**Information Type:** Statistical Analysis Plan (SAP)

# TITLE PAGE

**Protocol Title:** A Phase 3b, open-label, single-arm study in adolescent and adult female participants to evaluate clinical symptom improvement and the safety of gepotidacin during treatment of uncomplicated urinary tract infections (acute cystitis)

**Study Number:** 219575

**Compound Number:** GSK2140944

**Abbreviated Title:** A study in adolescent and adult female participants to evaluate clinical symptom improvement and the safety of gepotidacin during treatment of uncomplicated urinary tract infections (acute cystitis)

**Sponsor Name:** GlaxoSmithKline Research & Development Limited

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# VERSION HISTORY

| SAP Version | Approval Date | Protocol Version (Date) on which SAP is Based | Change | Rationale |
|---|---|---|---|---|
| SAP | 12 September 2024 | Protocol 27 July 2023<br><br>Protocol Amendment 10 September 2024 | Not Applicable | Original version |
| SAP Amendment 1 | 02 Apr 2025 | Protocol 27 July 2023<br><br>Protocol Amendment 10 September 2024 | Minor edits for clarification.<br><br>The CE definitions updated to include additional clarifications compared to the protocol<br><br>Clinical output table updated<br><br>TOI list removed<br><br>Imputation rules for missing concomitant medications times added<br><br>Imputation rules for missing AE times updated | To include further Subgroup analysis and define a new analysis population. |

| SAP Version | Approval Date | Protocol Version (Date) on which SAP is Based | Change | Rationale |
|---|---|---|---|---|
| | | | Additional Supplementary analysis added for CCI [redacted] CCI [redacted] | |

# 1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report (CSR) for Study 219575.

## 1.1. Objectives, Estimands and Endpoints

| Objectives | Endpoints |
|---|---|
| Primary | |
| • To evaluate clinical symptom improvement with gepotidacin treatment in female participants with uUTI at 24 hours (±4 hours). | • Achieving clinical symptom improvement, defined as a decrease from Baseline in CSS total score of at least 1 point at 24 hours (±4 hours), without the need for other systemic antimicrobials. |
| Secondary | |
| • To assess clinical symptom improvement with gepotidacin treatment over time in female participants with uUTI. | • Achieving clinical symptom improvement, defined as a decrease from Baseline of at least 1 point in the CSS total score at 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours), without the need for other systemic antimicrobials. |
| • To assess clinical symptom resolution with gepotidacin treatment over time in female participants with uUTI. | • Achieving clinical symptom resolution, defined as a decrease from Baseline to a CSS total score of 0 at 24 hours (±4 hours), 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours), without the need for other systemic antimicrobials. |
| • To assess safety and tolerability of gepotidacin treatment in female participants with uUTI. | • Participants with TEAEs, SAEs, and AESIs. |
| Exploratory | |
| CCI [redacted] | |

| Objectives | Endpoints |
|---|---|
| CCI | |

**Estimand for primary endpoint**

The primary clinical question of interest is to assess symptom improvement without the need for other systemic antimicrobials in participants at 24 hours (±4 hours) after the initial dose of gepotidacin and having received a second dose of gepotidacin prior to the primary CSS assessment at 24 hours (±4 hours).

The primary estimand is described by the following attributes:

**Population:**

- The population is female participants ≥12 years with suspected uUTI who can adhere to 2 doses of treatment as prescribed.

**Endpoint:**

- The primary endpoint is achieving clinical symptom improvement, defined as a decrease from Baseline in CSS total score of at least 1 point at 24 hours (±4 hours), without the need for other systemic antimicrobials on or before the time of this assessment.

**Treatment condition:**

- The treatment condition is Gepotidacin 1500 mg BID.

**Intercurrent Events and Strategies:**

- The intercurrent events (ICEs) and estimand strategies are:
    1. Participants unable to take 2 doses as prescribed before the CSS assessment at 24 hours (±4 hours) (Principal Stratum Strategy). Interest lies in the group of participants who complied with the 2 doses as prescribed before the CSS assessment at 24 hours (±4 hours).

2. A participant using other systemic antimicrobials, for uUTI on or before the CSS assessment at 24 hours (±4 hours) and/or for other infections before the CSS assessment at 24 hours (±4 hours) (Composite Strategy). These ICEs are incorporated into the definition of the endpoint.

**Population level summary**

- The population-level summary to be estimated is percentage of participants who achieve clinical symptom improvement and its 95% Exact Binomial CI.

**Rationale of estimand for primary endpoint:**

1. Interest lies in evaluating study intervention benefit through a decrease in CSS total score in participants who achieve 100% compliance to study intervention (by taking the 1500 mg (2 × 750 mg) dose orally twice daily (BID) as prescribed) before the CSS assessment at 24 hours (±4 hours).
2. Participants who take other antimicrobials for uUTI indicate lack of treatment benefit and will not be able to achieve symptom improvement (i.e., treatment failures). Participants who take other antimicrobials for other infections might confound the outcome by improving the symptoms. Therefore, such participants are also set to treatment failures.

**Supplementary estimand for primary endpoint:**

A supplementary estimand will be considered if CCI of enrolled participants are not able to comply with the 2 daily doses as prescribed before the CSS assessment at 24 hours (±4 hours).

The additional clinical question of interest is to assess symptom improvement without the need for other systemic antimicrobials in participants at 24 hours (±4 hours) after the initial dose of Gepotidacin.

The supplementary estimand is described by the following attributes:

**Population:**

- The population is female participants aged ≥12 years with suspected uUTI.

**Endpoint:**

- The endpoint is achieving clinical symptom improvement, defined as a decrease from Baseline in CSS total score of at least 1 point at 24 hours (±4 hours), without the need for other systemic antimicrobials on or before the time of this assessment.

**Treatment condition:**

- The treatment condition is Gepotidacin 1500 mg BID

**Intercurrent Events and Strategies:**

- The ICEs and estimand strategies are as follows:
    1. Participants unable to take 2 doses as prescribed before the CSS assessment at 24 hours (±4 hours) (Treatment Policy Strategy). Interest lies in the treatment effect regardless of compliance with the study intervention.
    2. A participant using other systemic antimicrobials, for uUTI on or before the CSS assessment at 24 hours (±4 hours) and/or for other infections before the CSS assessment at 24 hours (±4 hours) (Composite Strategy). These ICEs are incorporated into the definition of the endpoint.

**Population level summary**

- The population-level summary to be estimated is percentage of participants who achieve clinical symptom improvement and its 95% Exact Binomial CI.

**Rationale of supplementary estimand for primary endpoint:**

1. Interest lies in evaluating study intervention benefit through decrease in CSS total score in all participants whether or not compliant with the study intervention.
2. Participants who take other antimicrobials for uUTI indicate lack of treatment benefit and will not be able to achieve symptom improvement (i.e., treatment failures). Participants who take other antimicrobials for other infections might confound the outcome by reducing the symptoms. Therefore, such participants are also set to treatment failures.

**Estimands supporting Secondary Efficacy objectives:**

The secondary efficacy clinical questions of interest are to assess the following:

1. The **improvement** of clinical signs and symptoms without the need of any other systemic antimicrobials during the 5 days of treatment with gepotidacin in participants who complied with at least 80% of the total prescribed doses before each visit.
2. The **resolution** of clinical signs and symptoms without the need of any other systemic antimicrobials during the 5 days of treatment with gepotidacin in participants who complied with at least 80% of the total prescribed doses before each visit.

The estimand attributes for the secondary efficacy objectives are as follows:

**Population:**

- The population is female participants aged ≥12 years with suspected uUTI, who can comply with ≥80% doses of treatment as prescribed.

**Endpoints:**

- Achieving clinical symptom **improvement,** defined as a decrease from Baseline of at least 1 point in the CSS total score at 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours), without the need for other systemic antimicrobials on or before the time of the assessment.
- Achieving clinical symptom **resolution**, defined as a decrease from Baseline to a CSS total score of 0, at 24 hours (±4 hours), 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours), without the need for other systemic antimicrobials on or before the time of the assessment.

**Treatment condition:**

- The treatment condition is Gepotidacin 1500 mg BID

**The intercurrent events (ICEs) and estimand strategies are:**

1. Participants unable to take ≥80% doses of gepotidacin up to each time point i.e., 24 hours (±4 hours), 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours) ((Principal stratum) as applicable for each of the two endpoints. Interest lies in the group of participants who complied with ≥80% of the total prescribed doses of gepotidacin up to 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours).
2. A participant using other systemic antimicrobials for uUTI on or before each time point i.e., 24 hours (±4 hours), 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours) and/or for other infections before each time point i.e., 24 hours (±4 hours), 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours) (Composite Strategy) as applicable for each of the two endpoints. These ICEs are incorporated into the definition of the endpoints.
3. Study intervention discontinuation (due to any reason) (Treatment Policy Strategy). Interest lies in the treatment effect regardless of study intervention discontinuation.

**Population level summary**

- The population-level summary to be estimated is percentage of participants who achieve clinical symptom improvement and its 95% Exact Binomial CI.

**Rationale of estimands for secondary efficacy endpoints:**

1. Interest lies in evaluating study intervention benefit through decrease in CSS total score in participants who had at least 80% compliance to study intervention up to each time point i.e., 24 hours (±4 hours), 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours).
2. Participants who take other antimicrobials for uUTI on or before 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours) indicate lack of treatment benefit and will not be able to achieve symptom improvement (i.e., treatment failures) at the respective time points. Participants who take other antimicrobials for other infections before 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours) might confound the outcome of the visit by reducing the symptoms. Therefore, such participants are also set to treatment failures at the respective time points (Composite Strategy).

