MEDPACE

STATISTICAL ANALYSIS PLAN

Protocol Title:	A Multi-Center Randomized, Double-Blind Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of LBP-EC01 in Patients With Lower Urinary Tract Colonization Caused by *E. Coli*
Protocol Number:	LBx-1001
Protocol Version/Date:	1.4 / 01Oct2020
Investigational Product:	LBP-EC01
Sponsor:	Locus Biosciences, Inc 523 Davis Drive, Suite 350 Morrisville, NC 27560
SAP Version/Date:	1.0 / 17Dec2020

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SIGNATURE PAGE

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VERSION HISTORY

Version	Version Date	Description
1.0	17Dec2020	Initial approved version

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse event
ATC	Anatomical therapeutic chemical
AUC	Area under curve
BID	Twice daily
BLQ	Below limit of quantification
BMI	Body mass index
CDISC	Clinical Data Interchange Standards Consortium
CFU	Colony-Forming Unit
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRISPR	Clustered Regularly Interspersed Short Palindromic Repeats
crPhages	CRISPR-enhanced bacteriophage
CSR	Clinical Study Report
DAIDS	Division of AIDS (Acquired immunodeficiency syndrome)
DSMC	Data Safety Monitoring Committee
E. coli	*Escherichia coli*
ECG	Electrocardiogram
EOS	End of study
EOT	End of treatment
FIH	First in human
GM	Geometric mean
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	Investigational Medicinal Product
ITT	Intent-to-Treat
IVRS	Interactive voice/web-based response system
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamics
PK	Pharmacokinetics
PFU	Plaque-forming unit
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SDTM	Study Data Tabulation Model
SoA	Schedule of Assessments
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TFL	Table, figure, listing
USP	United States Pharmacopeia
UTI	Uninary tract infection
WBC	White blood cell
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number LBx-1001. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

To evaluate the safety, tolerability, and pharmacokinetics (PK) of LBP-EC01 in patients ≥18yrs of age with lower urinary tract colonization caused by *E. coli*.

2.1.2 Secondary Objectives

To evaluate the pharmacodynamics (PD) of LBP-EC01.

2.1.3 Exploratory Objectives

To explore the influence of LBP-EC01 on the urinary tract microbiota.

2.2 Study Design

2.2.1 Overview

This is a Phase 1b FIH study to assess safety, tolerability, PK, and PD of LBP-EC01 in patients who have significant colonization of the urinary tract by *E. coli*. It is a multi-center randomized, double-blind study in patients with indwelling urinary catheters, or who require intermittent urinary catheterization and/or patients with asymptomatic bacteriuria caused by *E. coli*.

No formal hypothesis will be tested. Thirty-six patients will be randomized 2:1 to receive either LBP-EC01 (at approximately 1.5×10^{7} - 1.5×10^{13} PFU/vial - the maximum feasible dose based on manufacturing process) or inert placebo given twice daily for 7 days by intravesical catheter. A new catheter will be installed at the beginning of the study and will be replaced at the discretion of the investigator. The study will be conducted in 7 sites in the US. Study duration for patients will be up to 56 days, which includes up to 21 days for screening, 7 days of Investigational Medicinal Product (IMP) treatment, a Day 14 assessment (14 days after first dose), a Day 28 assessment (28 days after first dose), and an End of Study (EOS) assessment (35 days after first dose). Patients will be in the clinic or hospital the evening prior to receiving the first dose of treatment and throughout the 7 days of treatment.

The study will consist of a Screening Period of up to 21 days. On Day -1 patients will either be hospitalized or in a facility that can provide proper administration of study drug and then randomized to LBP-EC01 or placebo. The entire 7-day Treatment Period in which patients will receive 13 doses of IMP will be conducted with the patient in the clinic/hospital. In circumstances where the patient may not be able to be in clinic/hospital for the full 7 days of treatment, upon consultation between the treating physician and the study Medical Monitor, patients may be considered to be treated and monitored in clinic/hospital for Days 1-3 and then may be allowed to come back to the clinic/hospital for the PM dose on Day 3 and the remaining treatment from Days 4-7. The end of treatment (EOT) will be after the 13th dose on Day 7, after

which the patient may be released from the clinic/hospital. The patient will return on Day 14 (±3 days) for the Day 14 Visit, and on Day 28 (±3 days) for the Day 28 Visit. AE data will be collected throughout the study, including Day 28 through Day 35. At Day 35, the patient will be contacted by telephone to assess any AEs or lab abnormalities since the Day 28 Visit. At the discretion of the investigator, the patient may be asked to return to the clinic/hospital for a Day 35 Visit (±3 days). Day 35 is the end of study. Assessments will be conducted as described in Table 1 and Table 2 of the Protocol.

