Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan Amendment 2 for 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)
Compound Number	:	GSK2140944
Clinical Study Identifier	:	204989
Effective Date	:	08 Sep 2022

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 204989.
- This RAP is intended to describe the full analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

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TABLE OF CONTENTS

PAGE

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol 204989.

<table>
<tr><td colspan="2">Revision Chronology:</td></tr>
<tr><td>Version</td><td>Date</td></tr>
<tr><td>Original</td><td>14JAN2022</td></tr>
<tr><td>Amendment No. 1</td><td>26JUL2022</td></tr>
<tr><td colspan="2">Updates include:
Clarifications that the primary analysis population will be “micro-ITT NTF-S (IA Set)” if the study is stopped early for success (and inclusion of corresponding outputs).
Clarifications that <18 years and ≥18 to 50 years strata will be combined for use as an analysis covariate to ensure participants with valid data are not excluded.
Other minor edits for clarification.</td></tr>
<tr><td>Amendment No. 2</td><td>Refer to Last Signature</td></tr>
<tr><td colspan="2">Updates include:
Updates to the IA recommendation framework to include a supplementary analysis performed on a supplementary analysis population defined as the primary analysis population excluding participants from investigators/sites which have had a corrective and preventative action (CAPA) put in place requiring that a supplementary analysis excluding data from these sites be performed. This population will be labeled micro-ITT NTF-S (CAPA) population and will be performed on the IA Set if applicable. The updated IA recommendation framework requires both the primary and supplementary analyses to meet the NI boundary to stop the study for efficacy at the interim analysis. If the study continues at the interim, demonstration of NI at the final analysis will remain based on the primary analysis only (micro-ITT NTF-S) and the supplementary analysis (micro-ITT NTF-S (CAPA)) performed at the final analysis will be provided for descriptive purposes only. This is detailed in Section 2.4 and Section 5.5.
Note: demonstration of NI at the final analysis will remain based on the primary analysis only.
Note: At the IA, for testing futility against the boundary only the primary population (micro-ITT NTF-S (IA Set) population) should be used to determine if the futility boundary has been met. The micro-ITT NTF-S (CAPA) (IA Set) supplementary analysis will also be available to the IDMC. The Z-Statistic boundaries in this supplementary analysis will be consistent with the primary analysis and presented for reference (i.e., should not be used as formal hypothesis testing for futility).
Note: Sensitivity analyses (i.e., unadjusted treatment difference and treatment difference adjusting for strata as randomized) will also be available to the IDMC. The Z-Statistic boundaries (for efficacy and/or futility) in these sensitivity analyses will be consistent with the primary analysis and presented for reference (i.e., should not be used as formal hypothesis testing).</td></tr>
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2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes to the planned statistical analysis specified in the protocol (Dated: 03-NOV-2021) are listed below.

- Whilst demonstration of NI at the final analysis (if the study continues at the IA) will remain based on the primary analysis only, the IA recommendation framework at the IA has been updated to include a supplementary analysis performed on a supplementary analysis population defined as the primary analysis population excluding participants from investigators/sites which have had a corrective and preventative action (CAPA) put in place requiring that a supplementary analysis excluding data from these sites be performed. This population will be labeled micro-ITT NTF-S (CAPA) population and will be performed on the IA Set if applicable. The updated IA recommendation framework requires both the primary and supplementary analyses to meet the NI boundary to stop the study for efficacy at the interim analysis. If the study continues at the interim analysis, demonstration of NI at the final analysis will remain based on the primary analysis only (micro-ITT NTF-S) and the supplementary analysis (micro-ITT NTF-S (CAPA)) performed at the final analysis will be provided for descriptive purposes only. This is detailed in Section 2.4 and Section 5.5.
    - Note: At the IA, for testing futility against the boundary only the primary population (micro-ITT NTF-S (IA Set) population) should be used to determine if the futility boundary has been met. The micro-ITT NTF-S (CAPA) (IA Set) supplementary analysis will also be available to the IDMC. The Z-Statistic boundaries in this supplementary analysis will be consistent with the primary analysis and presented for reference (i.e., should not be used as formal hypothesis testing for futility).
    - Note: Sensitivity analyses (i.e., unadjusted treatment difference and treatment difference adjusting for strata as randomized) will also be available to the IDMC. The Z-Statistic boundaries (for efficacy and/or futility) in these sensitivity analyses will be consistent with the primary analysis and presented for reference (i.e., should not be used as formal hypothesis testing).
- The covariates used for adjusting the primary analyses have been updated to combine the <18 and ≥18- to 50-year-old participants. Due to small number of participants if the age groups weren't combined <18-year-old participants with valid data may have been excluded from the primary analysis. This is because Miettinen and Nurminen method calculates the treatment difference within each stratum prior to combining stratum estimates to calculate a common risk difference. Therefore, as the treatment difference cannot be calculated within a stratum if there are only participants on one treatment arm within a stratum, and per current recruitment projections we do not expect the number of participants in the "<18 years, Nonrecurrent infection" and "<18 years, Recurrent infection" to increase substantially so there is a risk that there may be participants on only one treatment arm hence participants with valid data may have been excluded from

the primary analysis. To avoid this, it is statistically appropriate to combine these age groups. It is clinically appropriate to combine these age groups as there is no reason for differential susceptibility in adults compared to adolescents and no reason why the treatment difference between gepotidacin and nitrofurantoin would be different in these groups. For the primary analysis, the test statistics of the therapeutic success rate difference between the 2 treatment groups (gepotidacin - nitrofurantoin) for noninferiority (-10% margin) will be calculated using the Miettinen and Nurminen method stratified by age category (≤50 years, or >50 years) and acute cystitis recurrence (nonrecurrent infection or recurrent infection) combinations (4 strata).

- Additional exploratory endpoints were added, CCI [redacted]
- For superiority testing, *p*-value will be used instead of Z statistic.
- Clarity that a participant will be considered to have completed treatment if she has taken all doses of the randomly assigned study treatment, i.e. regardless of TOC Visit.

2.2. Study Objective(s) and Estimand(s) / Endpoint(s)

Objectives	Endpoints
Primary	**Primary**
To assess the combined clinical and microbiological efficacy of gepotidacin compared to nitrofurantoin, at the Test-of-Cure (TOC) Visit, in female participants with acute cystitis with qualifying uropathogen(s) at Baseline that all are susceptible to nitrofurantoin	Therapeutic response (combined per-participant microbiological and clinical response) at the TOC Visit.
Secondary	**Secondary**
To assess the clinical efficacy of gepotidacin compared to nitrofurantoin, at the TOC and Follow-up Visits, in female participants with acute cystitis	Clinical outcome and response at the TOC and Follow-up Visits.
To assess the clinical efficacy of gepotidacin compared to nitrofurantoin, at the TOC and Follow-up Visits, in female participants with acute cystitis with qualifying uropathogen(s) at Baseline that all are susceptible to nitrofurantoin	Clinical outcome and response at the TOC and Follow-up Visits.
To assess the microbiological efficacy of gepotidacin compared to nitrofurantoin, at the TOC and Follow-up Visits, in female participants with acute cystitis with qualifying uropathogen(s) at Baseline that all are susceptible to nitrofurantoin	Microbiological outcome and response at the TOC and Follow-up Visits.
To assess the combined clinical and microbiological efficacy of gepotidacin compared to nitrofurantoin, at the Follow-up Visit, in female participants with acute cystitis with qualifying uropathogen(s) at Baseline that all are susceptible to nitrofurantoin	Therapeutic response (combined per-participant microbiological and clinical response) at the Follow-up Visit.
To determine the plasma and urine pharmacokinetic (PK) concentrations of gepotidacin in female participants with acute cystitis	Gepotidacin plasma and urine concentrations
To assess the safety and tolerability of gepotidacin compared to nitrofurantoin in female participants with acute cystitis	Treatment-emergent AEs (TEAEs) and serious AEs (SAEs) and change from baseline results for clinical laboratory tests and vital sign measurements

Objectives	Endpoints
CCI	[redacted]

2.2.1. Primary Estimand

The primary clinical question of interest is: What is the treatment effect on therapeutic success rate after 5 days treatment with gepotidacin 1500 mg twice daily compared to 5 days treatment with nitrofurantoin 100 mg twice daily in participants with acute cystitis with qualifying uropathogen(s) at Baseline that all are susceptible to nitrofurantoin,

regardless of treatment discontinuation for any reason. Receipt of systemic antimicrobials impacts the endpoint definition (see Section 7.1.1.2 to Section 7.1.1.3).

