Statistical Analysis Plan Amendment 3

Study ID: 212943

Official Title of Study: A Double-Blind, Double Dummy, Randomized, Phase 1b, Nitrofurantoin Controlled, Repeat Oral Dose Study to Investigate the Safety, Tolerability, Pharmacokinetics and Microbiological Response of GSK3882347 in Female Participants with Acute Uncomplicated Urinary Tract Infection.

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TITLE PAGE

Protocol Title:	A Double-Blind, Double Dummy, Randomized, Phase 1b, Nitrofurantoin Controlled, Repeat Oral Dose Study to Investigate the Safety, Tolerability, Pharmacokinetics and Microbiological Response of GSK3882347 in Female Participants with Acute Uncomplicated Urinary Tract Infection.
Study Number:	212943
Compound Number:	GSK3882347
Abbreviated Title:	Safety, tolerability, pharmacokinetic and microbiological investigation of GSK3882347 in female participants with urinary tract infections.

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s)

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VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
Original	18-Nov-2021	20-Aug-2021	CCI [redacted]	
Amendment 1	23-Aug-2023	05-May-2023		

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			CCI [redacted]	
Amendment 2	03-Jan-2025	10-Jun-2024		
Amendment 3	20 Jan 2025	10-Jun-2024		

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			CCI [redacted]	

1. INTRODUCTION

The purpose of this SAP is to describe the planned analysis to be included in the Clinical Study Report for Protocol 212943. Details of the planned CCI [redacted] final analyses, are provided.

Additional details with regards to data handling conventions and the specification of data displays will be provided in the Output and Programming Specification (OPS) document.

Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
• To assess the microbiological efficacy of GSK3882347 at the Test of Cure (ToC) visit in participants with uUTI who have qualifying *E. coli* at baseline	• Microbiological response at the ToC Visit
Secondary	
• To evaluate the safety and tolerability following CCI [redacted] oral dosing for 5 days of GSK3882347 in participants with uUTI	• Occurrence of adverse events (AEs) and serious adverse events (SAEs) • Clinically significant changes from baseline in laboratory values (haematology, chemistry and urinalysis), vital signs and 12-lead electrocardiogram (ECG) readings at each visit
• To evaluate the plasma and urine pharmacokinetic (PK) concentrations following CCI [redacted] oral dosing for 5 days of GSK3882347 in participants with uUTI	Plasma: • GSK3882347 concentration Urine • Urine concentration at 22-24h interval collection post-dose

Objectives	Endpoints
Exploratory*	
CCI [redacted]	
• To evaluate the resolution of clinical symptoms over time of GSK3882347 in participants with uUTI caused by *E. coli*	• Clinical resolution response on Day 2 through to Day 6 (when collected and as data permit), ToC and Follow-up Visit
• To evaluate the resolution of clinical symptoms over time of GSK3882347 in participants with uUTI caused by *E. coli* using an exploratory scoring system	• Clinical symptom score outcome and response on Days 1 through to Day 6 (when collected and as data permit), ToC and Follow-up Visit
CCI [redacted]	

Objectives	Endpoints
CCI	

*Some exploratory data may not be available until after the main database lock and may be analysed/reported separately.

1.1.1. Estimand for Primary Endpoint

The primary clinical question of interest is: *What is the microbiological response for GSK3882347 assessed at ToC in participants with acute uUTI caused by E. coli at Baseline who completed the planned course of treatment (5 days) and had no major deviations from protocol that would prevent evaluation of microbiological response (as defined in the protocol deviation rules document).Use of rescue medication after last dose of study intervention will be set to non-responder in the endpoint definition.*

The Primary estimand is described by the following attributes:

- Population: Female participants with acute uUTI with a qualifying baseline *E. coli* (Section 6.4) at baseline who completed the planned course of treatment (5 days) and had no major deviations from protocol that would prevent evaluation of microbiological response
- Treatment condition: GSK3882347 CCI mg given orally CCI for 5 days or Nitrofurantoin 100mg given orally twice daily for 5 days.
- Variable: Microbiological response at ToC visit (see Section 4.2.1)
- Summary measure: Frequency and percentage of participants with microbiological response (responder/non-responder) in GSK3882347 treatment group
- Main intercurrent events anticipated:

- Use of rescue medication prior to ToC visit- Composite strategy
- This intercurrent event is captured through the definitions of microbiological response (see Section 4.2.1). Hence the participants who take rescue medication prior to ToC visit will be considered as non-responders.
- Participants who are lost to follow-up prior to ToC, have a missing/ unevaluable sample at ToC, discontinue study treatment due to any reason (withdrawal of consent/AEs/missed doses) will not be included in the analysis and may be replaced at the discretion of the Sponsor.

- Rationale for estimand:

  Use of rescue medication may impact microbiological outcomes and its use implies that the treatment the participant received is not working, therefore, the definition of a successful microbiological response precludes the use of rescue medications. In this small, early phase, proof of mechanism study, interest lies in the treatment effect of participants who completed the planned course of treatment and follow important components of the study protocol to establish proof of mechanism.

1.1.2. Estimand for Secondary Endpoints

The secondary clinical questions of interests are,

1. *What is the incidence of AEs, SAEs and clinically significant changes in safety data from baseline (laboratory, vitals and ECG) following* CCI *oral dosing for 5 days of GSK3882347 (or less than 5 days if study intervention is discontinued for any reason) in adult female participants with uUTI?*

The estimand is described by the following attributes:

- Population: Female participants with acute uUTI.
- Treatment condition: GSK3882347 CCI mg given orally CCI for 5 days or Nitrofurantoin 100mg given orally twice daily for 5 days.
- Variables:
  - Occurrence of adverse events (AEs) and serious adverse events (SAEs)
  - Clinically significant changes from baseline in laboratory values (haematology, chemistry and urinalysis), vital signs and 12 lead electrocardiogram (ECG) readings at each visit.
- Summary measure: Frequency and percentages for AEs, SAEs, laboratory values, vital signs and ECG values.
- Main intercurrent events anticipated:
  - Use of rescue medication - Treatment policy strategy
  - Discontinuation from the treatment due to any reason (withdrawal of consent /AEs (if not part of the endpoint definition, for example, in AE and SAE)/missed doses)-Treatment policy strategy

The interest lies in the full safety profile regardless of the occurrence of these intercurrent events. Hence safety data evaluated throughout the study will be considered for the analysis.

2. *To evaluate the plasma and urine PK concentrations following* CCI *oral dosing for 5 days of GSK3882347 or until discontinuation of treatment*

The estimand is described by the following attributes:

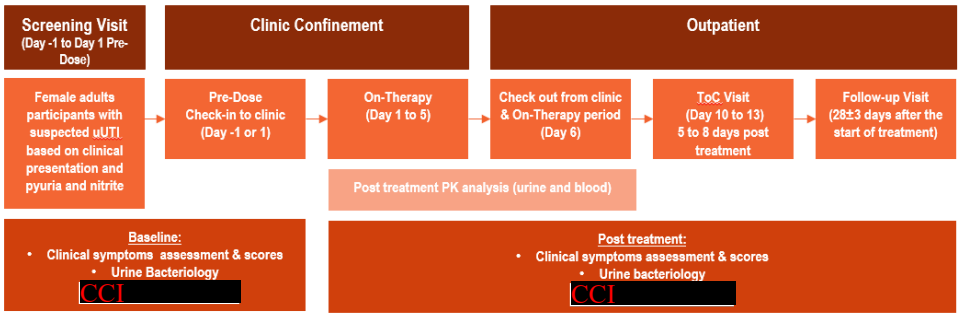
- Population: Female participants with acute uUTI
- Treatment condition: GSK3882347 given orally CCI for 5 days
- Variables:
  - Plasma:
    - GSK3882347 trough concentration on Day 1 and Day 5 (Ctau)
  - Urine:
    - Urine concentration at 22-24h collection following dose on Day 1 and Day 5
- Summary measure: Mean, 95% confidence interval (CI), standard deviation (SD), median, minimum, and maximum and geometric mean, 95% CI of geometric mean, and coefficient of variation (CV) of geometric mean, for log transformed data.
- Main intercurrent events anticipated:
  - Discontinuation from the treatment due to any reasons (AEs/withdrawal of consent/missed doses)
  - Administered incorrect dose based on adherence records

All these intercurrent events will be handled using while on treatment strategy as interest lies in PK data until whilst participants are receiving study intervention