Safety will be assessed throughout the study. Spleen evaluations will include ultrasound assessments for splenomegaly at Day -6 to -1, Day 3, and Day 7 and clinical examinations to assess for splenomegaly will be performed at all visits. In addition, attention will be focused on identifying any progression of a urinary colonization to an active infection, including the signs and symptoms of local vesicular reactions (e.g., bladder pain, hematuria). Symptoms of active infection will be solicited during daily observations throughout the 7 days of treatment and until the end of study. Symptoms of note in this population include dysuria, urinary frequency, urinary urgency, suprapubic discomfort and flank pain in addition to non-specific symptoms of urinary leakage, change in voiding habits, worsening muscle spasm, increasing autonomic dysreflexia, sweating, malaise, and fever or hypothermia. Urine microscopy and culture will be assessed frequently during the study (see Table 2 of the Protocol).

2.2.2 Randomization and Blinding

Study patients will be randomly assigned to LBP-EC01 or placebo treatment groups in a 2:1 ratio using IVRS.

This is a double-blind study. Blinding to study treatment allocation will be achieved through use of matching placebo solution and administration sets. Neither the patient, nor the Investigator, nor Medpace/Sponsor will be aware of the treatment allocation. Key pharmacy staff involved in the preparation of the IMP or placebo will need to be unblinded.

In the event of an emergency, the treatment code for an individual patient will be readily available to the Investigator and Sponsor/Medpace through the IVRS. If unblinding is necessary for patient management (in the case of an SAE), the Investigator will be able to break the treatment code by contacting the IVRS. Treatment codes should not be broken except in emergency situations. If the Investigator wishes to know the identity of the IMP for any other reason, he or she should contact the Medical Monitor directly. The Investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to an SAE).

As per Health Authority reporting requirements, the Sponsor/Medpace will break the treatment code for all unexpected SAEs (see Section 9.3 of the Protocol) that are considered by the Investigator to be related to IMP.

Whenever disclosure of the identity of the IMP is necessary, adequate procedures will be in place to ensure integrity of the data. Any unblinding, at the investigating site end, will be documented in the study report with date, reason for identifying the drug and the name of all the person(s) who required unblinding.

2.2.3 Study Drug

LBP-EC01 is a clear to opalescent, colorless to slightly yellow, aqueous solution. LBP-EC01 is a mixture of 3 crPhages internally named as p0031-8, p00ex-2, p004k-5, which are derived from wild-type myroviridae phages that target *E. coli*. These phages have been engineered to contain

an identical CRISPR-Cas3 construct and have been combined in equal amounts at 1×10^6 – 1×10^{12} PFU/mL (equivalent to approximately 1.5×10^7 – 1.5×10^{13} PFU/vial). One vial of LBP-EC01 containing approximately 15 mL of solution will be sterilely mixed with 45 mL of Lactated Ringer's solution (injection, USP) by the site pharmacy prior to each dose administered (details will be included in the pharmacy manual). LBP-EC01 and placebo solutions will be indistinguishable.

LBP-EC01 will be administered by bladder instillation via a newly placed urinary catheter BID at the maximum feasible dose, based on the manufacturing process (approximately 1.5×10^7 – 1.5×10^{13} PFU/vial), totaling approximately 60 mL of solution via sterile catheter tipped syringe (details will be included in the pharmacy manual). The urinary catheter will be clamped and the solution left in situ for a minimum of 30 minutes (to a maximum of 40 minutes) following instillation and then it will be placed on free drainage (duration of clamp should be documented).

LBP-EC01 will be provided in a 20 mL vial containing approximately 15 mL of the crPhage cocktail. This vial will be brought to room temperature prior to mixing with 45 mL of Lactated Ringer's solution (injection, USP) under sterile conditions and placed into a sterile syringe with a catheter tip. Handling and mixing of the vials making up LBP-EC01 will be done by the unblinded study pharmacist (details are provided in the pharmacy manual). Placebo solution Lactated Ringer's solution (injection, USP) will be brought to room temperature and will also be prepared by the pharmacist under aseptic technique and placed into a sterile catheter tipped syringe. The unblinded pharmacist will use the IVRS system to determine the randomization allocation.