The primary estimand is described by the following attributes:

- Population: Female participants with acute cystitis with qualifying uropathogen(s) at Baseline that all are susceptible to nitrofurantoin.
- Treatment condition: Gepotidacin 1500 mg twice daily for 5 days versus nitrofurantoin 100 mg twice daily for 5 days, regardless of adherence.
- Variable: Therapeutic response (combined per participant microbiological and clinical response) at the Test of Cure (TOC) Visit. Microbiological success is defined as eradication (i.e. reduction) of all qualifying uropathogens recovered at Baseline to $<10^3$ CFU/ml as observed on quantitative urine culture without the participant receiving other systemic antimicrobials. Clinical success is defined as resolution of signs and symptoms of acute cystitis present at Baseline (and no new signs and symptoms) without the participant receiving other systemic antimicrobials.
- Summary measure: difference in the therapeutic success rate in the gepotidacin and nitrofurantoin treatment groups (gepotidacin – nitrofurantoin).
- Intercurrent events (ICE):
    - Study treatment discontinuation (due to any reason) – treatment policy strategy (interest is in the treatment effect regardless of study treatment discontinuation).
    - Use of systemic antimicrobials - composite strategy. This intercurrent event is captured through the definitions of microbiological and clinical response (see Section 7.1.1.2 to Section 7.1.1.3) and will be counted as therapeutic failures.

  If the patient experiences both of these ICE then a composite strategy (assigning therapeutic response as a failure) will be used from the point that the relevant systemic antimicrobial was taken.

Rationale for estimand:

Interest lies in the treatment effect irrespective of whether the full course of 5 days of treatment was taken or not which reflects how patients may be treated in clinical practice. Hence a treatment policy strategy is appropriate for treatment withdrawal before completing 5 days of treatment. Use of other systemic antimicrobials may confound the bacterial culture results thus the microbiological response will be considered failure. For clinical data the use of a systemic antimicrobial for uUTI is a sign of treatment failure and use of a systemic antimicrobial for another infection can't be considered a success as it confounds the assessment of efficacy. Therefore, the definition of a successful therapeutic response precludes the use of other systemic antimicrobials.

2.2.2. Estimand for Secondary Endpoints

The secondary clinical questions of interest are: What is the treatment effect on each of the secondary efficacy endpoints after 5 days treatment with gepotidacin 1500 mg twice daily compared to 5 days treatment with nitrofurantoin 100 mg twice daily in participants with acute cystitis (clinical endpoints) and in participants with acute cystitis with qualifying uropathogen(s) at Baseline that all are susceptible to nitrofurantoin (therapeutic, clinical, and microbiological endpoints), regardless of treatment discontinuation for any reason. Receipt of systemic antimicrobials impacts the endpoint definitions (see Section 7.2.1.1, Section 7.2.1.2, and Section 7.2.1.3).

For each of the secondary efficacy endpoints the estimand will follow a similar approach to the estimand for the primary endpoint and use the same strategies for the intercurrent events. The exception is the summary measure for the outcome endpoints. These endpoints are descriptively summarized and therefore the summary measure will be the percentage in each clinical and microbiological outcome category in the gepotidacin and nitrofurantoin arms separately (as no direct comparison between treatment groups will be made).

The PK endpoint will use a while on treatment strategy for the intercurrent event of withdrawal from treatment since the PK will be assessed at all post baseline assessments irrespective of whether the patient completed the treatment.

The safety endpoint will use a treatment policy strategy for the intercurrent event of withdrawal from treatment since the safety will be assessed at all post baseline assessments irrespective of whether the patient completed the treatment. Components of estimand for all secondary endpoints are listed in Table 1.

Table 1 Estimand for Secondary Endpoints

	Population	Treatment condition	Variable	Summary measure	ICE
Clinical response at the TOC and FU Visits	Female participants with acute cystitis	Gepotidacin 1500 mg twice daily for 5 days versus nitrofurantoin 100 mg twice daily for 5 days regardless of adherence.	See Table 8 (Section 7.1.1) and Table 11 (Section 7.2.1)	Difference in the Clinical success rate in the gepotidacin and nitrofurantoin treatment groups.	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antimicrobials - composite strategy
Clinical outcome at the TOC and FU Visits	Female participants with acute cystitis	Gepotidacin 1500 mg twice daily for 5 days versus nitrofurantoin 100 mg twice daily for 5 days regardless of adherence.	See Table 8 (Section 7.1.1) and Table 11(Section 7.2.1)	Percentage of participants in each outcome category in the gepotidacin and nitrofurantoin arms separately	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antimicrobials - composite strategy
Clinical response at the TOC and FU Visits	Female participants with acute cystitis with qualifying uropathogen(s) at Baseline that all are susceptible to nitrofurantoin.	Gepotidacin 1500 mg twice daily for 5 days versus nitrofurantoin 100 mg twice daily for 5 days regardless of adherence.	See Table 8 (Section 7.1.1) and Table 11(Section 7.2.1)	Difference in the Clinical success rate in the gepotidacin and nitrofurantoin treatment groups.	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antimicrobials - composite strategy

	Population	Treatment condition	Variable	Summary measure	ICE
Clinical outcome at the TOC and FU Visits	Female participants with acute cystitis with qualifying uropathogen(s) at Baseline that all are susceptible to nitrofurantoin	Gepotidacin 1500 mg twice daily for 5 days versus nitrofurantoin 100 mg twice daily for 5 days regardless of adherence	See Table 8 (Section 7.1.1) and Table 11 (Section 7.2.1)	Percentage of participants in each outcome category in the gepotidacin and nitrofurantoin arms separately	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antimicrobials - composite strategy
Microbiological response at the TOC and FU Visits	Female participants with acute cystitis with qualifying uropathogen(s) at Baseline that all are susceptible to nitrofurantoin.	Gepotidacin 1500 mg twice daily for 5 days versus nitrofurantoin 100 mg twice daily for 5 days regardless of adherence.	See Table 7 (Section 7.1.1) and Table 10 (Section 7.2.1)	Difference in the microbiological success rate in the gepotidacin and nitrofurantoin treatment groups.	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antimicrobials - composite strategy
Microbiological outcome at the TOC and FU Visits	Female participants with acute cystitis with qualifying uropathogen(s) at Baseline that all are susceptible to nitrofurantoin.	Gepotidacin 1500 mg twice daily for 5 days versus nitrofurantoin 100 mg twice daily for 5 days regardless of adherence.	See Table 7 (Section 7.1.1) and Table 10 (Section 7.2.1)	Percentage of participants in each outcome category in the gepotidacin and nitrofurantoin arms separately	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antimicrobials - composite strategy
Therapeutic response at the FU Visit	Female participants with acute cystitis with qualifying uropathogen(s) at Baseline that all are	Gepotidacin 1500 mg twice daily for 5 days versus nitrofurantoin 100 mg twice daily for	See Table 10 and Table 11(Section 7.2.1)	Difference in the therapeutic success rate in the gepotidacin and nitrofurantoin treatment groups.	Study treatment discontinuation (due to any reason) – treatment policy