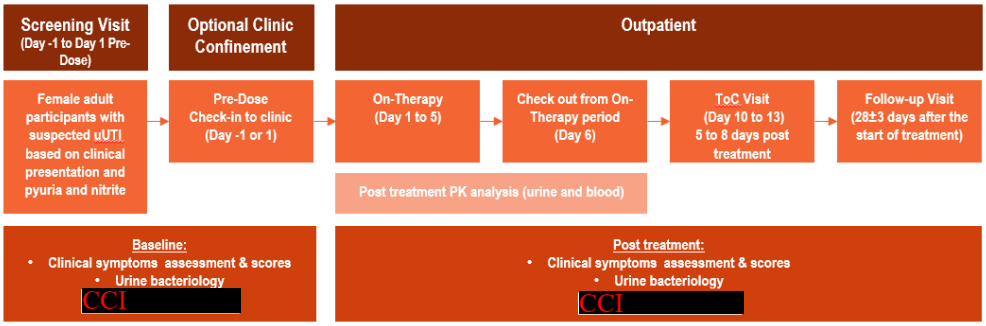
1.2. Study Design

Overview of Study Design and Key Features

Study Schematic for Cohort 1: Full Intensive PK Sampling as Inpatient



Study Schematic for Cohort 2: Reduced PK Sampling as Outpatient



Design Features	This Phase 1b study is a double-blind, double-dummy, nitrofurantoin-controlled study designed primarily to evaluate microbiological response at the ToC visit and safety, tolerability and PK response following CCI oral dosing for 5 days of GSK3882347 in adult female participants with uUTI. Nitrofurantoin will be included in the study to ensure unbiased reporting of safety events. The clinical response CCI with GSK3882347 will be evaluated as exploratory endpoints in this study. CCI The study will be separated into 2 cohorts. Cohort 1 will have an inpatient Treatment period and PK analysis will be conducted at frequent timepoints. Cohort 2 will have an outpatient Treatment period and PK analysis will be conducted less frequently, at key trough timepoints. The treatment period will consist of 5 days and the total study duration will be up to 31 days.
Study intervention	1. GSK3882347 CCI mg oral capsules CCI for 5 days. 2. Nitrofurantoin 100 mg oral capsule BID for 5 days.

Overview of Study Design and Key Features	
Study intervention Assignment	All participants who provide informed consent and meet the study entry criteria will be randomized to receive either CCI mg GSK3882347 or 100 mg BID nitrofurantoin in a 3:1 ratio.
CCI	

2. STATISTICAL HYPOTHESES

No formal statistical hypotheses will be tested in this study.

2.1. Multiplicity Adjustment

N/A

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	All participants who signed the ICF and were screened for eligibility.	• Study Population
Enrolled	All participants who passed screening and entered the study Note: screening failures [who never passed screening even if rescreened] and participants screened but never enrolled into the study [Met eligibility but not needed] are excluded from the Enrolled analysis set as they did not enter the study.)	• Study Population
Randomized	All participants in the Enrolled analysis set who were randomly assigned to study intervention in the study. Participants will be analyzed according to the intervention they were randomly assigned to.	• Study Population
Safety	All participants in the Randomized analysis set who receive at least 1 dose of study intervention. Participants will be analyzed according to their actual intervention received.	• Safety
Microbiological Modified Per Protocol (Micro-MPP)*	All participants in the Safety analysis set who: receive all planned doses of study intervention; have a Qualifying baseline *E. coli* from a quantitative bacteriological culture of a pre-treatment clean-catch midstream urine specimen; have completed a ToC visit; have no major protocol deviations that would prevent evaluation of microbiological response. Participants will be analyzed according to their actual intervention received.	• Efficacy
CCI [redacted]		

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Analysis Set	Definition / Criteria	Analyses Evaluated
CCI [redacted]		
Pharmacokinetic (PK)	All participants in the Safety analysis set who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). Participants will be analyzed according to their actual intervention received.	• Pharmacokinetic
CCI [redacted]		

*The algorithm for determining qualifying *E. coli* based on microbiology laboratory quantitative culture results is provided in the Appendix 4

CCI [redacted]

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

Summary tables will provide the following descriptive statistics as a minimum, unless otherwise specified:

- Continuous data (natural scale):

  n, mean, standard deviation (SD), median, minimum and maximum.

- Continuous data (log-transformed):

  n, geometric mean, %CV, median, minimum and maximum.

- Categorical data:

  number and percentage of participants in each category.

All analyses (excluding PK) will be presented on combined cohorts (Cohort1 + Cohort 2), unless otherwise specified.

Details of the planned displays are provided in OPS and will be based on GSK Data Standards and Statistical Principles.

4.1.2. Baseline Definition

For all endpoints the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

The mean will be considered for triplicate measurements taken at the latest pre-dose assessment. If the latest pre-dose assessment is missing, then the previous assessment time point would be considered as baseline where possible (i.e. if Day 1 (Pre-dose) is missing the Day -1 will be used) unless specified otherwise.

Parameter	Study Assessments Considered as Baseline		Baseline Used in Data Display
	Screening/ Day -1	Day 1 (pre-dose)	
Efficacy			
Microbiological response		x	Day 1(pre-dose)
UTI Clinical Symptom Score Assessment	x	x	Day 1(pre-dose)
CCI			
Quantitative Bacteriology Culture		x	Day 1(pre-dose)
CCI			
Safety			
12-lead ECG	x		Day -1
Vital sign	x	x	Day 1(pre-dose)
Haematology*	x	x	Day 1(pre-dose)
Clinical chemistry*	x	x	Day 1(pre-dose)
Urinalysis*	x	x	Day 1(pre-dose)
PK			
PK urine sample (Cohort 1)		x	Day 1(pre-dose)

Parameter	Study Assessments Considered as Baseline		Baseline Used in Data Display
	Screening/ Day -1	Day 1 (pre-dose)	
PK plasma sample (Cohort 1)		x	Day 1(pre-dose)

* If baseline data is missing, then change from baseline calculations will not be performed and will be set to missing.

4.2. Primary Endpoint(s) Analyses

The primary endpoint to be estimated is microbiological response at ToC visit in female participants with a qualifying baseline *E. coli.* The Micro-MPP analysis set will be used for the analysis and the results will be summarised by treatment group.

4.2.1. Definition of endpoint/estimand

The microbiological response to the study treatment will be determined by a prespecified programmed algorithm for each participant, considering the number of baseline qualifying uropathogens based on their microbiology laboratory quantitative culture results. The algorithm for determining qualifying *E. coli* is provided in the Appendix 4 and the detailed definitions for response are provided in Appendix 6.

Details on estimands are provided in the Section 1.1.1.

4.2.2. Main analytical approach

- Frequency and percentage of participants in each category of microbiological response (success/failure) at ToC visit will be summarized along with 95% Clopper-Pearson CI for the primary estimand and these results will be reported by treatment group, and will also be presented graphically.
- Primary estimand will be reported CCI [redacted] for the final reporting of the study.
- CCI [redacted].
- Details of the planned displays are provided in the OPS.

4.3. Secondary Endpoints Analyses

The secondary endpoints to be evaluated are safety and PK.

4.3.1. Pharmacokinetics

Urine and Plasma samples will be used to evaluate PK characteristics of GSK3882347. CCI [redacted] Final analyses and reporting will be performed by GSK Biostatistics and Programming.

Analysis of pharmacokinetic concentrations will be conducted by using the pharmacokinetic analysis set. Details on the pharmacokinetic estimand are given in Section 1.1.2

Descriptive summaries of plasma and urine concentrations will be presented by cohort. Individual subject level, and aggregate level plots of plasma concentration data will also be presented.

4.3.2. Safety

The following endpoints will be analysed:

- Occurrence of adverse events (AEs) and serious adverse events (SAEs)
- Clinically significant changes from baseline in laboratory values (haematology, chemistry and urinalysis), vital signs and 12-lead electrocardiogram (ECG) readings at each visit

Analysis of safety data will be conducted by using the Safety analysis set. Details on the safety estimand are given in Section 1.1.2. The details of the safety analyses are provided in Section 4.5.

4.4. Exploratory Endpoint(s) Analyses

Efficacy results will be presented on the Micro-MPP analysis set, unless otherwise specified.

CCI [redacted]

- Clinical resolution response
- Clinical symptom score outcome & response

CCI [redacted]

A blinded clinical review of concomitant medications will be conducted to determine use of systemic antibacterials.

4.4.1. PK Parameters

PK parameters will be calculated by standard non-compartmental methods.

The definition of the PK parameters of interest are given in the table below.