The mixed blinded solutions will be provided to the investigator/nursing staff for administration. If not used immediately, the IMP combined with Lactated Ringer's solution should be stored under refrigerated conditions and must be administered within 24 hours of preparation. Doses may be given at 8 AM within +/- a 2-hour window for the AM dose and 12 hours after the AM dose +/- a 3-hour window for the PM dose. The clinical site staff should consult with the Medical Monitor about any missed dose outside the allowable dosing window. Typically, these missed doses should be given and documented following standard procedure.

All patients will receive a total of 13 doses of drug product or placebo across 7 days of treatment (a single morning dose will be given on Day 7). All doses should be given using strict aseptic techniques and may be administered by clinic/hospital staff provided they have been given adequate training. Upon completion of the study, patients requiring subsequent catheterization should have their study catheter replaced. The catheter used in the study should be discarded per normal site policy.

2.2.4 Sample Size Determination

36 patients were randomized in a 2:1 ratio to LBP-EC01 or placebo. This is a FIH study and the sample size should be sufficient to establish early safety and PK at a single dose level.

2.3 Study Endpoints

2.3.1 Primary Endpoints

The primary endpoints involve summarizing the safety and tolerability of AEs and lab parameters, as well as the PK parameters of LBP-EC01. The PK parameters will be assessed as a combined set of all crPhages included in LBP-EC01 in both urine and blood.

The blood PK parameters will include the following assessments of LBP-EC01:

- Maximum concentration (C_{max})
- Time to C_{max} (T_{max})
- Area under the concentration versus time curve (AUC) from time 0 to the last measurable concentration (AUC_{0-t})

Other PK variables may be calculated as appropriate for the observed data.

2.3.2 Secondary Endpoints

The secondary endpoints involve summarizing PD parameters of LBP-EC01. These include:

- Reduction in urinary *E. coli* burden at any of the following timepoints: Day 2, Day 3, Day 5, Day 7 (EOT), Day 14, and Day 28
- Time to 1 log reduction in urinary *E. coli* count
- Recurrence of *E. coli* colonization or incidence of infection based on clinical signs and symptoms
- Changes in IgA, IgE, IgG, and IgM levels

2.3.3 Exploratory Endpoints

The exploratory endpoints involve exploring the effects of LBP-EC01 on the urinary tract microbiota. These include:

- Urine culture and sensitivity (persistent, recurrent *E. coli*, new colonizing new infections will be documented)
- Evaluation of bacterial biomarkers (e.g., phage sensitivity/resistance, bacterial antibiotic resistance, bacterial metagenomic analysis)

2.3.4 Exploratory Analyses

Exploratory analyses will include:

- Differences between indwelling and intermittent urinary catheterization populations will be compared
- Any persisting microbiological isolates will be fully explored with bacteriophage host range, antibiotic resistance patterns and genetic sequencing of isolates

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Definition of Baseline

Baseline is defined as the last measurement prior to the first dose of study drug unless otherwise specified.

3.1.2 End of Treatment Definition

The EOT is defined as the last date the patient received study drug, which is scheduled at Day 7.

3.1.3 End of Study Definition

A patient is considered to have completed the study if he or she has completed all portions of the study including the last visit or the last scheduled procedure shown in the SoA (Table 1 of the Protocol).

The EOS is defined as the last date that patient safety data is collected (i.e., Day 35). Once patients have completed Day 28, they may resume their regular medications and have any new intermittent catheters re-established as directed by their physician.

3.1.4 Summary Statistics

Categorical data will generally be summarized with counts and percentages of patients. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, minimum, and maximum. Geometric mean (GM), and GM CV% will also be provided for PK parameters. The value of zero will be excluded from the calculation of GM and GM CV%.

3.1.5 Hypothesis Testing

This is a Phase 1b study and primary outcomes are evaluation of safety, tolerability and PK. No formal hypothesis will be tested.

3.1.6 Handling of Dropouts and Missing Data

Generally, missing data will be noted but not be imputed unless otherwise specified.

3.2 Analysis Populations

3.2.1 Safety Population

The Safety Population is defined as all randomized patients who receive at least one dose of study drug. All safety data will be analyzed using the Safety Population.

