustained eradication or presumed sustained eradication.

Microbiologic recurrence: the outcome of at least 1 baseline pathogen is recurrence.

Microbiologic continued persistence: a per-patient microbiologic outcome of persistence at TOC will be considered a per-patient continued persistence.

Microbiologic indeterminate: the outcome of at least 1 baseline pathogen is indeterminate and there is no outcome of recurrence for any baseline pathogen.

5.1.5. Overall Response

The primary efficacy outcome is a composite outcome (overall response) and is programmatically determined based on the clinical and microbiologic outcomes based on FDA and EMA criteria as 1 of the following overall responses:

Overall success: a patient who is deemed a clinical cure AND who achieved microbiologic eradication.

Overall failure: a patient who is deemed a clinical failure OR is deemed to have microbiological persistence.

Overall indeterminate: insufficient data are available to determine if the patient is an overall success or failure.

5.2. Safety Assessments

The safety parameters include the incidence, severity, causality, and seriousness of treatment-emergent adverse events (TEAEs) and the evaluation of changes from baseline in safety laboratory test results, ECGs, vital signs, and physical examinations.

5.2.1. Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate electronic case report form (eCRF). Adverse events will be monitored and documented from the time of informed consent until study participation is complete. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 20.0).

5.2.2. Clinical Laboratory Evaluations

Standard clinical laboratory profiles for chemistry will be evaluated at Screening, Day 1, Day 3, Day 5, Day 7, the EOT Visit, the TOC Visit, and the LFU Visit. All Screening laboratories will be performed at the local laboratory and may have been collected as standard of care within 48 hours prior to randomization, with the exception of serum creatinine determination, which must be obtained at the local laboratory within 24 hours of the first dose of study drug. All other samples are to be sent to the central laboratory. The Day 5 safety chemistry panel will be performed at the local laboratory and sent to the central laboratory.

Standard clinical laboratory profiles for hematology will be performed at Screening, Day 1, Day 3, Day 5, Day 7, the EOT Visit, the TOC Visit, and the LFU Visit.

A urinalysis including urine dipstick analysis for leukocytes, nitrites, or a catalase test of the urine specimen, microscopic evaluation, specific gravity, and pH will be performed at Screening, Day 1, Day 3, Day 7, the EOT Visit, the TOC Visit, and the LFU Visit.

A highly sensitive urine or serum pregnancy test will be performed at Screening and at EOT on women of childbearing potential.

Standard of care safety laboratory profiles should also be performed by the local laboratory.

The chemistry, hematology, coagulation and urinalysis parameters assessed in this study include the following:

- Standard safety chemistry panel: alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALP), amylase, aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen, calcium, chloride, creatine kinase, creatinine, estimated glomerular filtration rate, gamma-glutamyl transferase, glucose, inorganic phosphorus, lactate dehydrogenase, lipase, potassium, sodium, total bilirubin, total protein, and uric acid.
- Hematology: hematocrit, hemoglobin, platelets, red blood cell count, white blood cell count and differential, basophils, eosinophils, lymphocytes, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, monocytes, and neutrophils.
- Coagulation: partial thromboplastin time, and prothrombin time.
- Urinalysis: bilirubin, blood, glucose, ketones, leukocyte esterase, microscopy, nitrite, pH, protein, specific gravity and urobilinogen.

Serum (beta human chorionic gonadotropin) or urine pregnancy test will be performed for female patients of childbearing potential only.

All Screening laboratories will be performed at the local laboratory and may have been collected as standard of care within 48 hours prior to randomization, with the exception of serum creatinine determination, which must be obtained at the local laboratory within 24 hours of the first dose of study drug. All other samples are to be sent to the central laboratory. The Day 5 safety chemistry panel will be performed at the local laboratory and sent to the central laboratory.

5.2.3. Vital Signs

Vital signs (including systolic and diastolic blood pressure, heart rate, and respiratory rate) will be taken after at least 5 minutes in a seated position. Vital signs will be recorded at Screening, all days that the patient receives study drug treatment, the EOT Visit, the TOC Visit, and the LFU Visit. Vital signs should be collected at the same time as assessments of signs and symptoms.