Parameter	Parameter Description	Cohort	Type
CCI			
C22-24,U	Concentration of GSK3882347 in urine during the 22-24 h collection interval	Combined cohorts, Day 1, 2, 3, 4, 5	Urine

CCI

[redacted]

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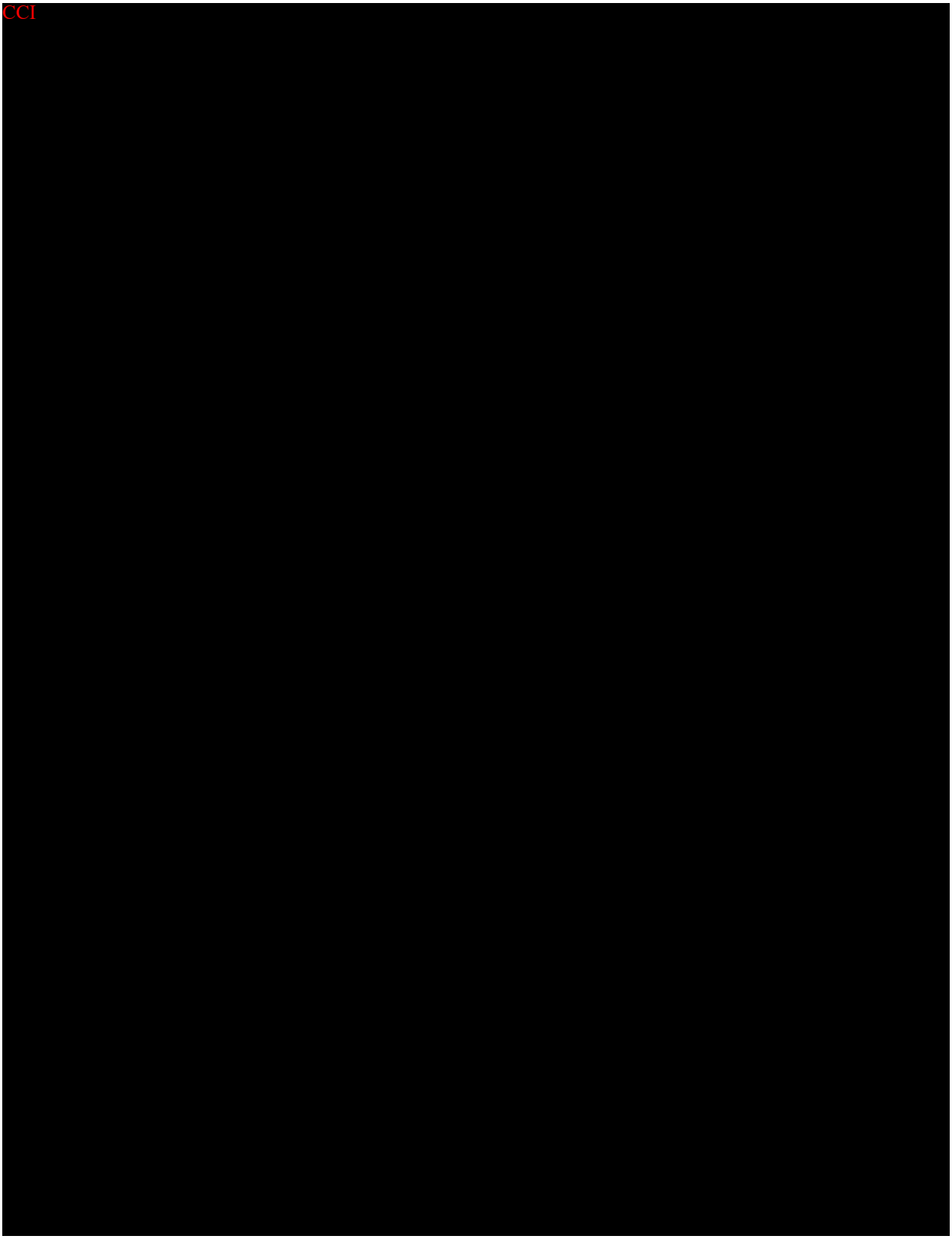

4.4.2. Microbiological Outcome and Response

Definition of endpoints/estimands

The microbiological outcome is determined by comparing the baseline culture results to the culture results at each subsequent visit by using a prespecified programmed algorithm for each participant, considering the number of baseline qualifying uropathogens. The algorithm for determining qualifying *E. coli* is provided in the Appendix 4 and the detailed definitions for outcome and response are provided in Appendix 6.

The estimand for microbiological outcome and response is detailed in Section 1.1.1.

Main analytical approach

- Frequency and percentage of participants in each category of microbiological outcome at CCI [redacted] ToC CCI [redacted] will be summarized along with 95% Clopper-Pearson CI by treatment group.
- Results will also be presented graphically over time and by treatment group.
- CCI [redacted]
- An exploratory statistical analysis to model the number of responders, adjusting for known covariates (e.g. age, history of UTIs) may be produced.
- CCI [redacted].

4.4.3. Clinical evaluation: Symptoms of uUTI and Clinical Resolution Response

Definition of endpoints

Investigator's Assessment of Clinical Resolution Response:

Outcome

- Investigator will examine the participants and will report the clinical resolution response in the eCRF as either resolved or unresolved at each visit.
- Refusal to consent to a clinical examination or failure to attend the visit will have an outcome of indeterminate (clinical resolution failure). This will be determined programmatically.
- At Follow-Up visit outcome will be determined programmatically, as outlined in Table 1.

Response

- No response will be determined for Day 2 through 6 visits.
- Response will be determined programmatically for ToC Visit, where response is a:
  - Clinical resolution success when investigator assessment is "resolved" at ToC

- Clinical resolution failure when investigator assessment is "unresolved" at ToC

- At Follow-Up visit response will be determined programmatically, as outlined in Table 1.

Table 1 Clinical Resolution Response (programmatic derivation)

Defining Criteria for Investigators Assessment of Clinical Symptom Resolution	Outcome	Response
Follow-up Visit		
• Clinically resolved at ToC and Follow-Up visit	Sustained clinical resolution	Clinical resolution success
• Clinically unresolved at ToC visit but clinically resolved at Follow-Up visit	Delayed clinical resolution	Clinical resolution failure
• Clinically resolved at ToC visit but clinically unresolved at Follow-Up visit	Clinical recurrence	Clinical resolution failure
• Clinically unresolved at ToC visit and Follow-Up visit	Clinically unresolved//Clinical worsening	Clinical resolution failure
• Refusal to consent to a clinical examination or, • Failure to attend the Follow-Up Visit or, achieved sustained or, • Achieved delayed clinical resolution but received other systemic antibacterials before the Follow-Up visit.	Indeterminate	Clinical resolution failure

ToC=Test of Cure

Clinical symptom score outcome and response:

Clinical outcome and response will be programmatically determined by comparing the scores of the signs and symptoms at each visit to those present at baseline. The detailed definitions are provided in Appendix 7.

Main analytical approach

- Frequency and percentage of participants in each outcome and response category of the investigator's assessment of clinical resolution response at Day 2 through Day 6 (when collected and as data permit), ToC and follow-up visits will be summarized along with 95% Clopper-Pearson CI by treatment group.
- Frequency and percentage of participants in each outcome and response category of clinical symptom score at Day 2 through Day 6 (when collected and as data permit), ToC and follow-up visits will be summarized along with 95% Clopper-Pearson CI by treatment group.
- Frequency and percentage of participants for each individual clinical symptom score (four individual clinical symptoms, each with four possible scores (ordinal categories)) will be summarised by visit and treatment group
- Total clinical symptom score over time will be summarized graphically in boxplots by visit and treatment group

4.4.6. Quantitative bacteriology culture results

- Bacteriology culture results categories (No Growth (<10^3), >=10^3 — <10^4, >=10^4 — <10^5, >=10^5, Indeterminate)
- Quantitative bacteriology culture results will be summarized by counts and percentages for each category by visit for Micro-MPP [redacted] analysis sets for each treatment arm.
- Number of participants in each bacteriology culture result category for each visit will be summarized graphically for Micro-MPP [redacted] analysis sets for each treatment arm.

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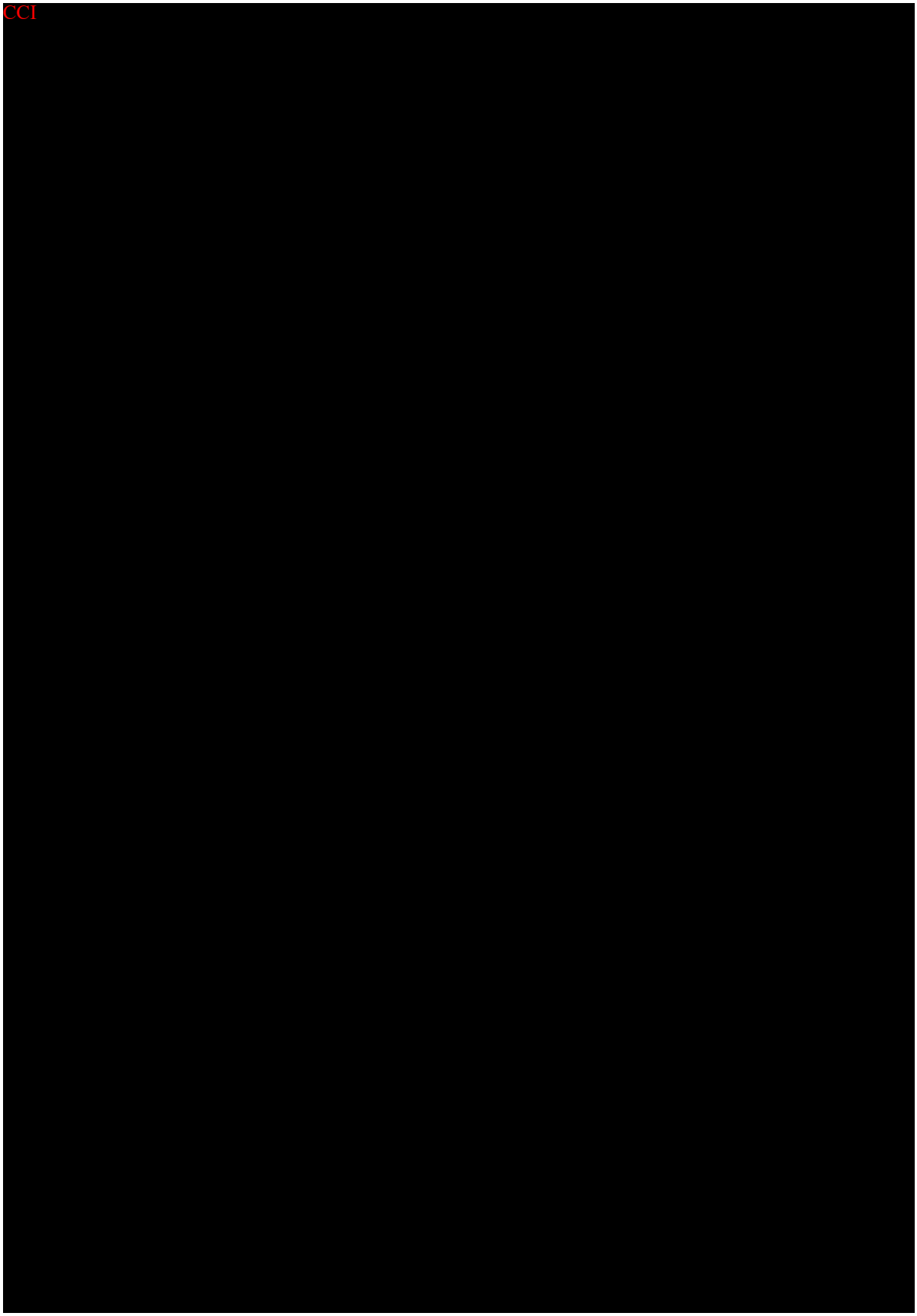