3.2.2 Intent-to-Treat (ITT) Population

The ITT Population is also defined as all randomized patients who receive at least one dose of study drug, thus the same as the Safety Population. The ITT Population will be the primary population for analysis of all secondary and exploratory endpoints except for those PD-related.

3.2.3 Evaluable Population

The Evaluable Population is defined as all patients in the ITT Population who completed the study and who have been dosed according to protocol for the first 4 days of treatment and who have not been subject to a suspension of treatment or who have not missed more than one dose of study drug during the remainder of treatment (i.e., Days 5-7). Patients who show disease progression to active infection will be discontinued from treatment and treated for their symptoms and will be followed for safety. These patients will be included in the Evaluable Population as long as they have been dosed according to protocol for the first 4 days of

treatment. The Evaluable Population will be a secondary population for analysis of the non-PD secondary and exploratory endpoints.

A list of patients excluded from the Evaluable Population will be finalized prior to unblinding the randomized treatment assignments.

3.2.4 PK Population

The PK Population is defined as all patients who receive at least one dose of LBP-EC01 and have at least one measurable post-dose concentration of LBP-EC01. The PK Population will be the population for all PK analysis.

3.2.5 PD Population

The PD Population is defined as all randomized patients who met enrollment criteria, who receive at least one dose of study drug, have a baseline PK assessment, and have a baseline *E. coli* measurement at or above $1x10^3$ Colony-Forming Unit (CFU)/mL. The PD Population will be the primary population for analysis of all PD-related secondary and exploratory endpoints.

3.2.6 Subgroup Analyses

Subgroup analyses of these Analysis populations may also be performed. Such subgroups include, but are not limited to:

- Patients with indwelling catheterizations and patients with intermittent catheterizations
- Patients with *E. coli* sensitive to LBP-EC01 and patients with *E. coli* insensitive to LBP-EC01

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

Counts and percentages of patients who were screened (signed informed consent), discontinued early during screening (screen failures), and randomized will be summarized in total based on all screened patients.

Counts and percentages of patients who were randomized, discontinued early from the study, and completed the study will be summarized by treatment and in total based on all randomized patients. Reasons for early discontinuation will also be summarized.

The disposition data, including screen failure reasons, will also be listed.

3.3.2 Protocol Deviations

Counts and percentages of patients with protocol deviations by deviation category will be summarized by treatment and in total based on all randomized patients and listed.

3.3.2.1 Eligibility Criteria

Eligibility criteria (inclusion/exclusion) will be listed based on randomized patients.

3.3.3 Analysis Populations

Counts and percentages of patients in each analysis population will be summarized by treatment and in total based on all randomized patients. Reasons for exclusion from each analysis population may also be summarized. Data will be listed including randomization data.

3.3.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age (years) at enrollment
- Sex
- Childbearing potential
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)
- Frequency and timing (within 1 month of Screening, within 1 year of Screening) of prior UTI
- Prior antibiotic use (within 30 days of Screening)
- Catheter use at Screening (none, indwelling, intermittent, other)

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of patients as appropriate by treatment and in total for all randomized patients and each defined analysis population. Data will also be listed.

3.3.5 Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0. Counts and percentages of patients with medical history by system organ class and preferred term will be summarized by treatment and in total based on all randomized patients. Data will also be listed.

3.3.6 Prior and Concomitant Medications

Medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the WHO Drug Dictionary version March 2019G B3. For summary purposes, medications will be considered prior medications if they stopped prior to the first dose of study drug and concomitant medications if they were taken at any time after the first dose of study drug (i.e., started prior to the first dose of study drug and were ongoing or started after the first dose of study drug).

If a medication has incomplete start or stop dates, dates will be imputed to determine whether a medication should be considered prior and/or concomitant. If a medication start date is incomplete, the first day of the month will be imputed for missing day and January will be imputed for missing month. If a medication stop date is incomplete, the last day of the month will be imputed for missing day and December will be imputed for missing month. Incomplete start and stop dates will be listed as collected without imputation.

Counts and percentages of patients taking prior and concomitant medications by ATC class and preferred term will be summarized by treatment and in total based on the Safety Population. Data will also be listed.

3.3.7 Catheterization

Catheter use from screening through the End of Study will be logged. All catheter data will be listed for the Safey Population.

3.3.8 Study Drug Administration and Exposure

Days of exposure to study drug will be calculated as date of last dose of study drug – date of first dose of study drug + 1. Days of exposure to study drug and number of doses received will be summarized by treatment based on the Safety Population with descriptive statistics and with counts and percentages of patients. Study administration data will be listed.