Participants who take other antimicrobials for uUTI on or before 24 hours (±4 hours), 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours) indicate lack of treatment benefit and will not be able to achieve symptom resolution (i.e., treatment failures) at the respective time points. Participants who take other antimicrobials for other infections before 24 hours (±4 hours), 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours) might confound the outcome of the visit by reducing the symptoms. Therefore, such participants are also set to treatment failures at the respective time points (Composite Strategy).

3. Interest lies in the treatment effect regardless of the 5-day treatment completion, which reflects how participants may be treated in clinical practice. Hence, a treatment policy strategy is appropriate for treatment withdrawal before completing the 5 days of treatment.

**Supplementary Estimands for Secondary Efficacy Endpoints:**

Supplementary estimands will be considered if CCI of enrolled participants are unable to comply with ≥80% of the total prescribed doses of gepotidacin up to each time point i.e., 24 hours (±4 hours), 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours).

The additional secondary efficacy clinical questions of interest are to assess the following:

1. The improvement of clinical signs and symptoms without the need of any other systemic antimicrobials during the 5 days of treatment with gepotidacin in all participants regardless of compliance with study intervention before 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours).
2. The resolution of clinical signs and symptoms without the need of any other systemic antimicrobials during the 5 days of treatment with gepotidacin in all participants regardless of compliance with study intervention before 24 hours (±4 hours), 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours).

The estimand attributes for the supplementary estimands for the secondary objectives are as follows:

**Population:**

- The population is female participants aged ≥12 years with suspected uUTI, who can comply with ≥80% doses of treatment as prescribed.

**Endpoints:**

- Achieving clinical symptom improvement, defined as a decrease from Baseline of at least 1 point in the CSS total score at 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours), without the need for other systemic antimicrobials on or before the time of the assessment.
- Achieving clinical symptom resolution, defined as a decrease from Baseline to a CSS total score of 0, at 24 hours (±4 hours), 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours), without the need for other systemic antimicrobials on or before the time of the assessment.

**Treatment condition:**

- The treatment condition is Gepotidacin 1500 mg BID.

**Intercurrent Events and Strategies:**

- The intercurrent events (ICEs) and estimand strategies are:
    1. Participants unable to take ≥80% doses of gepotidacin up to each time point i.e., 24 hours (±4 hours), 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours) (Treatment Policy Strategy). Interest lies in all participants regardless of compliance with study intervention.
    2. A participant using other systemic antimicrobials (for uUTI or other infections) on or before 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours) (Composite Strategy). This ICE is incorporated into the definition of the endpoint.
    3. Study intervention discontinuation (due to any reason) (Treatment Policy Strategy). Interest lies in the treatment effect regardless of study intervention discontinuation.

**Population level summary**

- The population-level summary to be estimated is percentage of participants who achieve clinical symptom improvement and its 95% Exact Binomial CI.

**Rationale of supplementary estimands for secondary efficacy endpoints:**

1. Interest lies in evaluating study intervention benefit through decrease in CSS total score in all participants, whether or not ≥80% compliant with study intervention.
2. Participants who take other antimicrobials for uUTI on or before 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours) indicate lack of treatment benefit and will not be able to achieve symptom improvement (i.e., treatment failures) at the respective time points. Participants who take other antimicrobials for other infections before 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours) might confound the outcome of the visit by reducing the symptoms. Therefore, such participants are also set to treatment failures at the respective time points (Composite Strategy).

   Participants who take other antimicrobials for uUTI on or before 24 hours (±4 hours), 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours) indicate lack of treatment benefit and will not be able to achieve symptom resolution (i.e., treatment failures) at the respective time points. Participants who take other antimicrobials for other infections before 24 hours (±4 hours), 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours) might confound the outcome of the visit by reducing the symptoms. Therefore, such participants are also set to treatment failures at the respective time points (Composite Strategy)
3. Interest lies in the treatment effect regardless of 5-day treatment completion, which reflects how participants may be treated in clinical practice. Hence, a treatment policy strategy is appropriate for treatment withdrawal before completing 5 days of treatment.

**Estimand for secondary safety objective:**

The estimand attributes for the secondary safety objectives are as follows:

**Population:**

- The population is female participants aged ≥12 years with suspected uUTI.

**Endpoints:**

The safety endpoints are Adverse Events (AE), Serious Adverse Events (SAE) and Adverse Events of Special Interests (AESI).

**Treatment condition:**

- The treatment condition is Gepotidacin 1500 mg BID

**Intercurrent Event and Strategy:**

The intercurrent event and estimand strategy is:

- Study treatment discontinuation due to any reason (treatment policy).

**Population level summary**

- The population-level summary to be estimated are counts and percentages of participants who have experienced AEs, SAEs, and AESIs.

**Rationale of estimands supporting secondary safety objectives:**

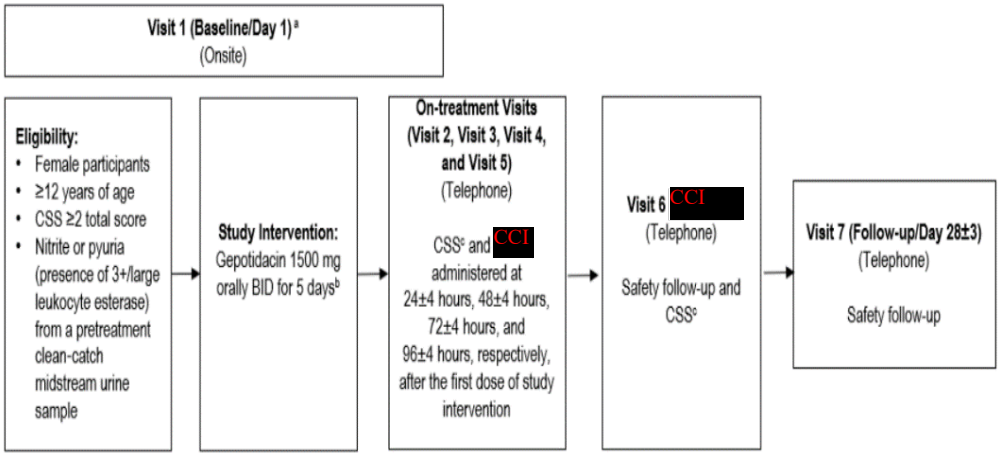
Interest lies in assessing safety of participants irrespective of whether they completed the study intervention or not. These safety endpoints will be captured and reported for each participant after the first dose of treatment regardless of study treatment completion.

## 1.2. Study Design

| Overview of Study Design and Key Features |
| --- |
| The study design schematic is shown below in **Figure 1** |

## Overview of Study Design and Key Features

**Figure 1 Study design overview**




a. During Visit 1, prior to first dose of study intervention, the Virtual Research Coordination Center (VRCC) will contact the participant by telephone to perform the CSS assessment and CCI CCI (in that specific order). This will be used as the Baseline CSS. The CSS will be reviewed (but not remeasured) by a study physician or otherwise appropriate medically trained staff from the study site onsite along with determination of whether other eligibility criteria are met before the first dose of study medication. Only If VRCC cannot do the telephone call, then the study physician or otherwise appropriate medically trained staff from the study site will ask the CSS questions and complete the CCI CCI before the first dose of study intervention. Only one CSS and CCI is to be performed at Visit.

b. The first dose of study intervention will be administered at the study site during Visit 1; the remaining 9 doses over the 5-day treatment course will be self-administered as outpatients. Each dose is to be taken after food consumption and with water to assist with tolerability.

c. At Visit 2, Visit 3, Visit 4, and Visit 5, the CSS assessment and CCI CCI will be completed (in that order) by VRCC. CCI [redacted]

| | |
|---|---|
| **Design Features** | Phase 3b, open-label, single-arm, multicentre study to evaluate clinical symptom improvement and the safety of gepotidacin during the treatment of uUTIs.<br>Female participants need to be ≥12 years of age with 2 or more clinical symptoms of uUTI and nitrite or pyuria from a pre-treatment clean-catch midstream urine sample.<br>The total duration of study participation is approximately 28 days, with at least 1 planned onsite study visit and 6 telephone calls study contacts, with allowance for unscheduled visits.<br>Visit Baseline/Day 1): onsite, Visit 2 (24 hours ±4 hours), Visit 3 (48 hours ±4 hours), Visit 4 (72 hours ±4 hours), and Visit 5 (96 hours ±4 hours): telephone, Visit 6 (CCI [redacted]): telephone, Visit 7 (Follow-up/Day 28): telephone, Unscheduled Visit: onsite or telephone.<br>Approximately 90 participants will be enrolled in the study to ensure at least 82 evaluable participants are included in the primary analysis.<br>Each visit will be assessed over a 24-hour period, beginning with the first dose of study intervention received for an individual participant. For example, participants who only receive 1 dose of study intervention on their first calendar day in the study due to a late afternoon/evening Visit 1 will take the second dose |

| Overview of Study Design and Key Features | |
|---|---|
| | on the following calendar day, which will complete Day 1. This pattern will continue until all 10 doses are received; thus, the tenth/last dose will be taken prior to Visit 5 (may be 5 or 6 calendar days, depending on when the first dose is taken).<br>The primary uUTI symptom assessment will be the CSS at 24 hours ±4 hours (Visit 2). Participants must have taken a total of 2 doses of gepotidacin before the 24 hours ±4 hours (Visit 2) assessment of CSS.<br>Other uUTI assessments will include the CCI CCI |
| **Study intervention** | Participants will receive oral study intervention BID for 5 days. Doses are to be taken approximately 12 hours apart, but the allowable window is 6 to 14 hours and must be at least a 6-hour minimum window between doses. The first oral dose will be administered at the study site at Baseline; participants will self-administer subsequent doses as outpatients thereafter. |
| **Study intervention Assignment** | Participants will be receiving the following study treatment once passed eligibility criteria as described in Figure 1<br>Gepotidacin: 1500 mg (2 × 750 mg) administered orally twice daily (BID) for 5 days to complete 3000 mg total daily dose. |
| **Interim Analysis** | An Interim Analysis (IA) is not planned in the study. |

# 2. STATISTICAL HYPOTHESES

No formal hypothesis testing will be performed for the primary, secondary, and exploratory endpoints.