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4.5. Safety Analyses

All safety analysis will be performed on the Safety analysis set and presented by treatment group and presenting combined cohorts (Cohort1 + Cohort 2), unless otherwise specified. Safety secondary endpoints are defined in Section 4.3.2 and estimand for safety are provided in the Section 1.1.2.

4.5.1. Extent of Exposure

Exposure to study treatment and compliance will be summarised descriptively overall and by cohort. Details of the derivations will be included in the OPS.

4.5.2. Adverse Events

An adverse event (AE) is considered on-intervention if the AE onset or worsening is on or after study intervention start. All AE summaries will present on-intervention events unless otherwise specified. SAE summaries will be based on all SAEs reported regardless of whether they meet the definition of on-intervention or not.

Adverse events will be coded using the standard Medical Dictionary for Regulatory Activity (MedDRA) and graded by the investigator according to Division of Microbiology and Infectious Diseases Adult Toxicity Tables for Adverse Event Assessment (see Protocol Section 10.7).

The following summary tables will be presented:

- AEs by SOC and PT and maximum intensity
- SAEs by SOC and PT and maximum intensity
- Common (≥10%) AEs
- Study intervention-related* AEs by SOC and PT and maximum intensity
- Study intervention-related* SAEs by SOC and PT and maximum intensity
- Study intervention-related* Common AEs (≥10%)
- Common (≥10%) Non-serious Adverse Events by SOC and PT

*A study intervention-related AE/SAE is defined as an AE/SAE for which the investigator classifies the relationship to study intervention as “Yes”.

4.5.2.1. Adverse Events of Special Interest

There are no adverse events of special interest in this study.

4.5.3. Additional Safety Assessments

4.5.3.1. Laboratory Data

Summary tables for laboratory data (haematology, clinical chemistry) will be produced:

- Change from baseline over time
- Frequency and percentage of laboratory results (relative to Normal Range) post-baseline relative to baseline
- Note: values of PCI will be flagged in listings only.

Separate summary tables for haematology and clinical chemistry laboratory tests will be produced. The following will be presented, at a minimum:

- Haematology parameters (including Platelet count, RBC count, Hemoglobin, Hematocrit, RBC Indices (Mean corpuscular volume (MCV), Mean corpuscular Hemoglobin (MCH), %Reticulocytes), WBC count (Lymphocytes, Neutrophils, Monocytes, Eosinophils, Basophils))
- Clinical chemistry parameters (including Blood urea nitrogen (BUN), Potassium, Sodium, Creatinine, Glucose(non-fasting), AST, SGOT, ALT, SGPT, Alkaline phosphatase, Total and direct bilirubin, calcium & Total Protein)

Additionally, summary tables for urinalysis data will be produced:

- Change from baseline in urine concentrations over time
- Frequency and percentage of urinalysis results post-baseline relative to baseline
- Note: values of PCI will be flagged in listings only.

The following will be presented, at a minimum:

- Urinalysis parameters (Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick. Microscopic examination (if blood or protein is abnormal), Protein/creatinine ratio)

4.5.3.2. Vital Signs

Summary tables for vital signs will be produced:

- Change from baseline in vital signs (temperature, systolic and diastolic blood pressure, pulse, and respiratory rate) over time
- Frequency and percentage of vital signs results (relative to Normal Range) post-baseline relative to baseline
- Note: values of PCI will be flagged in listings only.

4.5.3.3. ECG

Summary tables for ECG data will be produced:

- ECG findings
- Change from baseline in ECG values
- Maximum QTc values post-baseline relative to baseline by category
- Maximum increase in QTc values post-baseline relative to baseline by category
- Note: values of PCI will be flagged in listings only.

4.6. Other Analyses

4.6.1. Subgroup analyses

Microbiological outcome and response for each visit and treatment group will be also summarized based on the following subgroups for the Micro-MPP analysis set:

- Menopausal age groups: Pre-menopausal age vs post-menopausal age
  - Categories are considered pre-menopausal age: “potentially able to bear children” and “sterile of child-bearing age”. Categories for post-menopausal age: “post-menopausal”
- Frequency of recurrence of UTI in past 12 months: < 3 UTIs in past 12 months vs >=3 UTI in past 12 months.
- Frequency of recurrence of UTI in past 24 months: < 5 UTIs in past 24 months vs >=5 UTI in past 24 months.
- Baseline *E. coli*|: >=10^4 to <10^5 vs baseline *E. coli* > =10^5
  - If participants have multiple qualifying baseline *E. coli* the participant will be presented under the ‘higher’ of the multiple subgroups
- Baseline eGFR: >=60 to <90 vs eGFR >=90

If the number of participants is too small (less than 10%) within a subgroup, then the subgroup categories may be redefined.

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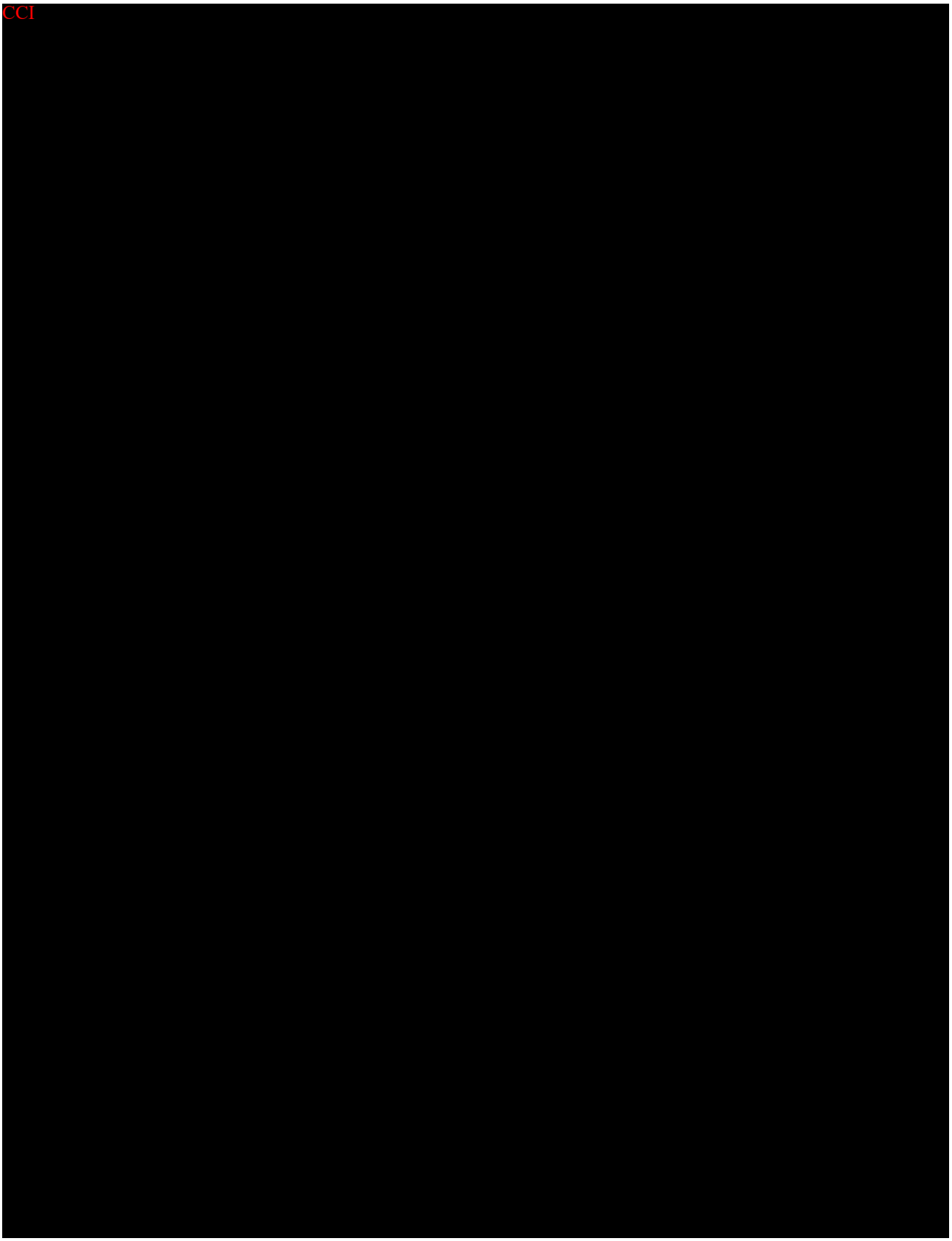

