Statistical Analysis Plan

Study ID: 214144

Official Title of Study: A Phase III, Multicenter, Randomized, Active Reference, Double Blind, Double-dummy Study in Japanese Female Participants to Evaluate the Efficacy and Safety of Gepotidacin in the Treatment of Uncomplicated Urinary Tract Infection (Acute Cystitis)

NCT ID: NCT05630833

Date of Document: 02-Apr-24

Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title:	A Phase III, Multicenter, Randomized, Active Reference, Double-blind, Double-dummy Study in Japanese Female Participants to Evaluate the Efficacy and Safety of Gepotidacin in the Treatment of Uncomplicated Urinary Tract Infection (Acute Cystitis)
Study Number:	214144
Compound Number:	*GSK2140944*
Abbreviated Title:	A study to investigate the efficacy and safety with gepotidacin in Japanese female participants with uncomplicated urinary tract infection (acute cystitis)
Acronym:	EAGLE-J

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s)

Registry	**ID**
Clintrials.gov	*NCT05630833*

XBU Statistical Analysis Plan (SAP) Template v2.0 17 January 2022

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	28 Nov 2022	Amendment 02 (07 Nov 2022)	Not Applicable	Original version
SAP Amendment 1	02 Apr 2024	Amendment 02 (07 Nov 2022)	• Modified the analysis populations to exclude the participants affected by GCP violation. • Modified the analysis population (micro-ITT NTF-S (Global)) to align with the primary analysis population in the global studies (204989 and 212390). • Added the analysis population including the participants affected by GCP violation for the supplementary analysis. • (Section 4.1.1.) Added the way of handling zero cell when computing the risk difference, and out-of-stability data for microbiological urine samples. • (Section 4.2.3.3.) Changed handling of missing data to that missing data will not be imputed in this study and missing data in the global studies will be imputed. • (Section 4.2.3.3.) Modified imputation model to align with the analyses in the global studies (204989 and 212390).	SAP was amended based on dry-run review comments impact on the analysis populations based on the GCP violation issues that occurred in one of the sites (Site ID: PPD), caused by CCI other minor edits or updates based on comparison with phase 3 studies.

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			• (Section 4.2.3.3. and4.2.3.4.) Removed the computation of posterior probability. • (Section 4.2.3.5. and 4.6.2.5.) Added the supplementary analysis including the participants affected by GCP violation for transparency. • (Section 4.3.1.3, and 4.3.4.3.) Clarified vague component of mixture prior has “weak” information. • (Section 4.3.1.3., and 4.3.4.3.) Added displaying median and 95%CrI of the prior for each initial weight. • (Section 4.3.7.2. and 4.4.9.2.) Changed the analysis population from micro-ITT to ITT) • (Section 4.3.8.2.) Added way of handling not quantifiable concentration data. • (Section 4.3.8.2.) Changed sampling window for PK summary • CCI [redacted]	

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			• CCI [redacted] • [redacted] • CCI [redacted] • (Section 4.6.1.) Clarified the definition of duration. • (Section 4.6.2.) Added the specification that missing grade of AE will be imputed as “severe”. • (Section 4.6.2.1.) Clarified the definition of the time of onset, duration, and time since end of treatment. • (Section 4.6.2.4.) Added summary of AE to screen potential adverse reactions. • (Section 4.6.3.1.) Corrected the definition of increasing fold in liver chemistry. • (Section 6.1.2.) Removed the summary of the participants who is	

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			ongoing in this study. • (Section 6.1.3.) Added and clarified some parameters in summary of baseline characteristics. • (Section 6.1.7.) Removed the summary of visit impact due to COVID-19. • (Table 15, 16 and 17) Clarified the derivation of clinical worsening. • (Section 6.2.1.4.) Clarified MIC50 and MIC90 • (Section 6.2.2.1.) Updated the list of AE term to identify AESI • (Section 6.2.4.1.) Clarified the derivation of DMID grading. • (Section 6.2.7) Amended the assessment window. • (Section 6.2.9) Amended missing/partial date of AE • (Section 6.2.11) Clarified the derivation of MDR	

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for Study 214144. Details of the final analyses are provided.

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
• To assess the consistency of therapeutic response of gepotidacin at the Test of cure (TOC) Visit (Day 10 to 13) in female participants with acute uncomplicated cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin in Japan, with that from global studies (Studies 204989 and 212390).	• Therapeutic response (combined per-participant microbiological and clinical response) at the TOC Visit
Secondary	
• To assess the therapeutic response of gepotidacin compared to nitrofurantoin as an active reference descriptively, at the TOC Visit, in female participants with acute uncomplicated cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin	• Therapeutic response at the TOC Visit
• To assess the clinical efficacy and microbiological efficacy of gepotidacin at the TOC Visit in female participants with acute uncomplicated cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin	• Clinical outcome and response at the TOC Visit • Microbiological outcome and response at the TOC Visit
• To assess the therapeutic response, clinical efficacy and microbiological efficacy of gepotidacin at the TOC Visit in female participants with acute uncomplicated cystitis who have qualifying uropathogen(s) resistant to two or more specific classes of antimicrobials at Baseline	• Therapeutic response at the TOC Visit • Clinical outcome and response at the TOC Visit • Microbiological outcome and response at the TOC Visit
• To assess the clinical efficacy of gepotidacin at the TOC Visit in female participants with acute uncomplicated cystitis	• Investigator assessment of clinical response at the TOC Visit
• To assess the safety and tolerability of gepotidacin in female participants with acute uncomplicated cystitis	• Occurrence of treatment-emergent adverse events (AEs), serious AEs (SAEs) and adverse events of special interest (AESIs) • Change from baseline in clinical laboratory tests • Change from baseline in electrocardiograms (ECGs) • Change from baseline in vital sign measurements
• To determine the plasma and urine PK concentrations of gepotidacin in female participants with acute uncomplicated cystitis	• Gepotidacin plasma and urine concentrations

Objectives	Endpoints
Exploratory	

CCI

[redacted]

Primary estimand

The primary clinical question of interest is: Whether the therapeutic response at the TOC visit in female participants with acute uncomplicated cystitis who have qualified uropathogen(s) at Baseline that all are susceptible to nitrofurantoin in this study is consistent with that from the global studies, regardless of intervention discontinuation for any reason. Receipt of systemic antimicrobials will impact the endpoint definition (see Section 6.2.1.1 and Section 6.2.1.2).

The estimand is described by the following attributes:

- Population: Japanese and non-Japanese (from Studies 204989 and 212390) female participants with acute uncomplicated cystitis who have qualifying uropathogen(s) at Baseline that all are susceptible to nitrofurantoin.
- Treatment condition: Gepotidacin 1500 mg BID for 5 days in this study versus gepotidacin 1500 mg BID for 5 days in the global studies (Studies 204989 and 212390) regardless of adherence.

- Variable: Therapeutic response (combined per-participant microbiological and clinical response) at the TOC Visit (the detailed definitions are provided in Section 6.2.1). Microbiological success is defined as eradication (i.e., reduction) of all qualifying bacterial uropathogens recovered at baseline to $<10^3$ colony-forming units/mL (CFU/mL) as observed on quantitative urine culture without the participant receiving other systemic antimicrobials. Clinical success is defined as resolution of signs and symptoms of acute cystitis present at Baseline (and no new signs and symptoms) without the participant receiving other systemic antimicrobials.
- Summary measure: Comparison of the proportion of Japanese participants achieving therapeutic success in this study with 10^{th} percentile of the predicted distribution for the proportion of participants achieving therapeutic success in this study derived from the global studies (Studies 204989 and 212390)
- Intercurrent events (ICEs):
    - Study treatment discontinuation (due to any reason) – treatment policy strategy (interest is in the treatment effect regardless of study treatment discontinuation)
    - Use of systemic antimicrobials – composite strategy. This ICE is captured through the definitions of microbiological and clinical response (see Section 6.2.1.1 and Section 6.2.1.2)

Rationale for estimand:

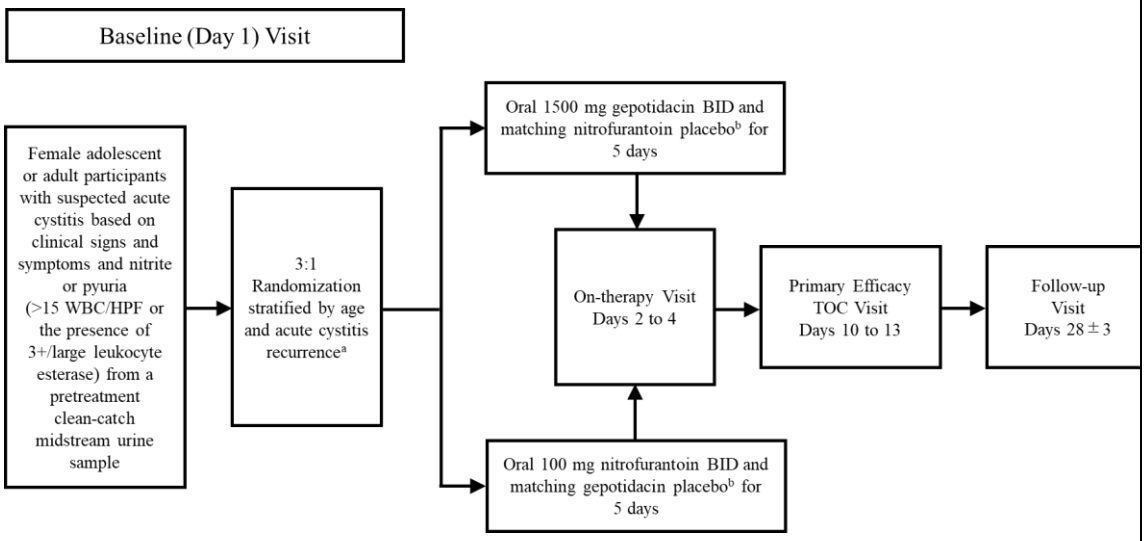
Interest in this study lies in whether the efficacy of gepotidacin treatment in this study is consistent with the global studies.

The clinical question of interest in this study and the global studies (Studies 204989 and 212390) lies in the treatment effect of gepotidacin regardless of whether the full course of 5 days of treatment was taken or not, which reflects how patients may be treated in clinical practice. Hence, a treatment policy strategy is appropriate for treatment withdrawal before completing 5 days of treatment. Use of other systemic antimicrobials may confound the bacterial culture results; thus, the microbiological response will be considered failure. For clinical data, the use of a systemic antimicrobial for acute uncomplicated cystitis is a sign of treatment failure and use of a systemic antimicrobial for another infection cannot be considered a success as it confounds the assessment of efficacy. Therefore, the definition of a successful therapeutic response precludes the use of other systemic antimicrobials.

Secondary estimands are provided in Section 4.3.

1.2. Study Design

Overview of Study Design and Key Features



Design Features	• This is a Phase III randomized, multicentre, active reference, double-blind, double-dummy study in adolescent and adult Japanese female participants to evaluate the efficacy and safety of gepotidacin. The primary objective is to assess consistency of this study with global studies (Studies 204989 and 212390) for therapeutic response of gepotidacin. • The study duration will be approximately 28 days with 4 visits. • Participants will be stratified by age category (≤50 years, or >50 years) and acute uncomplicated cystitis recurrence (recurrent or nonrecurrent) and will be randomly assigned in a 3:1 ratio to receive either oral gepotidacin or oral nitrofurantoin (active reference).
Study intervention	• Gepotidacin: 1500 mg administered orally BID for 5 days • Nitrofurantoin: 100 mg administered orally BID for 5 days
Study intervention Assignment	Participants will be stratified by age category and acute uncomplicated cystitis recurrence (recurrent or nonrecurrent). Recurrence is defined as a confirmed infection [not including the current infection in the calculation] with at least 1 prior episode within the past 3 months, at least 2 prior episodes within the past 6 months, or at least 3 prior episodes within the past 12 months before study entry). Participants will be randomly assigned in a 3:1 ratio to receive either oral gepotidacin or oral nitrofurantoin.
Interim Analysis	No formal interim analysis will be planned. Blinded review for therapeutic, clinical, and microbiological response at the TOC visit may be conducted during the study.

2. STATISTICAL HYPOTHESES

The primary objective is to assess the "consistency" of therapeutic success rate between the gepotidacin arm in this Eagle-J study with the pooled gepotidacin arm in the two global studies (Studies 204989 and 212390). The observed proportion of participants in the gepotidacin arm at the TOC visit achieving therapeutic success in this study will be compared with the predictive distribution of the therapeutic success rate estimated from the two global studies (Studies 204989 and 212390). "Consistency" is defined as:

$$\hat{p}_a > \frac{r_{aj}^{(10\%)}}{n_{aj}}$$

, where:
$\hat{p}_a$: Observed proportion of participants achieving therapeutic success on gepotidacin in this study
n_{aj}: Number of participants in gepotidacin of this study
$r_{aj}^{(10\%)}$: The lower 10th percentile of the cumulative distribution of the prior predictive distribution derived from the global study data for the expected number of participants achieving therapeutic success out of n_{aj} participants.

Therefore, $\frac{r_{aj}^{(10\%)}}{n_{aj}}$ is the threshold response rate that needs to be observed to meet therapeutic success, assuming the response rate is consistent with the global study response rate. The predictive distribution is defined as:

$$r_{aj} \sim \int Binomial(r_{aj}|n_{aj}, p_a) \times Beta(p_a|\alpha = r_{ag}, \beta = n_{ag} - r_{ag})dp_a$$

, where:
r_{aj}: The expected number of participants achieving therapeutic success in the gepotidacin arm of this study
r_{ag}: The pooled number of participants achieving therapeutic success in the gepotidacin arm across both global studies.
n_{ag}: The pooled number of participants in the gepotidacin arms across both global studies.

The two global studies (204989 and 212390) have almost the same study design and the therapeutic response would be similar as well. Therefore, the data will be simply pooled to derive the predictive distribution.

Example:

Assuming 884 participants on the gepotidacin arm and a 76% observed therapeutic response rate in the global studies, there is an approximately 10% probability of observing <= 56 out of 81 responders in this study if the true gepotidacin response rate in this study is consistent with the response rate estimated from the global studies. Therefore, the success rule for gepotidacin is set to require a therapeutic response rate greater than 69.1% (56/81) in order to demonstrate consistency with global results in this example.

The secondary objective is to assess the difference between the therapeutic response of gepotidacin with the nitrofurantoin therapeutic response at the TOC Visit in Japanese female participants with acute uncomplicated cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin. The difference in the therapeutic response rate between gepotidacin and nitrofurantoin will be assessed descriptively.

2.1. Multiplicity Adjustment

No multiplicity adjustment approaches will be used.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility	• Study Population
Intent-to-Treat (all participants) (ITT-ALL)	• All participants who were randomly assigned to study treatment in the study. • Participants will be analyzed according to their randomized study treatment.	• Listing
Intent-to-Treat (ITT)	• All participants in ITT-ALL population, except for participants from the site (Site ID: PPD) due to GCP violation • Participants will be analyzed according to their randomized study treatment.	• Study Population • Efficacy
Microbiological ITT (all participants) (micro-ITT-ALL)	• All participants randomly assigned to study treatment who receive at least 1 dose of study treatment and have a qualifying baseline uropathogen (defined in Section 6.2.10), from a quantitative bacteriological culture of a pretreatment clean-catch midstream urine specimen. • Participants will be analyzed according to their randomized study treatment. • Note that qualifying uropathogens include only the uropathogen species/groups [Gram-negative bacilli (e.g. *E. coli*, *K. pneumoniae*, *P. mirabilis*), S. *saprophyticus, and Enterococcus spp.*], defined in Section 6.2.10.	• Listing
Microbiological ITT (micro-ITT)	• All participants in micro-ITT-ALL, except for participants from the site (Site ID: PPD) due to GCP violation. • Participants will be analyzed according to their randomized study treatment.	• Study Population • Efficacy
Micro-ITT NTF-S (all participants) (micro-ITT-ALL NTF-S)	• All participants in the micro-ITT-ALL Population whose baseline qualifying bacterial	• Listing

Analysis Set	Definition / Criteria	Analyses Evaluated
	uropathogens that all are susceptible to nitrofurantoin (NTF-S). Broth microdilution nitrofurantoin MIC result from JMI Laboratories (if available) will take precedence over global central laboratory (GCL) nitrofurantoin MIC result for determining susceptibility to nitrofurantoin. • Nitrofurantoin susceptibility interpretations will be based on the Clinical and Laboratory Standards Institute (CLSI) guidelines • Participants with missing MIC susceptibility results for any qualifying uropathogens will not be included in the NTF-S subpopulation. • Participants will be analyzed according to their randomized study treatment.	
Micro-ITT NTF-S	• All participants in the micro-ITT Population whose baseline qualifying bacterial uropathogens that all are susceptible to nitrofurantoin (NTF-S). Broth microdilution nitrofurantoin MIC result from JMI Laboratories (if available) will take precedence over global central laboratory (GCL) nitrofurantoin MIC result for determining susceptibility to nitrofurantoin. • Nitrofurantoin susceptibility interpretations will be based on the Clinical and Laboratory Standards Institute (CLSI) guidelines • Participants with missing MIC susceptibility results for any qualifying uropathogens will not be included in the NTF-S subpopulation. • Participants will be analyzed according to their randomized study treatment. • Note that this population does not include the participants in the affected site by GCP violation (Site ID: PPD).	• Study Population • Efficacy

Analysis Set	Definition / Criteria	Analyses Evaluated
Micro-ITT NTF-S (Global Study)	• All participants from the global studies (Studies 204989 and 212390) in the micro-ITT NTF-S (IA set) Population defined in individual studies, who are not enrolled into this study but into each of the global studies. See the individual RAP for the detailed definition of this analysis population. • Note: this population will be referred as non-Japanese population. • Participants will be analyzed according to their randomized study treatment.	• NA
Micro-ITT NTF-S (Entire)	• All participants from micro-ITT NTF-S Population and micro-ITT NTF-S (Global Study) Population. • This is the primary analysis population. • Participants will be analyzed according to their randomized study treatment.	• Efficacy
Micro-ITT-ALL NTF-S (Entire)	• All participants from micro-ITT-ALL NTF-S Population and micro-ITT NTF-S (Global Study) Population. • Participants will be analyzed according to their randomized study treatment.	• Efficacy
Micro-ITT MDR	• All participants in the micro-ITT Population who have any qualifying baseline bacterial uropathogens that are resistant to two or more classes of antimicrobials. See the detail for MDR definition in Section 6.2.11. • Participants will be analyzed according to their randomized study treatment.	• Efficacy
Micro-ITT MDR (Global Study)	• All participants from the global studies (Studies 204989 and 212390) in the micro-ITT Population who have any qualifying baseline bacterial uropathogens that are resistant to two or more classes of antimicrobials. See the detail for MDR definition in Section 6.2.11.	• Efficacy

Analysis Set	Definition / Criteria	Analyses Evaluated
	• Participants will be analyzed according to their randomized study treatment.	
Micro-ITT MDR (Entire)	• All participants from micro-ITT MDR Population and micro-ITT MDR (Global Study) Population. • Participants will be analyzed according to their randomized study treatment.	• Efficacy
Safety (all participants) (Safety-ALL)	• All randomized participants who receive at least 1 dose of study treatment. • Participants will be analyzed according to their actual treatment received. • Note: if a participant receives both gepotidacin and nitrofurantoin, they will be summarized within gepotidacin 1500 mg BID.	• Safety
Safety	• All randomized participants in Safety-ALL population, except for the participants from the site (Site ID: PPD) due to GCP violation. • Note: if a participant receives both gepotidacin and nitrofurantoin, they will be summarized within gepotidacin 1500 mg BID. • Participants will be analyzed according to their actual study treatment received.	• Safety
Pharmacokinetics (all participants) (PK-ALL)	• All randomized participants who receive at least 1 dose of study treatment and have at least 1 non-missing plasma or urine PK concentration (Non-quantifiable [NQ] values will be considered as non-missing values). • This population will be used in the assessment and characterization of plasma and urine concentrations (summary table). Note: if a participant receives both gepotidacin and nitrofurantoin, they will be listed only (i.e. not summarized within gepotidacin 1500 mg BID). Plasma and/or urine samples for participant randomized	• Listing

Analysis Set	Definition / Criteria	Analyses Evaluated
	nitrofurantoin will not be measured.	
Pharmacokinetic (PK)	• All randomized participants in PK-ALL population, except for the participants from the site (Site ID: PPD) due to GCP violation. • This population will be used in the assessment and characterization of plasma and urine concentrations (summary table). Note: if a participant receives both gepotidacin and nitrofurantoin, they will be listed only (i.e., not summarized within gepotidacin 1500 mg BID). Plasma and/or urine samples for participant randomized nitrofurantoin will not be measured.	• PK

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

Participants who prematurely withdrew from study will not be replaced.

In the case of wrong stratification assigned at the time of randomization, the analyses will be performed based on the actual stratum per data collected in the CRF.

Confidence intervals will use 95% confidence levels unless otherwise specified.

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (std), median, minimum and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

It is anticipated that patient accrual will be spread thinly across centers and summaries of data by center would unlikely be informative and will not, therefore, be provided.

For any efficacy analyses of binary outcomes for which a risk difference will be estimated, if 100% (or 0%) success rates are observed in both treatment arms then a constant of 1E-10 will be added to each zero cell in the resultant contingency table to overcome software limitations and enable determination of the risk difference and two-sided 95% CI.

Out of stability (OOS) data may be delivered for microbiological urine samples. This data will not be included in any analysis, participants with OOS data will have their microbiological response missing and will be counted under the Unable to determine category.

Susceptibility interpretations will be based on CLSI M100 with the exception of nitroxoline and cefadroxil which are based on EUCAST guidelines and faropenem which is based on [Fuchs, 1995].

4.1.2. Baseline Definition

For all endpoints the baseline value will be the latest pre-dose assessment with a non-missing value (or randomization date in participants who are randomized but did not receive study treatment), including those from unscheduled visits. If time is not collected, Day 1 Pre-dose assessments are assumed to be taken prior to first dose and used as baseline.

For clinical signs and symptoms assessments and microbiological assessments, all Day 1 symptom assessments and urine samples (collected for identification of uropathogens) are used as baseline regardless of if they were taken pre or post dose. Urine samples collected on Day -1 or Day 1 can be considered as baseline.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing. If baseline data is missing, then change from baseline calculations will not be performed and will be set to missing.