5.2.4. Electrocardiograms

Twelve-lead ECGs will be performed at baseline at Screening and repeated as close as possible to the end of the infusion of study drug administration on the day on which the post-dose PK samples are drawn (Day 3, Day 4, or Day 5; day selected at the discretion of the Investigator). All 12-lead ECGs will be performed after the patient has been in a supine position for at least 10 minutes. The value at Screening will be used for assessing the QT interval corrected using Fridericia's formula (QTcF) exclusion criterion. All 12-lead ECGs will be performed and read locally. The following ECG parameters will be recorded:

- Heart rate,
- QRS interval,
- PR interval,

- RR interval,
- QT interval, and
- QTcF interval.

All ECGs will be evaluated for the presence of abnormalities by a qualified local physician. The ECGs will be classified as one of the following:

- Normal,
- Having a not clinically significant abnormality, or
- Having a clinically significant abnormality.

An example of a clinically significant abnormality may be a corrected QTcF >480 msec.

5.2.5. Physical Examinations

A complete physical examination will be performed at Screening, Day 3, Day 5, Day 7, and the EOT Visit. A limited physical examination will be performed at Day 2, Day 4, Day 6, Day 8 to Day 14 (if EOT has not already occurred), the TOC Visit, and the LFU Visit.

A complete physical examination must include source documentation of skin, head and neck, heart, lung, abdomen, extremities, back/flank/costo-vertebral angle tenderness, and neuromuscular assessments. Weight will be obtained at all complete physical examinations; height will only be collected at Screening. Limited physical examinations are symptom based and do not include weight. When clinically indicated, a prostate exam can be performed, at the discretion of the Investigator.

Physical examinations may be performed at unscheduled time points if deemed necessary by the Investigator.

5.3. Medical History

Medical/surgical history including urological/renal history inactive conditions diagnosed within the previous 5 years and all active conditions will be collected at screening. Medical/surgical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 20.0) except for urological/renal history.

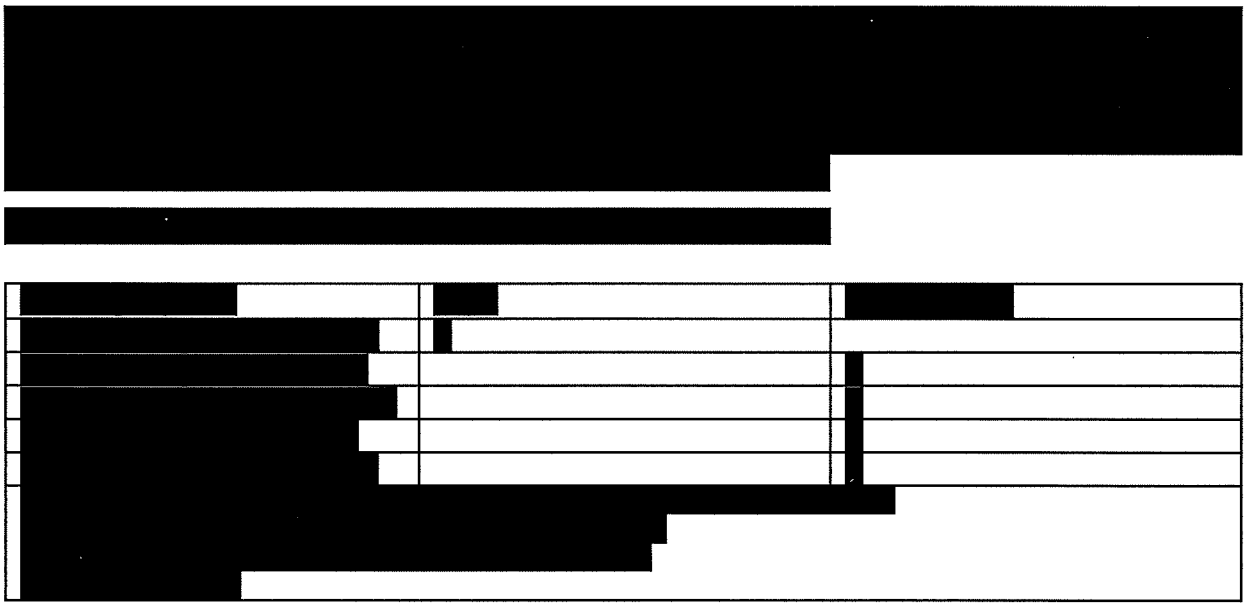
5.4. Prior and Concomitant Medications

All relevant treatments including all antibiotics, prescription and non-prescription medications, herbal medications and vitamin supplements, supportive therapies, and non-pharmacologic treatments received within 14 days before the first dose of study drug and during the study will be collected. The name, route of administration, dose, frequency, indication, and duration of the treatment will be recorded in the eCRF.