## 2.1. Multiplicity Adjustment

No multiplicity adjustment will be performed for the primary, secondary, and exploratory endpoints.

# 3. ANALYSIS SETS

| Analysis Set | Definition / Criteria | Analyses Evaluated |
|---|---|---|
| Screened (SCR) | • All participants who were screened for eligibility | • Study population |
| Intent to-treat (ITT) | • All participants who enrolled in the study (i.e., excluding screen failures). | • Study population<br>• Summary for disclosure documentation<br>• CCI [redacted] CCI<br>• Supplementary estimand of the primary endpoint as described in Section 1.1.<br>• Supplementary estimands for secondary efficacy endpoints as described in Section 1.1. (Clinical Improvement at 48 hours (±4 hours), 72 hours (±4 hours), 96 hours (±4 hours) and Clinical Resolution at 24 hours (±4 hours), 48 hours (±4 hours), 72 hours (±4 hours), 96 hours (±4 hours)) |
| Primary Clinically Evaluable at 24 hours (±4 hours) (CE24) | • All participants in the ITT analysis set who adhered to the 2 doses of treatment as prescribed before the 24 hours (±4 hours) CSS assessment (if available), or, before 24 hours (+4 hours) from first dose (if CSS assessment is missing). | • Primary estimand for primary efficacy endpoint as described in Section 1.1. (Clinical Improvement at 24 hours (±4 hours))<br>• Estimands for secondary efficacy endpoints as described in Section 1.1.<br>• (Clinical Improvement at 24 hours (±4 hours)) |
| Clinically Evaluable at 48 hours (±4 hours) (CE48) | • All participants in the ITT analysis set who adhered to at least 80% of planned doses of gepotidacin as prescribed before the 48 hours (±4 hours) CSS assessment (if available), or, before 48 hours (+4 hours) from first dose (if CSS assessment is missing). | • Estimands for secondary efficacy endpoints as described in Section 1.1.<br>• (Clinical Improvement and Clinical Resolution at 48 hours (±4 hours)) |
| Clinically Evaluable at 72 hours | • All participants in the ITT analysis set who adhered to at least 80% of planned doses of gepotidacin as | • Estimands for secondary efficacy endpoints as described in Section 1.1. |

| Analysis Set | Definition / Criteria | Analyses Evaluated |
|---|---|---|
| (±4 hours) (CE72) | prescribed before the 72 hours (±4 hours) CSS assessment (if available), or, before 72 hours (+4 hours) from first dose (if CSS assessment is missing). | • (Clinical Improvement and Clinical Resolution at 72 hours (±4 hours)) |
| Clinically Evaluable at 96 hours (±4 hours) (CE96) | • All participants in the ITT analysis set who adhered to at least 80% of planned doses of gepotidacin as prescribed before the 96 hours (±4 hours) CSS assessment (if available), or, before 96 hours (+4 hours) from first dose (if CSS assessment is missing). | • Estimands for secondary efficacy endpoints as described in Section 1.1. (Clinical Improvement and Clinical Resolution at 96 hours (±4 hours))<br>• CCI [redacted] |
| CCI [redacted] | | • |
| Safety (SAF) | • All enrolled participants who received at least 1 dose of study intervention. | • Estimand for secondary safety endpoints as described Section 1.1. |

# 4. STATISTICAL ANALYSES

## 4.1. General Considerations

The purposes of statistical analysis to estimate the percentage of participants showing an improvement/resolution of the clinical symptoms and safety and tolerability with gepotidacin treatment in female participants with uUTI.

Statistical analysis will be presented as per estimands for primary and secondary objectives. ICEs and strategies for primary and secondary estimands are defined in Section 1.1.

The following variables are:

- Age (continuous and ordered categorically)
- Race (categorical).
- Ethnicity (categorical).
- Site (categorical).

Any variable or combinations of variables which leads to a non-zero count (n) of <11 participants in a clinical study having this mix of characteristics must be considered as a risk to re-identification.

### 4.1.1. General Methodology

Participants who prematurely withdrew from study will not be replaced.

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.

Unless stated otherwise, confidence intervals (CI) will be produced using 95% confidence levels.

### 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 a participant is in the ITT but hasn't taken a dose, they will be included in study population summaries on ITT set. However, their change from baseline in CSS and CCI values will not be included in all the efficacy summary tables based on the CE sets. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

If any participant is enrolled with a baseline CSS score < 2, it will be flagged as a protocol deviation and such participants will be excluded from the ITT and all CE analysis sets. If they have taken the dose, then they will be included in the safety analysis set.

CCI

If either baseline or post-baseline data is missing, then change from baseline will be set to missing at that visit/timepoint.

The laboratory data, vital signs, ECG parameters are evaluated only at the baseline, but there could be assessments taken at unscheduled visits, which will only be included in the summary of worst-case post-baseline visit (only if there are at least 5 participants with data at unscheduled visits) and in the listings.

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. Clinical Outcomes

The Clinical Outcome variables of a participant will be programmatically determined by comparing their total clinical signs and symptoms score at each scheduled timepoints except CCI [redacted] (i.e., 24 hours ± 4 hours, 48 hours ± 4 hours, 72 hours ± 4 hours and 96 hours ± 4 hours) to the score at Baseline. The clinical outcomes at CCI [redacted] are defined in Section 4.4.2.

The clinical outcomes are then used to define the primary and secondary response variables:

**Table 1 Clinical outcome at each Visit/Timepoint**

| Definition Criteria | Outcome |
|---|---|
| Improvement of clinical signs and symptoms of uUTI present from Baseline, but not complete resolution, without the participant receiving other systemic antimicrobials for uUTI on/before each timepoint and without receiving other systemic antimicrobials for any other infections before each timepoint. | Clinical Improvement without Clinical Resolution |
| Improvement and complete resolution of clinical signs and symptoms of uUTI present from Baseline, without the participant receiving other systemic antimicrobials for uUTI on/before each timepoint and without receiving other systemic antimicrobials for any other infections before each timepoint. | Clinical Improvement with Clinical Resolution |
| Resolution of clinical signs and symptoms of uUTI present at Baseline (i.e., reduction of total CSS score to 0), without receiving other systemic antimicrobials for uUTI on/before each timepoint and without receiving systemic antimicrobials for other infections before each timepoint. | Clinical Resolution |
| No change is a change from baseline score of 0 at each timepoint, without the participant receiving other systemic antimicrobials for uUTI on/before each timepoint and without receiving systemic antimicrobials for other infections before each timepoint. | No Change |
| Worsening in clinical signs and symptoms from baseline (i.e., increase from baseline total CSS score >=1) and/or the participants receiving other systemic antimicrobials for uUTI on/before each timepoint. | Clinical Worsening |
| (1) The baseline score is missing, (unless clinical worsening outcome criteria were met) or<br>(2) Post baseline assessment is missing (unless clinical worsening outcome criteria were met):<br>• The post-baseline visit occurred but assessment is missing, or<br>• The post-baseline visit not occurred, or | Unable to determine |

| Definition Criteria | Outcome |
|---|---|
| • The post-baseline assessment is out of visit window, or<br>(3) The participant received any other systemic antimicrobials for other infections before the post-baseline timepoint (unless clinical worsening outcome criteria were met) | |

Note: Each timepoint is defined based on the date/time from the first dose.

Timepoints are 24 hours ± 4 hours, 48 hours ± 4 hours, 72 hours ± 4 hours, 96 hours ± 4 hours.

## 4.2. Primary Endpoint(s) Analyses

The primary estimand and supplementary estimands for the primary endpoint are defined in Section 1.1.

### 4.2.1. Definition of primary endpoint

The primary efficacy endpoint is achieving clinical symptom improvement (including clinical resolution). In this study, a participant will be considered to have clinical improvement (including clinical resolution) outcome if they attain either a "Clinical Improvement with Clinical Resolution" outcome or, a "Clinical Improvement without Clinical Resolution" outcome as defined in Table 1. And otherwise, as not improved/failure if they have any other outcomes.