3.4 Pharmacokinetic Assessment

Of note, systemic absorption of LBP-EC01 may not occur due to the local route of administration and consequently, may result in little to no quantifiable LBP-EC01 concentrations in the blood for a subject's PK profile.

3.4.1 Sample Collections for Pharmacokinetic Analysis

Blood and urine samples for PK will be collected at the times specified in Schedule of Blood and Urine Sampling of the Protocol (Table 2).

Pre-dosing PK samples for urine and blood will be collected after catheterization (if there is no existing catheter), up to 30 minutes prior to dosing. Post-dosing PK samples will be taken within 60 minutes after the catheter is released and re-clamped for 20 minutes to take additional urine and blood samples. 6 hour timepoint (±1 hour) will be collected after 6 hours following the AM dose

Of note, urine PK data will not include volumes since a 20 mL aliquot is taken rather than the whole void urine volume. Patients are allowed to urinate freely outside of the specified collections.

3.4.2 Handling Missing or Below the Lower Limit of Quantification Data

Blood and urine PK data will follow the same rules for handling of missing or below limit of quantification (BLQ) data.

For PK concentration data, if the actual sampling time is missing, but a valid concentration value has been measured, the concentration value will be flagged and the scheduled time point may be used for the calculation of PK parameters.

In cases of missing pre-dose for the first dose of each treatment period, the missing components may be assumed as zero. For the other cases, the missing data will not be imputed.

For semi-log plots, zero and BLQ values will be imputed as "0.1" for graphical purposes.

For the individual concentration and PK parameter calculation of each treatment period, the following rules will be applied:

- If one or more BLQ values occur before the first measurable concentration, they will be assigned a value of zero.
- If BLQ values occur between measurable concentrations in a profile, the BLQ should be omitted (set to missing).
- If BLQ values occur after the last measurable concentration in a profile, the BLQ should be omitted (set to missing).

For the concentration summary and mean concentration plot preparation of each treatment period, the following rules will be applied:

- Mean concentration at any individual time point or defined time interval will only be calculated if at least half of the patients have valid values (i.e., quantifiable and not missing) at this time point or defined time interval for each treatment period
- In cases where a mean value is not calculated due to the above criterion not being met, the value will be set to missing
- BLQ values will be set to zero.

3.4.3 Pharmacokinetic Concentration

LBP-EC01 concentrations will be determined in both blood and urine by using a plaque forming assay and expressed in units of plaque forming units (PFU)/mL.

Actual sampling times that are outside the sampling time windows may be excluded from concentration summary and mean concentration plotting but will still be used in the calculations of PK parameters and individual concentration plotting.

Blood

Individual blood concentrations of LBP-EC01 will be summarized by treatment at each nominal time point for the PK Population descriptively. Individual blood concentrations will also be listed for the PK Population.

Individual blood concentration will be plotted by treatment against actual sampling time points relative to dosing time. Mean (±SD) concentration will be plotted on a linear and semi logarithmic scale against nominal time points by treatment, when available.

Urine

Individual urine concentrations of LBP-EC01 will be summarized by treatment at each nominal time point for the PK Population descriptively. Individual urine concentrations will also be listed for the PK Population.

Individual urine concentration will be plotted by treatment against actual sampling time points relative to dosing time. Mean (±SD) concentration will be plotted against nominal time points by treatment, when available.

3.4.4 Pharmacokinetic Parameters

The following blood and urine PK parameters of LBP-EC01 will be determined using non-compartmental methods as appropriate:

Blood and Urine PK Parameters:

Parameters	Description
$C_{max,Dose\ 1}$	Maximum concentration; determined directly from the concentration time profile; if the maximum concentration occurs at more than one time point, C_{max} is defined as the first maximum value
$T_{max,Dose\ 1}$	Time to C_{max} of the first dose; determined directly from the concentration-time profile
AUC_{0-t}	Area under the concentration vs time curve (AUC) from predose (time 0) to the last quantifiable concentration (C_{last}) for Dose 1
$C_{trough,max}$	Minimum measured concentration from Day 1 (only including predose #2) through Day 7
$C_{max,all}$	Max post-dose concentration determined from Day 1 through Day 7
$AI_{Ctrough}$	Accumulation index using C_{trough} (predose Day 7 / $C_{trough,max}$)

The actual collection times will be used for the calculation of PK parameters. The Linear-Log Trapezoidal method (equivalent to the Linear Up/Log Down option in WinNonlin) will be used in the computation of all AUC values.