4.1.3. Strata

Participants will be randomized to a study treatment using stratification by age category (≤ 50 years, or >50 years) and acute cystitis recurrence (nonrecurrent infection or recurrent infection). In the case of a difference between the stratification assigned at the time of randomization and the data collected in the eCRF, the data collected in the eCRF will be considered actual and used unless specified.

Stratification Value (k)	Stratification Description
1	≤50 years, Nonrecurrent infection
2	≤50 years, Recurrent infection
3	>50 years, Nonrecurrent infection
4	>50 years, Recurrent infection

4.2. Primary Endpoint(s) Analyses

4.2.1. Definition of Estimands

Refer to Section 1.1.

4.2.2. Main analytical approach

The primary analysis of the primary estimand will be performed using the micro-ITT NTF-S (Entire) population.

The primary endpoint is therapeutic response (combined per-participant microbiological and clinical response) at the TOC Visit. Therapeutic success refers to participants who have been deemed both a microbiological success and a clinical success (i.e., responders).

The primary treatment effect will be estimated regardless of treatment discontinuation, as per the treatment policy strategy. The ICE of use of other systemic antimicrobial therapy is captured through the definitions of microbiological and clinical response and will be counted as failures (composite strategy). If a participant experiences both ICEs of study treatment discontinuation and use of systemic antimicrobials, then a composite strategy (assigning therapeutic response as a failure) will be used from the point that the relevant systemic antimicrobial was taken.

The number and proportion of participants achieving a therapeutic success will be presented along with its 95% Exact Clopper Pearson CI at the TOC visit and compared with the threshold for consistency with the global studies (Studies 204989 and 212390). The threshold will be derived with covariate adjustment, the covariates are the combinations of age-groups and uUTI recurrence of the participants (refer to Section 4.1.3, k=1, 2, 3, 4). For this analysis, participants who do not return for the TOC Visit or have missing data due to any reason at the TOC Visit will be treated as failures.

1. Derive the prior for therapeutic success rate in each stratum in EAGLE2/3 studies based on the definition of stratification factor (combination of age-groups and uUTI recurrence per CRF in this study

$$p_k \sim Beta\left(r_{k,global}, n_{k,global} - r_{k,global}\right)$$

, where $n_{k,global}$ and $r_{k,global}$ are the pooled number of participants and therapeutic responders who are assigned to the gepotidacin group of k^{th} stratum (k=1, 2, 3, 4) in the micro-ITT NTF-S (Global) population , respectively.

2. Derive the predictive distribution for the number of participants achieving therapeutic success in each stratum k, (k=1, 2, 3, 4)

$$r_{k,Japan} \sim Beta\ binomial\left(n_{k,Japan}, \alpha = r_{k,global}, \beta = n_{k,global} - r_{k,global}\right)$$

, where $n_{k,Japan}$ and $r_{k,Japan}$ are the number of participants and therapeutic responders who are assigned to the gepotidacin group of k^{th} stratum in the micro-ITT NTF-S population, respectively.

3. Derive lower 10 percentile as a threshold using simulation
   a. Set $j = 1$
   b. Sample $r_{k,Japan}^{(j)}$ from $Beta\ binomial\left(n_{k,Japan}, \alpha = r_{k,global}, \beta = n_{k,global} - r_{k,global}\right)$ for each stratum $(k = 1, \ldots, 4)$

c. Calculate $r_{Japan}^{(j)} = r_{1,Japan}^{(j)} + r_{2,Japan}^{(j)} + \cdots + r_{4,Japan}^{(j)}$ and set $j \leftarrow j + 1$

d. Repeat the step b and c until $j = 1{,}000{,}000$.

e. Obtain the lower 10th percentile value $\left(r_{Japan}^{(10\%)}\right)$ of $r_{Japan}^{(j)}$

f. Calculate the threshold as $r_{Japan}^{(10\%)}/n_{Japan}$ where n_{Japan} is the number of participants in the gepotidacin group.

4.2.3. Sensitivity analyses

4.2.3.1. Unadjusted threshold

The predictive distribution unadjusted of stratification factor (combination of age-groups and uUTI recurrence) is:

$$r_{aj} \sim \int Binomial(r_{aj}|n_{aj}, p_a) \times Beta(p_a|\alpha = r_{ag}, \beta = n_{ag} - r_{ag})dp_a$$

, where:
r_{aj}: The expected number of participants achieving therapeutic success in the gepotidacin arm of this study
r_{ag}: The pooled number of participants achieving therapeutic success in the gepotidacin arm across both global studies.
n_{ag}: The pooled number of participants in the gepotidacin arms across both global studies.

The unadjusted threshold value is defined as $r_{aj}^{(10\%)}/n_{aj}$, where $r_{aj}^{(10\%)}$ is the lower 10% tile of the above predictive distribution.

4.2.3.2. Adjustment with randomization strata

The adjusted threshold will be calculated based on the randomization stratum the participant was randomized to (instead of the actual stratum the participant should be assigned to) using the same approach as the primary analysis (Section 4.2.2)

4.2.3.3. Missing data in the global studies

Sensitivity analysis on the primary estimand will be done to assess the impact of missing data using the multiple imputation method in the global studies. If the entire TOC Visit, bacteriology samples or clinical signs and symptoms assessment were missing due to COVID-19 pandemic, then the missed values will be imputed under the missing at random (MAR) assumption. If the TOC bacteriology sample was taken but a result is not available for the sample for any reason then the missed values will also be imputed under the MAR assumption. All other missing data will be considered as a failure (i.e. non-responder). A conservative approach will be taken in this study where all missing data (regardless of the reason for missingness) will be imputed as therapeutic failure.

Missing microbiological response values and clinical response values (if any) in the global studies will be imputed using separate logistic regression models under the MAR assumption in the micro-ITT NTF-S (Global) Population. The imputation models for the global studies will be estimated using the data from the global studies, respectively. The missing data in each of the global studies will be imputed using the above imputation model of each individual study. Note that the imputation models will be estimated using data on the gepotidacin arm only. The variables to be included in the imputation models are:

Models for microbiological response in the global studies:

- Age (<=50 years, or >50 years)
- Acute cystitis recurrence (nonrecurrent infection or recurrent infection) at Baseline
- Interaction term between treatment, Baseline qualifying uropathogen species/group and MIC (gepotidacin or nitrofurantoin) for randomized treatment. This is the same variable used for multiple imputation analysis in the global studies. See the details in the study material of the global studies (204989 and 212390).
- Prior visit (On-therapy Visit) microbiological outcome

Models for clinical response in the global studies:

- Age (<=50 years, or >50 years)
- Acute cystitis recurrence (nonrecurrent infection or recurrent infection) at Baseline
- Baseline clinical signs and symptoms total score
- Prior visit (On-therapy Visit) clinical outcome
- Site (Sites with <10 participants in the micro-ITT NTF-S Population was combined prior to unblinding of the global studies)

Any subjects that had a missing value for one or more variables listed above were excluded from the relevant imputation model(s).

Proportion of Participants achieving therapeutic success in this study

The same approach as the primary analysis will be used.

Threshold using the data from both global studies.

The threshold = for the lower 10^{th} percentile of the predicted therapeutic success in this study will be calculated based on the pooled data from both global studies as follows. Note that the number of replication is set to 1,000,000.

1. Set $j = 1$
2. Impute missing values using separate logistic models that will be estimated using the data from both global studies.
3. Derive therapeutic response from the imputed values.

4. Sample $r_{k,Japan}^{(j)}$ from $Beta\ binomial\left(n_{k,Japan}, \alpha = r_{k,global}, \beta = n_{k,global} - r_{k,global}\right)$ for each stratum $(k = 1, \ldots, 4)$

   , where $n_{k,Japan}\ and\ r_{k,Japan}$ are the number of participants and therapeutic responders who are assigned to the gepotidacin group of k^{th} stratum in the micro-ITT NTF-S population, respectively after imputation.

5. Calculate $r_{Japan}^{(j)} = r_{1,Japan}^{(j)} + r_{2,Japan}^{(j)} + \cdots + r_{4,Japan}^{(j)}$
6. $j \leftarrow j + 1$
7. Repeat step 2-8 until $j = 1{,}000{,}000$
8. Obtain the 10th percentile value $\tilde{r}_{Japan}^{(10\%)}$ from $\left\{r_{Japan}^{(1)}, r_{Japan}^{(2)}, \ldots, r_{Japan}^{(j)}\right\}$ and calculate the threshold as $\tilde{r}_{Japan}^{(10\%)}/n_{Japan}$, where n_{Japan} is the number of participants in the gepotidacin group.

4.2.3.4. Tipping point analysis for missing data

The observed proportion of participants achieving therapeutic success on the gepotidacin arm in this study will be calculated using the same approach as the primary analysis.

The threshold will be derived given the assumed success rate as follows. Note that the number of replications is set to 1,000,000.

1. Set $p_{global}^{(i)}$ as the assumed success rate on the gepotidacin arm in the participants with missing therapeutic response of the global studies.
2. Set $j = 1$
   i. Set $k = 1$
   ii. Draw $r_{k,global}^{j,miss}$ from a binomial distribution $\left(size = n_{k,global}^{miss}, probability = p_{global}^{(i)}\right)$

   , where $n_{k,global}^{miss}$ and $r_{k,global}^{j,miss}$ are the number of subjects with missing therapeutic response and the number of responders out of those with missing therapeutic response, respectively.

   iii. Draw $r_{k,Japan}^{(j)}$ from Beta-binomial distribution $\left(size = n_{k,Japan}, \alpha = r_{k,global}^{*}, \beta = n_{k,global} - r_{k,global}^{*}\right)$

   $r_{k,global}^{*} = r_{k,global}^{obs} + r_{k,global}^{j,miss}$, where $r_{k,global}^{obs}$ is the observed number of participants achieving therapeutic success on the gepotidacin arm in k^{th} stratum of the global studies.

   iv. $k \leftarrow k + 1$
   v. Repeat step I-V until $k = K$
3. Calculate $r_{Japan}^{(j)} = r_{1,Japan}^{(j)} + r_{2,Japan}^{(j)} + \cdots + r_{4,Japan}^{(j)}$

4. $j \leftarrow j + 1$
5. Repeat step 2-8 until $j = 1{,}000{,}000$
6. Obtain 10th percentile $\tilde{r}_{Japan}^{(10\%)}$ from $\left\{r_{Japan}^{(1)}, r_{Japan}^{(2)}, \ldots, r_{Japan}^{(j)}\right\}$ and calculate the threshold as $\tilde{r}_{Japan}^{(10\%)} / n_{Japan}$, where n_{Japan} is the number of participants in the gepotidacin group.

Tipping point analysis will be done as follows.

1. A grid of values will be established, ranging from 0.0 to 1.00 in steps of 2.5%, establishing the assumed therapeutic success rates on the gepotidacin arm in participants with missing therapeutic response of the global studies.
2. For each assumed response rate, $p_{global}^{(i)}$, calculate the threshold through simulation steps which is shown above.

4.2.3.5. Impact by GCP violation

There was GCP violation in Site PPD and the participants from the site were excluded from the primary analysis. For transparency, the sensitivity analysis including those participants will be done. This analysis is based on micro-ITT-ALL NTF-S (Entire) population. The same approach as the primary analysis except for the analysis population will be done.

4.3. Secondary Endpoint(s) Analyses

4.3.1. Therapeutic Response at TOC Visit

4.3.1.1. Definition of Estimands

- **Population**: Japanese female participants with acute uncomplicated cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin
- **Treatment Condition**: Gepotidacin 1500mg BID for 5 days versus nitrofurantoin 100 mg BID for 5 days, regardless of adherence.
- **Variable**: Therapeutic response at the TOC Visit (see Section 6.2.1.1 and Section 6.2.1.2)
- **Summary Measure**: Difference in proportions of participants achieving therapeutic success in the gepotidacin and nitrofurantoin treatment groups.
- **Handling of Intercurrent Event**:
  - Study treatment discontinuation (due to any reason) – treatment policy
  - Use of systemic antimicrobials on or prior to the visit of interest – composite strategy. This ICE is captured through the definitions of microbiological and clinical response (see Section 6.2.1.1 and Section 6.2.1.2)

4.3.1.2. Main analytical approach

This analysis is based on micro-ITT NTF-S Population.

The number and proportion of participants achieving therapeutic success will be summarized, along with the 95% Exact Clopper Pearson CI at the TOC Visit by treatment group. ICE of use of other systemic antimicrobials is captured through the defining criteria of microbiological and clinical response (Section 6.2.1.1 and Section 6.2.1.2). Participants who do not return for the TOC Visit or have missing data at the TOC Visit will be treated as failures.

The difference in proportions of participants achieving therapeutic success for gepotidacin compared to nitrofurantoin and the 95%CI of the difference will be summarized at TOC Visit. Miettinen-Nurminen (score) confidence limits of the treatment difference will be computed. The MN estimate of the common risk difference and variance is computed by combining the point estimates and variances from individual strata using MN weights. The estimate uses inverse variance stratum weights to produce MN confidence limits for the stratum risk differences. The mathematics and algorithm of MN method can be found in the SAS procedure guide under "Summary Score Estimate of the Common Risk Difference" [SAS, 2018].

4.3.1.3. Supplementary analyses

Bayesian dynamic borrowing will be carried out to estimate the treatment difference in the Japanese population using data from each treatment group of the global studies (Studies 204989 and 212390).

The prior distribution is a mixture distribution with 2 components, one reflecting the results from the global studies, and a vague component reflecting 'weak information' about the treatment difference [Schmidli, 2014]

Denoting the difference (gepotidacin – nitrofurantoin) as Δ, the prior has the form:

$$f(\Delta) = w \times f_{inf}(\Delta) + (1 - w) \times f_{vag}(\Delta)$$

- $f_{inf}(\Delta) = Normal\left(\Delta \middle| \hat{\mu}_g, \hat{s}_g^2\right): informative\ component$
- $f_{vag}(\Delta) = Normal\left(\Delta \middle| -0.10, \hat{s}_g^2 / \left(\frac{1}{n_{ag}} + \frac{1}{n_{cg}}\right)\right): vague\ component$
- $w \in [0, 1]: fixed\ initial\ weight$

, where $\hat{\mu}_g, \hat{s}_g^2$ are the MN estimate of the common risk difference and variance on the proportion of participants achieving therapeutic success between gepotidacin and nitrofurantoin using the pooled data of both global studies. Similarly, $n_{ag}\ and\ n_{cg}$ are the pooled number of participants on the gepotidacin and nitrofurantoin arms in the global studies, respectively. Note that this prior will be based on micro-ITT NTF-S (Global) Population.

The prior mixture will be updated with the MN estimate of the common risk difference and variance on the proportion of participants achieving therapeutic success between gepotidacin and nitrofurantoin using the data from this study (micro-ITT NTF-S Population) to obtain the posterior mixture. The prior and posterior median of treatment difference and 95% credible interval will be presented by each initial weight (w = 0 to 1.0 by 0.05). The other set of initial weights may be explored.

4.3.2. Clinical Outcome and Response at the TOC Visit

4.3.2.1. Definition of Estimand

- **Population**: Japanese female participants with acute uncomplicated cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin
- **Treatment Condition**: Gepotidacin 1500 mg BID for 5 days, regardless of adherence
- **Variable**: Clinical outcome and response at the TOC Visit (see Section 6.2.1.2)
- **Summary Measure:**
  - Proportion of participants in each outcome category in the gepotidacin arm (Clinical outcome)
  - Proportion of participants achieving clinical success in the gepotidacin arm (Clinical response)
- **Handling of Intercurrent Event:**
  - Study treatment discontinuation (due to any reason) – treatment policy
  - Use of systemic antimicrobials on or prior to the visit of interest – composite strategy. This ICE is captured through the definitions of clinical response (see Section 6.2.1.2)

4.3.2.2. Main analytical approach

This analysis is based on micro-ITT NTF-S Population.

The number and proportion of participants achieving clinical success will be summarized, along with the 95% Exact Clopper Pearson CI at the TOC Visit by treatment group. In addition, the number and proportion of participants in each outcome category will be summarized at the TOC Visit by treatment group.

The ICE of use of other systemic antimicrobials is captured through the defining criteria of clinical outcome and response (Section 6.2.1.2). Participants who do not return for the TOC Visit or have missing data at the TOC Visit will be treated as failures.

4.3.3. Microbiological Outcome and Response at the TOC

4.3.3.1. Definition of Estimand

- **Population**: Japanese female participants with acute uncomplicated cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin
- **Treatment Condition**: Gepotidacin 1500 mg BID for 5 days, regardless of adherence
- **Variable**: Microbiological outcome and response at the TOC Visit (see Section 6.2.1.1)
- **Summary Measure:**
  - Proportion of participants in each outcome category in the gepotidacin arm (Microbiological outcome)
  - Proportion of participants achieving microbiological success in the gepotidacin arm (Microbiological response)
- **Handling of Intercurrent Event:**
  - Study treatment discontinuation (due to any reason) – treatment policy
  - Use of systemic antimicrobials prior to the visit of interest – composite strategy. This ICE is captured through the definitions of microbiological response (see Section 6.2.1.1)

4.3.3.2. Main analytical approach

This analysis is based on micro-ITT NTF-S Population.

The number and proportion of participants achieving microbiological success will be summarized, along with the 95% Exact Clopper Pearson CI at the TOC Visit by treatment group. In addition, the number and proportion of participants in each outcome category will be summarized at the TOC Visit by treatment group.

The ICE of use of other systemic antimicrobials is captured through the defining criteria of microbiological outcome and response (Section 6.2.1.1). Participants who do not return for the TOC Visit or have missing data at the TOC Visit will be treated as failures.

4.3.4. Therapeutic Response at the TOC Visit in MDR

4.3.4.1. Definition of Estimand

- **Population**: Japanese female participants with acute uncomplicated cystitis with qualifying bacterial uropathogen(s) resistance to “two or more” specific classes of antimicrobials at Baseline(see the details in Section 6.2.11)

- **Treatment Condition**: Gepotidacin 1500 mg BID for 5 days, regardless of adherence
- **Variable**: Therapeutic response at the TOC Visit (see Section 6.2.1.1 and Section 6.2.1.2)
- **Summary Measure:** Proportion of participants achieving therapeutic success in the gepotidacin arm
- **Handling of Intercurrent Event:**
  - Study treatment discontinuation (due to any reason) – treatment policy
  - Use of systemic antimicrobials on or prior to the visit of interest – composite strategy. This ICE is captured through the definitions of microbiological and clinical response (see Section 6.2.1.1 and Section 6.2.1.2)

4.3.4.2. Main analytical approach

This analysis is based on micro-ITT MDR Population.

The number and proportion of participants with therapeutic success will be presented by treatment group at the TOC Visit along with the 95% Exact Clopper Pearson CI. Participants who do not return for the TOC Visit or have missing data a t the TOC Visit will be treated as failures.

The ICE of use of other systemic antimicrobials is captured through the defining criteria of microbiological and clinical response (Section 6.2.1.1 and Section 6.2.1.2).

4.3.4.3. Supplementary analyses

Additional estimand is described by the following attributes:

- **Population**: Japanese female participants with acute uncomplicated cystitis with qualifying bacterial uropathogen(s) resistance to “two or more” specific classes of antimicrobials at Baseline
- **Treatment Condition**: Gepotidacin 1500 mg BID for 5 days vs Nitrofurantoin 100 mg BID for 5 days, regardless of adherence
- **Variable**: Therapeutic response at the TOC Visit
- **Summary Measure:** Proportion of participants achieving therapeutic success in the gepotidacin arm
- **Handling of Intercurrent Event:**
  - Study treatment discontinuation (due to any reason) – treatment policy
  - Use of systemic antimicrobials on or prior to the visit of interest – composite strategy. This ICE is captured through the definitions of microbiological and clinical response (see Section 6.2.1.1 and Section 6.2.1.2)

Bayesian dynamic borrowing will be carried out to estimate the treatment difference in MDR subgroup in the Japanese population using pooled data from each treatment group of the global studies (Studies 204989 and 212390).

The prior distribution is a mixture distribution with 2 components, one reflecting the results from the global studies, and a vague component reflecting 'weak information' about the treatment difference [Schmidli, 2014].

Denoting the difference (gepotidacin – nitrofurantoin) as Δ_{MDR}, the prior has the form:

$$h(\Delta_{\mathrm{MDR}}) = w \times h_{inf}(\Delta_{\mathrm{MDR}}) + (1-w) \times h_{vag}(\Delta_{\mathrm{MDR}})$$

- $h_{inf}(\Delta) = Normal\left(\Delta \middle| \hat{\mu}_{g,MDR}, \hat{s}^2_{g,MDR}\right): informative\ component$
- $h_{vag}(\Delta_{\mathrm{MDR}}) = Normal\left(\Delta \middle| -0.1, \hat{s}^2_{g,MDR} \middle/ \left(\frac{1}{n_{ag,MDR}} + \frac{1}{n_{cg,MDR}}\right)\right): vague\ component$
- $w \in [0,1]: fixed\ initial\ weight$

, where $\hat{\mu}_{g,MDR}, \hat{s}^2_{g,MDR}$ are crude estimate of the risk difference and variance on the proportion of participants achieving therapeutic success between gepotidacin and nitrofurantoin using the pooled data from MDR subgroup of both global studies. Similarly, $n_{ag,MDR}\ and\ n_{cg,MDR}$ are the pooled number of participants on the gepotidacin and nitrofurantoin arms in MDR subgroup of the global studies, respectively. Note that this prior will be based on micro-ITT MDR (Global) Population.

The prior mixture will be updated with the risk difference and its standard deviation derived from MDR subgroup data in this study (micro-ITT MDR population). The risk difference and its standard deviation will be obtained as follows to avoid 0 cell problem.

1. Beta (0.5, 0.5) will be updated with $\left(n_{aj,MDR}, r_{aj,MDR}\right)\ and\ \left(n_{cj,MDR}, r_{cj,MDR}\right)$, respectively.
2. Mean and variance on each treatment arm, $\left(\mu_{aj,MDR}, s^2_{aj,MDR}\right)\ and\ \left(\mu_{cj,MDR}, s^2_{cj,MDR}\right)$, will be obtained from each posterior.
3. Risk difference = $\mu_{aj,MDR} - \mu_{cj,MDR}$
4. Standard deviation = $\sqrt{s^2_{aj,MDR} + s^2_{cj,MDR}}$

, where $n_{aj,MDR}\ and\ n_{cj,MDR}$ are the number of participants on gepotidacin and nitrofurantoin arms, respectively, and $r_{aj,MDR}\ and\ r_{cj,MDR}$ are the number of participants achieving therapeutic success on gepotidacin and nitrofurantoin arms, respectively. The prior and posterior median and 95% credible interval will be presented by each initial weight (w = 0 to 1.0 by 0.05). The other set of initial weights may be explored.