Individual scores will be recorded by a study physician or otherwise appropriately medically trained staff, as recorded in the delegation log. Clinical symptom score (CSS) of acute cystitis participants will be recorded as per the protocol defined SoA using the following scoring system:

| **Clinical Signs and Symptoms** | **None** | **Mild**<br><br>Symptom is easily tolerated, causing minimal discomfort, and not interfering with everyday activities | **Moderate**<br><br>Symptom is sufficiently discomforting to interfere with normal everyday activities | **Severe**<br><br>Symptom prevents normal everyday activities |
|---|---|---|---|---|
| | SCORE 0 | SCORE 1 | SCORE 2 | SCORE 3 |
| Dysuria[a] | | | | |
| Frequency | | | | |
| Urgency | | | | |
| Lower abdominal | | | | |

| Clinical Signs and Symptoms | None | Mild<br><br>Symptom is easily tolerated, causing minimal discomfort, and not interfering with everyday activities | Moderate<br><br>Symptom is sufficiently discomforting to interfere with normal everyday activities | Severe<br><br>Symptom prevents normal everyday activities |
|---|---|---|---|---|
| | SCORE 0 | SCORE 1 | SCORE 2 | SCORE 3 |
| or suprapubic pain | | | | |

a. Dysuria is defined as pain or burning when passing urine.

- The clinical signs and symptoms include dysuria, frequency, urgency, and lower abdominal or suprapubic pain. Each of the signs and symptoms will be scored from 0 to 3.
- At Baseline, the participant must present with at least 2 signs and symptoms and have a total cumulative symptom score ≥ 2. 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. If the participant is missing baseline assessment, they will be considered 'Unable to determine' (refer Table 1) for outcome at the respective visit.
- The clinical symptoms improvement will be programmatically determined by comparing the total scores of the signs and symptoms of acute cystitis at the 24 hours (±4 hours) to those present at baseline as shown in Table 1.

### 4.2.2. Main analytical approach for primary endpoint

Participants achieving the primary efficacy endpoint of clinical symptom improvement with resolution at 24 hours ± 4 hours (refer definition in Section 4.2.1.) will be estimated by frequency and percentage using CE24 set.

Exact Binomial (Clopper Pearson) 95% confidence limits for percentage of participants with clinical symptom improvement at 24 hours ± 4 hours will be computed. Participants who are not able to complete the CSS assessment at 24 hours (±4 hours) will be considered as 'treatment failure' and included as 'not improvers' in primary analysis.

A stacked bar graph will be produced for:

- Individual component of clinical symptoms by severity. (none/mild/moderate/severe) at 24 hours and baseline which will be presented using the ITT and CE24 sets respectively.
- Total clinical symptom score categories classified as (<2, 2-5, 6-8, 9-12) will be presented by visits using the ITT and CE24 sets.

- Percentage of participants with clinical improvement, clinical resolution, Clinical worsening and UTD by visits for CE24 set.

A descriptive summary will be presented for CSS total and individual scores (Dysuria, Frequency, Urgency, and Lower abdominal or Suprapubic pain) including n, mean, standard deviation (std), median, minimum, and maximum at each timepoint (24 hours ± 4 hours, 48 hours ± 4 hours, 72 hours ± 4 hours and 96 hours ± 4 hours) for the ITT set. Participants listings for clinical outcome and response will also be produced for ITT set.

### 4.2.3. Sensitivity analyses for primary endpoint analysis

Sensitivity analysis will be conducted to examine the robustness of the primary efficacy results for the primary estimand. The sensitivity analysis will be performed using the CE24 set. A sensitivity analysis for the primary endpoint will be carried out to assess the impact for those participants who are unable to complete the CSS assessment at 24 hours (±4 hours). Missing clinical improvement data (without any antibiotic use) will be imputed under the missing at random (MAR) assumption. If an antibiotic is taken for uUTI before or at the timepoint of CSS assessment and/or for other infections before the timepoint of CSS assessment, the outcome variable will be imputed as ("Participants without Clinical Improvement or Resolution"). Multiple imputation method will be implemented to impute the incomplete (missing) CSS at 24 hours (±4 hours) using following steps -

Step 1: The missing clinical improvement with resolution outcome (without any antibiotics use) will be imputed using a logistic regression model. The following baseline covariates will be included in the imputation model. The number of imputations will be 1000 and SEED=219575.

- CCI
- [redacted]
- [redacted]

Any participants who have a missing value for one or more model covariates listed above will be excluded from the imputation model. The participants with missing covariates will be classified as "Participants without Clinical Improvement or Resolution."

Model for multiple imputation will be diagnosed to ensure the good fit for the data of clinical response.

Step 2: Step 1 will generate 1000 imputed datasets. From the imputed dataset, participants with clinical improvement will then be derived using the imputed and non-missing data per Section 4.2.1. and Table 1

Step 3: The estimated quantities in Step 2 will be combined across the imputed datasets using Rubin's rules to provide pooled estimates for the clinical symptom improvement rate.

Percentage of participants with "Clinical improvement with resolution outcome" at 24 hours ± 4 hours will be estimated and its corresponding 95% (Wald) CIs will also be presented.

### 4.2.4. Supplementary estimand for primary endpoint and analysis

A supplementary estimand analysis for primary endpoint will be conducted if CCI of participants in the ITT analysis set are unable to comply with the 2 doses of gepotidacin before 24 hours (±4 hours). Supplementary estimand analysis will be performed using ITT analysis set. Thereby including those participants who were unable to adhere to the 2 doses of treatment as prescribed before 24 hours (±4 hours) and were excluded from the CE24 set. Participants who are unable to complete the CSS assessment at 24 hours (±4 hours) will be considered treatment failures and included in the analysis as not improvers. Percentage of participants who achieve clinical symptom improvement along with the 95% exact Binomial CI will be produced in supplementary estimand analysis for primary efficacy endpoint.

#### 4.2.4.1. Sensitivity analysis of supplementary estimand for primary endpoint

- A sensitivity of the supplementary estimand for primary endpoint will be performed according to the rule mentioned in Section 4.2.4. considering ITT analysis set. The multiple imputation method will be used to impute the Responders (participants who achieve clinical symptom improvement) at 24 hours (±4 hours) as described in Section 4.2.3. step 1 & step 2.

Percentage of participants clinical symptom improvement at 24 hours ± 4 hours will be estimated and its corresponding 95% Exact Binomial CIs will also be presented.

## 4.3. Secondary Endpoint(s) Analyses

Estimands supporting secondary efficacy endpoints and Supplementary estimand (refer Section 1.1.) for secondary efficacy endpoints will be used for the secondary efficacy analysis.

### 4.3.1. Secondary endpoint(s)

The secondary efficacy endpoints and analyses are described in this Section.

- Achieving clinical symptom improvement, defined as a decrease from baseline of at least 1 point in the CSS total score at 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours), without the need for other systemic antimicrobials on or before the time of the assessments. A participant will be considered to have clinical improvement (including clinical resolution) outcome if they attain either a "Clinical Improvement with Clinical Resolution" outcome or, a "Clinical Improvement without Clinical Resolution" outcome as defined in Table 1. And otherwise, as not improved/failure if they have any other outcomes.
- Achieving clinical symptom resolution, defined as a decrease from baseline to a CSS total score of 0 at 24 hours (±4 hours), 48 hours (±4 hours), 72 hours (±4 hours), and

96 hours (±4 hours), without the need for other systemic antimicrobials on or before the time of the assessments, as defined in Table 1. A participant will be considered to have clinical symptom resolution if they attain an outcome (As defined in Table 1) of "Clinical Resolution". They will be considered as not achieving clinical resolution for all other outcomes in Table 1 (i.e. Clinical Improvement without Clinical Resolution, no change, clinical worsening and UTD).

#### 4.3.1.1. Definition of secondary endpoints

The clinical symptoms improvement (with and without resolution) and clinical resolution responses of a participant at each timepoint will be programmatically determined as defined in Table 1 of Section 4.1.3.

#### 4.3.1.2. Main analytical approach for secondary endpoints

The secondary efficacy endpoints will be estimated by number and percentage for participants with clinical symptom improvement at each timepoint (48 hours ± 4 hours, 72 hours ± 4 hours, and 96 hours ± 4 hours) using CE48, CE72 and CE96 sets respectively.

Additionally, the secondary efficacy endpoints will also be estimated by the number and percentage of participants with clinical symptom resolution at each timepoint, 24 hours (±4 hours), 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours) using CE24 , CE48 , CE72 and CE96 sets respectively, as described in Section 3.

Counts and percentage and Exact binomial (Clopper Pearson) 95% confidence limits for percentage of participants clinical symptom improvement and resolution at each timepoint will be computed.

Participants who are not able to complete the CSS assessment at each timepoint (48 hours ± 4 hours, 72 hours ± 4 hours and 96 hours ± 4 hours) will be considered as 'treatment failure' and included as not improved in the analysis of symptom improvement and not resolved in the analysis of symptom resolution.

A shift table will be created to explore the changes in the total CSS score and the individual symptoms score from baseline by visit. The analysis will be conducted on the ITT set at each timepoints (i.e. 24 hours (±4 hours), 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours).

#### 4.3.1.3. Sensitivity analyses for secondary endpoints

Sensitivity analysis will be executed to investigate the robustness of the secondary efficacy outcomes (Outcomes are "Clinical Improvement with resolution" and "Clinical Resolution").

This sensitivity analyses will measure the impact for those participants who are unable to complete the CSS assessment at each timepoint. Multiple imputation method will be used to impute the clinical outcome of interest at each timepoint (48 hours ± 4 hours, 72 hours

± 4 hours and 96 hours ± 4 hours) as described in Section 4.2.3. Step 1 & Step 2 with an additional covariate:

- CCI [redacted]

Counts and percentage of participants with the outcome of interest at each timepoint and its corresponding 95% Exact Binomial CIs will be presented.