Prior and concomitant medication will be coded using the World Health Organization (WHO) Drug Dictionary (March 2017E B2 Version).

Concomitant procedures/non-drug therapies will be coded using MedDRA, Version 20.0.

5.5. Pharmacokinetic Assessments



The PK samples will be collected for both treatment groups to maintain the blind. The PK samples obtained from the ETX2514SUL group will be analyzed (using a validated assay) by a central bioanalytical laboratory.

The PK plasma samples will be used to estimate PK parameters using non-compartmental methods, such as area under the concentration-time curve (AUC), maximum plasma concentration, time to maximum plasma concentration, drug clearance, half-life, minimum plasma concentration, and steady-state volume of distribution for ETX2514SUL. Population PK and PK-pharmacodynamic modeling will be performed and reported separately. The results will not be included in the clinical study report.

6. EFFICACY ENDPOINTS

6.1. Primary Endpoints

The primary efficacy parameter is the proportion of patients with an overall success (clinical cure and microbiologic eradication) in the m-MITT Population at the TOC Visit.

6.2. Secondary Endpoints

The secondary efficacy parameters include the following:

Proportion of patients with a response of clinical cure in the MITT, m-MITT, CE and ME Populations at the TOC Visit; and

Proportion of patients with a response of microbiologic eradication in the m-MITT and ME Populations at the TOC Visit.

6.3. Exploratory Endpoints

The exploratory efficacy parameters include the following:

- Proportion of patients with a response of sustained microbiologic eradication in the m-MITT and ME Populations at the LFU Visit,
- Proportion of patients with a response of sustained clinical cure in the MITT, m-MITT, CE, and ME Populations at the LFU Visit,
- Proportion of patients with a response of clinical cure in the MITT and m-MITT Populations at Day 5,
- All-cause mortality through the LFU Visit in the MITT Population,
- Summary (number and percentage of patients) of the assessment of clinical signs and symptoms of cUTI and AP at each time point throughout the study by treatment group in the MITT Population, and
- Descriptive statistics of the length of hospital stay by treatment group for the MITT Population.

7. ANALYSIS POPULATIONS

The following analysis populations will be included in the analyses.

7.1. Intent-to-Treat Population

The Intent-to-Treat (ITT) Population will include all patients randomized to study drug treatment (ETX2514SUL or placebo) regardless of whether the patient actually receives study drug.

7.2. Modified Intent-to-Treat Population

The Modified Intent-to-Treat (MITT) Population will include patients who meet ITT criteria and receive any amount of study drug.

7.3. Microbiologically Modified Intent-to-Treat Population

The Microbiologically Modified Intent-to-Treat (m-MITT) Population will include patients who meet MITT criteria and have at least 1 baseline uropathogen from an appropriately collected pre-treatment baseline urine or blood sample. To be considered a pathogen, the baseline urine culture must grow 1 or 2 bacteria isolates, each at $\geq 10^5$ CFU/mL. If ≥3 bacterial isolates are identified, the culture will be considered contaminated regardless of colony count unless 1 of the isolates, even if the CFU/mL is $<10^5$, that grows in the urine is also isolated from a blood culture obtained within 48 hours before the start of administration of the first dose of study drug. If the same pathogen is present in both blood and urine cultures, even if the CFU/mL is $<10^5$ in the urine, the organism will be considered a pathogen.

The m-MITT Population will be the primary efficacy population.

7.4. Clinically Evaluable Population

The Clinically Evaluable (CE) Population will include patients who meet the MITT criteria and meet evaluability criteria (meet key inclusion criteria, do not have key exclusion criteria, received a minimum of at least 12 doses of IV treatment to be a clinical cure [at least 8 doses of IV treatment to be a clinical failure], received ≥80% of anticipated doses, did not have a clinical response of indeterminate at the TOC visit).

7.5. Microbiologically Evaluable Population

The Microbiologically Evaluable (ME) Population will include patients who meet m-MITT criteria and CE criteria and have an appropriately collected urine culture specimen and interpretable urine culture result at the TOC Visit.

7.6. Safety Population

The Safety Population will include patients who meet ITT criteria and receive any amount of study drug. All safety analyses will be based on actual treatment received.