4.3.5. Clinical Outcome and Response at the TOC Visit in MDR

4.3.5.1. Definition of Estimand

- **Population**: Japanese female participants with acute uncomplicated cystitis who have qualifying uropathogen(s) resistance to "two or more" specific classes of antimicrobials at Baseline
- **Treatment Condition**: Gepotidacin 1500 mg BID for 5 days, regardless of adherence
- **Variable**: Clinical outcome and response at the TOC Visit (see Section 6.2.1.2)
- **Summary Measure:**
  - Proportion of participants in each outcome category in the gepotidacin arm (Clinical outcome)
  - Proportion of participants achieving clinical success in the gepotidacin arm (Clinical response)
- **Handling of Intercurrent Event:**
  - Study treatment discontinuation (due to any reason) – treatment policy
  - Use of systemic antimicrobials on or prior to the visit of interest – composite strategy. This ICE is captured through the definitions of clinical response (see Section 6.2.1.2)

4.3.5.2. Main analytical approach

This analysis is based on micro-ITT MDR Population.

The number and proportion of participants with clinical success will be presented by treatment group at the TOC Visit along with the 95% Exact Clopper Pearson CI. In addition, the number and proportion of participants in each outcome category will be summarized by treatment group at the TOC Visit.

The ICE of use of other systemic antimicrobials is captured through the defining criteria of clinical outcome and response (Section 6.2.1.2). Participants who do not return for the TOC Visit or have missing data at the TOC Visit will be treated as failures.

4.3.5.3. Supplementary analyses

Additional estimand is described by the following attributes:

- **Population**: Japanese female participants with acute uncomplicated cystitis with qualifying bacterial uropathogen(s) resistance to "two or more" specific classes of antimicrobials at Baseline
- **Treatment Condition**: Gepotidacin 1500 mg BID for 5 days vs Nitrofurantoin 100 mg BID for 5 days, regardless of adherence

- **Variable**: Clinical response at the TOC Visit
- **Summary Measure:** Proportion of participants achieving clinical success in the gepotidacin arm
- **Handling of Intercurrent Event:**
  - Study treatment discontinuation (due to any reason) – treatment policy
  - Use of systemic antimicrobials on or prior to the visit of interest – composite strategy. This ICE is captured through the definitions of clinical response (see Section 6.2.1.2)

The same BDB approach will be used as therapeutic response in MDR (Refer to Section 4.3.4.3).

4.3.6. Microbiological Outcome and Response at the TOC Visit in MDR

4.3.6.1. Definition of Estimand

- **Population**: Japanese female participants with acute uncomplicated cystitis who have qualifying uropathogen(s) resistance to "two or more" specific classes of antimicrobials at Baseline
- **Treatment Condition**: Gepotidacin 1500 mg BID for 5 days, regardless of adherence
- **Variable**: Microbiological outcome and response at the TOC Visit (see Section 6.2.1.1)
- **Summary Measure:**
  - Proportion of participants in each outcome category in the gepotidacin arm (Microbiological outcome)
  - Proportion of participants achieving clinical success in the gepotidacin arm (Microbiological response)
- **Handling of Intercurrent Event:**
  - Study treatment discontinuation (due to any reason) – treatment policy
  - Use of systemic antimicrobials prior to the visit of interest – composite strategy. This ICE is captured through the definitions of microbiological response (see Section 6.2.1.1)

4.3.6.2. Main analytical approach

This analysis is based on micro-ITT MDR Population.

The number and proportion of participants with microbiological success will be presented by treatment group at the TOC Visit along with the 95% Exact Clopper Pearson CI. In addition, the number and proportion of participants in each outcome category will be summarized by treatment group at the TOC Visit.

The ICE of use of other systemic antimicrobials is captured through the defining criteria of microbiological outcome and response (Section 6.2.1.1). Participants who do not return for the TOC Visit or have missing data at the TOC Visit will be treated as failures.

4.3.6.3. Supplementary analyses

Additional estimand is described by the following attributes:

- **Population**: Japanese female participants with acute uncomplicated cystitis with qualifying bacterial uropathogen(s) resistance to "two or more" specific classes of antimicrobials at Baseline
- **Treatment Condition**: Gepotidacin 1500 mg BID for 5 days vs Nitrofurantoin 100 mg BID for 5 days, regardless of adherence
- **Variable**: -Microbiological response at the TOC Visit
- **Summary Measure:** Proportion of participants achieving microbiological success in the gepotidacin arm
- **Handling of Intercurrent Event:**
  - Study treatment discontinuation (due to any reason) – treatment policy
  - Use of systemic antimicrobials prior to the visit of interest – composite strategy. This ICE is captured through the definitions of microbiological response (see Section 6.2.1.1)

The same BDB approach will be used as therapeutic response in MDR (Refer to Section 4.3.4.3).

4.3.7. Investigator Assessment of Clinical Response at the TOC Visit

4.3.7.1. Definition of Estimand

- **Population**: Japanese female participants with acute uncomplicated cystitis
- **Treatment Condition**: Gepotidacin 1500 mg BID for 5 days, regardless of adherence
- **Variable**: Investigator assessment of clinical response at the TOC Visit
- **Summary Measure:** Proportion of participants with investigator assessed clinical response of success, failure and indeterminate/missing on the gepotidacin arm
- **Handling of Intercurrent Event:**
  - Study treatment discontinuation (due to any reason) – treatment policy
  - Use of systemic antimicrobials on or prior to the visit of interest – composite strategy

4.3.7.2. Main analytical approach

This analysis is based on ITT Population. Below are the categories of response and response.

Definition	Clinical Response
Sufficient resolution of acute cystitis signs and symptoms such that no additional systemic antimicrobial therapy is required for the current infection	Clinical Success
Participant met any one of the criteria below: • No apparent response to treatment (persistence or progression of any pretreatment clinical signs and symptoms) • Use of additional systemic antibiotic(s) for the current infection • Death related to acute cystitis prior to the visit	Clinical Failure
Determination of clinical response could not be made at the visit for any of the following reasons: • Participant was lost to follow-up and/or the clinical assessment was not undertaken • Use of confounding systemic antibiotic(s) for another infection • Death prior to the visit where acute cystitis was clearly noncontributory	Indeterminate

The missing data at TOC visit including outside the analysis window will be handled as shown in Section 6.2.1.5.

The number and proportion of participants with investigator assessed clinical response of success, failure and indeterminate/missing at the TOC Visit by treatment group based on ITT Population. Reasons for an assessment of failure and indeterminate responses will also be summarized.

The 95% Exact Clopper Pearson CI for the proportion of participants with success will be presented as a binomial proportion for each treatment group.

4.3.8. Gepotidacin plasma and urine PK concentrations

4.3.8.1. Definition of Estimand

- **Population**: Japanese female participants with acute uncomplicated cystitis
- **Treatment Condition**: Gepotidacin 1500 mg BID for 5 days, regardless of adherence
- **Variable**: Gepotidacin plasma and urine PK concentrations
- **Summary Measure:** Summary statistics (appropriate for each type of endpoint) in the gepotidacin arm
- **Handling of Intercurrent Event:**
    - Study treatment discontinuation (due to any reason) – while on treatment strategy (treatment phase defined as from first dose to On-therapy Visit)

4.3.8.2. Main analytical approach

The analysis is based on the PK population.

All calculations of PK concentrations will be based on actual sampling times that fall within the set PK windows described below.

Summary statistics (n, arithmetic mean, geometric mean, median, standard deviation, minimum, maximum, 95% CI of the arithmetic and geometric means and between participant coefficient of variation [%CV and %CVb]) for plasma and urine gepotidacin concentrations will be provided by the sampling windows in Table 1. If PK concentrations are not quantifiable, these values will be imputed as 0.

PK samples collected outside of the treatment phase will only be listed.

If more than one concentration data is available within the same PK window at a scheduled time point, the data closer to 12 hours post-latest dose will only be used for the summary statistics of Pre-Dose. For Post-Dose, data closer to 2 hours post-latest dose will only be used for the summary statistics.

PK concentrations will be listed based on PK (Full) population (i.e. including the participants impacted by GCP violation).

Table 1 PK Summary by sampling windows

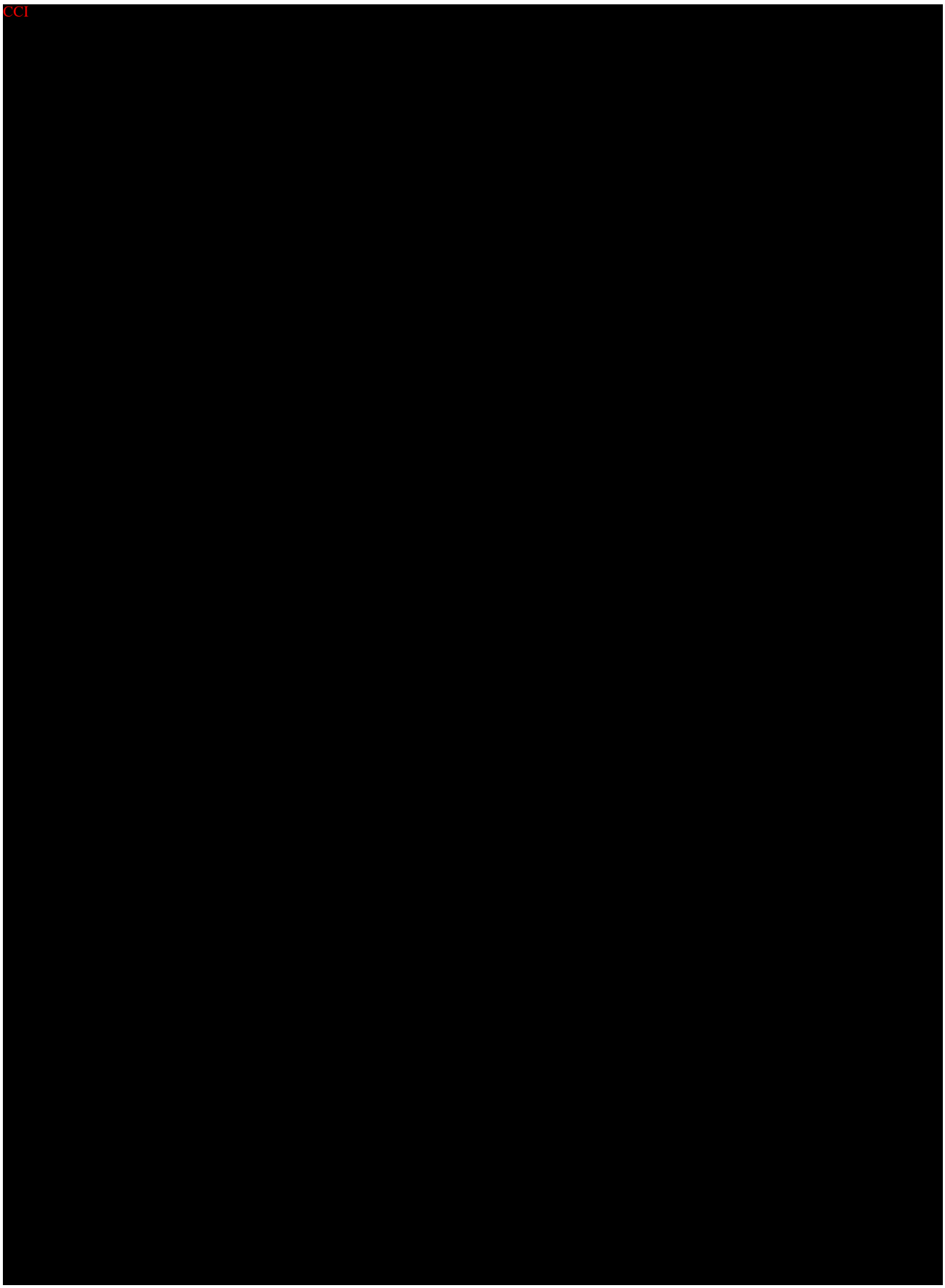
Visit	Parameter	PK Window
Baseline Study Day 1	$C_{day1, 0\text{-}2h}$	Average concentration post-dose 0 to ≤ 2 hours
	$C_{day1, >2h}$	Average concentration post-dose >2 hours
	$C_{day2\text{-}5, pre\text{-}dose}$	Average concentration pre-dose
On-Therapy Study Day 2 to 5	$C_{day2\text{-}5, 0\text{-}2h}$	Average concentration post-dose 0 to ≤ 2 hours
	$C_{day2\text{-}5, >2h}$	Average concentration post-dose >2 hours

4.4. Exploratory Endpoint(s) Analyses

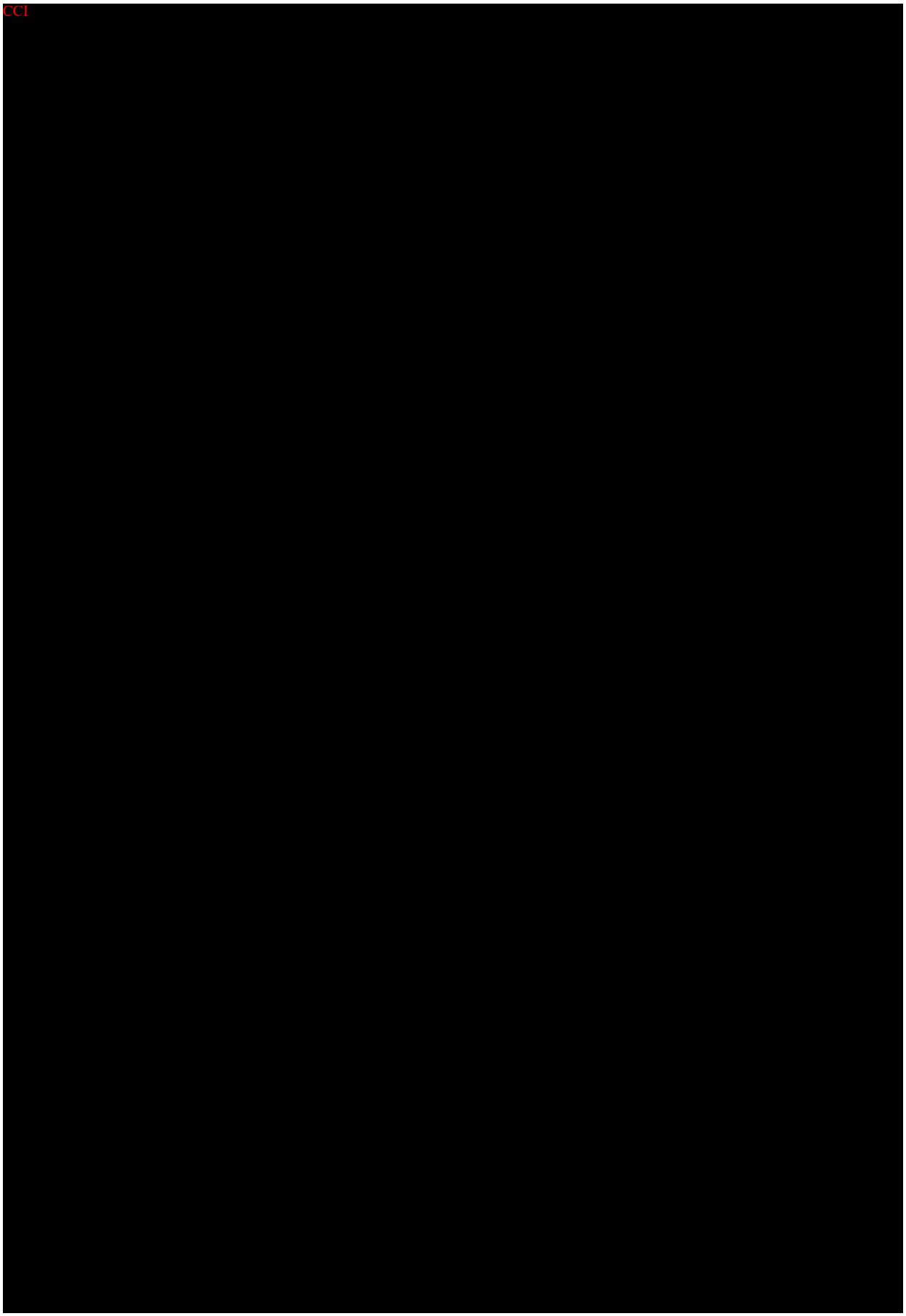
CCI

[redacted]