#### 4.3.1.4. Supplementary estimand for secondary endpoint analyses

A supplementary estimand analyses for secondary endpoints will be performed if CCI [redacted] of participants in the ITT analysis set are unable to take ≥80% doses of gepotidacin up to each of 24 hours ± 4, 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours). The supplementary estimand analysis will be performed using ITT analysis set. Participants who are unable to complete the CSS assessment at each timepoint (24 hours ± 4, 48 hours (±4 hours), 72 hours (±4 hours), and 96 hours (±4 hours) will be considered treatment failures and included in the analysis as not improved or not resolved for clinical symptom resolution.

Counts and percentage of participants with clinical symptom improvement and resolution at each timepoint and its corresponding 95% Exact Binomial CIs will be presented.

#### 4.3.1.5. Sensitivity analyses of supplementary estimand for secondary endpoints

Sensitivity of supplementary estimands analyses for secondary endpoints will be performed according to rule mentioned in Section 4.3.1.4. considering ITT analysis set. Multiple imputation method will be used to impute the missing outcome at each timepoint (24 hours ± 4, 48 hours ± 4 hours, 72 hours ± 4 hours and 96 hours ± 4 hours) as described in Section 4.2.3 for clinical symptom improvement and resolution, respectively.

Counts and percentage of participants with "Clinical improvement with resolution outcome" at each timepoint and its corresponding 95% (Wald) CIs will be presented.

### 4.3.2. Supportive secondary endpoint

No supportive secondary endpoint analysis will be performed.

## 4.4. Exploratory Analyses

CCI [redacted]

CCI

CCI

CCI

CCI

## 4.5. Safety Analyses

The safety analyses will be based on the safety analysis set.

### 4.5.1. Extent of Exposure

Treatment exposure will be summarized for gepotidacin treatment using the safety and CE24 analysis set. Duration of treatment (days), the number of doses administered, number of tablets, average daily dose and cumulative actual dose will be presented in treatment exposure summary. Dose administration and exposure data for all participants will be generated in the listing  Additionally, a separate table will be created for ICEs, summarizing the participants who did not adhere to two doses before the 24 hours (±4 hours) CSS assessment, and indicating whether the compliance was above or below 80% at 48 hours (±4 hours), 72 hours (±4 hours), 96 hours (±4 hours) assessment.

### 4.5.2. Adverse Events

The severity of TEAEs and treatment-emergent SAEs will be determined by the investigator according to the US National Institute of Allergy and Infectious Diseases [DAIDS, 2017] Table for grading the severity of adult and pediatric AEs. All reported TEAEs will be coded using standard Medical Dictionary for Regulatory Affairs (MedDRA) version 27.0 or later depending on the time of reporting and summarized by system organ class (SOC) and preferred term (PT).

A treatment emergent adverse event (TEAE) is defined as an adverse event (AE) with start date/time after the first dose date/time of the study treatment. If the time part is missing, dates will be considered and if date and time both are missing then eCRF question on whether the Adverse Event (AE) occurred before, after, or on the same day as the study intervention will be considered. Only TEAE will be included in summary tables, but all AEs will be displayed in detailed subject listings.

AEs will be summarized as the following:

- AEs by SOC, PT and maximum grade
- Serious adverse event (SAE) by SOC, PT and Maximum grade,
- Non-Serious adverse event (Non-SAE) by SOC and PT
- Drug-related adverse event (AE) by SOC, PT and Maximum grade,
- Drug-related non-serious adverse event by overall frequency,
- Drug-related fatal and non-fatal serious adverse event (SAE),
- Common AEs
- Adverse event (AE) leading to discontinuation of study intervention,
- Adverse event (AE) leading to withdrawal from study,
- Adverse events of special interests (AESIs) by SOC, PT and Maximum grade.
- Summary of deaths

**AEs, SAEs and Non-SAEs by SOC, PT and Severity grade:** Summary (counts & percentages) of adverse events (AEs), serious adverse events (SAE) and non-serious adverse events (non-SAEs**)** will be produced by system organ class (SOC), preferred term (PT). All adverse events (AEs) listing will be displayed at participant level in detail. Summary for serious adverse events (SAEs) will be summarised by System Organ Class, Preferred Term, and severity grade.

Adverse event severity is categorised as grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (potentially life threatening) and grade 5 (death). Adverse events starting after the first dose of study treatment with a missing severity will be classified as severe. If a participant reports an AE more than once within an SOC/PT, the AE with the worst-case (maximum) severity will be used in the corresponding severity summaries. A Summary table for adverse events leading to permanent discontinuation of study

treatment or withdrawal from study by system organ class (SOC) and preferred term (PT) and maximum grade will be generated.

**Common AEs:** A summary of (counts & percentages) of common AEs with incidence>=2% (before rounding) will be produced in descending order of the total incidence of PT.

**Common Non-SAEs:** A Summary of Common ([redacted]) Non-Serious Adverse Events by System Organ Class and Preferred Term will be produced.

**AEs and SAEs related to study intervention:** Relationship to gepotidacin, as indicated by the investigator, is classified as "not related" or "related". Adverse events with a missing relationship to gepotidacin will be recorded as "related" to study treatment. If a participant reports the same AE more than once within an SOC/PT, the AE with the worst-case relationship to gepotidacin will be used in the corresponding relationship summaries. Summary tables for drug-related adverse events (AEs) will be generated by system organ class (SOC), preferred term (PT) and maximum severity grade. The summary for drug-related non-serious adverse events and serious adverse events (SAEs) (fatal and non-fatal) will also be produced by preferred term (PT

Adverse events analyses including the analysis of AEs, SAEs and other significant AEs will be based on GSK Core Data Standards.

All AEs will be listed.

A Summary of deaths will be provided and participants profile for death will also be listed using enrolled analysis set.

In summary tables, system organ classes (SOCs) will be sorted in descending order of the total incidence then alphabetically, preferred terms (PTs) will be sorted in descending order of the total incidence then alphabetically within the SOC.

For completely missing or partial missing AE start date or end date, imputation rules will be applied following Appendix Section 6.3.8.

Details of the planned displays for AEs and SAEs are provided in Output programming specifications (OPS) and will be based on GSK Data Standards and statistical principles.

#### 4.5.2.1. Adverse Events of Special Interest

The following will be considered adverse events of special interest (AESI) for the purpose of analyses.

- Cardiovascular (CV) adverse events (AEs)
- Gastrointestinal (GI) adverse events (AEs)
- Clostridioides *difficile*-associated diarrhea (C. difficile AEs)
- Acetylcholinesterase Inhibition (AChE-I)

The AESIs Cardiovascular (CV) and Acetylcholinesterase Inhibition (AChE-I) will be identified using project-level Terms of Interest (ToI) lists obtained from the GSK coding specialist in consultation with the study safety expert.

Details of the planned displays for AESIs are provided in Output programming specifications (OPS) and will be based on GSK Data Standards and statistical principles.

#### *4.5.2.1.1.* Cardiovascular (CV) and Gastrointestinal (GI) AESIs

Gastrointestinal (GI) AESIs are defined as AEs within a gastrointestinal SOC.

Cardiovascular AESIs are defined as AEs with PTs that match the terms listed in the ToI list. The counts and percentages of participants with an event will be summarized and listed by PT, and the maximum grade for CV and GI AESIs. The most current version of MedDRA will be used as applicable at the time of this study SAC.

#### *4.5.2.1.2.* Clostridioides difficile-associated diarrhea (C. difficile AEs) AESIs

*Clostridioides difficile*-associated diarrhea (*C. difficile*) AESIs (PTs *Clostridium difficile* infection and *Clostridium difficile* colitis) will be included in the overview of summary of adverse events (AEs). *C. difficile* laboratory testing results are collected and recorded on distinct eCRF pages, which will be presented in a participant listing.

#### *4.5.2.1.3.* Acetylcholinesterase Inhibition (AChE-I) AESIs

Any reported AE listed in AChE-I TOI listing with a start time no later than 12 hours after the last dose administered, as evaluated by the investigator as per the [DAIDS, 2017]grading criteria provided in protocol Section 10.10 and Appendix 10: Division of AIDS table for grading the severity of adult and pediatric AEs, version 2.1, July 2017, will be included in the programmatic identification of AChE-I related AESI.The most current version of MedDRA will be used as applicable at the time of this study SAC.

Cumulative grade score of Acetylcholinesterase-Inhibition (AChE-I) 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 considered. The grading scale is defined as

| 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. This will be calculated for all AChE-I events, non-GI AChE-I events and GI AChE-I events. This will be calculated for All AChE-I events, non-GI AChE-I events and GI AChE-I events which will be summarized.

Acetylcholinesterase inhibition AESIs will be listed and tabulated by system organ class (SOC) and preferred term (PT) and maximum grade. Non-GI AChE-I events will also be

summarized. A separate table will summarize the AChE-I AESI by the number of events and unique preferred terms. In addition, time of onset (time from first dose to the onset of first event in hours), duration, and lag time (the time from last dose to the end date/time of the last event for subjects whose end date/time of the last event is after treatment end date/time) of AChE-I events will also be summarized, and repeated for non-GI AChE-I and GI AChE-I events.

AChE-I events with a start time less than 6 hours after the latest dose administered will also be flagged in listings.