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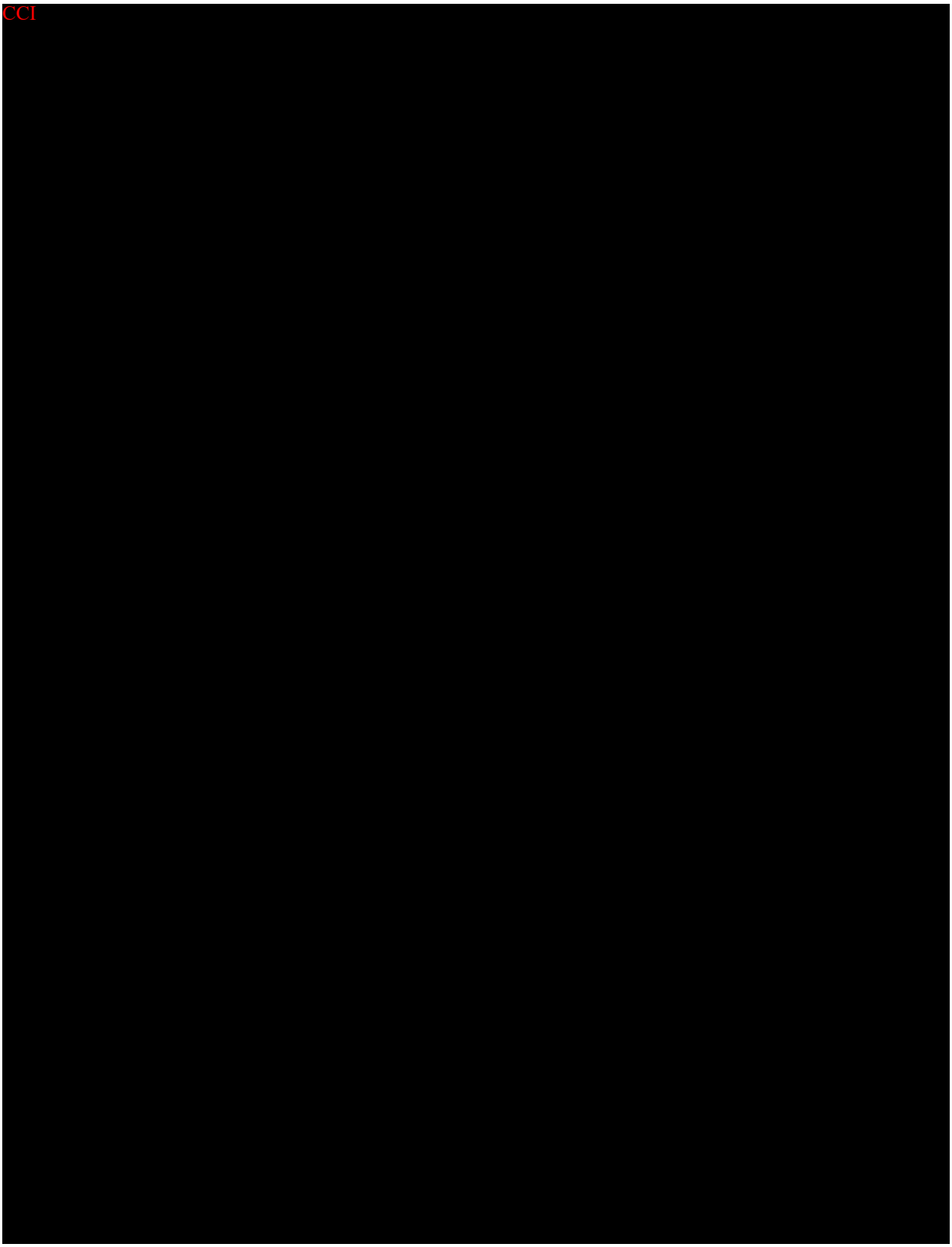


4.8. Changes to Protocol Defined Analyses

Changes from the originally planned statistical analysis specified in the protocol are detailed in Table 2

Table 2 Changes to Protocol Defined Analysis Plan

SAP version	Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
Original	• **Microbiological Success**: Microbiological response of $<10^3$ CFU/mL for all qualifying *E. coli* identified at Baseline in urine microbiology count at ToC visit, without receiving other systemic antimicrobials (rescue medications) prior to ToC. If the Baseline urine microbiology count has >1 *E. coli* strain present at $>10^4$ CFU/mL, both strains must have a response of $<10^3$ CFU/mL to achieve microbiological success. • **Microbiological Failure**: All other outcomes (for example but not limited to $\geq 10^3$ CFU/mL for any qualifying *E. coli* identified at Baseline, use of rescue medication prior to ToC, lost to follow-ups before ToC, missing/unevaluable samples at ToC, etc).	• **Microbiological Success:** Microbiological response of $<10^3$ CFU/mL for any *E. coli* (qualifying or non-qualifying at baseline) at test-of-cure. Any participant in the Micro-MPP population with *E. coli* <103 CFU/mL (no *E. coli*) at TOC. • **Microbiological Failure:** All other outcomes (for example, but not limited to, ≥103 CFU/mL for any *E. coli* (qualifying or non-qualifying at baseline), use of rescue medication prior to ToC, lost to follow-ups before ToC, missing/unevaluable samples at ToC). Any participants in the Micro-MPP population with *E. coli* ≥103 CFU/mL at TOC.	• Clarification to microbiological success/failure criteria based on FDA comment
Amendment 1	• Protocol amendment 4 updated definition of micro-ITT to require "all planned doses" rather than "at least 1 dose" and rename as Micro-MPP.	• Definition of Micro-MITT and CCI [redacted]: All eligible participants randomly assigned to study intervention who receive at least one dose of study intervention and have a Qualifying baseline *E.coli* (Micro) CCI [redacted]	• CCI [redacted]

SAP version	Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
		respectively (CCI from a quantitative bacteriological culture of a pre-treatment clean-catch midstream urine specimen.	
Amendment 3	CCI [redacted]		
	• For primary endpoint estimand: Use of rescue medication will be set to non-responder in the endpoint definition.	• Use of rescue medication after last dose of study intervention will be set to non-responder in the endpoint definition.	• Wording for primary estimand updated to clarify that rescue medication use for population of interest would only occur following the 5 day dosing period.
	• For secondary endpoints estimand: Use of rescue medication – While on treatment strategy	• Use of rescue medication – Treatment policy strategy	• Strategy for handling of ICE for estimand for Secondary endpoint – Safety so that all safety data is presented in summaries.
	• For secondary endpoints estimand: estimand specified for plasma and urine PK parameters	• For secondary endpoints estimand: estimand specified for plasma and urine PK concentrations	• Updated to align with protocol defined secondary endpoints

CCI [redacted]

CCI

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

Unless otherwise specified, the study population analyses will be based on the Screened, Enrolled, Randomised or Safety analysis set.

A summary of the number of participants in each of the participant level analysis sets will (defined in Section 3) be provided.

6.1.1. 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.

A participant is considered to have completed the study if all periods of the study up to and including the Follow-up Visit have been completed.

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

Rescreened participants will be summarized under their latest participant number.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics including age, gender, ethnicity, height/weight at screening and race will be summarized with descriptive statistics. . Pre/post-menopausal /childbearing potential age groups and Glomerular Filtration Rate (GFR) will also be presented. If the summary of demographics meets the criteria for de-identification, as described in the relevant procedural document, a de-identified version will be produced.

History of previous uUTI infections, baseline disease characteristics including baseline uropathogen recovery rate and clinical symptom score, will be summarized.

Past medical conditions and current medical conditions as of screening will be summarized separately.

6.1.3. Protocol Deviations

Important protocol deviations will be summarized by treatment.

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 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.

Protocol deviations which result in exclusion from the analysis set will also be summarized.

- Data will be reviewed prior to unblinding and freezing the database to ensure all deviations leading to analysis population exclusions are captured and categorised in the protocol deviations ADaM dataset.

6.1.4. Prior and Concomitant Medications

Concomitant medications including rescue medication will be coded using both the GSK Drug and WHO Drug dictionaries. However, the summary will be based on GSK Drug dictionary only. The summary of concomitant medications will be provided by ingredient, i.e. multi-ingredient medications will be summarized for each individual ingredient rather than a combination of ingredients. The summary will be created using ingredient base names, i.e. ingredients with the same base name but different salt will appear under one base name in the summary.