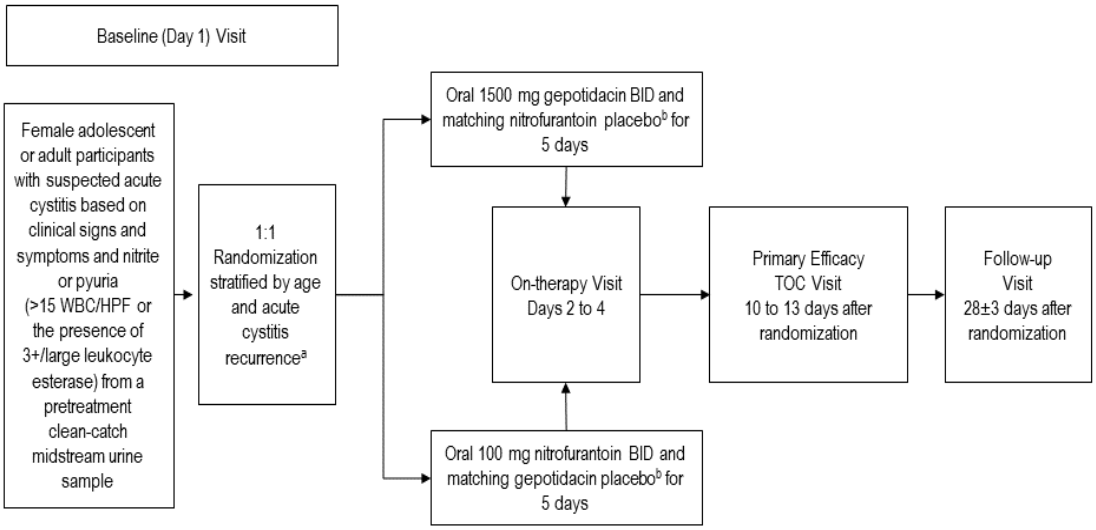
	Population	Treatment condition	Variable	Summary measure	ICE
	susceptible to nitrofurantoin.	5 days regardless of adherence.			Use of systemic antimicrobials - composite strategy
Pharmacokinetic (PK)	Female participants with acute cystitis	Gepotidacin 1500 mg twice daily for 5 days	See Section 9.1.1.1	Summary statistics (appropriate for each type of endpoint) in the gepotidacin arm	Study treatment discontinuation (due to any reason) – while on treatment strategy (treatment phase defined as from first dose to OT Visit)
Safety	Female participants with acute cystitis	Gepotidacin 1500 mg twice daily for 5 days versus nitrofurantoin 100 mg twice daily for 5 days regardless of adherence.	TEAEs, SAEs, as well as change from baseline results for clinical laboratory tests, and vital sign measurements.	Summary statistics (appropriate for each type of endpoint) in the gepotidacin and nitrofurantoin arms separately	Study treatment discontinuation (due to any reason) – treatment policy

2.3. Study Design

Overview of Study Design and Key Features

The study design schematic is shown in Figure 1.

Figure 1 Study Design Schematic



BID=twice daily; HPF=high-power field; TOC=Test-of-Cure; WBC=white blood cell.

a. There will be central randomization with stratification by age category (<18 years, ≥18 to 50 years, or >50 years) and acute cystitis recurrence (nonrecurrent infection or recurrent infection, defined as a confirmed infection [not including the current infection in the calculation] with at least 1 prior episode within the past 3 months, at least 2 prior episodes within the past 6 months, or at least 3 prior episodes within the past 12 months before study entry).

b. Study treatment will be administered under double-blind, double-dummy conditions. Each dose should be taken after food consumption and with water.

Design Features	• Phase III, randomized, multicenter, parallel-group, double blind, double-dummy, comparator-controlled, noninferiority study
	• The study duration is approximately 28 days with 4 planned study visits
	  • Baseline (Day 1) Visit
	  • On-Therapy (Day 2 to 4) Visit
	  • TOC (Day 10 to 13) Visit
	  • Follow-up (Day 28±3) Visit
	• The study will enroll approximately 2500 participants to fulfill the maximum target sample size of 884 participants with acute cystitis in the micro-ITT NTF-S Population, for an estimated total of approximately 442 evaluable participants per treatment group. The final number of randomized subjects may vary depending on the actual evaluability rate and review of qualifying uropathogens by an unblinded Statistical Data Analysis Center (SDAC). Therefore, enrollment will continue until the approximate target number of participants in the primary analysis population (micro-ITT NTF-S Population) has been reached.

Overview of Study Design and Key Features	
Dosing	• Participants will receive oral study treatment (gepotidacin [2 tablets] + nitrofurantoin matching placebo [1 capsule] or nitrofurantoin [1 capsule] + gepotidacin matching placebo [2 tablets]) BID (approximately every 12 hours) for 5 days. The first oral dose will be administered at the study site during the Baseline Visit; participants will self-administer subsequent doses as outpatients thereafter, beginning with the second dose, with the exception of 1 dose at the OT Visit that will be taken at the study site whenever possible.
Time & Events	• Refer to Appendix 1
Treatment Assignment	• Participants will be stratified, as described in Figure 1, and will be randomly assigned in a 1:1 ratio to receive one of the following study treatments: • Gepotidacin: 1500 mg administered orally twice daily (BID) for 5 days • Nitrofurantoin: 100 mg administered orally BID for 5 days
Interim Analysis	• One interim analysis will be planned to assess futility and efficacy or futility only. An independent data monitoring committee (IDMC) will review unblinded data to make recommendations to GSK. Details regarding the IDMC process will be available in relevant IDMC documents.

2.4. Statistical Hypotheses / Statistical Analyses

The study is designed to determine whether gepotidacin administered orally is noninferior compared with nitrofurantoin administered orally on the primary efficacy endpoint of therapeutic response (combined per-participant microbiological and clinical response) at the TOC Visit in participants with a qualifying uropathogen at Baseline that is susceptible to nitrofurantoin. Microbiological success per-participant is defined as eradication (i.e., reduction of all qualifying uropathogens recovered at Baseline to $<10^3$ CFU/mL as observed on quantitative urine culture) without the participant receiving other systemic antimicrobials prior to the urine culture assessment conducted at the TOC Visit (evaluated at the resolution of minutes). Clinical success is defined as resolution of all signs and symptoms of acute cystitis present at Baseline (and no new signs and symptoms) without the participant receiving other systemic antimicrobials. For systemic antimicrobials received for the current infection (as rescue treatment) prior to or on the TOC Visit will be considered a clinical failure. For systemic antimicrobials received for other infection (as non-rescue treatment) prior to the TOC Visit will be considered a clinical failure.

The following are null and alternative hypotheses for the primary analysis of the therapeutic success rates at the prespecified noninferiority margin of -10.0%:

H_0: therapeutic success rate of Gepotidacin 1500 mg BID – therapeutic success rate of Nitrofurantoin 100 mg BID $\leq$ -10.0%

H_1: therapeutic success rate of Gepotidacin 1500 mg BID – therapeutic success rate of Nitrofurantoin 100 mg BID >-10.0%

At the interim, if the Z statistic (for the primary analysis population) is higher than the Z statistic boundary for noninferiority, noninferiority will be tested in a supplementary analysis population (micro-ITT NTF-S (IA Set) (CAPA)) to ensure consistency. If the Z statistic (for the supplementary analysis population) is also higher than the Z statistic boundary for noninferiority the study will be stopped for efficacy and noninferiority will

be declared.
Note: The stopping boundaries for this key supplementary analysis will be consistent with the primary analysis (as will the null and alternative hypotheses), the futility bounds will be presented for reference only (and not to be used as formal futility hypothesis testing).

At the final analysis (if the study continues at the IA), if the Z statistic (for the primary analysis population) is higher than the Z statistic boundary for noninferiority the study will be declared successful and noninferiority will be declared. Refer to Section 5.5 for further details on study success definition and IA recommendation framework.

If noninferiority is declared between gepotidacin and nitrofurantoin, superiority will be tested in the primary analysis population with the following null and alternative hypotheses:

H_0: therapeutic success rate of gepotidacin 1500 mg BID – therapeutic success rate of nitrofurantoin 100 mg BID ≤0%

H_1: therapeutic success rate of gepotidacin 1500 mg BID – therapeutic success rate of nitrofurantoin 100 mg BID >0%

If the one-sided p-value is less than the p-value boundary superiority of gepotidacin will be declared.

The difference in therapeutic success rates between the two study treatment groups and its Z statistic use the Miettinen-Nurminen (MN) method Miettinen, 1985) stratified by age category (≤50 years, or >50 years) and acute cystitis recurrence (nonrecurrent infection or recurrent infection) combinations. In the event that any participants are mis-stratified, for the primary efficacy analysis, the actual age and acute cystitis collected in eCRF will be used to create actual pooled stratification. A sensitivity analysis of the primary efficacy analysis will also be conducted from the pooled stratification as randomized.