Additionally, Adverse Events of Torsade de Pointes/QT Prolongation SMQ by PT will also be summarized based on the SMQs listed in the OPS. The most current version of MedDRA will be used as applicable at the time of this study SAC.

#### 4.5.2.2. COVID-19 Assessment and COVID-19 AEs

Not Applicable.

#### 4.5.2.3. Impact of COVID-19 Pandemic on Safety Results

This study is conducted in the post-pandemic phase and therefore not applicable.

### 4.5.3. Classification and analysis of safety signals

As per GSK Guidance document (VQD-REF-019518 Statistical considerations for Assessment of Adverse Reaction for GDS and VDQ-REF-019393 Developing and Updating the Adverse Reaction of the Global datasheet) “Adverse reactions” (ARs) are undesirable effects, reasonably associated with use of a product that may occur as part of the pharmacological action of the product or may be unpredictable in its occurrence.”

CCI [redacted]. Qualitative evaluation of the potential ARs will be used to determine if there is sufficient evidence of a causal association with the investigational product.

#### 4.5.3.1. Multiplicity Adjustment

As screening for potential ARs is intended as an aid to medical judgment rather than to be used for decision making, no adjustment for multiplicity will be applied.

#### 4.5.3.2. Qualitative Causality Assessment

Qualitative evaluation of the potential ARs will be performed to determine if there is sufficient evidence of causal association with gepotidacin. The following data displays will be produced for each AE of potential ARs to support the qualitative causality assessments.

CCI

Additional data displays may be generated as needed to assist with further qualitative assessment of the potential ARs once the safety data is reviewed. The generated data displays may be useful in evaluating the likelihood of a causal association and the strength of causality by assessing the consistency according to clinically relevant attributes.

### 4.5.4. Additional Safety Assessments

#### 4.5.4.1. Laboratory Data

Laboratory evaluations including the analyses of chemistry laboratory tests, hematology laboratory tests, urinalysis, and liver function tests (as listed in Protocol Appendix 7) will be based on GSK Core Data Standards. Laboratory data will be graded by a Central Laboratory.

Descriptive statistics (n, mean, standard deviation (SD), median, minimum value (min), and maximum value (max)) will be presented for quantitative measurements of key continuous laboratory parameters at baseline and worst-case post-baseline assessments from unscheduled visits (only if there are at least 5 participants with data at unscheduled visits). Participants listing for all laboratory parameters will be produced.

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:

- 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
- (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

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

The severity of renal impairment will be evaluated using estimated by creatinine clearance (CCr) using the Cockcroft and Gault formula (1973):

$$\text{creatinine clearance (mL/min)} = \frac{(140 - \text{age in year}) \times (\text{weight in kg}) \times 0.85}{72 \times (\text{Serum creatinine in mg/dL})}$$

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

- Normal (≥90 mL/min)
- Mild (≥60 to 89 mL/min)

- Moderate (≥30 to 59 mL/min)
- Severe (<30 mL/min)

Details of the planned displays for clinical laboratory evaluations are provided in Output programming specifications (OPS) and will be based on GSK Data Standards and statistical principles.

#### 4.5.4.2. Vital Signs

The analyses of vital signs parameters will be based on GSK Core Data Standards.

The following vital signs measurements will be reported before blood collection for laboratory tests for the study at baseline.

- Temperature
- Systolic and Diastolic blood pressure
- Respiratory rate
- Pulse rate

Descriptive statistics (n, mean, standard deviation (SD), median, minimum value (min), and maximum value (max)) will be presented for quantitative measurements of vital signs parameters at baseline and worst-case post-baseline assessments from unscheduled visits (only if there are at least [redacted] participants with data at unscheduled visits) Participants listing for vital signs parameters will be presented.

Details of the planned displays for vital signs parameters are provided in Output programming specifications (OPS) and will be based on GSK Data Standards and statistical principles.

#### 4.5.4.3. ECG

The analyses of ECG parameters will be based on GSK Core Data Standards.

The arithmetic mean of the three recorded ECG measurements will be presented in all data summaries and participant listings. ECG measurements at baseline will be recorded, including heart rate, PR interval, QRS duration, QT interval, QRS axis and RR interval. Corrected QT intervals will be calculated in case of not correctly entered in eCRF by Bazett's formula.

$$\text{QTcB (msec )} = \frac{QT}{\sqrt{\text{RR}/1000}}$$

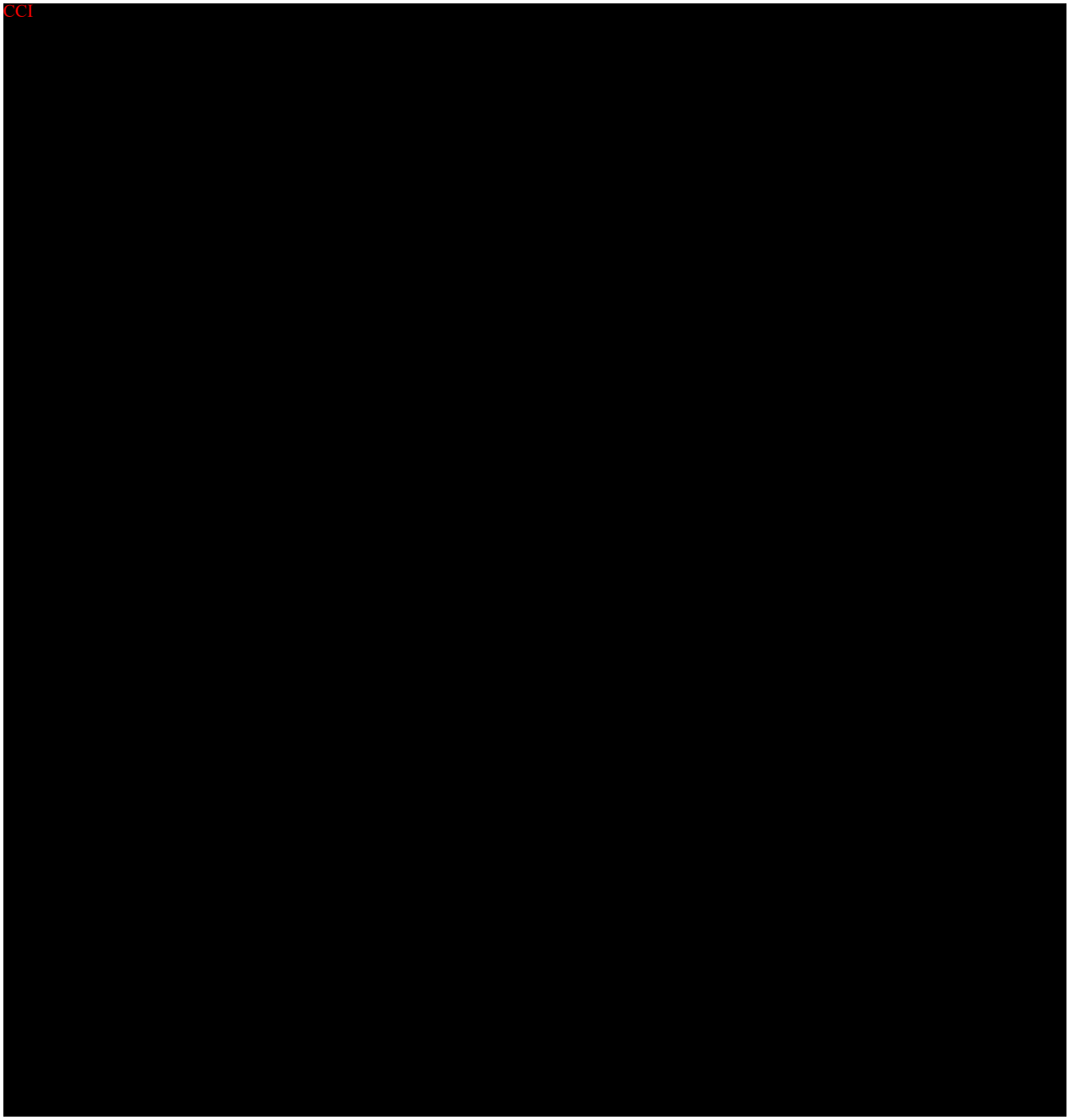
and by Fridericia's formula:

$$\text{QTcF (msec )} = \frac{QT}{\sqrt[3]{RR/1000}}$$

Descriptive statistics (n, mean, standard deviation (SD), median, minimum value (min), and maximum value (max)) will be presented for quantitative measurements of ECG parameters at baseline and worst-case post-baseline assessments from unscheduled visits (only if there are at least [redacted] participants with data at unscheduled visits) Participants listings will be provided for all parameters of ECG values and findings at baseline including abnormal ECGs including unscheduled visits.

Details of the planned displays for ECG parameters are provided in Output programming specifications (OPS) and will be based on GSK Data Standards and statistical principles.

## 4.6. Other Analyses



## 4.7 Interim Analyses

Not Applicable.

## 4.8 Changes to Protocol Defined Analyses

- The CE definitions here included additional clarifications compared to the protocol.
- CCI
- [redacted]

# 5 SAMPLE SIZE DETERMINATION

CCI

[redacted]

# 6 SUPPORTING DOCUMENTATION

## 6.1 Appendix 1 Study Population Analyses

The study population analyses will be based on the Intent to Treat (ITT) Analysis Set, unless otherwise specified. Some selected study population analyses will also be presented by the CE24 set.