Concomitant medications include any medication that was taken at some point during the on-intervention period as defined Section 6.3.2.

Prior medications will be included in listings.

6.1.5. Study Intervention Compliance

Frequencies and percentages for number of days dosed will be presented.

6.2. Appendix 2 Electronic Clinical Outcome Assessment (eCOA) Compliance

Not Applicable

6.3. Appendix 3 Data Derivations Rule

6.3.1. Criteria for Potential Clinical Importance

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern.

In addition, the following criteria will be used to flag potential clinical importance:

6.3.1.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Potential Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Haematocrit	Ratio of 1	Female	0.32	0.52
Haemoglobin	g/L	Female	10.0	17
Lymphocytes	$x10^9$/ L		0.8	
Neutrophil Count	$x10^9$/ L		1.5	
Platelet Count	$x10^9$/ L		100	550
White Blood Cell Count (WBC)	$x10^9$/ L		3	15

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Potential Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	mmol/L		30	
Calcium	mmol/L		2	2.75
Creatinine	µmol/L			120
Glucose	mmol/L		3	9
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150

Liver Function			
Test Analyte	**Units**	**Category**	**Potential Clinical Concern Range**
ALT/SGPT	U/L	High	≥ 2x ULN
AST/SGOT	U/L	High	≥ 2x ULN
AlkPhos	U/L	High	≥ 2x ULN
T Bilirubin	µmol/L	High	≥ 1.5x ULN
T. Bilirubin + ALT	µmol/L IU/L	High	Bilirubin≥1.5xULN AND ALT≥2xULN

6.3.1.2. ECG

ECG Parameter	Units	Potential Clinically Important Range	
		Lower	**Upper**
Absolute			
Absolute QTc Interval	msec		>450
Absolute PR Interval	msec	< 110	> 220
Absolute QRS Interval	msec	< 75	> 110
Change from Baseline			
Increase from Baseline QTc	msec		≥ 60

6.3.1.3. 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
Heart Rate	bpm	< 40	> 110

6.3.2. 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 End of Study (end of all follow up visits). 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 and time is considered the start of on-intervention for AE and concomitant medication.

6.3.3. Study Day and Reference Dates

The safety and efficacy reference date is the study intervention start date and will be used to calculate study day for safety and 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

6.3.4. Assessment Window

- Actual times will be used in the derivation of PK parameters and in the individual concentration-time plots.
- Planned times will be used in the descriptive summaries and in mean and median plots
- Planned time will be used for all other analysis

For data summaries by visit, scheduled visits with nominal visit description as well as the worst-case post baseline will be displayed. Unscheduled visits will not be displayed or slotted into a visit window but will be included in the derivation of worst-case post baseline assessment. All un-scheduled visits will be displayed in the listing.

6.3.5. Multiple measurements at One Analysis Time Point

When triplicate ECG assessments are taken, mean of the measurement will be calculated first and summary statistics will be based on the calculated mean. This will apply to both baseline and post baseline assessments.

For lab tests on a study day, if more than one assessment is taken on the same day, the test from a central lab will be taken over the test from a local lab. If multiple assessments are taken from the same type of lab, the worst case will be used.

6.3.6. 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.

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>• 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.</td></tr>
<tr><td>Adverse Events</td><td>• Partial dates for AE recorded in the CRF will be imputed using the following conventions:
<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month unless this is before the start date if the study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment.

Else if study intervention start date is not missing:

o 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.</td></tr>
<tr><td>Missing start day and month</td><td>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:

o 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.

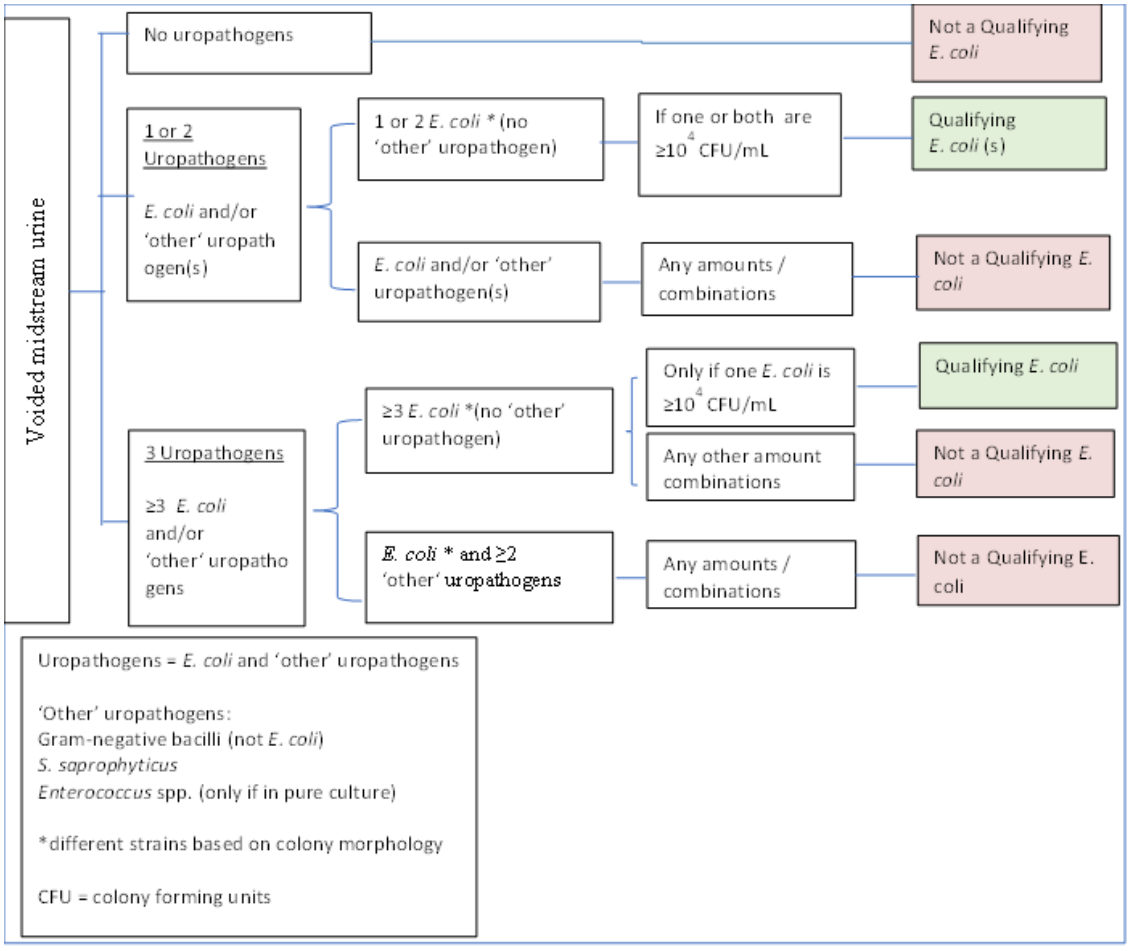
▪ Else set start date = study intervention start date.</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td><table>
<tr><td></td><td>Else set start date = January 1.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year).</td></tr>
<tr><td>Missing end day and month</td><td>No Imputation</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table></td></tr>
<tr><td>Concomitant Medications</td><td>• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:<table>
<tr><td>Missing start day</td><td>If start day of concomitant medications is missing , then set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>If concomitant medications start date is missing, then set start date = January 1.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year).</td></tr>
<tr><td>Missing end day and month</td><td>A '31' will be used for the day and 'Dec' will be used for the month.</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table></td></tr>
</table>