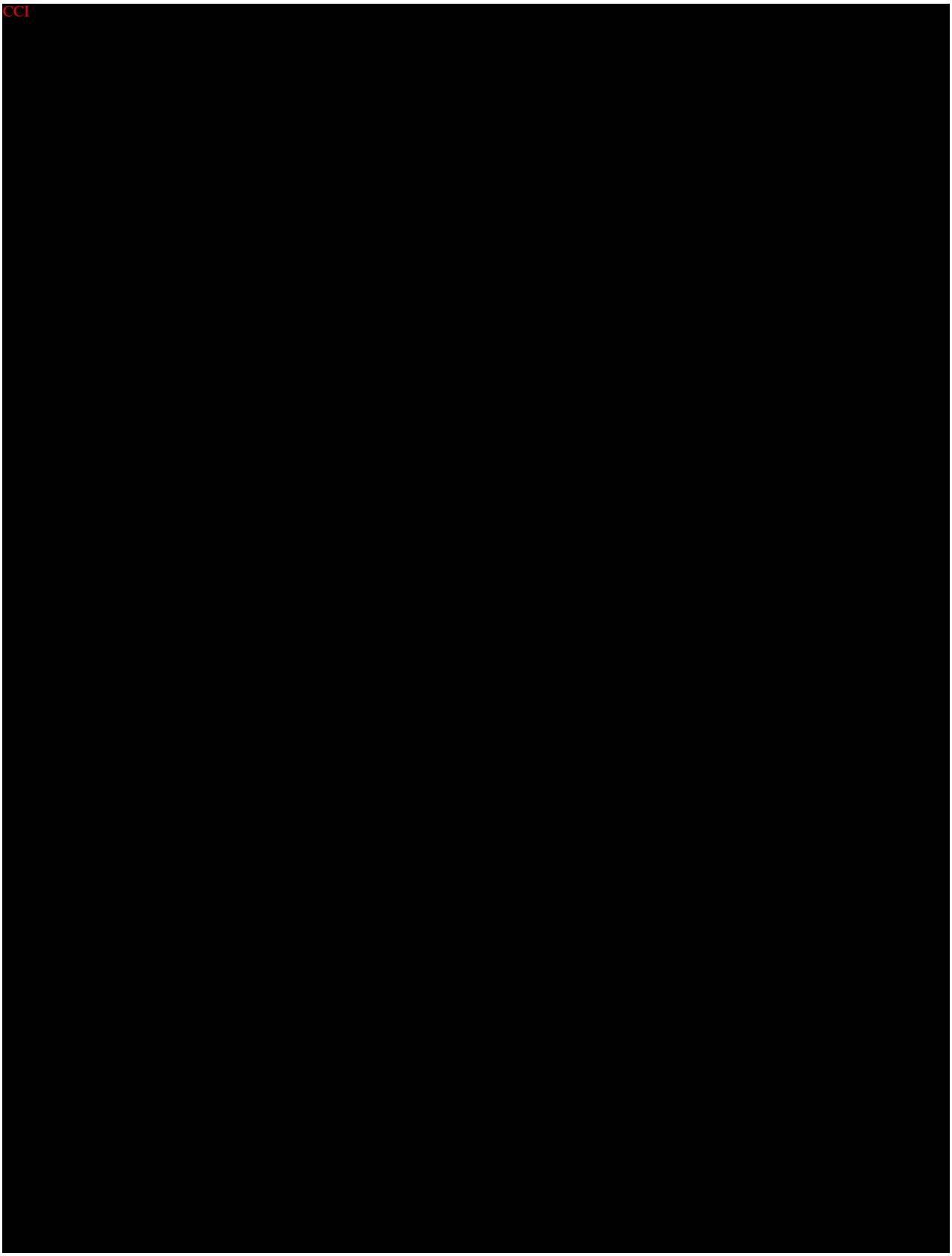
CCI



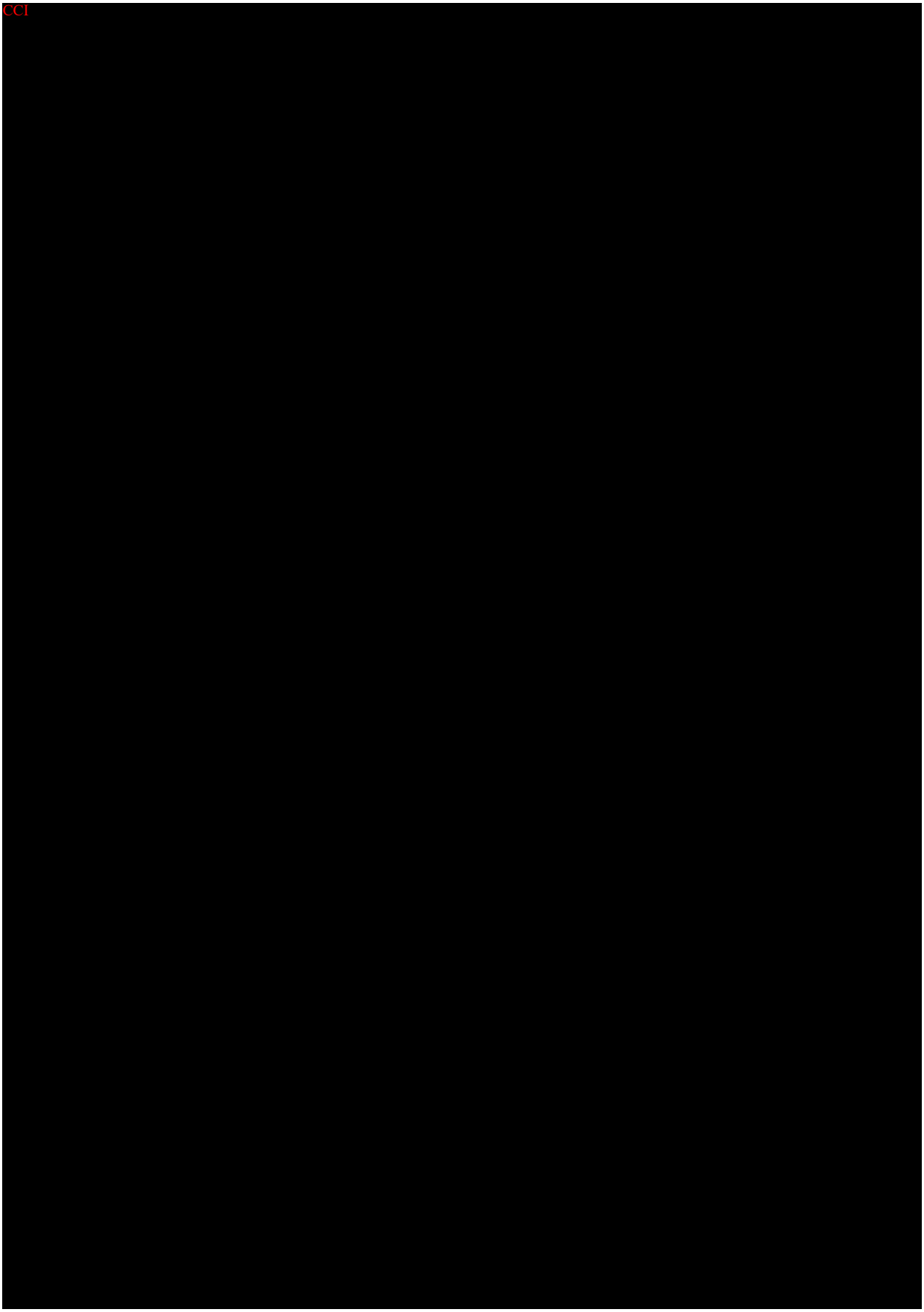
CCI



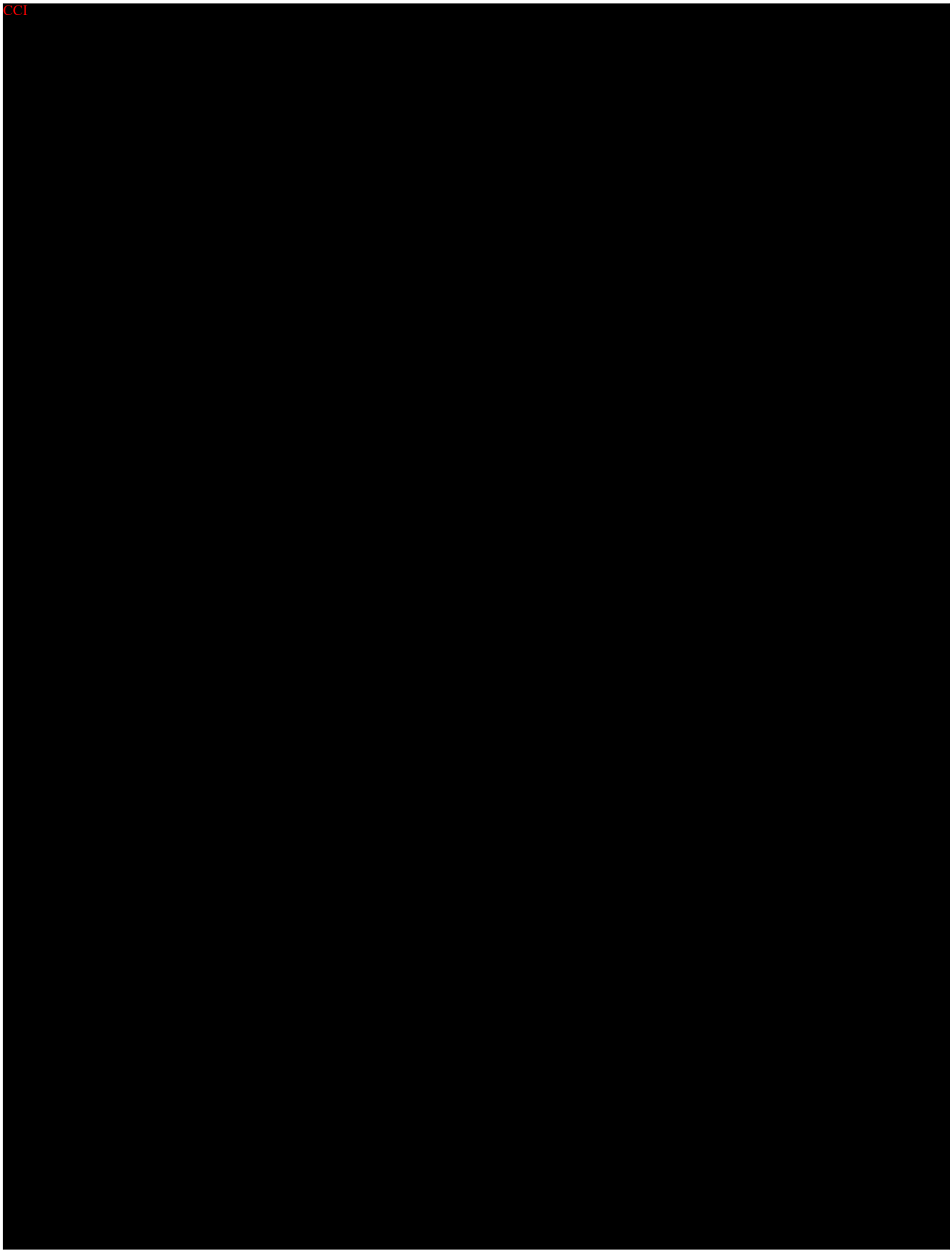
CCI



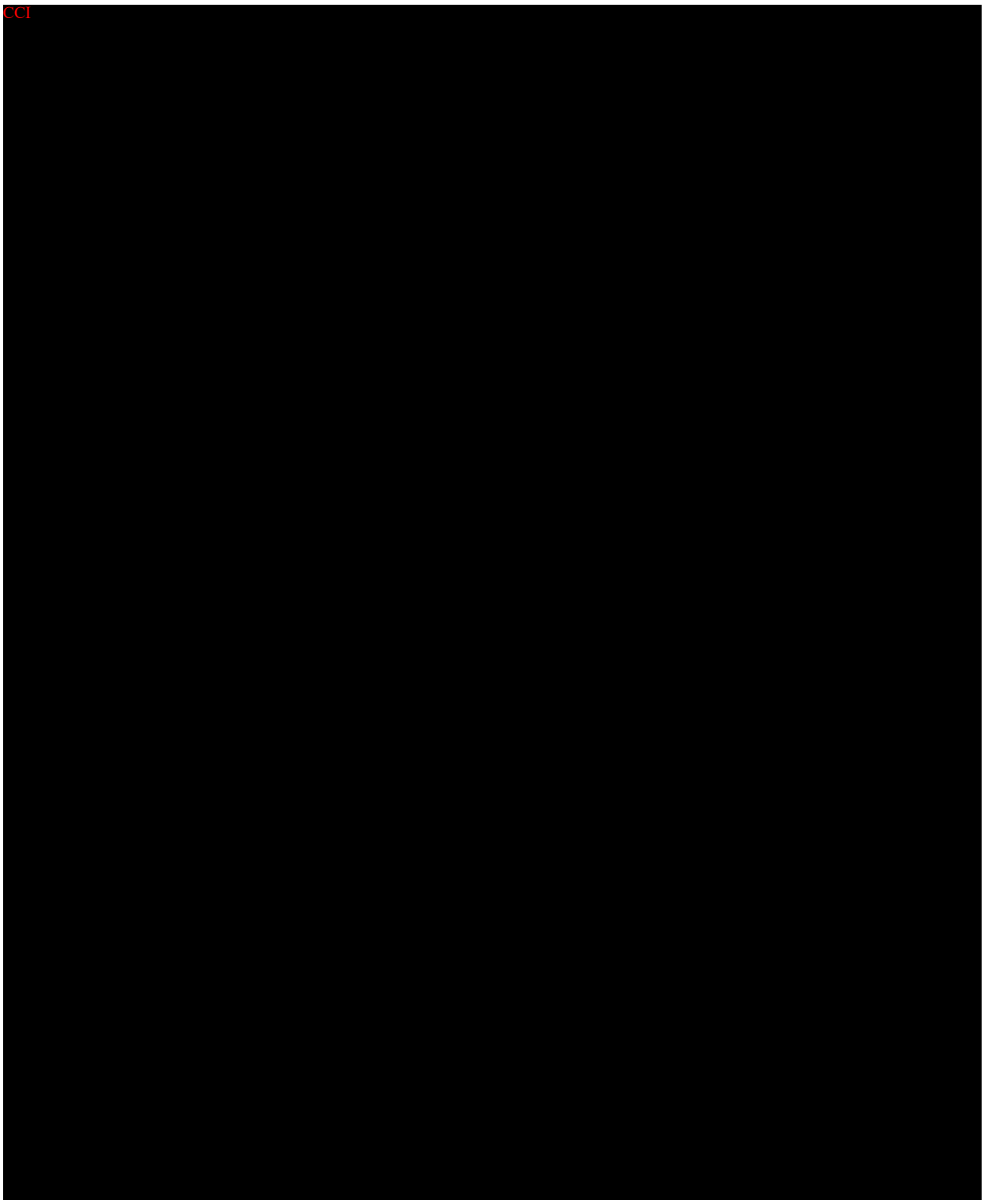
CCI



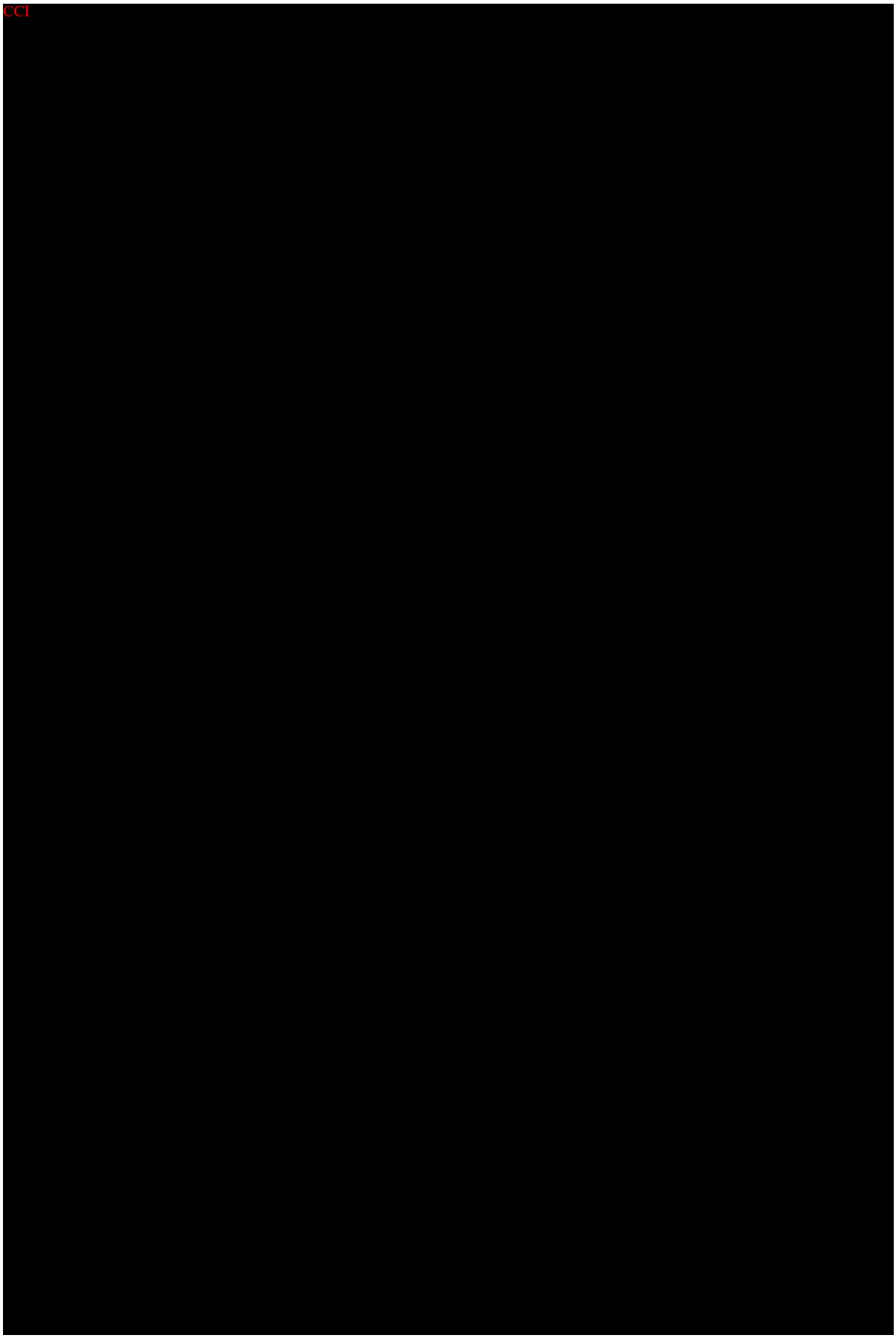
CCI



CCI



CCI



CCI

4.6. Safety Analyses

The safety analyses will be based on the Safety Analysis population, unless otherwise specified.

4.6.1. Extent of Exposure

Exposure will be summarized by treatment group for the Safety population using the following parameters.

- Duration of treatment (days): Rounding of the last dose date/time – the first dose date/time + (0.5 in days) to the nearest integer.
- Average daily dose (mg)
- Cumulative actual dose (mg)
- Compliance rate (%)

In addition, the number of participants with <80%, >=80%-<100% and 100% compliance rate will be summarized. In addition, listing will be produced for the exposure data.

Compliance rate (%) will be calculated as:

Study intervention	Formula
Gepotidacin/gepotidacin placebo	$\frac{total\ number\ of\ tablets\ taken}{20} * 100\ (\%)$
Nitrofurantoin/nitrofurantoin placebo	$\frac{total\ number\ of\ capsules\ taken}{10} * 100\ (\%)$

4.6.2. Adverse Events

An adverse event (AE) is considered treatment emergent if the AE onset date/time is on or after study intervention start date/time. If time is missing, only date will be compared. All AE and SAE summaries (including AESI) will be based on Treatment emergent adverse events unless otherwise specified.

Adverse events will be coded using the standard Medical Dictionary for Regulatory Affairs (MedDRA dictionary).

An overview summary of AEs, including counts and percentages of participants will be produced with:

- Any AE
- AE by maximum grade
- Study intervention related AEs
- AEs leading to withdrawal from study
- AEs leading to permanent discontinuation of study intervention
- AEs leading to permanent discontinuation of study intervention or withdrawal from study
- Study intervention related AEs leading to permanent discontinuation of study intervention
- SAEs
- Non-serious AEs
- Study intervention related SAE
- Fatal SAEs
- SAEs leading to permanent discontinuation of study intervention
- AEs of special interest (3 types of AESI will be provided separately)

In addition to overall summary, separate summaries of AE will be produced according to the below table. Note that missing grade of AE will be imputed as “Severe”.

	Summary by PT	Summary by PT and SOC	Summary by PT, SOC and Maximum Grade
Any AEs		Y	Y
Study intervention related AEs		Y	Y
AEs leading to permanent discontinuation of study intervention		Y	Y
Common (>= 1%) AEs	Y		
Serious AEs		Y	Y
Non-serious study intervention related AEs	Y		
Serious Fatal and Non-Fatal study intervention related AEs	Y		

Furthermore, the following summaries will be produced for disclosure purpose.

- Summary of Common (>=5%) non-serious Adverse Events by SOC and PT (Number of Subjects and Occurrences)
- Summary of SAEs by SOC and PT (Number of Subjects and Occurrences)

A study intervention-related AE is defined as an AE for which the investigator classifies the possible relationship to study intervention as "Yes". A worst-case scenario approach will be taken to handle missing relatedness data, i.e., the summary table will include events with the relationship to study intervention as 'Yes' or missing.

A study intervention-related SAE is defined as an SAE for which the investigator classifies the relationship to study intervention as "Yes". A worst-case scenario approach will be taken to handle missing data, i.e., the summary table will include events with the relationship to study intervention as 'Yes' or missing.

Common (>=X%) AEs are defined as AEs with >=X% incidence (before rounding) in any treatment group.

The following listings will be produced.

- All Adverse Events
- Serious Adverse Events and Reasons for Considering as a Serious Adverse Event.
- Subject Profile for Death

4.6.2.1. Adverse Events of Special Interest

The following will be considered adverse events of special interest (AESI) for the purpose of analyses: Clostridium difficile, Cardiovascular, Gastrointestinal, and Potential Acetylcholinesterase-Inhibition AESIs. The definitions and derivations are provided for each AESI in Section 6.2.2.1.

Clostridium difficile AESIs

This will be included in the overall summary of AEs.

Cardiovascular and Gastrointestinal AESIs

The number and percentage of participants with an event will be summarized by PT, SOC and maximum grade. In addition, the incidence of AEs of GI effects and time to the first occurrence will be summarized.

Potential Acetylcholinesterase-Inhibition AESIs

Any reported AE listed in the Section 6.2.2.1 with a start time no later than 12 hours after the latest dose administered, as evaluated by the investigator as per the DMID grading criteria provided in the protocol Section 10.12 Appendix 12: Division of Microbiology and Infectious Disease Adult Toxicity Tables for Adverse Event Assessment, will be included in the programmatic identification of a potential Acetylcholinesterase-Inhibition (AchE-I) AESI.

Cumulative grade score of potential AchE-I events will be calculated as the sum of the grade of each reported AE. This enables the number of AEs and the severity of each AE to be taken into account. The grading scale is defined in Table 2.

Table 2 AchE-I Cumulative Grade Score Scale

Cumulative Grade:	0	1	2	3	4
Cumulative Grade Score:	0	1 to 3	4 to 6	7 to 10	≥11

For instance, if a participant reports two AEs, one of Grade 1 and the other of Grade 3, their cumulative grade score of 4 would result in cumulative grade 2. If a participant reports no AEs, their cumulative grade score of 0 would result in cumulative grade 0. This will be calculated for All AchE-I events, non-GI AchE-I events and GI aChE-T events, however only All AchE-I events and non-GI AchE-I events will be summarized.

AchE-I AESIs and non-GI AchE-I events will be summarized by SOC, PT and maximum grade. Separate tables will summarize AchE-I AESI by number of events and unique PT. In addition, the following parameters of AchE-I events will also be summarized, and repeated for non-GI AchE-I and GI AchE-I events.

Time of onset (hours):

1. **Definition**

   Time of onset (hours) is defined as time from first dose to the start date of the first event in hours. The first event is defined as the treatment emergent AE of which start date is the earliest within each participant. If the start time of the first event is missing, 00:00 will be imputed to calculate the time of onset. Time of onset will be rounded to the nearest hour, which will be zero hour if time of onset is <30 minutes.

2. Analytical approach

Time of onset will be summarised for each type of AChE-I by treatment group.

Time since end of treatment (hours):

1. Definition

Time since end of treatment is defined as the time from the end date of the treatment to the non-missing end date of the last event, which will be derived as follows.

1) For missing end date of the treatment emergent AEs, the earliest date of death and the last contact date will be imputed.
2) The last event will be identified as the treatment emergent AEs of the latest end date including the imputed end date per each participant. If there are more than one AEs that have the same end date but some AEs have missing end time and the other has non-missing end time, the AE with non-missing end time will be chosen as the last event.
3) For missing end time of the last event, 23:59 will be imputed.
4) Time since end of treatment will be computed as (End date/time of the last event – treatment end date/time)

2. Analytical approach

For participants with the positive value of time since end of treatment which was calculated from non-missing end date, the time since end of treatment will be summarised for each category of AChE-I event (if any) by treatment group.

In addition, the following numbers will be presented for each AChE-I categories by treatment group.

1) The number of participants with the last AChE-I event end date imputed
2) The number of participants who have no event of any type of AChE-I with an end date after the end of treatment

Duration (days):

1. Definition

Duration in days will be computed as the difference from the start date of the first event to the end date of the last event (imputed end date of last event – start date of first event + 1). The first and last events defined are the same also for the time of onset and time since end of treatment, respectively.

2. Analytical approach

Duration will be summarised for each AChE-I categories by treatment group.

AchE-I events with a start time less than or equal to 6 hours after the latest dose administered will also be flagged in the dataset.

4.6.2.2. COVID-19 Assessment and COVID-19 AEs

A standardized MedDRA Query (SMQ) will be used to identify all COVID-19 AEs. COVID-19 assessments for participants with COVID-19 AEs will be summarized.

4.6.2.3. Impact of COVID-19 Pandemic on Safety Results

The summary of the incident rates of AE before and after the start of the COVID-19 will not be producedsince this study starts after the beginning of the COVID-19 pandemic.

4.6.2.4. Quantitative Screening for Identification of Potential Adverse Reaction

Frequentist approach to screen for potential ARs will be used. Specifically, the Crowe method [Crowe, 2013] will be applied for initial screening of the large number of adverse events to generate a "short list" of potential ARs. Due to the smaller sample size than the global studies, this method is based on the HLT relative risk (incidence rate on gepotidacin arm divided by that on nitrofurantoin arm).

Screening criteria endorsed are displayed in Table 3.

Table 3 Criteria for Quantitative Screening for Potential ARs.

Absolute Incidence in Nitrofurantoin Subjects	HLT relative risk (Gepotidacin vs Nitrofurantoin)	95% CI for HLT RR*
No condition	≥1.25	No condition

Note that any event which has not occurred on nitrofurantoin arm but occurred on gepotidacin arm will be included in the "short list". In addition, the following AEs will automatically be included in the "short list" of potential ARs for further qualitative evaluation:

- QT Prolongation: It is a very rare serious event that has been observed in early phase gepotidacin studies and therefore needs further evaluation. It is identified using HLT "ECG investigations".
- Serious and severe adverse events: The incidence of serious and severe AEs is expected to be very low and the qualitative assessment will be applied directly to these events without going through the quantitative screening process.
- Fungal infections: It is a known AR for nitrofurantoin. It is identified using HLT "Fungal infections NEC".
- Hepatobiliary disorders: It is a known AR for nitrofurantoin. It is identified using HLT "Hepatic and hepatobiliary disorders".
- AESI specified in Section 6.2.2.1.
- AEs with PT as "Hyperhidrosis" or "Dysarthria"

A summary table of treatment emergent adverse events meeting the pre-specified quantitative screening criteria by SOC, HLTs and PTs with incidence (%) for each treatment group, RR, and the associated 95% CI will be generated.

In addition, the following outputs will be generated.