Study population analyses will be included analyses of participant's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, study intervention compliance based on GSK Core Data Standards.

CCI

[redacted]

Details of the planned displays for study population analyses are provided in Output programming specifications (OPS) and will be based on GSK Data Standards and statistical principles.

### 6.1.1 Participant Disposition

Participant disposition will be tabulated for study treatment (gepotidacin) with the counts and percentages of participants who complete the study, prematurely withdraw, and the reason for study withdrawal for ITT analysis set and primary clinically evaluable at 24 hours (±4 hours) analysis set. Participant listing of the reasons for study withdrawal will be provided.

Summary of treatment status and reasons for discontinuation of study treatment will be produced for study treatment (gepotidacin), with the number of participants who completed treatment, or prematurely discontinued treatment, and the primary reasons for treatment discontinuation tabulated for the ITT analysis set and primary clinically evaluable at 24 hours (±4 hours) analysis set. Participant listing of the reasons for treatment discontinuation will also be provided.

Summary of reasons for screen failure (did not meet inclusion/exclusion criteria, adverse event, protocol deviation, lost to follow-up investigator discretion, participant withdrew consent, or other) will be provided for screened participants. A listing for participants with inclusion/exclusion criteria deviations will be generated.

A summary of the number of subjects by site will be produced using ITT analysis set and primary clinically evaluable at 24 hours (±4 hours) analysis set.

A table will be generated for summarizing the number of participants in each analysis set for all participants who provided informed consent. A listing for exclusion of participants from each analysis set will be produced. A separate table will also be constructed that summarizes the reasons for exclusion from each study analysis set for all participants in the ITT analysis set.

### 6.1.2 Demographic and Baseline Characteristics

Demographic characteristics such as age, sex, race, ethnicity, childbearing potential, baseline renal impairment category, height, weight, and body mass index (BMI), and baseline history of acute cystitis recurrence will be summarized and tabulated for study treatment using participants in ITT and primary clinically evaluable at 24 hours (±4 hours) analysis set.

Descriptive statistics will be presented for age, height, weight, and BMI. Counts and percentages will be presented for age category (<=50 and >50), sex, race, ethnicity, childbearing potential.

Individual participant demographics characteristics will be presented in listings.

CCI

[redacted]

### 6.1.3 Protocol Deviations

Important protocol deviations will be summarized.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan, entitled Study Deviation Tool and Rules. These protocol deviations will be reviewed to identify those considered as important as follows:

Data will be reviewed prior to freezing the database to ensure all important deviations. which may lead to exclusion of a participant from the analysis sets are captured and categorised in the protocol deviations dataset.

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

A separate participant listing of all inclusion/exclusion criteria deviations will also be provided. This listing will be based on data as recorded on the inclusion/exclusion page of the eCRF.

### 6.1.4 Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the WHO Drug dictionary at the time of reporting. Counts and percentages will be presented for prior and concomitant medication by Anatomical Therapeutic Chemical (ATC) classification Level 1 (Body System) information and Ingredient using ITT analysis set and primary clinically evaluable at 24 hours (±4 hours) analysis set. A systemic antimicrobial is regarded as an antibiotic used for treating uUTI or other infections.

CCI [redacted]

The summary of concomitant medications will present separate summaries for systemic concomitant medications, non-systemic concomitant medications, systemic antibiotics taken for the disease under study (either started before treatment start date and continued in the treatment period, or, started on/after treatment start date), systemic antibiotics taken for another disease/condition (either started before treatment start date and continued in the treatment period, or, started on/after treatment start date) and prohibited (non-antibiotic) medications.

An antibiotic is considered systemic if the route is oral, subcutaneous, intramuscular, intravenous, or rectal.

All prior and concomitant medications, as well as prior and concomitant antibiotic medications for uUTI, will be provided in separate listings.

### 6.1.5 Medical History and Current Medical Conditions

Counts and percentages for medical history and current medical conditions will be presented for each body system of participants using ITT analysis set. General medical history, previous *Clostridioides difficile* infection, and liver/cardiovascular related medical conditions will be summarized separately in tables and listings. A distinct summary table will also be produced for history of previous uncomplicated UTIs during the past 3 months, past 3-6 months, past 6-12 months, and past 5 years, and pre-existing conditions with similar symptoms in past 12 months for the ITT analysis set and primary clinically evaluable at 24 hours (±4 hours) analysis set. All data will be listed.

### 6.1.6 Study Intervention Compliance

A summary of overall compliance and compliance up to each timepoints of CSS assessments from start of gepotidacin treatment based on the exposure data will be produced. Counts & percentages for below categories as applicable will be presented using safety and CE24 set.

- <80%
- ≥80% - <100%
- =100%

- >=100%

Overall Compliance rate (%) will be calculated as per following formula:

CCI [redacted]

Compliance rate (%) upto each visit/timepoint will be calculated as per following formula:

CCI [redacted]

### 6.1.7 Additional Analyses Due to the COVID-19 Pandemic

No additional analysis will be performed due to COVID-19 pandemic.

## 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

#### 6.3.1.1 ECG

| ECG Parameter | Units | Potential Clinically Important Range | |
|---|---|---|---|
| | | Lower | Upper |
| Absolute | | | |
| Absolute QTc Interval | msec | NA | >450 |
| Absolute PR Interval | msec | <110 | >220 |
| Absolute QRS Interval | msec | <75 | >110 |

#### 6.3.1.2 Vital Signs

| Vital Sign Parameter (Absolute) | Units | Potential Clinically Important Range | |
|---|---|---|---|
| | | Lower | Upper |
| Systolic Blood Pressure | mmHg | <85 | >160 |
| Diastolic Blood Pressure | mmHg | <45 | >100 |
| Pulse Rate | bpm | <40 | >110 |
| Temperature | C | ≤35 | ≥38 |
| Respiratory Rate | bpm | <10 | >20 |

### 6.3.2 Laboratory Values

For this study, Division of AIDS [DAIDS, 2017] for Grading the Severity of Adult and Pediatric Adverse Events defined in Section 6.3.11 will be utilized. This differs from the EAGLE-2 and EAGLE-3 phase III studies, where AE grading was done using the Division of Microbiology and Infectious Diseases (DMID) table, which is no longer used.

### 6.3.3 Study Period

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

| Study Period | Definition |
|---|---|
| CCI [redacted] | |

#### 6.3.3.1 Study Period for Concomitant Medication

| Study Period | Definition |
|---|---|
| Prior | If medication started prior to the first dose date (or ICF 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 ICF date if first dose date is missing) |

**NOTES:**

- Please refer Section 6.3.8 for handling of missing and partial dates for concomitant medication. Use the rules which is mentioned in table of Section 6.3.8 if concomitant medication date is completely missing.
- If a participant has taken single medication on the same date as the first dose date, then time will be used to determine if it's prior or concomitant. If time is missing, it will be considered concomitant.

### 6.3.4 Treatment Emergent Flag for Adverse Events

| Flag | Definition |
|---|---|
| Treatment Emergent | If adverse event (AE) onset date/time is on or after treatment start date/time, i.e., study intervention starts date/time ≤ adverse event (AE) starts date/time. If time is missing, only date will be compared. |

**NOTES:**
Time of study intervention dosing and start/stop time of adverse events (AEs) should be considered, if collected.

### 6.3.5 Study Day and Reference Dates

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

The efficacy reference date is the study intervention start date 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:

CCI [redacted]

### 6.3.6 Assessment Window

CCI [redacted]

For adverse events (AEs) and concomitant medications, study data will not be reported by visit as this assessment are collected through the study.

Analysis timepoint labels will be assigned to each post-baseline record (including records from unscheduled and early termination timepoints where date/time is collected for safety data Labs, ECG, Vitals etc.) based on the corresponding study hours/day (relative to first study intervention).

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 timepoint window and irrespective of whether they are scheduled or unscheduled.

**Table 3 Analysis Assessment Window for Post-Baseline**

| Timepoints Analysis Set / Domain | Protocol Visit Window/ Extended Visit Window | Target | Analysis Timepoint Window | |
|---|---|---|---|---|
| | | | Beginning Timepoint | Ending Timepoint |
| Efficacy (Primary, Secondary and Exploratory) | 24 hours ± 4 hours | 24 hours | ≥20 hours | ≤28 hours |
| | 24 hours ± 12 hours | | >12 hours | ≤ 36 hours |
| | 48 hours ± 4 hours | 48 hours | ≥44 hours | ≤52 hours |
| | 48 hours ± 12 hours | | >36 hours | ≤60 hours |
| | 72 hours ± 4 hours | 72 hours | ≥68 hours | <76 hours |
| | 72 hours ± 12 hours | | >60 hours | ≤84 hours |
| | 96 hours ± 4 hours | 96 hours | ≥92 hours | ≤100 hours |
| | 96 hours ± 12 hours | | >84 hours | ≤108 hours |
| CCI [redacted] | | | | |

If multiple records exist within the same analysis timepoint window, then the record occurring closest to the target hours/day will be utilized in all analyses and analysis set determinations. If multiple records are equally close to the target hours/day, then the later record will be utilized. If multiple records occur on the same hours/day and time is not collected, then the record with the larger Study Data Tabulation Model (SDTM) record sequence number will be utilized in all analyses. All protocol assessments (including unscheduled and early termination timepoints) will be presented in participant listings. Both the nominal and analysis timepoint will be presented in listings.

### 6.3.7 Multiple measurements at One Analysis Time Point

Analysis visits will be created based on visit windows as described in Section 6.3.6.