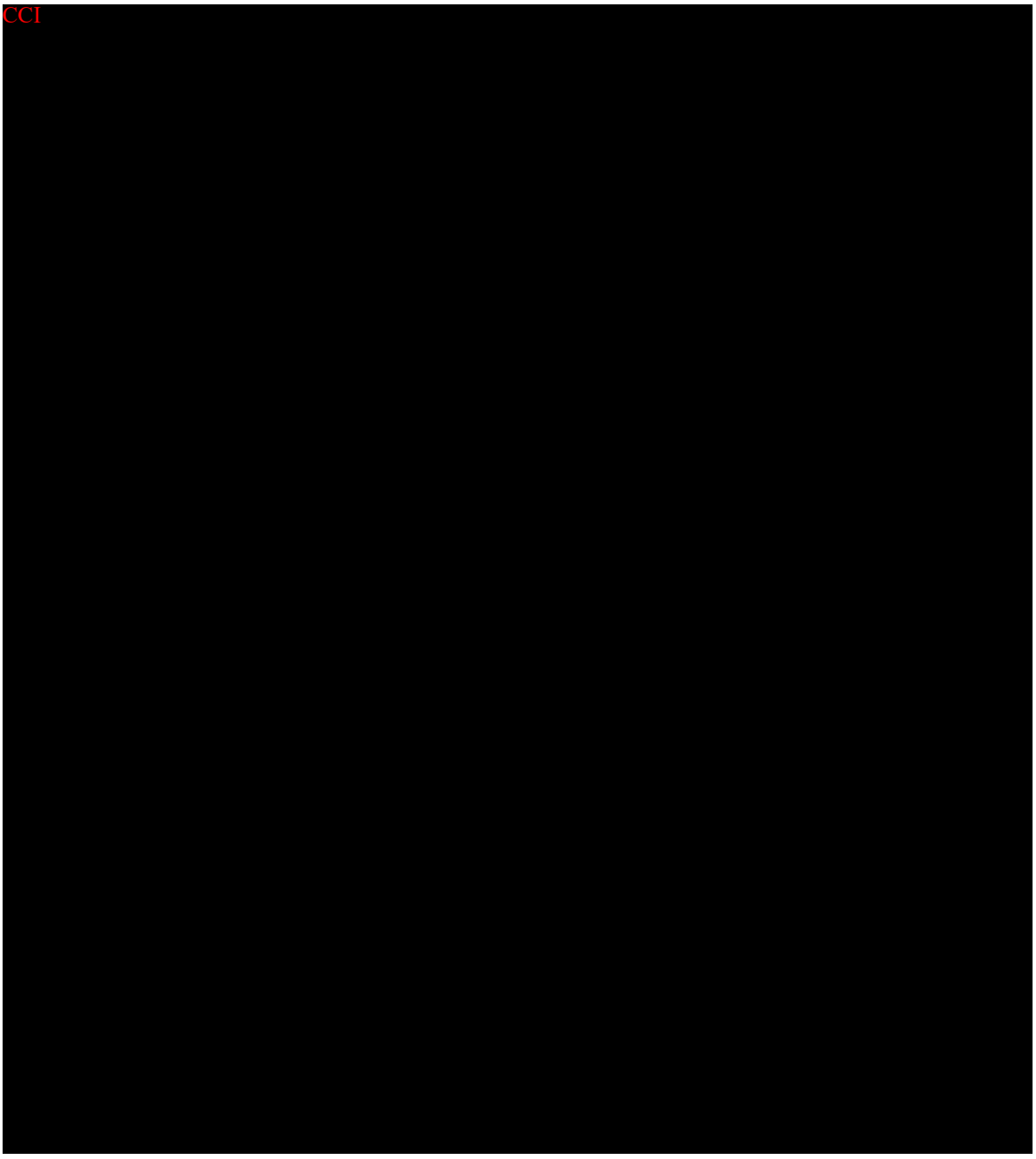
6.4. Appendix 4: Algorithm for Determining Qualifying *E. coli* Pathogen

In addition to other criteria defined in the Inclusion Criteria, only participants with a qualifying *E. coli* uropathogen at Baseline from a quantitative bacteriology culture of a pre-treatment clean-catch midstream urine specimen will be included in the Micro-MPP/CCI analysis sets. The algorithm for determining qualifying *E. coli* uropathogen based on microbiology laboratory quantitative culture results is provided below.

Figure 1 Algorithm for qualifying *E. coli* Pathogen



CCI



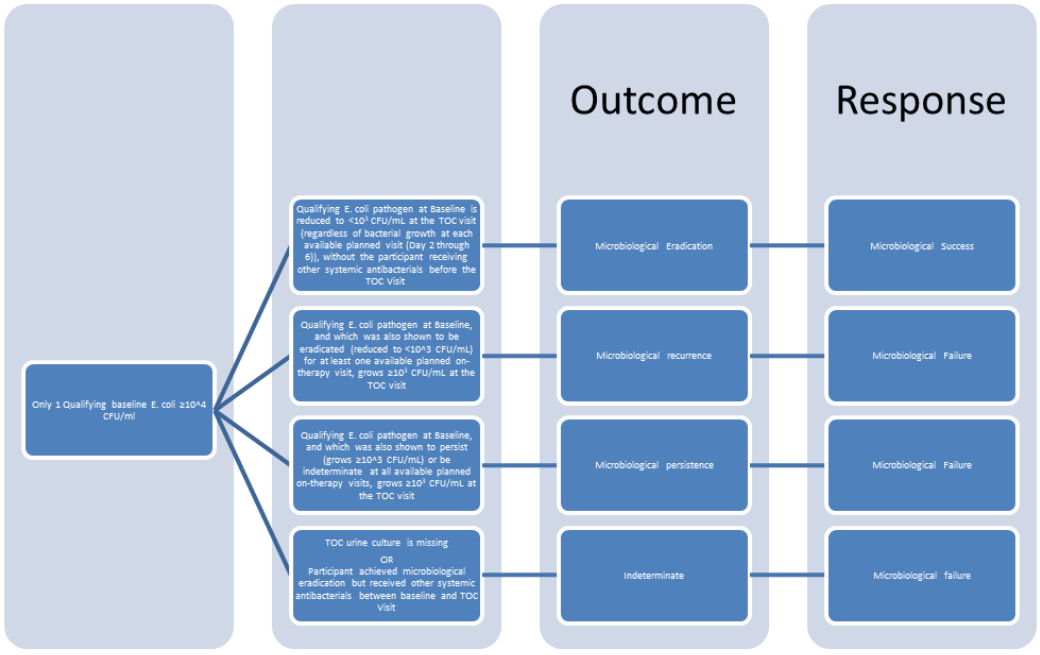
6.6. Appendix 6: Microbiological outcome and response

Microbiological outcome and response is determined as follows for qualifying *E. coli* pathogen. CCI

6.6.1. One qualifying Baseline E. coli Pathogen

CCI

6.6.1.2. ToC Visit



CCI

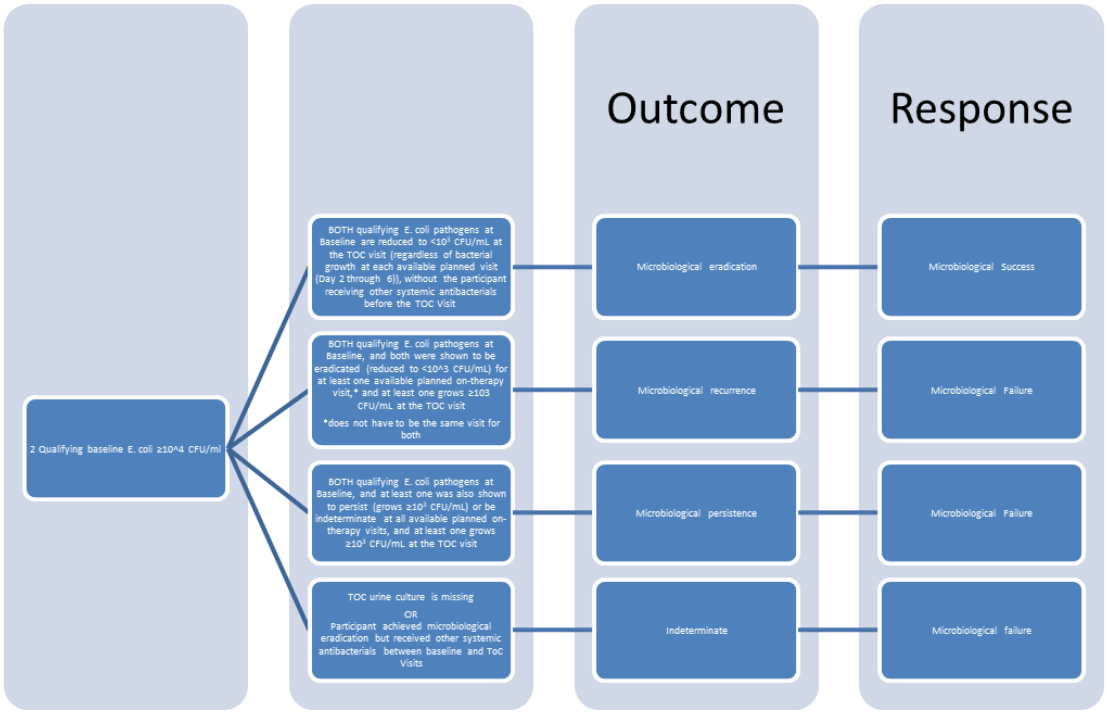
[redacted]

6.6.2. Two qualifying Baseline E. coli pathogen

CCI

[redacted]