- Summary of treatment emergent adverse events by SOC, HLT and PTs by subgroups (Consistency check between subgroups: Actual Age Category, and Renal Impairment Evaluated by Baseline CrCL)
    - Actual Age Category: <18, 18-64 and >=65
    - Renal Impairment (Baseline Creatinine Clearance): Normal (>=90mL/min), Mid-Impairment (>=60 to 89 mL/min), Moderate Impairment (>= 30 to 59 mL/min), Severe Impairment (< 30mL/min), Missing
- Incidence rate of treatment emergent AEs according to different attributes by HLT and treatment group (Consistency check in AE attribute: AEs related to study treatment, AEs leading to permanent discontinuation of study treatment, AE leading to dose reduction, AE leading to dose interruption /delay, SAEs related to study treatment, Fatal SAEs, and Fatal SAEs related to study treatment)
- Summary of treatment emergent AEs by HLT and Maximum Grade (Consistency check in AE attribute)
- Summary of Cumulative Incidence of Treatment Emergent Adverse Events (HLTs) by Time to First Occurrence (Temporal association). The categories of time to first occurrence are below.
    - <= 2 days, <= 3 days, <= 4 days, <= 5 days, <= 6 days, <= 7 days, <= 8 days, <= 9 days, >= 10 days

4.6.2.5. Impact of GCP violation

This analysis is based on Safety-ALL population. For transparency, the number and percentage of participants experiencing any adverse events will be presented by treatment arm, SOC and PT.

4.6.3. Additional Safety Assessments

4.6.3.1. Laboratory Data

Summaries of worst-case grade increase from baseline grade will be provided for all the lab tests that are gradable by DMID criteria (Section 6.2.4). These summaries will display the number and percentage of subjects with a maximum post-baseline grade increasing from their baseline grade. Any increase in grade from baseline will be summarized along with any increase to a maximum grade of 3 and any increase to a maximum grade of 4. Missing baseline grade will be assumed as grade 0. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia separately. The determination of worst case post-baseline takes into account both planned and unscheduled assessments.

For lab tests that are not gradable by DMID criteria (Section 6.2.4), summaries of worst-case changes from baseline with respect to normal range will be generated. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarized for the worst-case post-baseline. If a subject has a decrease to low and an increase to high during the same time interval, then the subject is counted in both the "Decrease to Low" categories and the "Increase to High" categories.

Separate summary tables for change from baseline in haematology, and chemistry laboratory tests will be produced. Liver function laboratory tests will be included with chemistry lab tests.

A summary of Liver Monitoring/Stopping Event Reporting will be summarized. For participants with more than one liver stopping or liver monitoring event, only data related to the earliest most severe criteria event is included in the summary.

Abnormal liver chemistry results will be summarized by increasing folds above the upper limit of normal (ULN) including tests of interest and thresholds as follows (including data at all the visit including unscheduled visits):

- ALT or AST > 3xULN and Total Bilirubin > 2xULN*
- ALT or AST > 3xULN and ALP < 2xULN and Total Bilirubin ≥ 2xULN
- ALT or AST > 3xULN and Total Bilirubin > 1.5xULN
- Hepatocellular injury: (ALT/ALT ULN)/(ALP/ALP ULN)) >= 5 and ALT >= 3xULN **
- ALT or AST ≥ 20xULN
- ALT or AST ≥ 10xULN
- ALT or AST ≥ 8xULN
- ALT or AST ≥ 5xULN
- ALT or AST ≥ 3xULN
- ALT ≥ 20xULN
- ALT ≥ 10xULN
- ALT ≥ 8xULN
- ALT ≥ 5xULN
- ALT ≥ 3xULN
- AST ≥ 20xULN
- AST ≥ 10xULN
- AST ≥ 8xULN
- AST ≥ 5xULN
- AST ≥ 3xULN

- Total Bilirubin > 2xULN
- Total Bilirubin > 1.5xULN
- Total Bilirubin > 2xULN and a portion of Direct Bilirubin >= 35% on the same day
- Total Bilirubin > 1.5xULN and a portion of Direct Bilirubin >= 35% on the same day

*: The total Bilirubin elevation must occur on or up to 28 days after the ALT elevation

**: sign of hepatocellular injury, ALT and ALP values must occur on the same day.

Urinalysis results will be summarized using descriptive statistics. The severity of renal impairment will be evaluated and summarized according to the method in Section 6.2.2.2.

4.6.3.2. Vital Signs

The number of participants with worst case vital sign results relative to potential clinical importance (PCI) criteria which are post-baseline relative to baseline will be summarised by test and category. The summary will include baseline data and worst case post-baseline, and planned visit. The baseline categories are: Low, within Range and High for PCI criteria. The change categories for PCI criteria are: To Low, To within Range or No Change, To High. The determination of worst case post-baseline takes into account both planned and unscheduled assessments. Changes in value from baseline for each vital sign will be summarized at every assessed time point. All vital sign data will be listed.

4.6.3.3. ECG

The number of participants with worst case QTc values relative to potential clinical importance criteria which are post-baseline relative to baseline will be summarised. The summary will include baseline data and worst case post-baseline, and visits (i.e. On-Therapy and TOC visits). The baseline categories are: Low, within Range and High for PCI criteria. The change categories for PCI criteria are: To Low, To within Range or No Change, To High. The determination of worst case post-baseline takes into account both planned and unscheduled assessments. A summary of change from baseline in ECG values will be produced by visit.

4.7. Other Analyses

4.7.1. Subgroup analyses

The estimands of these subgroup analyses are the same as that provided in the Section 4.3.1.1 (therapeutic response), Section 4.3.2.1 (clinical response) and Section 4.3.3.1 (microbiological response).

These analyses are based on the micro-ITT NTF-S Population. The number and proportion of participants achieving therapeutic, clinical and microbiological success at the TOC Visit will be presented by treatment arm and the following subgroup:

- Age group: < 65 vs ≥ 65 years
- Age category (<=50, >50)
- Acute cystitis recurrence
- Actual stratification combinations as above for age category and acute cystitis recurrence
- Qualifying uropathogen species/group isolated at Baseline (including phenotypic (e.g., ESBL, MDR) and genotypic subcategories), which is defined in Section 6.2.10.
- Number of Qualified Uropathogens at Baseline (only 1 qualifying uropathogen, two qualified uropathogens, one qualified plus additional any number of non-qualified uropathogens, only for therapeutic response). If the number of participants in each subgroup is >=10, the data will be summarized. Otherwise, these will be provided in the dataset.

4.8. Interim Analyses

No formal interim analysis is planned. Blinded review for therapeutic, clinical and microbiological response will be conducted.

4.8.1. Blinded review

This blinded review aims to assess if the blinded results for the response rates are far from the expected. Once approximately 30 participants in micro-ITT NTF-S Population have completed the TOC visit, the blinded review will be done using the data from those participants. If the following criterion has been met, we will consider the response rate may be more variable than planned and the mitigation will be conducted (e.g. training for sites).

$$\Pr(p < 0.6) > 0.5$$

This is based on the Bayesian probability and p is pooled therapeutic success rate among gepotidacin and nitrofurantoin arms. The prior for p is Beta(0.5, 0.5) and this prior will be updated with the number of participants achieving therapeutic success and the number of participants in the blinded review (i.e. approximately 30 participants).

The maximum number of participants achieving therapeutic success to trigger considering the mitigation is provided in the Table 4. For example, if we observe <= 18 participants achieving therapeutic success in 30 participants, we will consider the mitigation.

Table 4 Maximum number of participants achieving therapeutic success

Number of Participants in blinded review	Maximum number of participants achieving therapeutic success
25	15
26	15
27	16
28	16
29	17
30	18
31	18
32	19
33	19
34	20
35	21

4.9. Changes to Protocol Defined Analyses

There were changes below to the originally planned statistical analysis specified in the protocol amendment 2 (Dated: [07-NOV-2022]).

- Added the analysis populations due to GCP violation
- Amended the micro-ITT NTF-S (Global) population to align with the primary analysis population (i.e., IA set) in the global studies (204989 and 212390).
- Originally, missing data in this study was to be imputed for tipping point analysis and multiple imputation sensitivity analysis for missing data. However, a conservative approach will be taken in this study where all missing data (regardless of the reason for missingness) will be imputed as therapeutic failure. Note that the missing data in the global studies (204989 and 212390) will be imputed for tipping point analysis and multiple imputation sensitivity analysis.

5. SAMPLE SIZE DETERMINATION

This study is not designed to demonstrate non-inferiority of the gepotidacin to nitrofurantoin but designed to demonstrate consistency of this study with the global studies for therapeutic response of the gepotidacin.

5.1. Gepotidacin Sample Size

Approximately 81 participants in the gepotidacin treatment group is considered an appropriate sample size to evaluate consistency between this study and both global studies (Studies 204989 and 212390).

Assuming 81 participants in the micro-ITT NTF-S population on gepotidacin and an observed 76% therapeutic success rate out of 884 participants in the global studies, the

therapeutic response in the gepotidacin arm in this study would need to be greater than 69.1% to declare "consistency" with the global studies.

5.1.1. Sample Size Sensitivity

Table 5 demonstrates a range of observed therapeutic response rates and the number of participants on the gepotidacin arm in this study against the corresponding consistency thresholds required in this study assuming 884 participants on the gepotidacin arm in both global studies.

Table 5 Gepotidacin Consistency Thresholds for Different Observed Gepotidacin Therapeutic Response Rate in the Global Studies and the Number of Participants on the Gepotidacin arm in this study

Observed Therapeutic Response Rate in the Global Studies	Number of Participants on the Gepotidacin arm in this study						
	75	77	79	81	83	85	87
45%	37.3%	37.7%	38.0%	37.0%	37.3%	37.6%	37.9%
50%	42.7%	42.9%	43.0%	42.0%	42.2%	42.4%	42.5%
55%	46.7%	46.8%	48.1%	48.1%	48.2%	48.2%	48.3%
60%	52.0%	51.9%	53.2%	53.1%	53.0%	52.9%	52.9%
65%	57.3%	57.1%	58.2%	58.0%	57.8%	57.6%	58.6%
70%	62.7%	63.6%	63.3%	63.0%	62.7%	63.5%	63.2%
75%	68.0%	68.8%	68.4%	67.9%	68.7%	68.2%	69.0%
80%	73.3%	74.0%	73.4%	74.1%	73.5%	74.1%	74.7%

5.1.2. Nitrofurantoin Sample Size

The sample size on the nitrofurantoin arm is based on the precision estimate of 95%CI for the treatment difference.

The treatment difference between gepotidacin and nitrofurantoin will be assessed descriptively. Table 6 demonstrates a range of observed differences and corresponding 95% CIs assuming a 3:1 randomization (i.e. 81 participants on gepotidacin and 27 on nitrofurantoin in micro-ITT NTF-S population).

Table 6 95% Confidence Intervals for Different Observed Therapeutic Response Rates on the Gepotidacin arm across a Range of Differences in Therapeutic Response Rate in Gepotidacin – Nitrofurantoin assuming a 3:1 randomization.

Observed Gepo TRR	Observed difference of TRR in Gepotidacin from that in Nitrofurantoin and corresponding 95% CI (%)				
	10%	5%	0%	-5%	-10%
45%	(-11.0,31.0)	(-16.4,26.4)	(-21.7,21.7)	(-26.8,16.8)	(-31.7,11.7)
50%	(-11.4,31.4)	(-16.7,26.7)	(-21.8,21.8)	(-26.7,16.7)	(-31.4,11.4)
55%	(-11.7,31.7)	(-16.8,26.8)	(-21.7,21.7)	(-26.4,16.4)	(-31.0,11.0)
60%	(-11.7,31.7)	(-16.6,26.6)	(-21.3,21.3)	(-25.9,15.9)	(-30.3,10.3)
65%	(-11.4,31.4)	(-16.2,26.2)	(-20.8,20.8)	(-25.2,15.2)	(-29.4,9.4)
70%	(-11.0,31.0)	(-15.6,25.6)	(-20.0,20.0)	(-24.1,14.1)	(-28.1,8.1)
75%	(-10.3,30.3)	(-14.7,24.7)	(-18.9,18.9)	(-22.8,12.8)	(-26.4,6.4)
80%	(-9.4,29.4)	(-13.5,23.5)	(-17.4,17.4)	(-21.0,11.0)	(-24.3,4.3)

5.1.3. Proposed Sample Size

Assuming a 36% evaluability rate, approximately 300 participants will be enrolled and randomized to either gepotidacin or nitrofurantoin in a 3:1 ratio to achieve 108 participants in the micro-ITT NTF-S population (i.e. approximately 81 participants on gepotidacin and 27 on nitrofurantoin). Enrolment will continue until the approximate target number of participants in the micro-ITT NTF-S Population has been reached. This study will be conducted at multiple sites in Japan.

Note: Enrolled means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

Unless otherwise specified, the study population analyses will be based on the ITT and, micro-ITT NTF-S Population. A summary of the number of participants in each of the participant level analysis set will be provided.

6.1.1. Study Population

A summary of the number of participants included in each population will be displayed based on the Screened Population. In addition, a summary and listing of exclusions from study population will be produced based on the ITT population.

6.1.2. Participant Disposition

A summary of the number and percentage of participants who completed the study as well as those who prematurely withdrew from the study will be provided. Reasons for study withdrawal will be summarized. Reasons for study withdrawal will be listed.

A summary of study intervention status will be provided. This display will show the number and percentage of participants who have completed the study intervention and the ToC visit or have discontinued the study intervention prematurely, as well as primary reasons for discontinuation of study intervention and the ToC visit.

A summary of the number and percentage of participants who passed screening and entered the study, who failed screening and therefore were not entered into the study, and participants who met eligibility criteria but were not needed will be provided along with the reasons for screen failure. The number of participants will be summarized by Country, ~~Site~~ Id and Investigator Id based on micro-ITT NTF-S Population.

6.1.3. Demographic and Baseline Characteristics

The demographic characteristics including age, gender, ethnicity, height/weight, BMI at screening and race will be summarized with descriptive statistics. In addition, the following age categories will be summarized: <18, 18-64 and >=65 based on the ITT and micro-ITT NTF-S populations. The listing of demographic characteristics will be produced as well.

A summary of baseline characteristics will be provided as follows. Data will be listed and summarized using descriptive statistics or frequency counts and percentages as applicable.

Analysis set	Baseline characteristics
ITT Population	• Cardiovascular family history

ITT, and micro-ITT NTF-S Populations	• Actual randomization strata as per IRT system
	  • Age category
	  • Baseline acute cystitis recurrence
	• Age category as per cCRF (<=50 years, >50 years)
	• Baseline acute cystitis recurrence
	• The number of episodes of uncomplicated UTI in the past 3 months, 3-6 months and 6-12 months.
	• Baseline renal impairment category (refer to Section 6.2.2.2 for the details)
	• Baseline quantitative bacterial counts by uropathogen
	• Number of participants with at least one baseline qualifying uropathogen identified by uropathogen.
	• Number of baseline uropathogens identified per participant
	• Number of baseline qualifying uropathogens identified per participant
	• Baseline clinical symptom score

Micro-ITT Population	• Baseline qualifying uropathogens (including phenotypic and genotypic subcategories) • Baseline qualifying uropathogens by species and group (e.g. Klebsiella spp., other Enterobacterales, gram-negative nonfermenters, gram-positive species) The proportion in the above summaries is calculated using the total number of baseline qualifying uropathogens as denominator. Note that for the participants who have the same species of more than one baseline qualifying uropathogens (e.g. 2 *E coli.*), this will be counted multiple times. For example, suppose a participant has 2 identical *E coli.* and another participant has 1 *E coli.* and 1 *Klebsiella spp*. For the proportion of *E coli over both patients* is 0.75 (3/4).

Past medical conditions and current medical conditions as of screening will be summarized respectively based on the ITT Population and micro-ITT NTF-S Population. If the reported medical condition was resolved before screening, this will be regarded as past medical condition. Otherwise, this will be regarded as current medical condition.

Substance use, including smoking history, cigarettes per day, alcohol and caffeine consumption will be summarized based on the ITT Population.

6.1.4. Protocol Deviations

Important protocol deviations will be summarized based on ITT Population.

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations (where possible without knowing the study intervention details) are captured and categorised in the protocol deviations dataset.

- This dataset will be the basis for the summaries of important protocol deviations.

In addition to the overall summary of important protocol deviations, separate summaries will be produced for important protocol deviations related to COVID-19 based on the ITT Population. Listings of important protocol deviations and subjects with inclusion/exclusions criteria deviations will be produced.

6.1.5. Prior and Concomitant Medications

The analysis is based on the ITT and micro-ITT NTF-S Populations.

Prior and concomitant medications will be coded using WHO Drug dictionaries. The summary of concomitant medications will be provided by Anatomical Therapeutic Chemical (ATC) classification Level 1 and ingredient. Note that multi-ingredient medications will be summarized for a combination of ingredients. Listing of prior and concomitant medications will be produced.

Separate summaries of prior and concomitant medications will be provided for systemic antibiotics as well. An antibiotic is considered systemic if the route is oral, subcutaneous, intramuscular, intravenous, or rectal.

6.1.6. Study Intervention Compliance

Refer to Section 4.6.1.

6.1.7. Additional Analyses Due to the COVID-19 Pandemic

A participant is defined as having a suspected, probable or confirmed COVID-19 infection during the study if the answer is “Confirmed”, “Probable” or “Suspected” to the case diagnosis question from the COVID-19 coronavirus infection assessment eCRF. Numbers of participants with a suspected, probable or confirmed COVID-19 infection, and of COVID-19 test results will be summarized based on the Safety Population.

Additionally, if greater than 30 participants have a suspected, probable of confirmed COVID-19 infection, the following data displays will be produced:

- Summary of current (and/or past) medical conditions for participants with COVID-19 adverse events.
- Summary of baseline characteristics for participants with COVID-19 adverse events.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Efficacy

6.2.1.1. Microbiological Outcome and Response

Microbiological response by Baseline Qualifying Uropathogen will be derived at On-therapy, TOC and Follow-up Visits according to Table 7, Table 8 and Table 9. Only start date (not time) of antibiotics use will be considered when deriving the outcome and response.

Participant-level microbiological outcome and response will be derived at On-therapy, TOC and Follow-up Visits according to Table 10.

Microbiological outcome by New Qualifying Uropathogen will be derived at On-therapy Visit according to Table 11, Table 12 and Table 13.

Table 7 Microbiological Outcome by Baseline Qualifying Uropathogen at the On-Therapy Visit

Defining Criteria	Outcome
A quantitative urine culture taken at the On-therapy Visit shows that the qualifying bacterial uropathogen recovered at Baseline is reduced to $<10^3$ CFU/mL, without the participant receiving other systemic antimicrobials before the On-therapy Visit	Microbiological eradication
A quantitative urine culture taken at the On-therapy Visit shows that the qualifying bacterial uropathogen recovered at Baseline grows $\geq 10^3$ CFU/mL, without the participant receiving other systemic antimicrobials before the On-therapy Visit	Microbiological persistence
• The On-therapy urine culture result is missing, or • The participant received other systemic antimicrobials before the Ontherapy Visit	Unable to determine

CFU=colony-forming units.

Table 8 Microbiological Outcome and Response by Baseline Qualifying Uropathogen at the Test of Cure Visit

Defining Criteria	Outcome	Response
Participants considered microbiological failures at the TOC Visit will also be considered microbiological failures at the Follow-up Visit.		
A quantitative urine culture taken at the TOC Visit shows reduction of the qualifying bacterial uropathogen recovered at Baseline to $<10^3$ CFU/mL, without the participant receiving other systemic antimicrobials before the TOC Visit	Microbiological eradication	Microbiological success
A quantitative urine culture taken at the TOC Visit shows that the qualifying bacterial uropathogen recovered at Baseline, and which was also shown to persist or unable to determine at the On-therapy Visit, grows $\geq 10^3$ CFU/mL, without the participant receiving other systemic antimicrobials before the TOC Visit	Microbiological persistence	Microbiological failure

Defining Criteria	Outcome	Response
A quantitative urine culture taken at the TOC Visit shows that the qualifying bacterial uropathogen recovered at Baseline, and which was also shown to be eradicated at the On-therapy Visit, grows ≥103 CFU/mL, without the participant receiving other systemic antimicrobials before the TOC Visit	Microbiological recurrence	Microbiological failure
• The TOC urine culture result is missing, or • The participant received other systemic antimicrobials before the TOC Visit	Unable to determine	Microbiological failure

CFU=colony-forming units; TOC=Test-of-Cure.

Table 9 Microbiological Outcome and Response by Baseline Qualifying Uropathogen at the Follow Up Visit

Defining Criteria	Outcome	Response
Participants considered microbiological failures at the TOC Visit will also be considered microbiological failures at the Follow-up Visit.		
A quantitative urine culture taken at the Follow-up Visit shows reduction of the qualifying bacterial uropathogen recovered at Baseline to $<10^3$ CFU/mL, following microbiological eradication at the TOC Visit, without the participant receiving other systemic antimicrobials before the Follow-up Visit	Sustained microbiological eradication	Microbiological success
A quantitative urine culture taken at the Follow-up Visit shows that the qualifying bacterial uropathogen recovered at Baseline grows $\geq 10^3$ CFU/mL, following microbiological eradication at the TOC Visit, without the participant receiving other systemic antimicrobials before the Follow-up Visit	Microbiological recurrence	Microbiological failure
A quantitative urine culture taken at the Follow-up Visit shows that the qualifying bacterial uropathogen recovered at Baseline grows $\geq 10^3$ CFU/mL, and also did not achieve an outcome of microbiological eradication at the TOC Visit, without the participant receiving other systemic antimicrobials before the Follow-up Visit	Microbiological persistence	Microbiological failure
A quantitative urine culture taken at the Follow-up Visit shows reduction of the qualifying bacterial uropathogen recovered at Baseline to $<10^3$ CFU/mL, and also did not achieve an outcome of microbiological eradication at the TOC Visit, without the participant receiving other systemic antimicrobials before the Follow-up Visit	Delayed microbiological eradication	Microbiological failure
• The Follow-up urine culture result is missing, or • The participant received other systemic antimicrobials before the Follow-up Visit	Unable to determine	Microbiological failure

CFU=colony-forming units; TOC=Test-of-Cure.