Additional PK parameters may be determined as appropriate.

The blood and urine PK parameters will be listed and summarized by treatment using descriptive statistics for the PK Population.

3.5 Pharmacodynamic Assessment

The secondary endpoints concern the pharmacodynamics of LBP-EC01. These will be summarized by treatment based on the PD Population.

E. coli assessments will be made at the timepoints specified in the SoA of the protocol. Incidence of the following endpoints will also be summarized with counts and percentages of patients at Day 1 (Baseline), Day 2, Day 3, Day 5, Day 7 (EOT), Day 14 and Day 28:

- Reduction in urinary *E. coli* burden at timepoint from Baseline
- Biological elimination of *E. coli* at timepoint after Baseline. Biological elimination is defined as measurement below $1x10^3$ CFU/mL

The following *E. coli* parameters will be derived based on all available post-Baseline data and summarized and listed:

- Time to 1 log reduction in urinary *E. coli* from Baseline
- Biological elimination at any timepoint.
- Incidence and time to recurrence of *E. coli* colonization. Recurrence is defined as past biological elimination followed by increase above the patient's baseline CFU/mL.
- Incidence of infection based on clinical signs and symptoms defined as an adverse event marked as a UTI symptom and followed by antibiotic use.

E. coli parameters will be summarized first for the total CFU/mL in a patient (sum of CFU/mL for all *E. coli* strains) but may also be summarized by strain specific *E. coli* colonization (individual strain CFU/mL per patient).

All *E. coli* assessment data will be listed.

3.6 Exploratory Assessment

The exploratory endpoints explore the influence of LBP-EC01 on the urinary tract microbiota. These will be summarized based by treatment on the ITT Population and Evaluable Population.

3.6.1 Urine Culture and Sensitivity

Urine culture and sensitivity assessments will be made at the timepoints specified in the SoA of the protocol. Incidence and summaries of CFU/mL levels of all non-*E. coli* bacteria isolated will be presented at each scheduled visit. Overall summaries of all bacteria (including *E. coli*) may also be presented. All data will be listed.

3.6.2 Bacterial Biomarkers

Bacterial biomarkers will be collected at the timepoints specified in the SoA of the protocol.

3.6.2.1 Phage Sensitivity/Resistance

Phage sensitivity and resistance by *E. coli* isolates will be collected at the timepoints specified in the SoA of the protocol. Incidence of the following will be summarized by isolate for the cocktail and each individual phage:

- Isolates that yield ennumerable plaques (PFU/mL)
- Isolates that yield ennumerable plaques (PFU/mL) or that demonstrate “lysis from without”
- Insensitive isolates (no ennumerable plaques or no “lysis from without”)

All phage sensitivity and resistance will be listed by patient for each *E. coli* isolate, including *E. coli* sensitivity to the cocktail and to each individual phage.

3.6.2.2 Bacterial Antibiotic Resistance

Patient incidence of antibiotic resistance will be summarized across all *E. coli* isolates. All patient antibiotic resistance data will be listed, including MIC values and interpretations.

3.6.2.3 Bacterial Metagenomics Analysis

The metagenomics data will be available following the study’s completion, and this analysis will be described in a separate analysis plan.

3.6.3 Microbiological Isolates

Any persisting microbiological isolates identified will have all related data listed, including bacteriophage host range and antibiotic resistance patterns. Genetic sequencing of isolates will be included in the separate metagenomics analysis.

3.7 Safety Assessment

Safety data will be summarized by actual treatment received (and in total for selected analyses) based on the Safety Population.

3.7.1 Adverse Events (AEs)

AEs will be captured from the date of informed consent through study completion. All AEs will be coded to system organ class and preferred term using MedDRA version 22.0. Treatment-emergent adverse events (TEAEs) are defined as AEs that start after the first dose of study drug.

Adverse events of special interest include signs and symptoms of a urinary tract infection (UTI) and local vesicular reaction.

An overview of AEs will be provided including counts and percentages of patients (and event counts) with the following:

- Any TEAEs (overall and by maximum severity)
- Any study drug related TEAEs (overall and by maximum severity)
- Any TEAEs of special interest (overall and by maximum severity)
- Any serious AEs (SAEs)
- Any treatment-emergent serious AEs (TESEAEs)
- Any TEAEs leading to discontinuation of study drug
- Any TEAEs leading to discontinuation of study
- Any AEs leading to death

Counts and percentages of patients (and event counts) will also be presented by system organ class and preferred term for each of the categories in the overview.