8. STATISTICAL ANALYSIS

8.1. General Statistical Considerations

Summary statistics will be presented by treatment group. For continuous variables, the number of observations (n), mean, standard deviation, median, minimum, and maximum will be provided. For categorical variables, the frequency and percentage in each category will be displayed.

For summary statistics, the mean and median will be displayed to one decimal place greater than the original value and the measure of variability (e.g. standard deviation) will be displayed to two decimal places greater than the original value. All analyses will be performed using SAS® Version 9.3 or higher.

Descriptive statistics will be provided for each treatment group (ETX2514SUL and placebo [background imipenem/cilastatin therapy]). Statistical tests and/or confidence intervals (CIs) will be used to compare treatment groups.

8.2. Handling of Dropouts/Missing data

For the primary efficacy outcome measure of overall response, patients with missing data or who are lost to follow-up will be considered as an indeterminate response and are included in the denominator for the calculation of overall success rate. Thus, patients with an indeterminate outcome are considered as failures for the primary analysis. A clinical failure occurring at an earlier time point will be carried forward to the subsequent visits.

In cases of missing or incomplete dates (e.g. AE and concomitant medications), the missing component(s) will be assumed as the most conservative value possible. For example, AEs with missing start dates, but with stop dates either overlapping into the treatment period or missing, will be counted as treatment-emergent, taking the worst-case approach. When partial dates are present in the data, both a partial start date and/or a partial stop date will be evaluated to determine whether it can be conclusively established that the AE started prior to the start of study drug or ended prior to the start of study drug. If the above cannot be conclusively established based on the partial and/or present dates, then the AE will be considered as treatment-emergent. Actual data values as they appear in the original eCRF will be presented in the data listings.

Missing values for other variables will not be imputed and only observed values will be used in data analyses and summaries.

8.3. Baseline Definition

For microbiological data, baseline pathogen(s) are determined from all specimens collected prior to the first dose of study drug.

For all efficacy and safety endpoints, baseline is defined as the last measurement or assessment prior to the first dose of study drug.

8.4. Patient Disposition

Patient disposition will be summarized for the ITT and MITT Populations for each treatment group and in total. The following patient disposition categories will be included in the summary for the ITT and MITT Populations:

- Patients who were randomized,
- Patients who received study drug,
- Patients who did not receive study drug,
- Patients who completed the study treatment,
- Patients who did not complete the study treatment,
- Patients who completed the study, and
- Patients who did not complete the study.

For patients who did not complete the treatment, and patients who did not complete the study, a summary will be provided by reason of discontinuation. A summary of screen failures and the reason for screen failures will be provided. In addition, the reason(s) for exclusion from an analysis population (m-MITT, CE, and ME) will be summarized by treatment group and a corresponding listing will be provided showing each patient's inclusion/exclusion from each population and reason(s) for exclusion.

8.5. Protocol Deviations

The number of patients with at least one reportable protocol deviation, and the number of patients with at least one reportable deviation in each category will be presented by treatment group and overall for the ITT Population.

8.6. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively for the ITT, MITT, m-MITT, CE, and ME Populations by treatment group and overall. Age, weight, height, body mass index (BMI), and screening creatinine clearance will be summarized descriptively (n, mean, standard deviation, median, minimum, and maximum). Sex, race, ethnicity, age group (<65, 65- <75, and ≥75 years) and screening creatinine clearance group (<30 mL/min, 30- <70 mL/min and ≥70 mL/min) at baseline will be summarized with contingency tables.

8.7. Baseline Infection Characteristics

Baseline infection characteristics will be summarized with descriptive statistics for the ITT, MITT, m-MITT, CE, and ME Populations. Infection type (cUTI or AP) will be summarized to show the

number and percentage of patients in each category. Signs/symptoms and evidence of pyuria criteria the patient met at enrolment will be summarized by infection type with contingency tables. Riske associated with cUTI will also be summarized for patients with cUTI.

All baseline pathogens will also be summarized for the m-MITT and ME Populations.

The number and percentage of patients with each sign and symptom present at baseline (urinary frequency, urinary urgency, dysuria, nausea, vomiting, abdominal pain, suprapubic pain or discomfort, flank pain, and costo-vertebral angle tenderness, by severity (absent, mild, moderate and severe), will be tabulated for the MITT, m-MITT, CE and ME Populations. Additional tables will summarize each sign and symptom at baseline separately for patients with cUTI and AP in the MITT, m-MITT, CE and ME Populations.