Table 10 Participant-Level Microbiological Outcome and Response Definitions per Study Visit

Defining Criteria at the On-Therapy Visit	Outcome	Response
All qualifying baseline uropathogens have a microbiological outcome of eradication at On-therapy	Microbiological eradication	NA
At least one qualifying baseline uropathogen has an outcome of persistence at On-therapy	Microbiological persistence	NA
All qualifying baseline uropathogen outcomes are unable to determine at On-therapy	Unable to determine	NA
Defining Criteria at the TOC Visit	**Outcome**	**Response**
All qualifying baseline uropathogens have a microbiological outcome of eradication at TOC	Microbiological eradication	Microbiological success
At least one qualifying baseline uropathogen has an outcome of persistence at TOC	Microbiological persistence	Microbiological failure
At least one qualifying baseline uropathogen has an outcome of recurrence and none have an outcome of persistence at TOC	Microbiological recurrence	Microbiological failure
All qualifying baseline uropathogen outcomes are unable to determine at TOC	Unable to determine	Microbiological failure
Defining Criteria at the Follow-up Visit	**Outcome**	**Response**
All qualifying baseline uropathogens have a microbiological outcome of sustained eradication at Follow-up	Sustained microbiological eradication	Microbiological success
At least one qualifying baseline uropathogen has an outcome of recurrence and none have an outcome of persistence at Follow-up	Microbiological recurrence	Microbiological failure
At least one qualifying baseline uropathogen has an outcome of persistence at Follow-up	Microbiological persistence	Microbiological failure
At least one qualifying baseline uropathogen has an outcome of delayed eradication and none have an outcome of persistence or recurrence at Follow-up	Delayed microbiological eradication	Microbiological failure
All qualifying baseline uropathogen outcomes are unable to determine at Follow-up	Unable to determine	Microbiological failure

NA=Not applicable; TOC=Test-of-Cure.

Table 11 Microbiological Outcome by New Qualifying Uropathogen at the On Therapy Visit

Defining Criteria	Outcome
A new qualifying bacterial uropathogen, not identified at Baseline, is documented by quantitative urine culture at the On-therapy Visit	New uropathogen

Table 12 Microbiological Outcome by New Qualifying Uropathogen at the Test-of-Cure Visit

Defining Criteria	Outcome
A new qualifying bacterial uropathogen, not identified at Baseline, is documented by quantitative urine culture at the Test-of-Cure Visit in a participant who did not achieve a clinical outcome of clinical resolution at the Test-of-Cure Visit	New infection
A new qualifying bacterial uropathogen, not identified at Baseline, is documented by quantitative urine culture at the Test-of-Cure Visit in a participant who did achieve a clinical outcome of clinical resolution at the Test-of-Cure Visit	Colonization

Table 13 Microbiological Outcome by New Qualifying Uropathogen at the Follow up Visit

Defining Criteria	Outcome
A new qualifying bacterial uropathogen, not identified at Baseline, is documented by quantitative urine culture at the Follow-up Visit in a participant who did not achieve a clinical resolution at the Follow-up Visit	New infection
A new qualifying bacterial uropathogen, not identified at Baseline, is documented by quantitative urine culture at the Follow-up Visit in a participant who did achieve a clinical resolution at the Follow-up Visit	Colonization

6.2.1.2. Clinical Outcome and Response

Clinical signs and symptoms of acute cystitis will be recorded based on participant interview per the SoA (Protocol Section 1.3) using the scoring system and instructions (Table 14). The total cumulative symptom score is derived by summing the score for each individual sign and symptom. If any individual sign and symptom scores are missing, then total symptom score will also be missing.

At TOC, success is defined as normal presentation of signs and symptoms with a total cumulative symptom score of zero. Clinical outcome and response will be derived at On-therapy (Table 15), TOC (Table 16) and Follow-up (Table 17) Visits. Note that "resolution", "improvement" and "worsening or no change" in total symptom score as used in the tables below are defined as:

- "Resolution": Total cumulative symptom score is zero.
- "Improvement": Change from baseline in total cumulative symptom score is less than zero.
- "Worsening or no change": Change from baseline in total cumulative symptom score is greater than or equal to zero.

Note that only start date of antibiotics use will be considered when deriving the outcome and response.

Table 14 Clinical Signs and Symptoms Scoring System

Clinical Signs and Symptoms	None	Mild Symptom is easily tolerated, causing minimal discomfort and not interfering with everyday activities	Moderate Symptom is sufficiently discomforting to interfere with normal everyday activities	Severe Symptom prevents normal everyday activities
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
Dysuria				
Frequency				
Urgency				
Lower abdominal or suprapubic pain				

Table 15 Clinical Outcome at the On-Therapy Visit

Defining Criteria	Outcome[a]
Resolution of signs and symptoms of acute cystitis present at Baseline (and no new signs and symptoms), without the participant receiving other systemic antimicrobials not for the current infection before the On-therapy Visit and also without receiving an other systemic antimicrobials for the current infection prior to or at the On-therapy Visit.	Clinical resolution
Improvement in total symptom scores from Baseline, but not complete resolution, without the participant receiving other systemic antimicrobials (not for the current infection) before the On-therapy Visit and also without receiving an other systemic antimicrobials for the current infection prior to or at the On-therapy Visit.	Clinical improvement
Worsening or no change in total symptom scores from Baseline or the participant received other systemic antimicrobials for the current infection prior to or on the date of the On-therapy Visit (if the date of On-therapy Visit is missing, the end date of the analysis window will be used as the date of On-therapy visit)	Clinical worsening
• The Baseline score is missing (unless On-therapy score is 0 and no antibiotics use (either not for current infection or for current infection) then outcome will be clinical resolution OR unless Clinical Worsening outcome criteria were met then outcome will be Clinical worsening), or • The On-therapy assessment is missing, (unless clinical worsening outcome criteria were met then outcome is worsening) or • The participant received other systemic antimicrobials not for the current infection prior to	Unable to determine

Defining Criteria	Outcome[a]
the assessment (unless clinical worsening outcome criteria were met)	

a. A study physician or otherwise appropriately medically trained staff will determine the individual clinical signs and symptoms scores for acute cystitis (Table 14), which will then be used to programmatically determine the clinical outcome. The same scorer will be used at all assessment time points for each participant, on all occasions, whenever possible.

The text with underline is additional clarification to derive the clinical outcome in addition to the protocol table.

Table 16 Clinical Outcome and Response at the Test-of-Cure Visit

Defining Criteria	Outcome[a]	Response
Resolution of signs and symptoms of acute cystitis present at Baseline (and no new signs or symptoms), without the participant receiving other systemic antimicrobials not for the current infection before the TOC Visit and also without receiving an other systemic antimicrobials for the current infection prior to or at the TOC Visit	Clinical resolution	Clinical success
Improvement in total symptom scores from Baseline, but not complete resolution, without the participant receiving other systemic antimicrobials not for the current infection before the TOC Visit and also without receiving an other systemic antimicrobials for the current infection prior to or at the TOC Visit	Clinical improvement	Clinical failure
Worsening or no change in total symptom scores from Baseline or the participant received other systemic antimicrobials for the current infection before or on the date of the TOC Visit (if the date of TOC Visit is missing, the end date of the analysis window will be used as the date of TOC visit)	Clinical worsening	Clinical failure
• The Baseline score is missing (unless TOC score is 0 and no antibiotics use (either not for current infection or for current infection) then outcome will be clinical resolution OR unless Clinical worsening outcome criteria were met then outcome will be Clinical worsening), or • The TOC assessment is missing (unless clinical worsening outcome criteria were met then outcome is worsening), or • The participant received other systemic antimicrobials not for the current infection prior to the assessment (unless clinical worsening criteria were met)	Unable to determine	Clinical failure

TOC = Test-of-Cure

a. A study physician or otherwise appropriately medically trained staff will determine the individual clinical signs and symptoms scores for acute cystitis (Table 14), which will then be used to programmatically determine the clinical outcome. The same scorer will be used at all assessment time points for each participant, on all occasions, whenever possible.

The text with underline is additional clarification to derive the clinical outcome and response in addition to the protocol table.

Table 17 Clinical Outcome and Response at the Follow-up Visit

Defining Criteria	Outcome[a]	Response
Resolution of signs and symptoms of acute cystitis demonstrated at the TOC Visit persist at the Follow-up Visit (and no new signs and symptoms), without the participant receiving other systemic antimicrobials not for the current infection before the Follow-up Visit and also without receiving an other systemic antimicrobials for the current infection prior to or at the Follow Up Visit	Sustained clinical resolution	Clinical success
Resolution of signs and symptoms of acute cystitis present at Baseline (and no new signs or symptoms), after clinical failure at TOC, without the participant receiving other systemic antimicrobials not for the current infection before the Follow-up Visit and also without receiving an other systemic antimicrobials for the current infection prior to or at the Follow-Up Visit	Delayed clinical resolution	Clinical failure
Improvement in total symptom scores from Baseline, but not complete resolution after clinical failure at the TOC visit, without the participant receiving other systemic antimicrobials not for the current infection before the Follow-up Visit and also without receiving an other systemic antimicrobials for the current infection prior to or at the Follow-Up Visit	Clinical improvement	Clinical failure
Worsening or no change in total symptom scores at Follow-up compared to Baseline after clinical failure at TOC, or the participant received other systemic antimicrobials for the current infection before or on the date of the Follow-up Visit (if the date of Follow-Up Visit is missing, the end date of the analysis window will be used as the date of Follow-Up visit)	Clinical worsening	Clinical failure
Signs and symptoms of acute cystitis reoccur at the Follow-up Visit (can be improved (but not resolution) OR worsening or no change from baseline i.e., (1) change from baseline at Follow-Up visit < 0 AND score is not 0 at Follow-Up Visit (2) change from baseline at the Follow-Up visit >= 0) after clinical success at TOC without the participant receiving an other systemic antimicrobials for the current infection prior to or at the Follow-Up visit	Clinical recurrence	Clinical failure
1) The Baseline score is missing (unless Follow-Up score is 0 and no antibiotics use (either not for current infection or for current infection) then outcome will be clinical resolution (delayed or sustained as appropriate) OR unless Clinical worsening outcome criteria were met then outcome will be clinical worsening), or 2) The Follow-up assessment is missing (unless clinical worsening outcome criteria were met then outcome is clinical worsening), or	Unable to determine	Clinical failure

Defining Criteria	Outcome[a]	Response
3) The participant received other systemic antimicrobials not for the current infection prior to the assessment (unless the clinical worsening or recurrence outcome criteria were met)		

TOC = Test-of-Cure

a. A study physician or otherwise appropriately medically trained staff will determine the individual clinical signs and symptoms scores for acute cystitis (Table 14), which will then be used to programmatically determine the clinical outcome. The same scorer will be used at all assessment time points for each participant, on all occasions, whenever possible.

The text with underline is additional clarification to derive the clinical outcome in addition to the protocol table.

6.2.1.3. Fold change on susceptibility

Fold change will be used to describe how much the MIC for gepotidacin and nitrofurantoin changes between baseline and subsequent visits for the same bacterial species from the same participant based on the broth microdilution results. Fold change will be calculated (in doubling dilutions) as the ratio of the MIC at the subsequent visit to the MIC at Baseline Visit. However, ratio of 1 will be reported as 0-fold ratio. Ratio less than 1 will be reported in reciprocal with negative sign (e.g. ratio of 0.5 will be reported as -2 fold). Examples:

Baseline MIC (mcg/mL)	Post-baseline MIC (mcg/mL)	Fold-change
1	1	0-fold
1	2	2-fold
1	4	4-fold
1	8	8-fold
1	16	16-fold
1	0.5	- 2-fold
1	0.25	- 4-fold
1	>32	>/=64-fold
1	>/=32	>/=32-fold
1	<0.125	>/= - 16-fold
1	</=0.125	>/= - 8-fold

6.2.1.4. MIC50 and MIC90

MIC50 and MIC90 are defined as the 50th and 90th percentile of the MIC values. They will only be reported if the number of uropathogens is larger or equal to 10. MICxx is defined as follows.

$$MICxx = \min_j \{x_j; \hat{F}(x_j) \geq xx\%\}$$

$$, where\ x_j\ is\ MIC\ value\ and\ \hat{F}(\cdot)\ is\ empirical\ cumulative\ distribution.$$

For an even number of samples, the MIC50 is the next one above the median. Similar algorithm applied to MIC90.

6.2.1.5. Investigator-Assessed Clinical Response

Definitions	Clinical Response
Sufficient resolution of acute cystitis signs and symptoms such that no additional systemic antimicrobial therapy is required for the current infection	Clinical Success
Participant met any one of the criteria below: • No apparent response to treatment (persistence or progression of any pretreatment clinical signs and symptoms) • Use of additional systemic antibiotic(s) for the current infection • Death related to acute cystitis prior to the visit	Clinical Failure
Determination of clinical response could not be made at the visit for any of the following reasons: • Participant was lost to follow-up and/or the clinical assessment was not undertaken • Use of confounding systemic antibiotic(s) for another infection • Death prior to the visit where acute cystitis was clearly noncontributory	Indeterminate

Missing data will be handled based on the table below.

Scenario	Date of data at EW (early withdrawal) Visit	Response at EW visit	Reason for response at EW visit	Start date of Antibiotics use for uUTI	Derivation of data
Missing at TOC	Date < 17 days + baseline	Clinical Failure OR Indeterminate	"Death" is contained	NA	Same as data at EW visit
Missing at TOC	Any date	Clinical Failure	"Use of additional systemic antibiotic(s) for the current infection"	Baseline <= date <= 17 days + baseline	Same as data at EW visit
Missing at Follow-Up	Date < 31 days + baseline	Clinical Failure OR Indeterminate	"Death" is contained	NA	Same as data at EW visit
Missing at Follow-Up	Any date	Clinical Failure	"Use of additional systemic antibiotic(s) for the current infection"	Baseline <= date <= 31 days + baseline	Same as data at EW visit
Any other missing other than the above					Response: Indeterminate/missing Reason: Participant was lost to follow-up and/or the clinical assessment was not undertaken/missing

CCI

6.2.2. Safety

6.2.2.1. Adverse Events of Special Interest

Cardiovascular (CV) AEs, gastrointestinal (GI) AEs, C. difficile AEs, and AEs related to Acetylcholinesterase Inhibition (AChE-I) as determined by algorithm will be considered AESIs.

Clostridium difficile AESIs

AEs will be regarded as C. difficile AESIs if the preferred terms are either *Clostridium difficile* infection or *Clostridium difficile* colitis.

Cardiovascular and Gastrointestinal AESIs

Gastrointestinal AESIs are defined as AEs with a "Gastrointestinal disorders" SOC. AEs will be regarded as Cardiovascular AESIs if the preferred terms are any one of the following PTs below. **Term**	**Code**	**Term**	**Code**
Degenerative aortic valve disease	10075846	Tachycardia	10043071
Supraventricular extrasystoles	10042602	Ventricular tachyarrhythmia	10065341
Rebound tachycardia	10067207	Torsade de pointes	10044066
Cardio-respiratory arrest neonatal	10007618	Fascicular block	10086740
Cardiac flutter	10052840	Lown-Ganong-Levine syndrome	10024984
Paroxysmal arrhythmia	10050106	Conduction disorder	10010276
Cardiac death	10049993	Congenital supraventricular tachycardia	10082343
Atrial conduction time prolongation	10064191	Pacemaker generated arrhythmia	10053486
Neonatal bradyarrhythmia	10082054	Wolff-Parkinson-White syndrome	10048015
Bradycardia foetal	10006094	Long QT syndrome	10024803
Neonatal sinus bradycardia	10082188	Parasystole	10033929
Sinus bradycardia	10040741	Cardiac arrest neonatal	10007516
Marshall-White syndrome	10088084	Foetal tachyarrhythmia	10077575
Junctional ectopic tachycardia	10074640	Neonatal sinus tachycardia	10082191
Ventricular fibrillation	10047290	Congenital tricuspid valve stenosis	10010656
Ventricular parasystole	10058184	Parachute mitral valve	10064192
Pulseless electrical activity	10058151	Stroke in evolution	10059613
Accessory cardiac pathway	10067618	Subarachnoid haemorrhage	10042316
Sinoatrial block	10040736	Ischaemic cerebral infarction	10060840
Paroxysmal atrioventricular block	10077503	Spinal subdural haematoma	10050164
Ogden syndrome	10082376	Thrombotic stroke	10043647
Familial atrial fibrillation	10088317	Pituitary infarction	10035092
Nodal rhythm	10029470	Cerebral haemorrhage neonatal	10008112
Bundle branch block left	10006580	Cerebral haemorrhage	10008111
Precerebral artery embolism	10085250	Claude's syndrome	10085447
Cerebral septic infarct	10070671	Vertebrobasilar stroke	10082484
Cerebellar ischaemia	10068621	Intraoperative cerebral artery occlusion	10056382
Pseudostroke	10078090	Cerebral gas embolism	10070813
Basal ganglia stroke	10071043	Brain stem thrombosis	10062573
Lacunar infarction	10051078	Basal ganglia haemorrhage	10067057
Ruptured cerebral aneurysm	10039330	Vertebral artery perforation	10075735
Malignant middle cerebral artery syndrome	10086546	Carotid artery perforation	10075728
Cerebral artery perforation	10075734	Ischaemic stroke	10061256

Gastrointestinal AESIs are defined as AEs with a "Gastrointestinal disorders" SOC. AEs will be regarded as Cardiovascular AESIs if the preferred terms are any one of the following PTs below. **Term**	**Code**	**Term**	**Code**
Spinal cord haemorrhage	10048992	Cerebral arteriovenous malformation haemorrhagic	10008086
Subarachnoid haematoma	10076701	Cerebrovascular disorder	10008196
Mitral valve disease	10061532	Myxomatous mitral valve degeneration	10077377
Pulmonary oil microembolism	10069388	Mitral valve stenosis	10027733
Heritable pulmonary arterial hypertension	10085244	Pulmonary tumour thrombotic microangiopathy	10079988
Cor pulmonale acute	10010969	Pulmonary venous thrombosis	10037459
Neonatal pulmonary hypertension	10088909	Cement embolism	10050484
Pulmonary hypertensive crisis	10068726	Pulmonary veno-occlusive disease	10037458
Pulmonary valve incompetence	10037448	Newborn persistent pulmonary hypertension	10053592
Transient aphasia	10080106	Pulmonary valve thickening	10079337
Subclavian steal syndrome	10042335	Capsular warning syndrome	10067744
Tricuspid valve thrombosis	10088062	Tricuspid valve incompetence	10044640
Tricuspid valve disease mixed	10086096	Transmyocardial revascularisation	10059211
Heart valve stenosis	10061996	Deep vein thrombosis postoperative	10066881
Peripheral revascularisation	10053351	Carotid revascularisation	10072559
Respiratory sinus arrhythmia magnitude increased	10079115	Progressive encephalopathy, hypsarrhythmia and optic atrophy syndrome	10086607
Renal artery revascularisation	10087816	Unicuspid aortic valve	10081548
Acute myocardial infarction	10000891	Aortic valve atresia	10066801
Aortic valve disease	10061589	Arrhythmia supraventricular	10003130
Congenital aortic valve incompetence	10010370	Reperfusion arrhythmia	10058156
Supravalvular aortic stenosis	10042598	Heart alternation	10058155
Arrhythmia neonatal	10003124	Timothy syndrome	10079205
Central bradycardia	10078310	Foetal heart rate disorder	10061158
Sinus arrest	10040738	Atrial parasystole	10071666
Cardiac fibrillation	10061592	Atrial tachycardia	10003668
Trifascicular block	10044644	Bifascicular block	10057393
Accelerated idioventricular rhythm	10049003	Sudden cardiac death	10049418
Ventricular tachycardia	10047302	Atrioventricular block complete	10003673
Bundle branch block right	10006582	Sinus node dysfunction	10075889
Bundle branch block bilateral	10006579	Sudden death	10042434
Bezold-Jarisch reflex	10076999	Cardio-respiratory arrest	10007617
Chronotropic incompetence	10068627	Neonatal tachyarrhythmia	10082055

Gastrointestinal AESIs are defined as AEs with a "Gastrointestinal disorders" SOC. AEs will be regarded as Cardiovascular AESIs if the preferred terms are any one of the following PTs below. **Term**	**Code**	**Term**	**Code**
Baseline foetal heart rate variability disorder	10074638	Bradycardia	10006093
Inherited cardiac conduction disorder	10070294	Congenital heart valve incompetence	10077594
Ventricular flutter	10047294	Mitral valve atresia	10066800
Straddling tricuspid valve	10083223	Congenital tricuspid valve incompetence	10067887
Extraischaemic cerebral haematoma	10080347	Congenital heart valve disorder	10064086
Central nervous system haemorrhage	10072043	Congenital tricuspid valve atresia	10049767
Vertebral artery thrombosis	10057777	Cerebral microembolism	10078311
Vertebral artery occlusion	10048965	Carotid aneurysm rupture	10051328
Pituitary haemorrhage	10049760	Cerebral artery occlusion	10008089
Thalamic infarction	10064961	Cerebellar infarction	10008034
Cerebellar artery occlusion	10053633	Cerebral microinfarction	10083668
Reversible ischaemic neurological deficit	10050496	Post stroke depression	10070606
Cerebral infarction foetal	10008119	Precerebral artery thrombosis	10074717
Brain stem haemorrhage	10006145	Brain stem infarction	10006147
Medullary compression syndrome	10087065	Basal ganglia haematoma	10077031
Lacunar stroke	10076994	Mitral valve incompetence	10027727
Embolic cerebellar infarction	10084072	Pulmonary thrombosis	10037437
Cerebral artery embolism	10008088	Pulmonary microemboli	10037421
Embolism arterial	10014513	Hoigne's syndrome	10059393
Mitral valve calcification	10050558	Post procedural pulmonary embolism	10063909
Systolic anterior motion of mitral valve	10076976	Cor pulmonale	10010968
Pulmonary embolism	10037377	Pulmonary arterial hypertension	10064911
Embolic pneumonia	10065680	Pulmonary artery wall hypertrophy	10063561
Cor pulmonale chronic	10010970	Right ventricular hypertension	10074301
Lambl's excrescences	10083691	Tricuspid valve disease	10061389
Arrhythmia prophylaxis	10051305	Cardiac valve rupture	10068165
ECG signs of myocardial infarction	10075299	Heart valve calcification	10058968
Bicuspid aortic valve	10004552	Cardiac valve discolouration	10079467
Arrhythmia	10003119	Cardiac valve vegetation	10057651
Atrioventricular node dysfunction	10084085	Cerebral revascularisation	10071508
Ventricular pre-excitation	10049761	Aortic valve stenosis	10002918
Supraventricular tachyarrhythmia	10065342	Tachyarrhythmia	10049447
Cardiac arrest	10007515	Sinus arrhythmia	10040739
Atrioventricular node dispersion	10077893	Atrioventricular conduction time shortened	10068180
Holiday heart syndrome	10083709	Postural orthostatic tachycardia syndrome	10063080
Anomalous atrioventricular excitation	10002611	Supraventricular tachycardia	10042604