3. PLANNED ANALYSES

3.1. Interim Analyses

One IA is planned to assess either both efficacy (noninferiority) and futility or just futility by the IDMC. The IDMC will meet when approximately 60% of participants in the micro-ITT NTF-S Population have achieved the TOC Visit to evaluate the primary endpoint, identify potential treatment benefit, and make recommendations for continuing or stopping the study, as per the IDMC charter. The scope of data for the IA reporting will include (a) participants who had the opportunity to reach their Test of Cure (TOC) visit and (b) participants who have not yet reached their TOC visit, but are already known to be failures (e.g., subjects who took other systemic antimicrobial or withdrew from the study before the TOC visit). The IDMC members will include at least 3 independent experts (from a total of 5 planned), including an infectious disease specialist, a chairperson with experience chairing IDMC meetings, and a statistician. Details regarding the IDMC process will be described in the IDMC charter.

The Statistical Data Analysis Centre (SDAC), a PPD unblinded statistical team, will conduct and provide all unblinded analyses to the IDMC before the meeting is held. The GSK and PPD study teams that are operating the study and conducting the final analysis will remain blinded. The IDMC and SDAC will maintain unblinded data in a secure area to ensure the integrity of the data until the study is completed. Details on protecting blind and data integrity will be described in a blinding plan.

At the time the IA is conducted, the IDMC will review unblinded data to confirm that sufficient microbiological data exist for the unblinded gepotidacin treatment arm before deciding how to proceed as detailed in the IA RAP.

If the IDMC confirms there is sufficient microbiology data in the gepotidacin arm, an IA with stopping rules for both efficacy and futility will be performed. The nominal significance levels for the interim and final analyses will be determined by the Lan-DeMets spending functions approach [Lan , 1983]. This will be based on the Pocock stopping boundary for efficacy and the O'Brien-Fleming stopping boundary for futility. The futility bounds of this study are nonbinding and are considered guidance rather than strict bounds. The IA recommendation framework requires both the primary and supplementary analyses to meet the NI boundary to stop the study for efficacy at the interim analysis as described in Section 5.5. For futility, only the micro-ITT NTF-S population will be used to determine if the futility boundary has been met (i.e., not the micro-ITT NTF-S (CAPA) population).

During the course of the IA, patients will continue to be randomized. If efficacy success (i.e., noninferiority) is reached at the IA and the study is stopped early, the IA efficacy results will be the primary analysis to support the effectiveness of the study. If efficacy success is not reached at the IA, the study will continue to the maximum target sample size for the micro-ITT NTF-S Population of approximately 884 participants.

If, at the IA, the IDMC confirms that there is not sufficient microbiology data in the gepotidacin arm, then a futility-only IA will be conducted. The nominal significance levels for the interim and final analyses will be determined by the Lan-DeMets spending

functions approach [Lan , 1983]. This will be based on the O'Brien-Fleming stopping boundary for futility. The futility bounds of this study are nonbinding and are considered guidance rather than strict bounds. Note: only the micro-ITT NTF-S population will be used to determine if the futility boundary has been met (i.e., not the micro-ITT NTF-S (CAPA) population). The stopping boundaries will be calculated under the assumption of an approximate maximum sample size of 768 participants in the micro-ITT NTF-S Population, a 76% therapeutic success rate for nitrofurantoin, a -10.0% noninferiority margin and a 0.025 one-sided alpha level. If the decision is to continue at IA, the boundary for final analyses will not be updated as it is based on the planned sample size.

Table 2 summarizes the information fraction, sample size and decision guidance (boundaries in *Z*-statistics and *p*-value, cumulative alpha, and beta) for the planned IA at 60% timing (i.e., a planned end of study sample size of 884 participants in the micro-ITT NTF-S Population) with a -10.0% noninferiority margin, 0.025 one-sided type I error and a 0.1 type II error approximately and assuming a 76% therapeutic success rate for nitrofurantoin. If the decision is to continue at IA, the boundary for final analyses will not be updated as it is based on the planned sample size of 884.

Table 2 Information Fraction and Stopping Boundaries for Efficacy and Futility IA

Information Fraction	Target Sample Size for each study	Efficacy Boundary			Non-Binding Futility Boundary		
		Z statistics	*p*-value	Cumulative alpha	*Z* statistics	*p*-value	Cumulative beta
60%	530	>2.104	<0.018	0.018	<0.854	>0.197	0.033
100%	884	>2.23	<0.013	0.025	<2.23	>0.013	0.098

Information fraction is determined using CLSI based micro-ITT NTF-S. Testing for noninferiority and superiority share the same Z statistics and *p*-value boundaries.

Table 3 summarizes the information fraction, sample size, and decision guidance (boundaries in Z-statistics and p-values, cumulative beta) for the planned IA for futility only. The IA will occur at 530 participants and this corresponds to 69% information fraction for futility-only IA (i.e., a planned end of study sample size of 768 participants in the micro-ITT NTF-S Population) with a -10.0% noninferiority margin, 0.025 one-sided type I error and assuming a 76% therapeutic success rate for nitrofurantoin. The actual boundaries will be determined based on the actual information fraction in the micro-ITT NTF-S (IA Set) population at the time of IA. If the decision is to continue at IA, the boundary for final analyses will not be updated as it is based on the planned sample size of 768. Boundaries are calculated in software EAST using Wald statistics without adjusting for strata.

Table 3 Information Fraction and Stopping Boundaries for Futility Only IA

Information Fraction	Target Sample Size for each study	Non-Binding Futility Boundary		
		Z statistics	*p*-value	Cumulative beta
69%	530	<1.128	>0.13	0.059
100%	768	<1.96	>0.025	0.116

Information fraction is determined using CLSI based micro-ITT NTF-S

The efficacy boundaries and non-binding futility boundaries in Table 2 and Table 3 are based on initially assigned information fraction and are calculated in software EAST using Wald statistics without adjusting for strata. The actual boundaries will be determined based on the actual information fraction in the micro-ITT NTF-S (IA Set) population at the time of IA. If the decision is to continue at IA, the boundary for end of study analyses will not be updated as it is based on the planned sample size.

Sensitivity analyses (i.e., unadjusted treatment difference and treatment difference adjusting for strata as randomized) will also be available to the IDMC. The Z-Statistic boundaries (for efficacy and/or futility) in these sensitivity analyses will be consistent with the primary analysis and presented for reference (i.e., should not be used as formal hypothesis testing).

Conditional power will be calculated based on the observed data at the time of the IA for each study individually and will be provided purely for additional information to facilitate the decision around stopping for futility. It will not be used to facilitate any decision on stopping for success.

Additional details on IA designs, microbiological data criteria, stopping boundaries, content, and structure of the data output for IA are described in the IDMC charter and a separate IA analysis plan.

3.2. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All participants have completed the study as defined in the protocol at the FU Visit.
2. If the study is stopped for success at the IA, primary inferential analysis and a small set of supporting analyses will be repeated on the complete data for participants included in the IA to ensure consistency. Data collected after the IA data cut are considered overrun. Overrun participants will be pooled with the IA participants for all analyses defined in this document except the primary inferential analysis. If the study is not stopped for success, all analyses will be performed on all participant data after study completion.