8.8. Medical History

Medical history of renal/urological conditions will be summarized descriptively by treatment group and in total for MITT and m-MITT Populations. All other medical and surgical history will be summarized for the MITT and m-MITT Populations for each treatment group and in total by system organ class (SOC) and preferred term (PT).

All Medical and surgical history will be listed by patient.

8.9. Prior and Concomitant Medications

Prior medications are medications used before the first dose of study drug. Concomitant medical are medications used on or after the first dose of study drug.

The prior and concomitant medications will be summarized with the number and percentages by Anatomical Therapeutic Chemical (ATC) class and preferred term for each treatment group and overall in the m-MITT Population. Although a patient may have taken two or more medications, the patient is counted only once within an ATC classification. The same patient may contribute to two or more preferred terms in the same classification.

The proportion of patients who receive the prior and concomitant medications will be summarized by treatment group and overall for the following:

- Systemic antibacterial medications taken prior to (within 14 days) the first dose of study drug,
- Systemic antibacterial medications taken within 72 hours prior to the first dose of study drug,
- Non-antibacterial medications taken prior to (within 14 days) the first dose of study drug, and
- Concomitant medications taken on or after the first dose of study drug.

All prior and concomitant medications and procedures will be listed by patient.

8.10. Dosing and Extent of Exposure

Descriptive statistics for the duration of study drug will be summarized by treatment group for the Safety, m-MITT, CE, and ME Populations. Treatment duration is defined as the date of the last dose of study medication - first dose of study mediation +1 day. The number and percentage of patients receiving 1-3, 4-6, 7, 8-10 and 11-14 days of study drug will be provided. The total number of doses of study drug received will also be summarized by treatment group using descriptive statistics.

Compliance with study drug will be summarized, and will be defined as the total number of doses of study drug taken, divided by the total number of doses expected multiplied by 100. Total number of expected doses will be derived based on elapsed time between first and last doses of study drug and its prescribed frequency. Percent compliance as a continuous variable and the proportion of patients with <80% and ≥80% compliance will be summarized by treatment group for the Safety, m-MITT, CE and ME Populations.

8.11. Efficacy Analyses

8.11.1. Analysis of Primary Efficacy Endpoints

The primary efficacy endpoint for this study is the proportion of patients with an overall success (clinical cure and microbiologic eradication) in the m-MITT Population at the TOC Visit.

Patients will be programmatically categorized as a success, failure, or indeterminate response. Patients with missing data or who are lost to follow-up are defined as indeterminate for the primary analysis and are included in the denominator for the calculation of overall success rate. Thus, patients with an indeterminate outcome are considered failures for the primary analysis. The number and percentage of patients in each treatment group in each response category will be reported.

The proportion of patients with overall success will be summarized by treatment group in the m-MITT and ME Populations. Two-sided 95% CIs will be presented for the observed difference in the overall success rate (EXT2514SUL group minus placebo group [background imipenem/cilastatin therapy]). The primary analysis is based on a CI computed using a continuity-corrected Z-statistic.

8.11.2. Additional Analyses of the Primary Efficacy Endpoint

The primary efficacy outcome will also be assessed separately across the randomization stratification factor of baseline diagnosis (symptomatic cUTI versus AP) for the m-MITT Population. For each baseline diagnosis stratum, a 95% CI will be computed for the difference in the overall success rate using a continuity-corrected Z-statistic. Exploratory analyses in other subgroups may also be conducted.

8.11.3. Analysis of Secondary Efficacy Endpoints

The number and percentage of patients determined to be a clinical cure, clinical failure and indeterminate response at the TOC visit in the MITT, m-MITT, CE and ME Populations will be presented by treatment group. Two-sided 95% CIs for the observed difference in the clinical cure rates between the EXT2514SUL group and the placebo group (background imipenem/cilastatin therapy) will be presented based on a continuity-corrected Z-statistic.

The number and percentage of patients with a per-patient microbiologic eradication, persistence, and indeterminate response at the TOC Visit in the m-MITT and ME Populations will be presented by treatment group. Two-sided 95% CIs for the observed difference in the per-patient microbiological eradication rates between the EXT2514SUL group and the placebo group (background imipenem/cilastatin therapy) will be presented based on a continuity-corrected Z-statistic.