Gastrointestinal AESIs are defined as AEs with a "Gastrointestinal disorders" SOC. AEs will be regarded as Cardiovascular AESIs if the preferred terms are any one of the following PTs below. **Term**	**Code**	**Term**	**Code**
Bundle branch block	10006578	Sinusoidal foetal heart rate pattern	10074643
Adams-Stokes syndrome	10001115	Bradyarrhythmia	10049765
Atrioventricular dissociation	10069571	Withdrawal arrhythmia	10047997
Atrial escape rhythm	10085756	Tachycardia paroxysmal	10043079
Atrial flutter	10003662	Wandering pacemaker	10047818
Cardiac failure congestive	10007559	Sinus tachycardia	10040752
Bicuspid pulmonary valve	10063730	Arrhythmic storm	10067339
Weber's syndrome	10085448	Ictal bradycardia syndrome	10088979
Cerebral haemorrhage foetal	10050157	Foetal heart rate acceleration abnormality	10074642
Spinal epidural haematoma	10050162	Pacemaker syndrome	10051994
Basal ganglia infarction	10069020	Atrial standstill	10087237
Cerebellar embolism	10067167	Congenital pulmonary valve disorder	10061075
Spinal subarachnoid haemorrhage	10073564	Congenital pulmonary valve atresia	10052644
Septic cerebral embolism	10086435	Congenital mitral valve stenosis	10010548
Intracranial tumour haemorrhage	10022775	Thalamic stroke	10087626
Post procedural stroke	10066591	Basilar artery perforation	10075736
Embolic cerebral infarction	10060839	Brain stem embolism	10074422
Meningorrhagia	10052593	Lateral medullary syndrome	10024033
Intraventricular haemorrhage neonatal	10022841	Occipital lobe stroke	10089110
Cerebellar haemorrhage	10008030	Intracranial haemorrhage neonatal	10086946
Internal capsule infarction	10083408	Pseudo-occlusion of internal carotid artery	10085779
Pituitary apoplexy	10056447	Cerebral vascular occlusion	10076895
Cerebellar artery thrombosis	10008023	Perinatal stroke	10073945
Brain stem stroke	10068644	Cerebral artery thrombosis	10008092
Mitral valve thickening	10079336	Periventricular haemorrhage neonatal	10076706
Ischaemic mitral regurgitation	10077864	Spinal epidural haemorrhage	10049236
Mitral perforation	10068138	Middle cerebral artery stroke	10027580
Portopulmonary hypertension	10067281	Intraventricular haemorrhage	10022840
Right-to-left cardiac shunt	10076605	Haemorrhagic cerebral infarction	10019005
Congenital pulmonary hypertension	10050701	Cerebral infarction	10008118
Pulmonary valve calcification	10057464	Thrombotic cerebral infarction	10067347
Pulmonary valve disease	10061541	Basilar artery thrombosis	10063093
Pulmonary valve sclerosis	10057465	Myocardial infarction	10028596
Pulmonary valve stenosis	10037450	Septic pulmonary embolism	10083093
Tricuspid valve prolapse	10066862	Alveolar capillary dysplasia	10077023
Prosthetic cardiac valve thrombosis	10063176	Coronary sinus dilatation	10082615
Heart valve incompetence	10067660	Pulmonary venous hypertension	10085364

Gastrointestinal AESIs are defined as AEs with a “Gastrointestinal disorders” SOC. AEs will be regarded as Cardiovascular AESIs if the preferred terms are any one of the following PTs below. **Term**	**Code**	**Term**	**Code**
Cardiac valve disease	10061406	Amaurosis fugax	10001903
Prosthetic cardiac valve regurgitation	10087802	Tricuspid valve sclerosis	10057467
Cardiac valve fatty infiltration	10087637	Tricuspid valve thickening	10079338
Deep vein thrombosis	10051055	Cardiac valve thickening	10079587
Periprocedural myocardial infarction	10079319	Silent myocardial infarction	10049768
Cerebrovascular pseudoaneurysm	10084087	Coronary revascularisation	10049887
Revascularisation procedure	10084091	Foetal cerebrovascular disorder	10053601
Angina unstable	10002388	Aortic annulus rupture	10079586
Aortic valve prolapse	10057454	Subvalvular aortic stenosis	10042431
Aortic valve thickening	10075851	Heart block congenital	10019263
Aortic valve sclerosis	10002917	Extrasystoles	10015856
Williams syndrome	10049644	Atrioventricular block second degree	10003677
Ventricular extrasystoles	10047289	Brugada syndrome	10059027
Ectopic atrial rhythm	10088339	Wolff-Parkinson-White syndrome congenital	10049291
Lenegre's disease	10071710	BRASH syndrome	10084073
Nodal arrhythmia	10029458	Ventricular arrhythmia	10047281
Foetal cardiac arrest	10084280	Early repolarisation syndrome	10086230
Rhythm idioventricular	10039111	Foetal heart rate deceleration abnormality	10074636
Atrioventricular block	10003671	Long QT syndrome congenital	10057926
Nonreassuring foetal heart rate pattern	10074641	Agonal rhythm	10054015
Ventricular asystole	10047284	Chronic atrial and intestinal dysrhythmia syndrome	10086078
Defect conduction intraventricular	10012118	Frederick's syndrome	10082089
Tachycardia foetal	10043074	Bradycardia neonatal	10056471
Atrial fibrillation	10003658	Shone complex	10066802
Foetal arrhythmia	10016847	Pulmonary valve stenosis congenital	10037451
Atrioventricular block first degree	10003674	Ebstein's anomaly	10014075
Neonatal tachycardia	10049775	Carotid artery occlusion	10048964
Mitral valve dysplasia	10089005	Cerebellar haematoma	10061038
Congenital mitral valve incompetence	10010547	Spinal cord infarction	10058571
Carotid blowout syndrome	10088005	Migrainous infarction	10056237
Brain stem haematoma	10073230	Cerebral haematoma	10053942
Spinal stroke	10082031	Haemorrhage intracranial	10018985
Putamen haemorrhage	10058940	Embolic stroke	10014498
Carotid artery thrombosis	10007688	Parietal lobe stroke	10089109
Spinal subdural haemorrhage	10073563	Spinal cord haematoma	10076051

Gastrointestinal AESIs are defined as AEs with a "Gastrointestinal disorders" SOC. AEs will be regarded as Cardiovascular AESIs if the preferred terms are any one of the following PTs below. **Term**	**Code**	**Term**	**Code**
Basilar artery occlusion	10048963	Haemorrhagic transformation stroke	10055677
Cerebellar stroke	10079062	Precerebral artery occlusion	10036511
Inner ear infarction	10070754	Brain stem ischaemia	10006148
Cerebral ischaemia	10008120	Cerebral aneurysm perforation	10075394
Benedikt's syndrome	10085451	Thalamus haemorrhage	10058939
Intracranial haematoma	10059491	Carotid arterial embolus	10007684
Haemorrhagic stroke	10019016	Subdural haemorrhage neonatal	10042365
Cerebral thrombosis	10008132	Subarachnoid haemorrhage neonatal	10042317
Mitral valve disease mixed	10027724	Haemorrhagic cerebellar infarction	10085944
Degenerative mitral valve disease	10075847	Cerebrovascular accident	10008190
Metastatic pulmonary embolism	10069909	Mitral valve sclerosis	10051538
Carcinoid heart disease	10069010	Mitral face	10073380
Cardiac valve replacement complication	10053748	Mitral valve prolapse	10027730
Degenerative multivalvular disease	10081779	Obstetrical pulmonary embolism	10029925
Cardiac valve sclerosis	10061082	Anaphylactoid syndrome of pregnancy	10067010
Cardiac valve abscess	10064267	Pulmonary artery thrombosis	10037340
Respiratory sinus arrhythmia magnitude	10079114	Pulmonary hypertension	10037400
Respiratory sinus arrhythmia magnitude abnormal	10079117	Transient ischaemic attack	10044390
Congenital aortic valve stenosis	10010371	Tricuspid valve stenosis	10044642
Aortic valve calcification	10050559	Degenerative tricuspid valve disease	10078909
Aortic valve incompetence	10002915	Tricuspid valve calcification	10057466
Heyde's syndrome	10049251	Post procedural myocardial infarction	10066592
Aortic valve disease mixed	10002912	Respiratory sinus arrhythmia magnitude decreased	10079116
-	-	Arterial revascularisation	10084482

Acetylcholinesterase Inhibition AESIs

AEs will be regarded as Acetylcholinesterase Inhibition AESIs if the preferred terms are any one of the following PTs below.

Term	**Code**	**Term**	**Code**
Atrioventricular block first degree	10003674	Convulsions local	10010920
Atonic seizures	10003628	Diarrhoea	10012735
Bradycardia foetal	10006094	Status epilepticus	10041962
Diarrhoea haemorrhagic	10012741	Laryngeal dyspnoea	10052390
Dysarthria	10013887	Prophylaxis against bronchospasm	10054927

Term	Code	Term	Code
Dyspnoea paroxysmal nocturnal	10013974	Post procedural diarrhoea	10057585
Retching	10038776	Procedural vomiting	10066963
Simple partial seizures	10040703	Idiopathic generalised epilepsy	10071081
Sinus bradycardia	10040741	Bradycardia	10006093
Vomiting projectile	10047708	Convulsive threshold lowered	10010927
Self-induced vomiting	10048636	Diarrhoea infectious neonatal	10012744
Hypoglycaemic seizure	10048803	Dyspnoea at rest	10013969
Lennox-Gastaut syndrome	10048816	Frequent bowel movements	10017367
Nocturnal dyspnoea	10049235	Haematemesis	10018830
Atypical benign partial epilepsy	10056699	Nausea	10028813
Hyponatraemic seizure	10073183	Tonic convulsion	10043994
Infantile vomiting	10075315	Frontal lobe epilepsy	10049424
Neonatal sinus bradycardia	10082188	Tonic clonic movements	10051171
Abdominal discomfort	10000059	Clonic convulsion	10053398
Defaecation urgency	10012110	Lafora's myoclonic epilepsy	10054030
Drooling	10013642	Psychogenic seizure	10058895
Epilepsy	10015037	Partial seizures	10061334
Flatulence	10016766	Seizure like phenomena	10071048
Heart rate decreased	10019301	Change in seizure presentation	10075606
Hyperkinesia	10020651	Idiopathic partial epilepsy	10076552
Petit mal epilepsy	10034759	Post stroke seizure	10076981
Psychomotor hyperactivity	10037211	Abdominal pain lower	10000084
Vomiting	10047700	Cold sweat	10009866
Myoclonic epilepsy	10054859	Diarrhoea infectious	10012742
Partial seizures with secondary generalisation	10056209	Dyspnoea exertional	10013971
Alcoholic seizure	10056347	Febrile convulsion	10016284
Therapeutic emesis	10058324	Generalised tonic-clonic seizure	10018100
Faecal vomiting	10064670	Night sweats	10029410
Psychogenic pseudosyncope	10075190	Presyncope	10036653
Central bradycardia	10078310	Sweat gland disorder	10042653
Gastrointestinal disorder	10017944	Bradyarrhythmia	10049765
Hyperemesis gravidarum	10020614	Convulsion in childhood	10052391
Lacrimation decreased	10023642	Prophylaxis of nausea and vomiting	10054133
Vomiting psychogenic	10047709	Increased bronchial secretion	10062530
Wheezing	10047924	Transfusion-associated dyspnoea	10072266
Viral diarrhoea	10051511	Hypocalcaemic seizure	10072456
Epigastric discomfort	10053155	Abdominal pain	10000081
Antidiarrhoeal supportive care	10055660	Abdominal pain upper	10000087
Bronchial hyperreactivity	10066091	Bronchospasm	10006482
Gastrointestinal tract irritation	10070840	Gastrointestinal pain	10017999

Term	Code	Term	Code
Focal dyscognitive seizures	10079424	Hyperhidrosis	10020642
Febrile infection-related epilepsy syndrome	10079438	Salivary hypersecretion	10039424
Neonatal epileptic seizure	10082068	Seizure	10039906
Gelastic seizure	10082918	Sweating fever	10042666
Abdominal tenderness	10000097	Syncope	10042772
Drug withdrawal convulsions	10013752	Bradycardia neonatal	10056471
Dyspnoea	10013968	Acetonaemic vomiting	10058938
Lacrimation increased	10023644	Abdominal symptom	10060926
Seizure anoxic	10039907	Cyclic vomiting syndrome	10062937
Autonomic seizure	10049612	Prophylaxis against diarrhoea	10064065
Benign familial neonatal convulsions	10067866	Post-tussive vomiting	10066220
Hyperglycaemic seizure	10071394	Procedural nausea	10066962
Unilateral bronchospasm	10072338	Seizure cluster	10071350
Faeces soft	10074859	Migraine-triggered seizure	10076676
Irregular breathing	10076213	Acute encephalitis with refractory, repetitive partial seizures	10076948
Asthma	10003553	Discoloured vomit	10079120
Bacterial diarrhoea	10004016	Epilepsy with myoclonic-atonic seizures	10081179
Bronchospasm paradoxical	10006486	Seizure prophylaxis	10081601
-	-	Neonatal seizure	10082067

6.2.2.2. Renal impairment

The severity of renal impairment will be evaluated using estimated by creatinine clearance (Ccr).

Severity of renal impairment will be categorized based on creatinine clearance as below (rounded to the nearest integer):

- Normal ($\geq 90\ mL/min$)
- Mild ($\geq 60\ to\ 89\ mL/min$)
- Moderate ($\geq 30\ to\ 59\ mL/min$)
- Severe ($< 30\ mL/min$)

6.2.3. Criteria for Potential Clinical Importance

6.2.3.1. ECG

ECG Parameter	Units	Potential Clinically Important Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec	N/A	>450
Absolute PR Interval	msec	< 110	> 220
Absolute QRS Interval	msec	< 75	> 110

6.2.3.2. Vital Signs

Vital Sign Parameter (Absolute)	Units	Potentially Clinically Important Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	< 85	> 160
Diastolic Blood Pressure	mmHg	< 45	> 100
Pulse Rate	bpm	< 40	> 110

6.2.4. Division of Microbiology and Infectious Diseases Adult Toxicity Tables for Adverse Event Assessment

6.2.4.1. Laboratory Values

For grading, only numerical criteria will be used in the derivation rules as follows.

Adults:

For adults, laboratory abnormalities will be graded according to the modified US National institute of Allergy and Infectious Diseases Division of Microbiology and Infectious Diseases (DMID) criteria, which is aligned with the global studies (204989 and 212390). Laboratory results are converted to SI units.

HEMATOLOGY						
	Laboratory parameter	**Display label**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin	Hemoglobin	Hemoglobin (Low)	9.5 to 10.5 g/dL	8.0 to 9.4 g/dL	6.5 to 7.9 g/dL	<6.5 g/dL
Absolute Neutrophil Count	Neutrophils	Neutrophils (Low)	1000 to 1500 /mm^3	750 to 999 /mm^3	500 to 749 /mm^3	<500 /mm^3
Platelets	Platelets	Platelets (Low)	75,000 to 99,999 /mm^3	50,000 to 74,999 /mm^3	20,000 to 49,999 /mm^3	<20,000 /mm^3
White Blood Cells	Leukocytes	Leukocytes (High)	11,000 to 13,000 /mm^3	13,001 to 15,000 /mm^3	15,001 to 30,000 /mm^3	>30,000 or <1000 /mm^3
% Polymorphonuclear Leukocytes + Band Cells	NA	NA	>80%	90 to 95%	>95%	N/A
Abnormal Fibrinogen	NA	NA	Low: 100 to 200 mg/dL High: 400 to 600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: <50 mg/dL High: N/A	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	NA	NA	20 to 40 mcg/mL	41 to 50 mcg/mL	51 to 60 mcg/dL	>60 mcg/dL
Prothrombin Time (PT)	NA	NA	1.01 to 1.25 × ULN	1.26 to 1.5 × ULN	1.51 to 3.0 × ULN	>3 × ULN
Activated Partial Thromboplastin (APTT)	NA	NA	1.01 to 1.66 × ULN	1.67 to 2.33 × ULN	2.34 to 3 × ULN	>3 ×ULN
Methemoglobin	NA	NA	5.0 to 9.9%	10.0 to 14.9%	15.0 to 19.9%	>20%

N/A=not applicable; ULN=upper limit of normal.

CHEMISTRIES						
	Laboratory parameter	**Display label**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	Sodium	Sodium (Low)	130 to 135 mEq/L	123 to 129 mEq/L	116 to 122 mEq/L	<116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	Sodium	Sodium (High)	146 to 150 mEq/L	151 to 157 mEq/L	158 to 165 mEq/L	>165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	Potassium	Potassium (Low)	3.0 to 3.4 mEq/L	2.5 to 2.9 mEq/L	2.0 to 2.4 mEq/L or intensive replacement therapy of hospitalization required	<2.0 mEq/L or abnormal potassium *with* paresis, ileus, or life-threatening arrhythmia
Hyperkalemia	Potassium	Potassium (High)	5.6 to 6.0 mEq/L	6.1 to 6.5 mEq/L	6.6 to 7.0 mEq/L	>7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	Glucose	Glucose (Low)	55 to 64 mg/dL	40 to 54 mg/dL	30 to 39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	Glucose	Glucose (High)	116 to 160 mg/dL	161 to 250 mg/dL	251 to 500 mg/dL	>500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	Calcium	Calcium (Low)	8.4 to 7.8 mg/dL	7.7 to 7.0 mg/dL	6.9 to 6.1 mg/dL	<6.1 mg/dL or abnormal calcium *with* life-threatening arrhythmia or tetany
Hypercalcemia (corrected for albumin)	Calcium	Calcium (High)	10.6 to 11.5 mg/dL	11.6 to 12.5 mg/dL	12.6 to 13.5 mg/dL	>13.5 mg/dL or abnormal calcium *with* life-threatening arrhythmia
Hypomagnesemia	Magnesium	Magnesium (Low)	1.4 to 1.2 mEq/L	1.1 to 0.9 mEq/L	0.8 to 0.6 mEq/L	<0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	Phosphate	Phosphate (Low)	2.0 to 2.4 mg/dL	1.5 to 1.9 mg/dL or replacement Rx required	1.0 to 1.4 mg/dL intensive therapy or hospitalization required	<1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia

CHEMISTRIES						
	Laboratory parameter	**Display label**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	Bilirubin (when any of AST, ALT and ALP is greater than the upper limit of normal range at the same analysis visit)	Bilirubin (High)	1.1 to <1.25 × ULN	1.25 to <1.5 × ULN	1.5 to 1.75 × ULN	>1.75 × ULN
Hyperbilirubinemia (when other liver function tests are in the normal range)	Bilirubin (when all of AST, ALT and ALP are within the normal range at the same analysis visit)	Bilirubin (High)	1.1 to <1.5 × ULN	1.5 to <2.0 × ULN	2.0 to 3.0 × ULN	>3.0 × ULN
Blood urea nitrogen	Urea	Urea Nitrogen (High)	1.25 to 2.5 × ULN	2.6 to 5 × ULN	5.1 to 10 × ULN	>10 × ULN
Hyperuricemia (uric acid)	NA	NA	7.5 to 10.0 mg/dL	10.1 to 12.0 mg/dL	12.1 to 15.0 mg/dL	>15.0 mg/dL
Creatinine	Creatinine	Creatinine (High)	1.1 to 1.5 × ULN	1.6 to 3.0 × ULN	3.1 to 6.0 × ULN	>6 × ULN or dialysis required

Rx=therapy; ULN=upper limit of normal

ENZYMES						
	Laboratory parameter	**Display label**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Aspartate aminotransferase (AST)	Aspartate aminotransferase	Aspartate aminotransferase (High)	1.1 to <2.0 × ULN	2.0 to <3.0 × ULN	3.0 to 8.0 × ULN	>8.0 × ULN
Alanine aminotransferase (ALT)	Alanine aminotransferase	Alanine aminotransferase (High)	1.1 to <2.0 × ULN	2.0 to <3.0 × ULN	3.0 to 8.0 × ULN	>8.0 × ULN
Gamma to glutamyl transferase (GGT)	NA	NA	1.1 to <2.0 × ULN	2.0 to <3.0 × ULN	3.0 to 8.0 × ULN	>8.0 × ULN
Alkaline Phosphatase	Alkaline Phosphatase	Alkaline Phosphatase (High)	1.1 to <2.0 × ULN	2.0 to <3.0 × ULN	3.0 to 8.0 × ULN	>8.0 × ULN
Amylase	NA	NA	1.1 to 1.5 × ULN	1.6 to 2.0 × ULN	2.1 to 5.0 × ULN	>5.1 × ULN
Lipase	NA	NA	1.1 to 1.5 × ULN	1.6 to 2.0 × ULN	2.1 to 5.0 × ULN	>5.1 × ULN

ULN=upper limit of normal.

URINALYSIS						
	Laboratory parameter	**Display label**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Proteinuria	NA	NA	1+ or 200 mg to 1 gm loss/day	2 to 3+ or 1 to 2 gm loss/day	4+ or 2 to 3.5 gm loss/day	Nephrotic syndrome or >3.5 gm loss/day
Hematuria	NA	NA	Microscopic only <10 RBC/hpf	Gross, no clots >10 RBC/hpf	Gross, with or without clots, or red blood cells casts	Obstructive or required transfusion

HPF=high powered field; RBC=red blood cells.

Adolescent Participants:

For adolescent participants over 12 years of age and less than 18 years of age, the adult DMID will be applied for all parameters with the exception of serum creatinine which will be graded programmatically according to the modified DMID pediatric toxicity criteria , which is aligned with the global studies (204989 and 212390) . Laboratory results are converted to SI units.

CHEMISTRIES						
	Laboratory parameter	**Display label**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Creatinine	Creatinine	Creatinine (High)	1.0 to 1.7 x ULN	1.8 to 2.4 x ULN	2.5 to 3.5 x ULN	>3.5 x ULN

ULN=upper limit of normal.

6.2.5. Study Period

Assessments and events will be classified according to the time of occurrence relative to the study intervention period.

Pre-Intervention is defined as time prior to the first dose of study intervention.

On-Intervention is defined as time from first dose to last date. If time of assessment or study intervention is not collected, the following assessment on the first dose date will be assumed to be taken prior to the first dose and therefore considered pre-intervention: ECG, Lab, and vital signs, and first dose date is considered on-intervention for AE and concomitant medication.