3. All protocol deviations captured and categorized, and analysis populations defined.
4. All final database cleaning and data lock activities completed by data management.
5. All criteria for the unblinding of subject randomization codes have been achieved.
6. All randomization codes have been distributed per standard operating procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened Population	• All participants who were screened for eligibility • Participants will be analyzed according to their randomized study treatment.	• Study Population •
Intent-to-Treat (ITT) Population	• All participants randomly assigned to study treatment. • Participants will be analyzed according to their randomized study treatment.	• Study Population • Efficacy
Microbiological ITT (micro-ITT) Population	• All participants randomly assigned to study treatment who receive at least 1 dose of study treatment and have a qualifying baseline uropathogen from a quantitative bacteriological culture of a pretreatment clean-catch midstream urine specimen. • Participants will be analyzed according to their randomized study treatment.	• Study Population • Efficacy
micro-ITT NTF-S Population	• All participants in the micro-ITT Population whose baseline qualifying uropathogens are all susceptible to nitrofurantoin (NTF-S)[1]. Participants with missing MIC susceptibility results for any qualifying uropathogens will not be included in the NTF-S sub-Population. • Participants will be analyzed according to their randomized study treatment.	• Study Population • Efficacy (including the primary efficacy analysis if the study does not stop for efficacy)
micro-ITT NTF-S (IA Set) Population	• All participants in the micro-ITT NTF-S Population who, per the interim analysis data, had: a) the opportunity to reach their Test of Cure (TOC) visit, or b) had not yet reached their TOC visit, but were already known to be failures (e.g., subjects who took other systemic antimicrobial or withdrew from the study before the TOC visit) • Participants will be analyzed according to their randomized study treatment. Note: this population will only be used as the primary analysis population if the study stops for efficacy. [2]	• Study Population • Efficacy (including the primary efficacy analysis if the study stops for efficacy)
micro-ITT NTF-NS Population	• All participants in the micro-ITT Population who have any baseline qualifying uropathogens that are NTF-NS, defined as resistant to nitrofurantoin (NTF-R), or intermediate to nitrofurantoin (NTF-I), or no interpretation to nitrofurantoin (NTF-NI), Participants missing MIC susceptibility results for all qualifying	• Study Population • Efficacy

Population	Definition / Criteria	Analyses Evaluated
	uropathogens will not be included in the NTF-NS sub-Population. • Participants will be analyzed according to their randomized study treatment.	
Microbiologically Evaluable at OT (ME-OT) Population	• Participants who meet the definition of the micro-ITT Population, follow important components of the study (i.e., (1) receive at least 80% of planned doses as randomized and actual treatment received is the same as randomized, (2) have an interpretable quantitative urine culture at the OT Visit and evaluable clinical scores at the baseline and the OT Visit, (3) have not taken any other systemic antimicrobial before OT unless it was taken for the current infection (therapeutic failure), and (4) have no other major protocol deviation that prevents evaluation of efficacy. • Participants will be analyzed according to their randomized study treatment, however, by definition, for all participants in this analysis population the actual treatment received is the same as randomized.	• Efficacy
Microbiologically Evaluable at TOC (ME-TOC) Population	• Participants who meet the definition of the micro-ITT Population, follow important components of the study (i.e., (1) receive at least 80% of planned doses as randomized and actual treatment received is the same as randomized, (2) have an interpretable quantitative urine culture at the TOC Visit and evaluable clinical scores at the baseline and the TOC Visit, (3) have not taken any other systemic antimicrobial before TOC unless it was taken for the current infection, and (4) have no other major protocol deviation that prevents evaluation of efficacy. • Participants will be analyzed according to their randomized study treatment, however, by definition, for all participants in this analysis population the actual treatment received is the same as randomized.	• Efficacy
Microbiologically Evaluable at FU (ME-FU) Population	• Participants who meet the definition of the micro-ITT Population, follow important components of the study (i.e., (1) receive at least 80% of planned doses as randomized and actual treatment received is the same as randomized, (2) have an interpretable quantitative urine culture at FU Visit (unless microbiological outcome at TOC is persistence or recurrence) and evaluable clinical scores at the baseline and the FU Visit (unless clinical outcome at TOC is clinical improvement or worsening), (3) have not taken any other systemic antimicrobial	• Efficacy

Population	Definition / Criteria	Analyses Evaluated
	before FU unless it was taken for the current infection (therapeutic failure), and (4) have no other major protocol deviation that prevents evaluation of efficacy. • Participants will be analyzed according to their randomized study treatment, however, by definition, for all participants in this analysis population the actual treatment received is the same as randomized.	
ME-OT NTF-S Population	• All participants in the ME-OT Population whose baseline qualifying uropathogens are all susceptible to nitrofurantoin. • Participants will be analyzed according to their randomized study treatment, however, by definition, for all participants in this analysis population the actual treatment received is the same as randomized.	• Efficacy
ME-OT NTF-NS Population	• All participants in the ME-OT Population who have any baseline qualifying uropathogens that are NTF-NS. • Participants will be analyzed according to their randomized study treatment, however, by definition, for all participants in this analysis population the actual treatment received is the same as randomized.	• Efficacy
ME-TOC NTF-S Population	• All participants in the ME-TOC Population whose baseline qualifying uropathogens are all susceptible to nitrofurantoin. • Participants will be analyzed according to their randomized study treatment, however, by definition, for all participants in this analysis population the actual treatment received is the same as randomized.	• Efficacy
ME-TOC NTF-NS Population	• All participants in the ME-TOC Population who have any baseline qualifying uropathogens that are NTF-NS. • Participants will be analyzed according to their randomized study treatment, however, by definition, for all participants in this analysis population the actual treatment received is the same as randomized.	• Efficacy
ME-FU NTF-S Population	• All participants in the ME-FU Population whose baseline qualifying uropathogens are all susceptible to nitrofurantoin. • Participants will be analyzed according to their randomized study treatment, however, by definition, for all participants in this analysis population the actual treatment received is the same as randomized.	• Efficacy

Population	Definition / Criteria	Analyses Evaluated
ME-FU NTF-NS Population	• All participants in the ME-FU Population who have any baseline qualifying uropathogens that are NTF-NS. • Participants will be analyzed according to their randomized study treatment, however, by definition, for all participants in this analysis population the actual treatment received is the same as randomized.	• Efficacy
Clinically Evaluable at OT (CE-OT) Population	• All participants in the ITT Population who follow important components of the study as specified in the protocol (i.e., (1) receive at least 80% of planned doses as randomized and actual treatment received is the same as randomized, (2) have evaluable clinical scores of signs and symptoms at the baseline and the OT Visit, (3) have not received other systemic antimicrobials before OT unless it was for the current infection (therapeutic failure), and (4) have no other major protocol deviation that prevents evaluation of efficacy). • Participants will be analyzed according to their randomized study treatment, however, by definition, for all participants in this analysis population the actual treatment received is the same as randomized.	• Efficacy
Clinically Evaluable at TOC (CE-TOC) Population	• All participants in the ITT Population who follow important components of the study as specified in the protocol (i.e., (1) receive at least 80% of planned doses as randomized and actual treatment received is the same as randomized, (2) have evaluable clinical scores of signs and symptoms at the baseline and the TOC Visits, (3) have not received other systemic antimicrobials before TOC unless it was for the current infection (therapeutic failure), and (4) have no other major protocol deviation that prevents evaluation of efficacy. • Participants will be analyzed according to their randomized study treatment, however, by definition, for all participants in this analysis population the actual treatment received is the same as randomized.	• Study Population • Efficacy
Clinically Evaluable at FU (CE-FU) Population	• All participants in the ITT Population who follow important components of the study as specified in the protocol (i.e., (1) receive at least 80% of planned doses as randomized and actual treatment received is the same as randomized, (2) have evaluable clinical scores of signs and symptoms at the baseline and the FU Visit (unless clinical outcome at TOC is clinical	• Efficacy

Population	Definition / Criteria	Analyses Evaluated
	improvement or worsening), (3) have not received other systemic antimicrobials before FU unless it was for the current infection (therapeutic failure), and (4) have no other major protocol deviation that prevents evaluation of efficacy). • Participants will be analyzed according to their randomized study treatment, however, by definition, for all participants in this analysis population the actual treatment received is the same as randomized.	
Safety Population	• All randomized participants who receive at least 1 dose of study treatment. • Participants will be analyzed according to their actual treatment received. Note: if a participant receives both gepotidacin and nitrofurantoin they will be summarized within gepotidacin 1500 mg BID.	• Safety
Pharmacokinetic (PK) Population	• All randomized participants who receive at least 1 dose of study treatment and have at least 1 nonmissing plasma or urine PK concentration. This population will be used for listing and summary of plasma and urine gepotidacin concentration-time data and population PK (plasma) analysis, as data permit. • Participants will be reported according to their actual treatment received. Note: if a participant receives both gepotidacin and nitrofurantoin they will be listed only (i.e., not summarized within gepotidacin 1500 mg BID). . Note: Plasma and/or urine samples for participant randomized to Nitrofurantoin will not be measured.	• PK

1. Broth microdilution nitrofurantoin MIC result from JMI Laboratories (if available) will take precedence over global central laboratory (GCL) nitrofurantoin MIC result for determining susceptibility to nitrofurantoin.
2. The micro-ITT NTF-S (IA Set) Population will include participants who have completed their TOC Visit or had the opportunity to reach their TOC visit (determined by the last day of the TOC visit analysis window per Table 5) as of the IA data cut-off. Participants who have not had the opportunity to reach their TOC Visit but are known failures (per the SDTM datasets used in the interim analyses) will be in scope of the IA Set if they are randomized prior to the IA data cut-off.