[redacted]

[redacted]

8.12. Safety Analyses

All safety summaries and analyses will be performed on the Safety Population. All patients will be summarized based on the actual treatment received. Safety endpoints include the assessment of TEAEs and the evaluation of changes from baseline in safety laboratory test results, ECGs, vital signs, and physical examinations.

8.12.1. Adverse Events

A TEAE is defined as an adverse event occurring on or after the administration of the first dose of study drug. An overview of adverse events will be provided which summarizes the incidence of the following categories:

- All AEs,
- All TEAEs,
- Drug-related TEAEs,
- Mild TEAEs,
- Moderate TEAEs,
- Severe TEAEs,
- SAEs,
- Drug-related SAEs,
- SAE leading to death,
- TEAE leading to discontinuation of study drug, and
- SAE leading to discontinuation of study drug.

Patients with multiple events will be counted only once within each category. Severity grade and relationship will be counted using the maximum severity and the strongest relationship respectively for a patient with multiple TEAEs.

The number and percentage of patients reporting a TEAE in each treatment group will be tabulated by SOC and PT; by SOC, PT, and severity; and by SOC, PT, and relationship (related or unrelated to study drug and imipenem/cilastatin). Summary tables will be presented alphabetically by SOC and decreasing frequency of PT in the EXT2514SUL group within SOC. For all analyses of TEAEs, if the same AE (based on PT) is reported for the same patient more than once, the AE is counted only once for that PT and at the highest severity and strongest relationship to study drug.

The number and percentage of patients reporting a SAE and reporting a TEAE leading to discontinuation of study drug in each treatment group will be summarized by SOC and PT.

A list of patients who have SAEs, a list of patients who discontinue from study drug, and a list of death will be provided. All adverse events will be listed.

8.12.2. Clinical Laboratory Evaluations

Laboratory test results (hematology, serum chemistry, and urinalysis) at each scheduled visit and change from baseline will be summarized by treatment group.

Shift tables from baseline to each scheduled post-baseline visit will be provided for selected chemistry parameters (ALT, AST, total bilirubin, creatinine, creatine kinase, ALP, potassium) and hematology parameters (hematocrit, hemoglobin, platelets, white blood cell count and differential). For chemistry parameters, the following categories will be used: < the lower limit of normal (LLN), normal, > the upper limit of normal (ULN) to ≤3×ULN, >3×ULN to ≤5×ULN, >5×ULN, and missing. For hematology parameters, the following categories will be used: low, normal, high, and missing. Boxplots over time by treatment group of total white blood cell and absolute neutrophil counts will also be provided.

The number and percentage (based on the number of patients with a normal level at baseline) of patients in each treatment group with an ALT (>3×ULN, >5×ULN, and >10×ULN), an AST (>3×ULN, >5×ULN, and >10×ULN), an ALT or AST >3×ULN, and a total bilirubin (>1.5×ULN and >2×ULN) will be presented by study visit. A listing of patients who meet the laboratory criteria for Hy's law will also be provided. The laboratory criteria for Hy's law is defined as ALT or AST>3×ULN, ALP ≤2.0×ULN, and total bilirubin >2×ULN. A listing will also be provided for the potentially clinically significant (PCS) values for the above parameters.

All clinical laboratory data will be listed. Values outside the normal ranges will be flagged.

8.12.3. Vital Signs

Descriptive statistics will be provided for vital sign data (systolic and diastolic blood pressure, heart rate, and respiratory rate) presented as both actual values and changes from baseline over time.

A listing of all vital signs will be provided by patient.

8.12.4. Electrocardiograms

Descriptive statistics will be provided for 12-lead ECG findings (heart rate, QRS, PR, RR, QT, and QTcF) and changes from baseline for each scheduled visit in the Safety Population.

Change from baseline will be calculated for each patient as the post-baseline value minus the baseline value. Boxplots by treatment group of the ECG parameters will also be provided for the baseline and post-baseline ECG assessments.

The number and percentage of patients with notable ECG changes in maximum QTcF (>450 msec, >480 msec, and >500 msec) over all post-baseline evaluations, as well as in QTcF maximum changes from baseline (>30 msec and >60 msec) over all post-baseline evaluations will be summarized by treatment group.

All 12-lead ECG findings will be listed by patient.

8.12.5. Physical Examination

Physical examination findings will be listed by patient.

8.13. Pharmacokinetic Analyses

The pharmacokinetic analyses will be performed by another vendor and reported separately.

8.14. Interim Analysis

No interim analysis of efficacy has been planned.