All AE data will be listed. Listings will be presented specifically for SAEs and TEAEs leading to discontinuation of study drug, as well as TEAEs of special interest.

3.7.2 Clinical Laboratory Tests

Blood and urine samples for clinical laboratory tests will be collected at timepoints specified in the SoA of the protocol and processed by a central laboratory. A list of laboratory tests to be performed is included in Appendix A.

3.7.2.1 Hematology, Chemistry, Coagulation, Lipids, and Urinalysis

Values and changes from baseline will be presented at each scheduled visit and baseline by laboratory test. The incidence of abnormalities (as defined by normal ranges) prior to the first dose of study drug and after the first dose of study drug will be summarized with counts and percentages of patients. Data will be listed.

3.7.2.2 Pregnancy

Pregnancy data will be listed.

3.7.3 Immunoglobulins

Total levels of each immunoglobulin (IgA, IgE, IgG, and IgM) from Baseline will be measured at the timepoints specified in the SoA and Schedule of Blood and Urine Sampling of the Protocol.

Values and changes from baseline will be summarized at each scheduled visit and baseline by immunoglobulin. The incidence of positive detection (defined as above normal range; see below) will also be summarized with counts and percentages of patients at the same timepoints.

Immunoglobulin	Normal Range	Positive Detection
IgA	70 – 400 mg/dL (0.7 – 4.0 g/L)	> 400 mg/dL (> 4.0 g/L)
IgE	<= 100 IU/mL	> 100 IU/mL
IgG	700 – 1600 mg/dL (7.0 – 16.0 g/L)	> 1600 mg/dL (> 16.0 g/L)
IgM	40 – 230 mg/dL (0.4 – 2.3 g/L)	> 230 mg/dL (> 2.3 g/L)

All immunoglobulin data will be listed.

3.7.4 Vital Signs

Vital signs will be measured at timepoints specified in the SoA of the protocol. Vital signs will consist of blood pressure, heart rate, respiratory rate, and oral body temperature. Values and changes from baseline will be presented at each scheduled visit and baseline by vital sign. Data will be listed.

3.7.5 Body Weight, Height, and Body Mass Index

Body weight, height, and BMI will be measured/calculated at the timepoints indicated in the SoA of the protocol and the values at Screening will be used to calculate BMI. Data will be listed.

3.7.6 Electrocardiograms

Triplicate 12-lead ECG recordings (i.e., 3 useful ECGs without artifacts) will be obtained within approximately 2-5 minutes at each specified timepoint indicated in the SoA of the protocol. The average of the 3 readings will be used to determine ECG intervals and inclusion in summaries. The following ECG parameters will be recorded:

- Heart rate
- PR interval
- QRS interval
- QT interval
- QTc using Fridericia's interval
- RR interval

Values and changes from baseline will be presented at each scheduled visit and baseline by ECG parameter.

All ECGs will be evaluated by a qualified Investigator for the presence of abnormalities. All ECG data will be listed.

3.7.7 Physical Examinations

Targeted physical examinations will be performed at the specified timepoints in the SoA of the protocol (or as clinically indicated). These will be a limited, symptom-directed physical examination only. Conditions noted prior to study drug dosing will be recorded as medical history and those recorded after study drug dosing will be recorded as AEs.

3.7.8 Spleen Examinations

Spleen evaluations will include ultrasound assessments for splenomegaly at the specified timepoints in the SoA of the protocol and clinical examinations to assess for splenomegaly will be performed at all visits. A clinical examination may also be performed at a clinic visit on Day 35 at the discretion of the study investigator if there are abnormal or clinically significant findings at Day 28.

Splenomegaly is defined as a doubling of the largest dimension of the spleen from baseline or hematologic evidence of splenic sequestration defined as a hematologic abnormality (i.e., anemia, leukopenia, thrombocytopenia) of Grade 3 or greater based on DAIDS criteria.

Counts and percentages of patients with a doubling of the largest dimension of the spleen from baseline will be presented. The largest diameter of the spleen value and changes from baseline will be summarized at each scheduled visit and baseline. All spleen evaluation data will be listed.