Handling of multiple CSS assessment - If a second assessment of CSS is taken on any specific day corresponding to 24h, 48h, 72h, 96h after taking CCI [redacted] due to tolerability issues, the former assessment (taken before the CCI [redacted] use) will be considered for reporting.

All assessments (including unscheduled and early termination visits) will be presented in participant listings. The arithmetic mean of the three recorded ECG measurements will be presented at baseline as described in Section 4.5.4.3.

If multiple assessments are taken from the same type of lab parameters from the same visit, then worst case will be used.

### 6.3.8 Handling of Missing and Partial Dates

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>General</td><td>
<ul>
<li>Partial dates will be displayed as captured by the in-participant listing displays.</li>
<li>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.</li>
</ul>
</td></tr>
<tr><td>Adverse Events</td><td>
<ul>
<li>The eCRF allows for the possibility of partial dates to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event:</li>
</ul>
<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.<br>Else if study intervention start date is not missing:<ul><li>If month and year of start date = month and year of study intervention start date, then<ul><li>If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.</li><li>Else set start date = study intervention start date.</li></ul></li></ul>Else set start date = 1st of month.<br>In this case, event is considered On-treatment and treatment emergent as per Section 6.3.4.</td></tr>
<tr><td>Missing start time</td><td>Midnight 0:00:00 will be used for AEs with missing start<br>time to determine if it’s AChE-I<ul><li>Treatment start time will be used for AEs with missing start time if treatment start date is same as AEs start date.</li></ul></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.<br>Else if study intervention start date is not missing:<ul><li>If year of start date = year of study intervention start date, then<ul><li>If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.</li></ul></li></ul></td></tr>
</table>
</td></tr>
</table>

| Element | Reporting Detail | |
|---|---|---|
| | | – Else set start date = study intervention start date.<br>Else set start date = January 1.<br>In this case, event is considered On-treatment and treatment emergent as per Section 6.3.4. |
| | Missing end day | Last day (dependent on the month and year example '28/29/30/31') of the month will be used will be used for the day, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used. |
| | Missing end day and month | No Imputation will be applied in case of AE with missing end day and month |
| | Missing end time | 23:59 will be used for AEs with missing time |
| | Completely missing start/end date | • Completely missing start or end dates will remain missing, with no imputation applied. Information on AE occurred before, after, or on the same day as the study intervention will be used.<br>• Consequently, time to onset and duration of such events will be missing.<br>• Adverse events with entirely missing or unknown start dates will be assumed to be on-treatment and treatment emergent for reporting. |
| Concomitant Medications including Antibiotics and Prohibited medications/Medical History | • Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention and the recorded partial date will be displayed in listings: | |
| | 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.<br>Else if study intervention start date is not missing:<br>• If month and year of start date = month and year of study intervention start date, then<br>– If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.<br>– Else set start date = study intervention start date.<br>Else set start date = 1st of month. |
| | Missing start time | Midnight 0:00:00 will be used for concomitant medications with missing start time if treatment start date is not same as the concomitant medication start date. |

| Element | Reporting Detail | |
|---|---|---|
| | | • Treatment start time will be used for concomitant medications with missing start time if treatment start date is same as concomitant start date |
| | 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.<br>Else if study intervention start date is not missing:<br>• If year of start date = year of study intervention start date, then<br>– If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.<br>– Else set start date = study. intervention start date.<br>Else set start date = January 1. |
| | Missing end day | If the partial date is a end date, 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. |
| | Missing end time | 23:59 will be used for concomitant medications with missing time |
| | Completely missing start/end date | Completely missing start or end dates will remain missing, with no imputation applied. |
| Age | Age is derived using the date of first dose. When first dose date is missing, the ICF 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:<br>(First Dose Date – 30 Jun of collected birth year +1)/365.25 | |

### 6.3.9 Premature Withdrawals

| Element | Reporting Detail |
|---|---|
| General | • Participant study intervention completion is defined as if the participant has taken all doses of the study intervention. Participants who discontinue study intervention will not be considered withdrawn from the study and should attend Follow-up Visits as applicable. |
| | • Participants study completion (i.e., as specified in the protocol) is defined as if the<br>participant has completed all study visits including the Follow-up Visit |
| | • All available data from participants who were withdrawn from the study will be listed and all available CSS, CCI CCI and AEs data will be included in summary tables and figures as described in Section 6.3.6. on Analysis timepoints. |

### 6.3.10 Handling of Missing Data

| Element | Reporting Detail |
|---|---|
| General | • Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument:<br>o These data will be indicated using a "blank" in participant listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table.<br>o Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such. |
| Efficacy | • As defined in the endpoint variables, participants with missing measurements will be treated as failures for corresponding visits (unless otherwise specified for sensitivity analyses). |
| Outliers | • Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report. |

### 6.3.11 Division of AIDS table for grading the severity of adult and pediatric AEs, version 2.1, July 2017

The Division of AIDS Table for Grading the Severity of Adult and pediatric Adverse Events [DHHS, 2017] is a descriptive terminology which can be utilized for AE reporting. A grading (severity) scale is provided for each AE term.

The DAIDS Table is available at this link:
https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

**Estimating Severity Grade for Parameters Not Identified in the Grading Table**

The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as Grade 5.

| Parameter | Grade 1 Mild | Grade 2 Moderate | Grade 3 Severe | Grade 4 Potentially Life-Threatening |
|---|---|---|---|---|
| **Clinical** AE NOT identified elsewhere in the grading table | Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated | Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated | Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated | Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death |

### 6.3.12 Reporting Process

| Software |
|---|
| • The currently supported versions of SAS software will be used. |
| **Analysis Datasets** |
| • Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.3 & ADaM IG Version 1.1)<br>• For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM. |
| **Generation of RTF Files** |
| • RTF files will be generated for all reporting efforts described in the Statistical Analysis Plan. |

### 6.3.13 Reporting Standards

| Planned and Actual Time |
|---|
| • Reporting for tables, figures, and formal statistical analyses:<br>  • The impact of any major deviation from the planned assessment times and/or scheduled timepoint on the analyses and interpretation of the results will be assessed as appropriate.<br>• Reporting for Data Listings:<br>  • Planned and actual time relative to study drug dosing will be shown in listings.<br>  • Unscheduled or unplanned readings will be presented within the participant's listings. |
| **Unscheduled Visits** |
| • Unscheduled visits and Early withdrawal visits may be included in summary tables and/or figures as described in Section 6.3.6. on Analysis Timepoints and analyses such as "all post baseline", "worst case post baseline", and "max post baseline" etc. All unscheduled visits and Early Withdrawal visits will be included in listings. |

### 6.3.14 Maintaining Integrity of Accumulating Data in the Open-Label Single-Arm Study

The following measures will be taken to maintain the integrity of the study before DBL:

- Limited distribution of accumulating study data and dry run 1 TFLs to the core study team (includes study CSLs, study Safety leads and study medical writer only)
- Review of dry run 2 to be limited within study Biostatistics team only
- MDT and the wider team will be able to view study results after DBL starting from HDL data as documented in the Study Results Dissemination Plan
- Study safety leads will discuss any safety data at a very high-level only to get inputs from the SRT (if required), a case by case review may not be conducted at the SRT (unless the SRT lead considers this essential for a particular patient).

### 6.3.15 Early PK Access Key Activities

Early PK access key activities are not applicable for the study as no PK data is collected.

## 6.4 Appendix 4 Abbreviations & Trademarks

### 6.4.1 Abbreviations

| Abbreviation | Description |
|---|---|
| AChE-I | Acetylcholinesterase Inhibition AE Adverse Event |
| ADaM | Analysis Data Model |
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| CCI [redacted] | |
| BID | Twice Daily |
| CE | Clinically Evaluable |
| CI | Confidence Interval |
| CV | Cardiovascular |
| eCRF | Electronic Case Report Form |
| GI | Gastrointestinal |
| GSK | GlaxoSmithKline |
| ICE | Intercurrent Event |
| ITT | Intent-To-Treat |
| MAR | Missing at Random |
| SAC | Statistical Analysis Complete |
| SAE | Serious AE |
| SDTM | Study Data Tabulation Model |

| Abbreviation | Description |
|---|---|
| TEAE | Treatment-Emergent Adverse Event |
| UTI | Urinary Tract Infection |
| uUTI | Uncomplicated Urinary Tract Infection |
| WHO | World Health Organization |

### 6.4.2 Trademarks

| Trademarks of the GlaxoSmithKline Group of Companies |
|---|
| GSK Drug |

| Trademarks not owned by the GlaxoSmithKline Group of Companies |
|---|
| MedDRA |
| SAS |

# 7 REFERENCES

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GSK Study Report NCT04020341. Study 204989. A Phase III, randomized, multicenter, parallel-group, double-blind, double-dummy study in adolescent and adult female participants comparing the efficacy and safety of gepotidacin to nitrofurantoin in the treatment of uncomplicated urinary tract infection (acute cystitis). 2023.

GSK Study Report NCT04187144. Study 212390. A Phase III, randomized, multicenter, parallel-group, double-blind, double-dummy study in adolescent and adult female participants comparing the efficacy and safety of gepotidacin to nitrofurantoin in the treatment of uncomplicated urinary tract infection (acute cystitis). 2023.

Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events, Corrected Version 2.1 (July 2017).

Department of Health and Human Services (DHHS), National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. July 2017. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

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