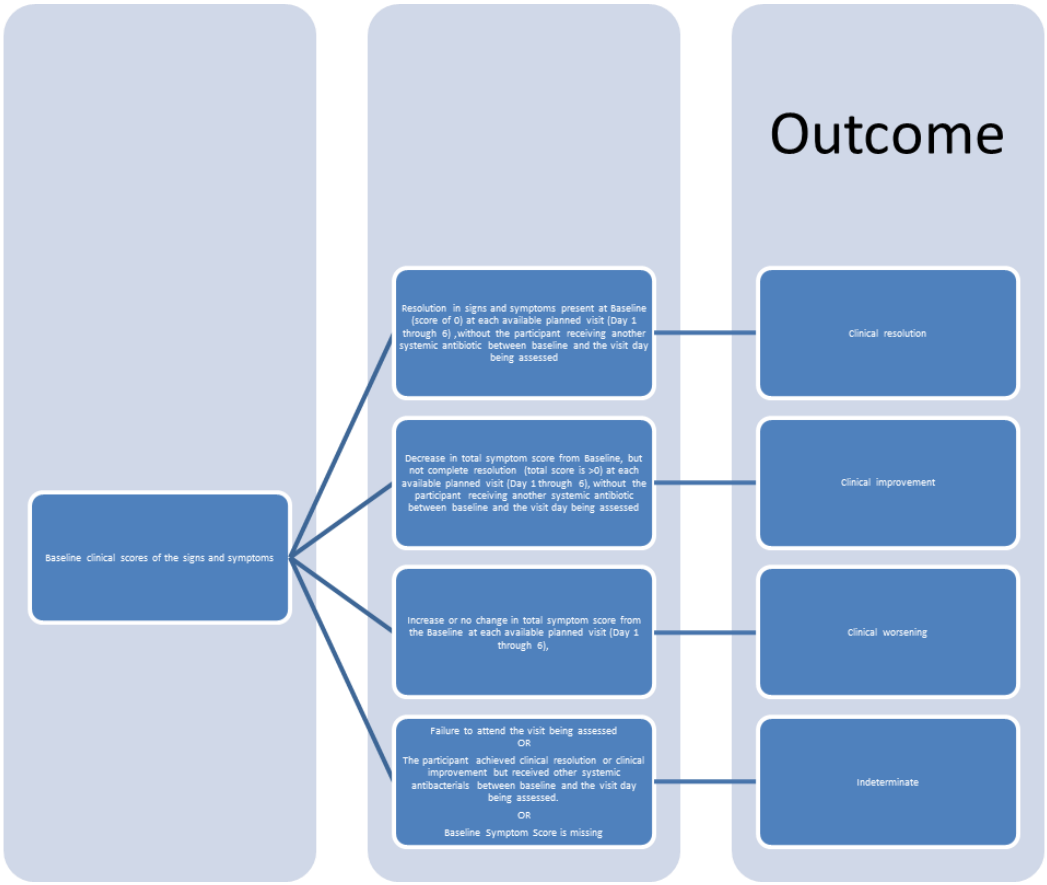
6.6.2.2. ToC Visit



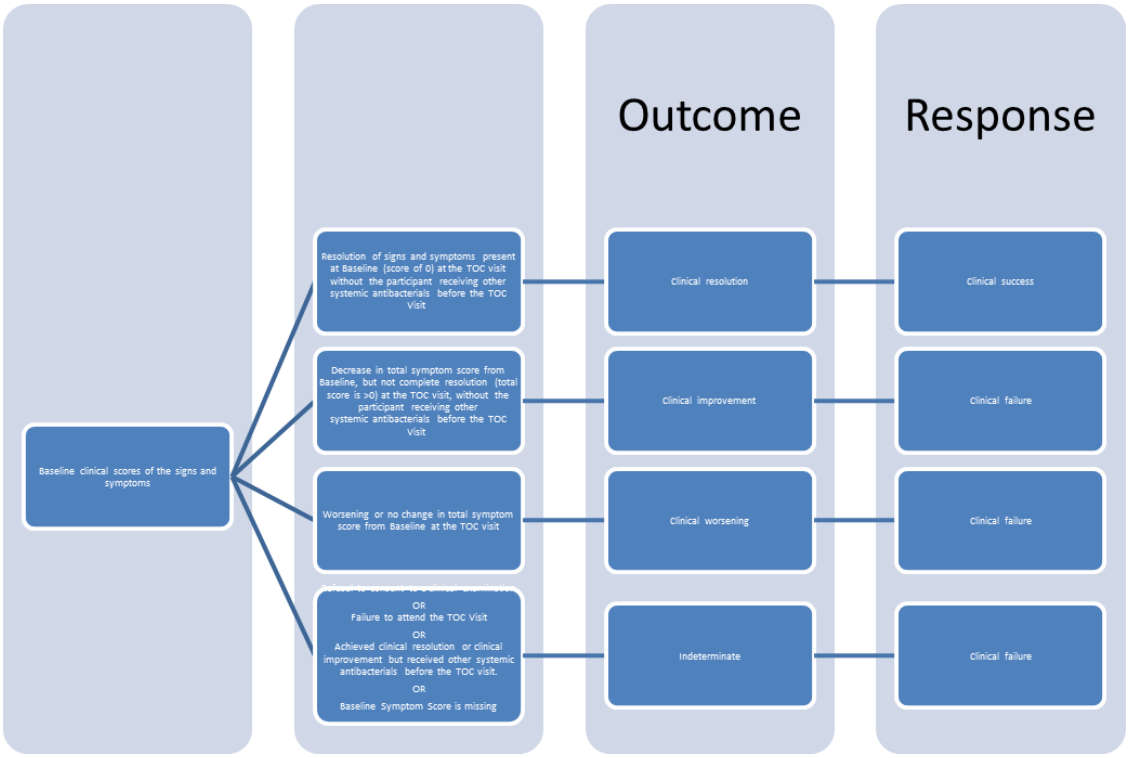
CCI

6.7. Appendix 7: Clinical symptom score outcome and response

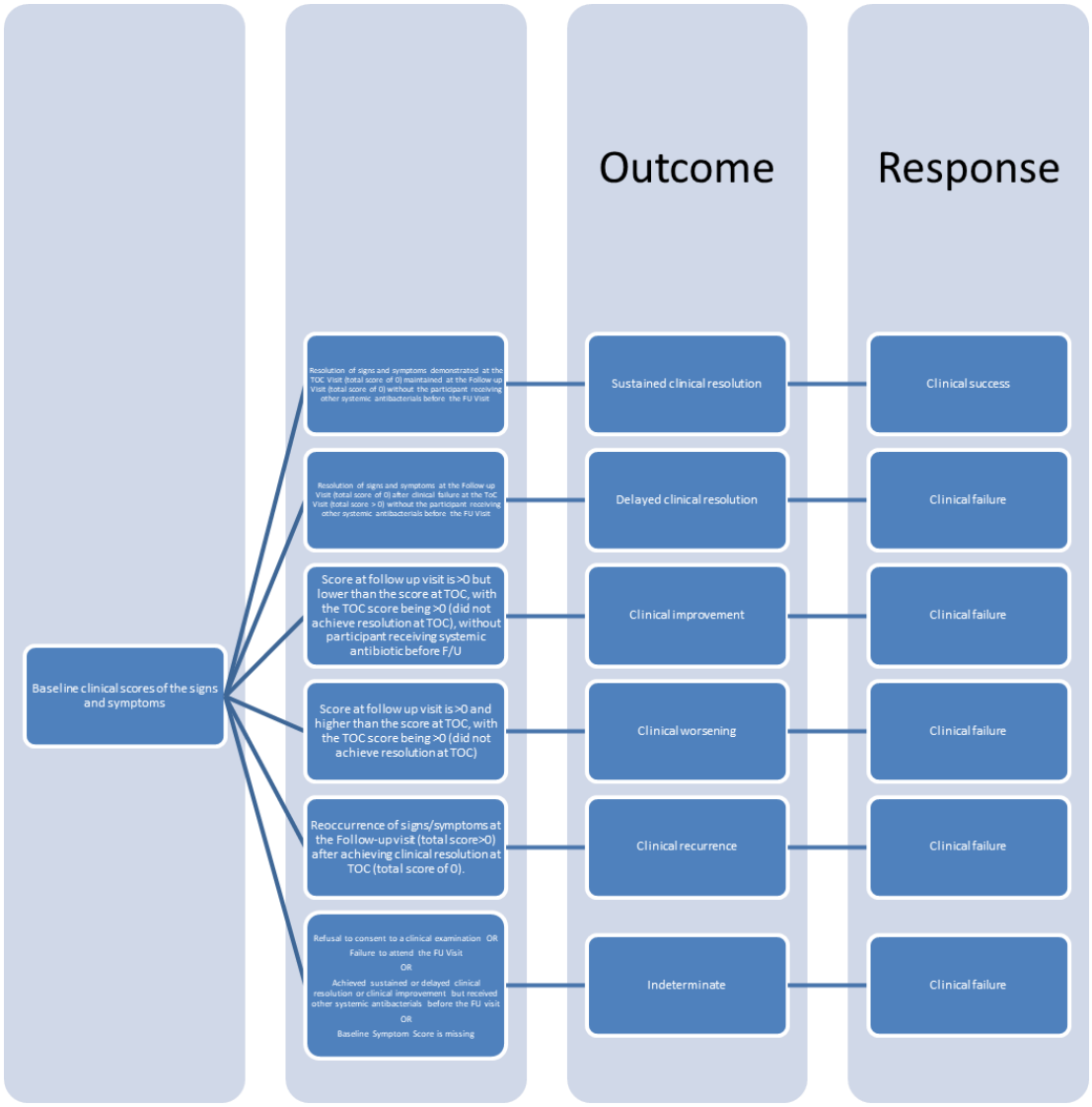
6.7.1.1. Day 2 through 6 Visits



6.7.1.2. ToC Visit



6.7.1.3. Follow-Up Visit



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HARP	WinNonlin

8. REFERENCES

Not Applicable