Notes:

- Refer to Appendix 9: List of Data Displays.
- Qualifying uropathogens specified in any study populations above include only the uropathogen species/groups [Gram-negative bacilli (e.g. *E. coli, K. pneumoniae, P. mirabilis*), *S. saprophyticus*, and *Enterococcus* spp.], as described in Section 7.3.2.
- Evaluable clinical score means non-missing clinical score.
- Significant deviations which prevent evaluation of efficacy and result in exclusion from CE/ME analysis populations will be determined by the study team throughout the conduct of the study before database lock

The term “CE Population” is used to refer to all CE Populations. The term “ME Population” is used to refer to all ME Populations.

Inclusion into the ITT, Safety, and PK Population will be determined programmatically from eCRF data.

Inclusion criteria for the micro-ITT/NTF-S/NTF-NS, ME Populations, and CE Populations will be determined programmatically and through manual review conducted by the Sponsor. The Sponsor will be blinded to treatment assignment and may review the data concurrent with conduct of the study. Final determination of population inclusion will be performed after database lock and prior to unblinding. Exclusion from ME/CE Populations related to receipt of incorrect study drug will be determined programmatically after unblinding.

Nitrofurantoin susceptibility interpretations will be based on the Clinical and Laboratory Standards Institute (CLSI) guidelines to determine participant inclusion into the NTF-S/NTF-NS subpopulations except as described in Section 7.1.6.3.

If the study stops for efficacy the primary analysis population will be the micro-ITT NTF-S (IA Set) Population, and the micro-ITT NTF-S Population (complete trial data including participants included in the IA and overrun participants) will be used for sensitivity analyses (as described in Section 7.1.6.2) to provide a nominal estimate of the treatment difference and 95% CI. If the study does not stop for efficacy the primary analysis population will be the micro-ITT NTF-S Population (complete trial data).

In the event that one or more investigators/sites have had a corrective and preventative action (CAPA) put in place requiring that a supplementary analysis excluding data from these sites be performed, a supplementary analysis will be performed. A flag will be included to identify subjects enrolled by those investigators/sites. This will enable further subpopulations to be defined for the primary analysis populations (micro-ITT NTF-S if the study continues / micro-ITT NTF-S (IA Set) if the study stops for futility). The sub population will consist of all subjects in the primary analysis population except subjects from those investigative sites (e.g., micro-ITT NTF-S (CAPA)/ micro-ITT NTF-S (IA Set) (CAPA) respectively) and will be used to perform the additional supplemental analysis for the primary efficacy endpoint only. Note: this analysis is included in the IA recommendation framework per Section 5.5.

4.1. Protocol Deviations

Significant protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, participant management or participant assessment) will be summarized and listed. Separately, significant deviations which result in exclusion from analysis populations and events that result in exclusion from analysis populations will be summarized and listed.

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.

- Data will be reviewed prior to freezing the database to ensure all significant deviations and deviations which may lead to exclusion of a participant from the analysis populations are captured and categorized in the protocol deviations dataset. This will occur prior to unblinding.
- This dataset will be the basis for the summaries and listings of significant protocol deviations.

A separate 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.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Subgroup Display Descriptors

Randomized and actual treatment will be reported per Table 4. This accounts for potential treatment misallocations due to double-dummy treatments, if applicable.

Table 4 Randomized and Actual Treatment Group Descriptions

Randomized Treatment Group Descriptions			
Randomized Treatments (double-dummy)		**Data Displays for Reporting**	
Tablet	**Capsule**	**Description**	**Order in TFL**
Gepotidacin	Placebo (matched to Nitrofurantoin)	Gepotidacin 1500 mg BID	1
Placebo (matched to Gepotidacin)	Nitrofurantoin	Nitrofurantoin 100 mg BID	2
Actual Treatment Group Descriptions (Listing of actual and randomized treatment, PK)			
Actual Treatments (double-dummy)		**Data Displays for Reporting[1]**	
Tablet	**Capsule**	**Description**	**Order in TFL**
Placebo (matched to Gepotidacin)	Placebo (matched to Nitrofurantoin)	Placebo	1
Gepotidacin	Nitrofurantoin	Gepotidacin 1500 mg BID + Nitrofurantoin 100 mg BID	2
Gepotidacin	Placebo (matched to Nitrofurantoin)	Gepotidacin 1500 mg BID	3
Placebo (matched to Gepotidacin)	Nitrofurantoin	Nitrofurantoin 100 mg BID	4
Actual Treatment Group Descriptions (Safety TFL)			
Actual Treatments (double-dummy)		**Data Displays for Reporting[2]**	
Tablet	**Capsule**	**Description**	**Order in TFL**
Placebo (matched to Gepotidacin)	Placebo (matched to Nitrofurantoin)	Placebo	1
Gepotidacin	Nitrofurantoin	Gepotidacin 1500 mg BID	2
Gepotidacin	Placebo (matched to Nitrofurantoin)	Gepotidacin 1500 mg BID	2
Placebo (matched to Gepotidacin)	Nitrofurantoin	Nitrofurantoin 100 mg BID	3

1. PK Summaries will only include “Gepotidacin 1500 mg BID” arms only, all other data will be listed only
2. Safety Summaries will include “Gepotidacin 1500 mg BID” and “Nitrofurantoin 100 mg BID” arms only, all other data will be listed only

Total (across all treatment groups) will be presented for study population, safety, and selected microbiology displays.

5.2. Baseline Definitions

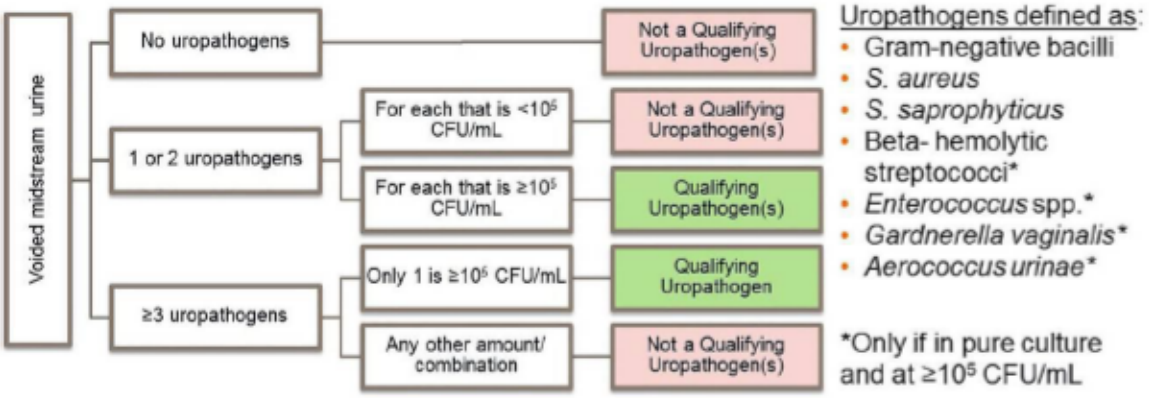
For all endpoints, the baseline value will be the latest predose assessment with a non-missing value (or randomization date in participants who are randomized but did not receive study treatment), including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline. For clinical signs and symptoms assessments, CCI and microbiological assessments, all Day 1 symptom assessments and urine samples (collected for identification of uropathogens) are used as baseline regardless of if they were taken pre or post dose. Urine samples collected on Day -1 or Day 1 can be considered as baseline. If baseline data is missing, then change from baseline calculations will not be performed and will be set to missing.