Post-Intervention is defined as any time post on-intervention window, i.e. > last dose date.

6.2.5.1. Study Phases for Concomitant medication

Study Phase	Definition
Prior	If medication started prior to the first dose date (or randomized date if first dose date is missing)
Concomitant	If medication ended after the first dose date or is ongoing regardless of the start date (or randomized date if first dose date is missing)

Study phases for concomitant medication will be derived after handling of missing and partial dates for medication (see Section 6.2.9). If a single medication taken on the same date as the first dose date, time will be used to determine if it's prior or concomitant. If time is missing, it will be considered concomitant.

6.2.5.2. Treatment Emergent Flag for Adverse Events

Adverse events are defined as treatment emergent AEs if AE onset date/time is on or after treatment start date/time. That is, study treatment start date/time <= AE start date/time. If time is missing, only date will be compared.

6.2.5.3. Participant and Study Completion

A participant is considered to have completed study treatment if she has taken all doses of the randomly assigned study treatment and also completed the ToC visit. A participant is considered to have completed the study if she has completed all study visits including the Follow-up Visit.

6.2.6. Study Day and Reference Dates

The safety reference date is the study intervention start date (or randomization date if not dosed) and will be used to calculate study day for safety measures.

The efficacy reference date is the study intervention start date (or randomization date if not dosed) and will be used to calculate study day for efficacy measures and baseline characteristics, as well as efficacy durations.

The study day is calculated as below:

- Assessment Date = Missing → Study Day = Missing
- Assessment Date < Reference Date → Study Day = Assessment Date – Ref Date
- Assessment Date ≥ Reference Date → Study Day = Assessment Date – Ref Date + 1

6.2.7. Assessment Window

Unscheduled and withdrawal visit data will be slotted into a target visit based on visit window defined in the table below. If there are multiple assessments within the same window, the closest one to the target day will be taken in the slotting. If multiple records are equally close to the target day, then the later record will be utilized. For post-baseline records collected outside the analysis visit window, a blank analysis visit label will be assigned.

Analysis Set / Domain	Parameter (if applicable)	Target	Analysis Window		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	
All	All	Day 3	Day 2	Day 5	On-therapy
All	All	Day 12	Day 9	Day 16	Test-of-Cure
All	All	Day 28	Day 21	Day 31	Follow-up

The procedure of the analysis visit assignment is as follows.

1. Calculate the analysis days for planned visit, unscheduled visit, and early withdrawal visit with non-missing outcome if applicable. The calculation of the analysis days is provided in Section 6.2.6.
2. Slot the visits to each of analysis timepoint according to the above table.
    a. If there are multiple assessments within the same windows, the closest one to the target day will be taken in the slotting.
    b. If multiple records are equally close to the target day, then the later record will be utilized using the sequence number in SDTM dataset.
    c. For post-baseline records collected outside the analysis visit window, a blank analysis visit label will be assigned. Such assessments will not be included in any of the by visit summaries. Descriptive summaries that are shown for “any assessment post baseline” e.g. maximum/minimum/ worst case post baseline, will use all assessments irrespective of whether they fall in an analysis visit window.

6.2.8. Multiple measurements at One Analysis Time Point

Not applicable.

6.2.9. Handling of Partial Dates

Element	Reporting Detail	
General	• Partial dates will be displayed as captured in participant listing displays. • However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for 'slotting' data to study phases or for specific analysis purposes as outlined below. • Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.	
Adverse Events	• Partial dates for AE recorded in the CRF will be imputed using the following conventions:	
	Missing start time (AChE-I only)	Midnight 0:00:00 will be used for AEs with missing start time to determine if it's AChE-I.
Concomitant Medications/Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:	

	Missing start day	If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.
		Else if study intervention start date is not missing:
		• If month and year of start date = month and year of study intervention start date, then
		  • If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.
		  • Else set start date = study intervention start date.
		Else set start date = 1st of month.

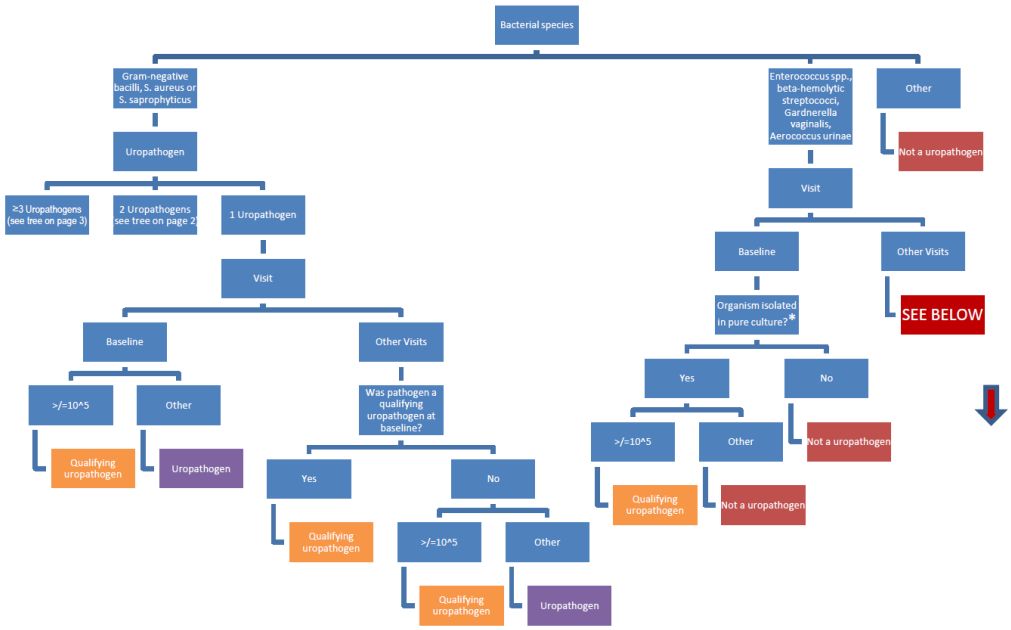
	Missing start day and month	If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.
		Else if study intervention start date is not missing:
		• If year of start date = year of study intervention start date, then
		  • If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.
		  • Else set start date = study. intervention start date.
		Else set start date = January 1.

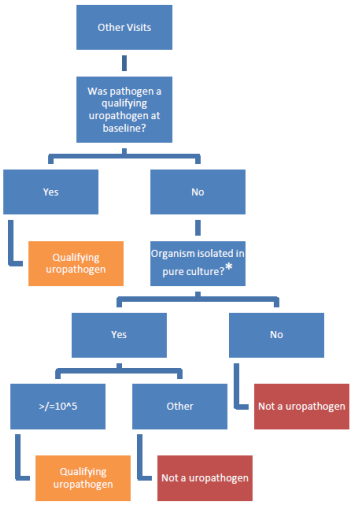
	Missing end day	A '28/29/30/31' will be used for the day (dependent on the month and year).
	Missing end day and month	A '31' will be used for the day and 'Dec' will be used for the month.

Element	Reporting Detail	
	Completely missing start/end date	No imputation
Age	Age is derived using the date of first dose. When first dose date is missing, the informed consent date is used. Only year of birth is collected so Day and Month of birth are imputed as 30 June. Formula for deriving age is the integer component of: • (First Dose Date – 30 Jun of collected birth year + 1) / 365.25	

6.2.10. Qualifying Uropathogen Algorithm

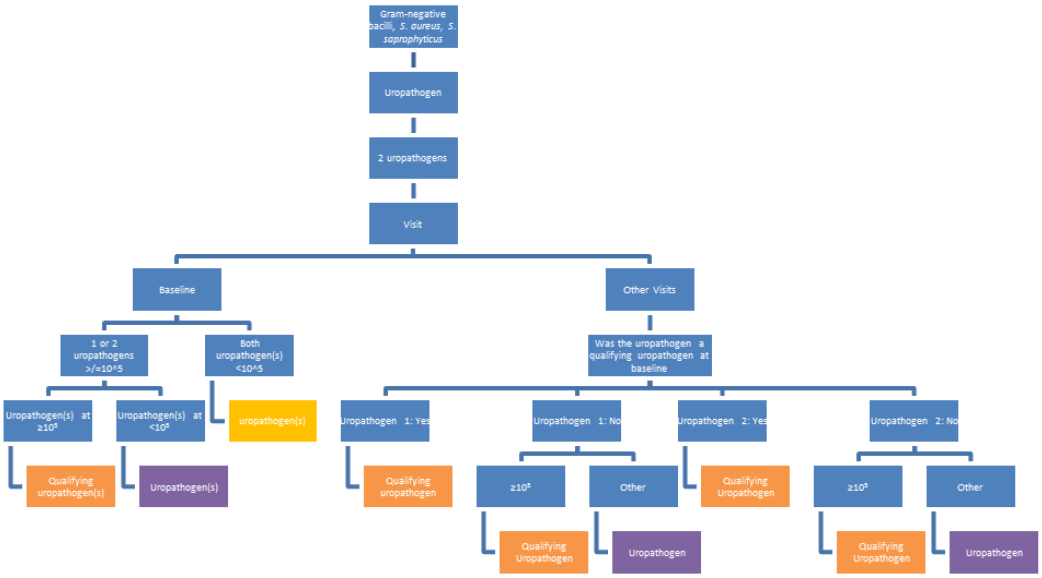
Qualifying Uropathogen Decision Tree: Single Uropathogen





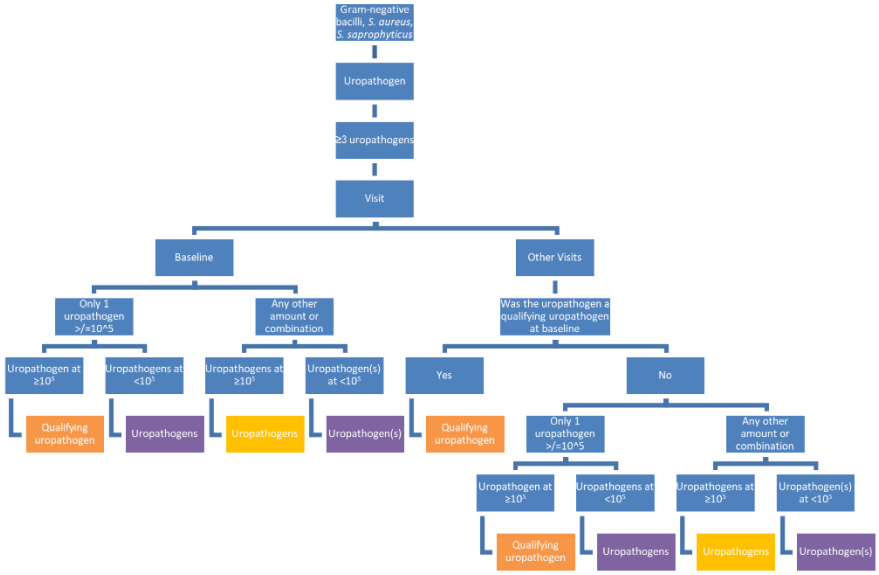
*Pure culture: a culture containing the growth of a single strain of organism free from other pathogens or normal flora.

Qualifying Uropathogen Decision Tree: 2 Uropathogens



Note: Since *Enterococcus* spp., beta-hemolytic streptococci, *Gardnerella vaginalis* and *Aerococcus urinae* must be present in pure culture to be considered a uropathogen, the 2 or ≥3 uropathogens trees do not apply to these organisms.

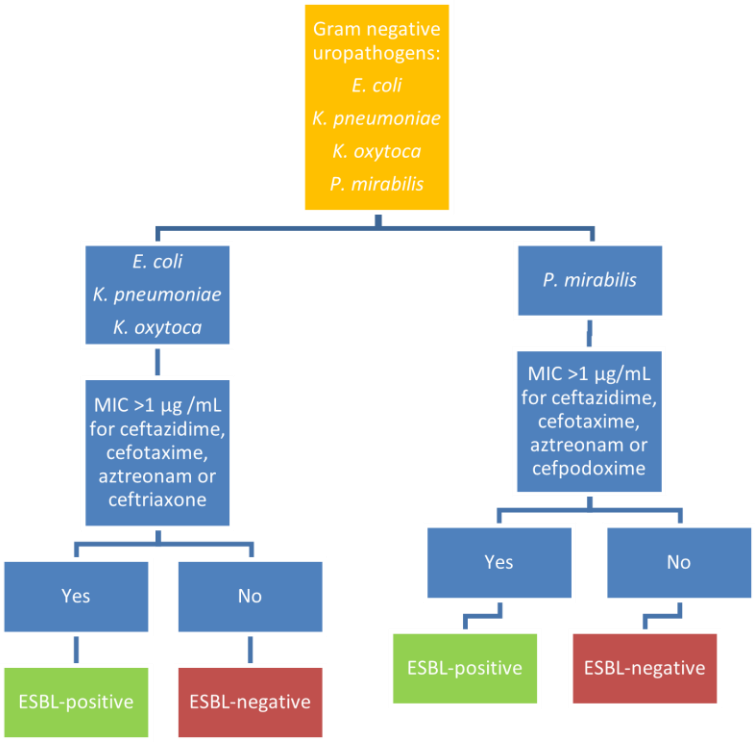
Qualifying Uropathogen Decision Tree: >= 3 Uropathogens



Note: Since *Enterococcus* spp., beta-hemolytic streptococci, *Gardnerella vaginalis* and *Aerococcus urinae* must be present in pure culture to be considered a uropathogen, the 2 or ≥3 uropathogens trees do not apply to these organisms.

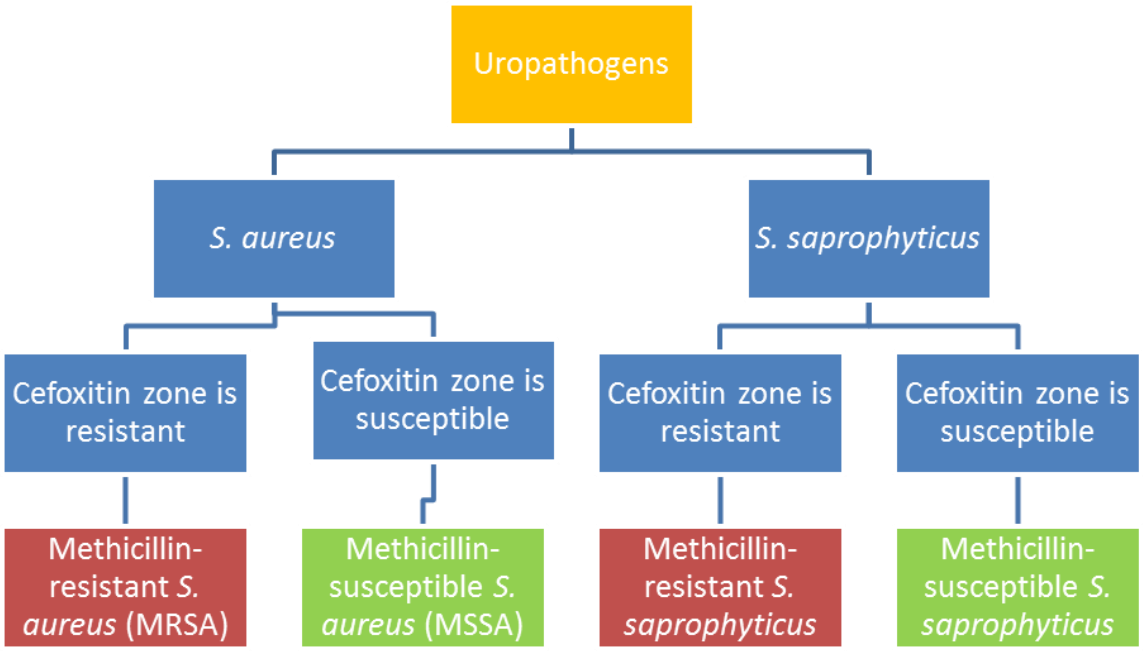
6.2.11. Uropathogen Phenotype Algorithm

ESBL. Decision Tree:



Note: ESBL not determined for other Gram-negative organisms.

Methicillin* Decision Tree:



*Cefoxitin is tested as a surrogate test for oxacillin to determine methicillin susceptibility/resistance. Methicillin-(oxacillin) resistant staphylococci are resistant to all currently available beta-lactams, cephalosporin and carbapenem antimicrobial agents, with the exception of ceftaroline.

Multidrug Resistance (MDR):

Definition 1: A uropathogen will be regarded as multidrug-resistant if the uropathogen is resistant to >= 1 drugs in each class among >= 2 antimicrobial classes (β-lactam, Fluoroquinolone, Fosfomycin and Aminoglycoside). This definition will be used for micro-ITT MDR Population.

Definition 2: A uropathogen will be regarded as multidrug-resistant (3 or more) if the uropathogen is resistance to >= 1 drugs in each class among >= 3 antimicrobial classes (β-lactam, Fluoroquinolone, Fosfomycin and Aminoglycoside). This phenotype will be included in the subgroup analyses.

Below is the table of antimicrobial classes, susceptibility test and the guideline of susceptibility interpretation for the MDR definitions above.

Antimicrobial class	Antimicrobial	Susceptibility test (MSMETHOD)	Guideline (MSSCAT)
Beta-lactam	Ampicillin	Micro Broth Dilution	CLSI
	Mecillinam	Disk diffusion	CLSI
	Penicillin	Disk diffusion	CLSI
	Amoxicillin/clavulanic acid	Micro Broth Dilution	CLSI
	Ceftolozane/tazobactam	Micro Broth Dilution	CLSI
	Ceftazidime/avibactam	Micro Broth Dilution	CLSI
	Piperacillin/tazobactam	Micro Broth Dilution	CLSI
	Cefazolin	Micro Broth Dilution	CLSI
	Ceftriaxone	Micro Broth Dilution	CLSI
	Cefadroxil	Disk diffusion	EUCAST
	Cefoxitin	Disk diffusion	CLSI
	Meropenem	Micro Broth Dilution	CLSI
	Faropenem	Disk diffusion	[Fuchs, 1995]
Aminoglycoside	Amikacin	Micro Broth Dilution	CLSI
	Gentamicin	Micro Broth Dilution	CLSI
Fluoroquinolone	Ciprofloxacin	Micro Broth Dilution	CLSI
	Levofloxacin	Micro Broth Dilution	CLSI
Fosfomycin	Fosfomycin	Agar dilution	CLSI

List of Antimicrobials Being Tested

Antimicrobial Class	Sub-class	Antimicrobial
β-lactam	Penicillin	Ampicillin
		Mecillinam
		Penicillin
	β-lactam combination	Amoxicillin/clavulanic acid
		Ceftolozane/tazobactam

Antimicrobial Class	Sub-class	Antimicrobial
		Ceftazidime/avibactam
		Piperacillin/tazobactam
	Cephalosporin	Cefazolin
		Ceftriaxone
		Cefotaxime
		Ceftazidime
		Cefpodoxime
		Cefoxitin
		Cefadroxil
		Cefoxitin
	Carbapenem/Penem	Meropenem
		Faropenem
	Monobactam	Aztrenam
Fluoroquinolone		Ciprofloxacin
		Levofloxacin
Fosfomycin		Fosfomycin
Aminoglycoside		Amikacin
		Gentamicin
Folate pathway Antagonist		Trimethoprim-sulfamethoxazole
		Trimethoprim
		Sulfisoxazole
Nitrofuran		Nitrofurantoin
Glycopeptide		Vancomycin
Nitroxoline		Nitroxoline

Antimicrobial-Resistant Phenotypes:

Antimicrobial class	Antimicrobial	Drug relevant to Gram-negatives	Drug relevant to Gram-positives	Resistant phenotype to be reported by GCL if interpretation is resistant*
Penicillin	Ampicillin	X	X	AMP-R
	Mecillinam	X		MEC-R
	Penicillin		X	PEN-R
B-lactam combination	Amoxicillin/clavulanic acid	X		AUG-R
	Ceftolozane/tazobactam	X		C/T-R
	Ceftazidime/avibactam	X		CZA-R
	Piperacillin/tazobactam	X		P/T-R
Cephalosporin	Cefazolin	X		FAZ-R
	Ceftriaxone	X		AXO-R
	Cefadroxil	X		CFR-R
	Cefoxitin**		X	See methicillin resistance tree

Antimicrobial class	Antimicrobial	Drug relevant to Gram-negatives	Drug relevant to Gram-positives	Resistant phenotype to be reported by GCL if interpretation is resistant*
Carbapenem/Penem	Meropenem	X		MERO-R
	Faropenem	X	X	FPM-R
Aminoglycoside	Amikacin	X		AMI-R
	Gentamicin	X		GEN-R
Folate Pathway Antagonist	Trimethoprim-sulfamethoxazole	X	X	SXT-R
	Trimethoprim	X	X	TMP-R
	Sulfisoxazole	X	X	SFX-R
Fluoroquinolone	Ciprofloxacin	X	X	CIP-R
	Levofloxacin	X	X	LEVO-R
Nitrofuran	Nitrofurantoin	X	X	NIT-R
Glycopeptide	Vancomycin		X	VAN-R
Fosfomycin	Fosfomycin	X	X	FOF-R
Nitroxoline	Nitroxoline	X	X	NOX-R

*Resistant phenotype based on CLSI M100 interpretations with the exception of nitroxoline and cefadroxil which are based on EUCAST interpretations and faropenem which is based on [Fuchs, 1995].

** Surrogate test for oxacillin to determine methicillin susceptibility/resistance.

R=resistant

6.2.12. Trademarks

Trademarks of the [GlaxoSmithKline / ViiV Healthcare] Group of Companies
ADVAIR

Trademarks not owned by the [GlaxoSmithKline / ViiV Healthcare] Group of Companies
NONMEM
SAS
WinNonlin

7. REFERENCES

Crowe B, Brueckner A, Beasley C, Kulkarni P. Current Practices, Challenges, and Statistical Issues With Product Safety Labeling 2013;5(3): 180-193. *Statistics in Biopharmaceutical Research.* 2013;5(3):180-193.

Fuchs PC, Barry AL, Sewell DL. Antibacterial activity of WY-49605 compared with those of six other oral agents and selection of disk content for disk diffusion susceptibility testing. *Antimicrob Agents Chemother.* 1995;39:1472-9.

SAS Institute Inc. *SAS/STAT User's Guide.* Version 15.1 ed. Cary, NC:SAS; 2018.

Schmidli HS, Gsteiger S, Roychoudhury S, O'Hagan A, Spiegelhalter D, Neuenschwander B. Robust meta-analytic-predictive priors in clinical trials with historical control information. *Biometrics.* 2014;70:1023-1032.