4 DATA SAFETY MONITORING COMMITTEE

A Data Safety Monitoring Committee (DSMC) will monitor the safety of patients over the course of the study. The DSMC will meet once or more during the patient enrollment period to examine the unblinded accumulated safety data. Patients, investigators, site staff and in general all personnel directly involved in the conduct of the study will remain blinded to the patients' treatment assignment until the completion of the study.

Details related to the DSMC responsibilities, authorities, and procedures will be documented in a DSMC charter which will be finalized prior the first patient being enrolled in the study.

5 ANALYSIS TIMING

5.1 Interim Analysis

No interim analysis is planned.

5.2 Pre-Final Analysis

After the database is locked and the Evaluable Population status has been determined for all patients, the randomized treatment assignments will be unblinded and the pre-final analysis will be generated. Pre-final TFLs will be provided for review.

5.3 Final Analysis

After all comments on the pre-final analysis have been resolved and the study database is declared final, the final analysis will be generated. Final TFLs will be provided, as well as SDTM data and ADaM data along with associated files, if requested. Associated files may include: annotated case report forms (CRFs), SDTM specifications, SDTM programs, ADaM specifications, ADaM programs, TFL programs, and CDISC Define packages for both SDTM and ADaM data.

6 ADDITIONAL ANALYSES ON THE IMPACT OF COVID-19

6.1 General Consideration

The COVID-19 pandemic may impact the conduct of the study from different aspects including quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product, or other considerations if site personnel or trial patients become infected with COVID-19.

Start date and end date of COVID-19 impact will be determined to assess the impact of the COVID-19 pandemic to the study. COVID-19 impact date is defined as the date at which the site and/or overall study was impacted by COVID-19, resulting in changes to how assessments where conducted at the site and/or for the study overall.

6.2 Analysis Populations

6.2.1 COVID-19 Population

The COVID-19 Population may be added and defined as all randomized patients who have been seriously impacted by COVID-19 and have missed critical endpoint assessments.

Endpoint/safety analyses may be performed separately by including/excluding these patients.

6.3 Subject Disposition

Summaries of patients who discontinued early from the study due to COVID-19 impact will be added to the disposition summaries.

In addition, subject disposition may be summarized and stratified by COVID-19 status (prior to/post to COVID-19 impact date).

6.4 Protocol Deviations

Protocol deviations related to COVID-19 will be categorized and summarized and listed separately.

6.5 Concomitant Medications

Counts and percentages of patients taking prior and concomitant medications that are used to treat COVID-19 by ATC class and preferred term may be summarized by treatment and in total based on the Safety Population.

6.6 Safety Assessment

6.6.1 Adverse Events (AEs)

An overview of AEs may be provided including counts and percentages of patients (and event counts) and stratified by COVID-19 status (AEs start prior to/post to COVID-19 impact date).

Counts and percentages of patients (and event counts) will be presented by system organ class and preferred term for COVID-19 related AEs.

7 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

No changes from the protocol-specified analyses have been made except for those detailed above to assess any impact of COVID-19.

8 PROGRAMMING SPECIFICATIONS

The creation of analysis datasets and all analyses will be performed using SAS® (version 9.4 or higher). PK parameters will be calculated via SAS® and confirmed with the results of Phoenix WinNonlin™ (version 8.1 or higher).

All available data will be presented in patient data listings which will be sorted by patient and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

APPENDIX A: LABORATORY TESTS

Samples for the following laboratory tests will be sent to the central laboratory for analysis:

• **Hematology:** Hemoglobin, hematocrit, platelet count, red blood cell (RBC) count, mean corpuscular volume, absolute reticulocyte count, total and differential leucocyte (WBC) absolute count (neutrophils, eosinophils, lymphocytes, monocytes and basophils).

• **Serum chemistry:** Albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, C-reactive protein, calcium, chloride, creatinine phosphokinase, gamma-glutamyl transferase, glucose, phosphate, potassium, creatinine, sodium, total bilirubin, total protein, troponin, urea, IL-6 and an immunoglobulin panel (IgA, IgE, IgG and IgM).

• **Coagulation:** activated partial thromboplastin time, prothrombin time

• **Lipids:** High density lipoprotein-cholesterol, low density lipoprotein cholesterol, triglycerides, total cholesterol.

• **Urinalysis and Microscopy** A pre-dose catheter urine specimen will be collected for dipstick analysis of protein, blood, white blood cells, glucose, and pH and microscopy.