No change from baseline will be derived for ECGs since the protocol only requires ECG evaluations at the Baseline Visit.

5.2.1. Qualifying Uropathogens

The algorithm for determining baseline qualifying uropathogens based on microbiology laboratory quantitative culture results is provided in Figure 2 and Section 12.10:

Figure 2 Baseline Algorithm for Determining Qualifying Uropathogens



Only the following uropathogen species/groups, including Gram-negative bacilli (e.g., *E. coli, K. pneumoniae, P. mirabilis*), *S. saprophyticus*, and *Enterococcus* spp., will be considered for inclusion in the micro-ITT and other microbiological populations.

5.3. Multicenter Studies

In this multicenter global study, enrollment will be presented by investigative site, country, and region for descriptive summaries. Data from all sites will be combined for statistical analyses; analyses will not be adjusted by site.

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

The list of covariates and other strata may be used in descriptive summaries and statistical analyses, some of which may also be used for subgroup analyses. Additional covariates and other strata of clinical interest may also be considered.

- If the number of participants is small within a category of a covariate or strata, then the covariate/strata categories may be refined prior to unblinding the trial.
- If the category cannot be refined further, then the covariate may be included as a continuous measure.

Participants will be randomized to a study treatment using stratification by age category (<18 years, ≥18 to 50 years, or >50 years) and acute cystitis recurrence (nonrecurrent infection or recurrent infection). In the case of a difference between the stratification assigned at the time of randomization and the data collected in the eCRF, the data collected in the eCRF will be considered actual and used unless specified.

Stratification Factor	Stratification Level
Age Category	<18 years
	≥18 to 50 years
	>50 years
Acute Cystitis Recurrence	Nonrecurrent infection
	Recurrent infection

Stratification combinations will thus include:

Stratification Value	Stratification Description
1	<18 years, Nonrecurrent infection
2	<18 years, Recurrent infection
3	≥18 to 50 years, Nonrecurrent infection
4	≥18 to 50 years, Recurrent infection
5	>50 years, Nonrecurrent infection
6	>50 years, Recurrent infection

For use as an analysis covariate, pooled strata combining the <18 and ≥18 to 50-year-old participants are defined as follows:

Pooled Stratification Factor	Stratification Level
Age Category	≤ 50 years
	>50 years
Acute Cystitis Recurrence	Nonrecurrent infection
	Recurrent infection

Pooled stratification combinations will thus include:

Pooled Stratification Value	Stratification Description
1	≤50 years, Nonrecurrent infection
2	≤50 years, Recurrent infection
3	>50 years, Nonrecurrent infection
4	>50 years, Recurrent infection

Covariates
Treatment
Pooled strata (≤50 years, Nonrecurrent infection; ≤50 years, Recurrent infection; >50 years, Nonrecurrent infection; or >50 years, Recurrent infection†
Age (≤50 years, or >50 years)*
Acute cystitis recurrence (nonrecurrent infection or recurrent infection) at Baseline*
Baseline clinical signs and symptoms total score* (clinical response only)
Interaction term between treatment, Baseline uropathogen species/group and MIC (gepotidacin or nitrofurantoin) for randomized treatment* (microbiology response only).
Prior visit (On-therapy Visit) clinical outcome* (clinical response only)
Prior visit (On-therapy Visit) microbiological outcome* (microbiological response only)
Site (Sites with <10 participants in the micro-ITT NTF-S Population may be combined prior to unblinding)* (clinical response only)

†In the case of a difference between the stratification assigned at the time of randomization and the data collected in the eCRF, the data collected in the eCRF will be considered actual and used unless specified.
*Included in the multiple imputation logistic regression models only

5.4.2. Examination of Subgroups

Subgroup analyses will be performed using the following categories for efficacy analysis; treatment group differences will be displayed for subgroups with ≥10 participants across both treatment groups. For the subgroup analyses related to age category and acute cystitis, in the event that participants are mis-stratified, the actual stratification will be created using actual age and recurrent status collected from eCRF. If the number of participants is small within a subgroup, then the subgroup categories may be refined prior to unblinding the trial.

- Age category (<18, ≥18 to 50, >50) (only for therapeutic, clinical and (participant-level) microbiological response analyses)
- Acute cystitis recurrence (nonrecurrent infection, recurrent infection) (nonrecurrent infection or recurrent infection, defined as a confirmed infection with at least 1 episode within the past 3 months, at least 2 episodes within the past 6 months, or at least 3 episodes within the past 12 months before study entry)

(only for therapeutic, clinical and (participant-level) microbiological response analyses)
- (Unpooled) Stratification combinations as above for age and acute cystitis recurrence (only for therapeutic, clinical and (participant-level) microbiological response analyses)
- Qualifying uropathogen species/group isolated at Baseline (including phenotypic and genotypic subcategories), which is defined in Section 7.3.2. (only for therapeutic, clinical and (uropathogen-level) microbiological response analyses)
- Number of Qualified Uropathogens at Baseline (only 1 qualifying uropathogen, two qualified uropathogens, one qualified plus additional any number of non-qualified uropathogens) (only for therapeutic response analyses)
- Region (only for therapeutic, clinical and (participant-level) microbiological response analyses):
    - Americas: United States and Mexico
    - Europe: Bulgaria, Czech Republic, Germany, Greece, Hungary, Romania, Slovakia, Spain, and United Kingdom
    - Asia-Pacific: India
    - Others
- Race (only for therapeutic, clinical and (participant-level) microbiological response analyses)
- Ethnicity (only for therapeutic, clinical and (participant-level) microbiological response analyses)
- Menopausal status: Post-menopausal vs. Non post-menopausal (only for therapeutic, clinical and (participant-level) microbiological response analyses)
- Baseline symptom total scores (2-5, 6-8, 9-12) (only for therapeutic, clinical and (participant-level) microbiological response analyses).

For primary efficacy endpoint, additional subgroup analyses by age, acute cystitis recurrence and their combinations as randomized will be included.

For safety analysis, the below subgroup analysis related to age will be explored:

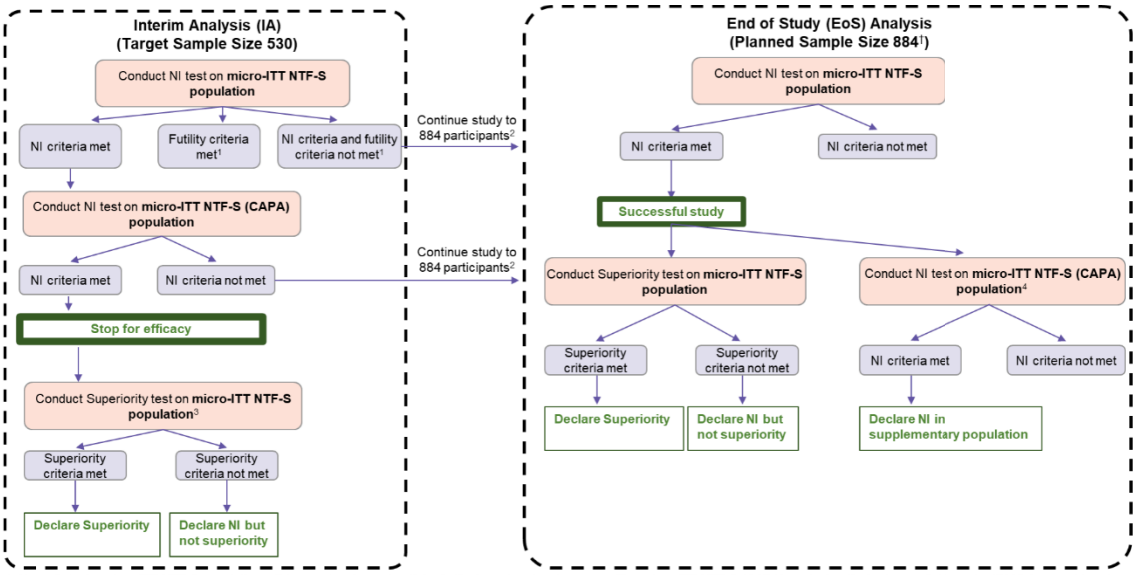
- Age: <18, ≥18 to 64, ≥ 65 to 74, ≥75

5.5. Multiple Comparisons and Multiplicity

The primary comparison of interest is the comparison between gepotidacin to nitrofurantoin for the primary endpoint of therapeutic response rate at TOC in the micro-ITT NTF-S Population. This analysis will be adjusted for stratification factors. The issue of multiple comparisons in the primary analysis will be addressed by testing the noninferiority of gepotidacin to treatment with nitrofurantoin prior to testing for superiority as described in Section 2.4. Further to this, the IA recommendation framework is defined per Figure 3. The IA recommendation framework required that both the noninferiority criteria is met in both the primary analysis population and the supplementary population for the study to be stopped for efficacy and noninferiority to be declared. Note: If the study continues at the interim, demonstration of NI at the final analysis will remain based on the primary analysis only (micro-ITT NTF-S) and the

supplementary analysis (micro-ITT NTF-S (CAPA)) performed at the final analysis will be provided for descriptive purposes only.

Figure 3 Study Success Definition and IA Recommendation Framework



1. Note: Only the micro-ITT NTF-S population will be used to determine if the futility boundary has been met. The micro-ITT NTF-S (CAPA) analysis will also be available to the IDMC for consideration.
2. Note: If there is not sufficient microbiology data the IDMC will perform the IA for futility with a planned sample size of 768 rather than 884
3. Note: For the interim analysis, the efficacy evidence used to stop or continue a study is based on the noninferiority testing only, i.e. not superiority testing.
4. Note: The supplementary analysis at the EOS may exclude more investigators/sites than the supplementary analysis at the IA

The statistical analyses of all other efficacy endpoints will be descriptive in nature, and therefore, will not be subject to multiplicity adjustments.

5.6. Analysis Visits

Analysis visit windows will be defined for by-visit summary and analysis purposes as illustrated in Table 5. Data not reported by-visit, including adverse events and concomitant medications, will not employ analysis visits. Analysis visit labels will be assigned to each post-baseline record (including records from unscheduled and early termination visits) based on the corresponding study day (relative to first study treatment or randomization if not treated). For post-baseline records collected outside the analysis visit window, a blank analysis visit label will be assigned. For example, a record collected at study Day 6 will not be utilized in any analyses or by visit descriptive summaries conducted at the OT or TOC scheduled visit. Descriptive summaries that are shown for “any assessment post baseline” e.g. maximum/minimum/ worst case post baseline, will use all assessments irrespective of whether they fall in an analysis visit window.

Table 5 Analysis Visit Windows

Post-Baseline Scheduled Visit	Protocol Window (Days)	Target Day	Analysis Visit Window (Days)
On-therapy	2 to 4	3	2 to 5
Test-of-Cure	10 to 13	12	9 to 16
Follow-up	25 to 31	28	21 to 31

If multiple records exist within the same analysis visit window, then the record occurring closest to the target day will be utilized in all analyses and analysis population determinations. If multiple records are equally close to the target day, then the later record will be utilized. If multiple records occur on the same 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 visits) will be presented in subject listings. Both the nominal and analysis visit will be presented in listings.

5.7. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
Section 12.1	Appendix 1: Schedule of Activities
Section 12.2	Appendix 2: Study Phases and Treatment Emergent Adverse Events
Section 12.3	Appendix 3: Data Display Standards & Handling Conventions
Section 12.4	Appendix 4: : Derived and Transformed Data
Section 12.5	Appendix 5: Reporting Standards for Missing Data
Section 12.6	Appendix 6: Values of Potential Clinical Importance
Section 12.7	Appendix 7: Division of Microbiology and Infectious Diseases Adult Toxicity Tables for Adverse Event Assessment
Section 12.8	Appendix 8: Abbreviations & Trademarks
Section 12.9	Appendix 9: List of Data Displays
Section 12.10	Appendix 10: Qualifying Uropathogen
Section 12.11	Appendix 11: Uropathogen Phenotype
Section 12.12	Appendix 12: Uropathogen Genotype
Section 12.13	Appendix 13: Uropathogen Grouping and Order Example

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be mainly based on the ITT Population and the primary analysis population (micro-ITT NTF-S/micro-ITT NTF-S (IA Set)), unless otherwise specified. Study population analyses including subject disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards. Baseline disease characteristics including baseline clinical symptom score, baseline uropathogens (including phenotypic and genotypic subcategories), past and current medical conditions, history of uncomplicated UTI, and exposure data will also be summarized.

6.1.1. Disposition and Protocol Deviations

All participants who provided informed consent will be accounted for. Participant disposition will be tabulated for each treatment group and overall, with the number of participants who completed the study, or prematurely withdrew, with the reason for early withdrawal presented for the ITT and micro-ITT NTF-S Populations and micro-ITT NTF-S (IA Set) Population if the study stops for efficacy. Separately, a summary of treatment status and reasons for discontinuation of study treatment will be provided for each treatment group and overall, with the number of participants who completed treatment, or prematurely discontinued treatment, and the primary reasons for treatment discontinuation tabulated for the ITT and micro-ITT NTF-S Populations and micro-ITT NTF-S (IA Set) Population if the study stops for efficacy.

The number and percentage of participants enrolled by country and site will be summarized for each treatment group and overall for the ITT Population.

For the Screened Population, a summary of reasons for screen failure (did not meet inclusion/exclusion criteria, adverse event, protocol deviation, lost to follow up, investigator discretion, withdrew consent, or other) will be provided.

A table will be produced summarizing the number of participants in each analysis population for all participants who provided informed consent. A separate table will also be constructed that summarizes the reasons for exclusion from each study population for all participants in the ITT Population. For each study population, failure to meet specific study population requirements will be summarized by treatment group and overall. Note that only participants with pre-defined uropathogens [Gram-negative bacilli (e.g. *E. coli, K. pneumoniae, P. mirabilis*), *S. saprophyticus*, and *Enterococcus* spp. as described in Section 7.3.2] will be considered for inclusion in the relevant microbiological populations.

The number and percentage of participants in the ITT Population with significant protocol deviations will be summarized by category and coded term.

All data will be listed by participant (paginated by treatment group).

6.1.2. Demographic and Baseline Disease Characteristics

Demographic and other baseline characteristics such as age, sex, race, ethnicity, childbearing potential, height, weight, body mass index (BMI), baseline acute cystitis recurrence and baseline renal impairment category will be summarized and tabulated by treatment group and for all participants in ITT, micro-ITT NTF-S, CE-TOC, and ME-TOC NTF-S Populations and micro-ITT NTF-S (IA Set) Population if the study stops for efficacy. Descriptive statistics will be presented for age, height, weight, and BMI. Frequency counts and percentages will be presented for age category, sex, race, ethnicity, childbearing potential, and baseline acute cystitis recurrence. Age is computed as integer part of (First Dose Date - JUN30 of Collected Birth Year + 1)/365.25; when first dose date is missing, the informed consent date is used. Individual participant demographics (including baseline acute cystitis status) will be presented in listings.

Baseline disease characteristics will summarize baseline quantitative bacterial counts, number of subjects with at least one baseline qualifying uropathogen identified, number of baseline qualifying uropathogens identified per subject, baseline qualifying uropathogens identified, and baseline clinical symptom score in ITT, micro-ITT and its derivatives (including micro-ITT NTF-S (IA Set) Population if the study stops for efficacy), CE-TOC, ME-TOC and its derivatives, ME-FU and its derivative populations. Separately, baseline uropathogens and qualifying uropathogens (including phenotypic and genotypic subcategories) will be summarized for ITT, micro-ITT and its derivatives, ME-TOC and its derivatives, ME-FU and its derivative populations. Baseline qualifying uropathogens will also be summarized separately by species and group (e.g., *Klebsiella* spp., other Enterobacterales, gram-negative nonfermenters, gram-positive species) for micro-ITT and its derivatives, ME-TOC and its derivatives, ME-FU and its derivative populations. Data will be listed and summarized using descriptive statistics or frequency counts and percentages as applicable.

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

$$\mathrm{Ccr(mL\ /\ min\ )} = \frac{\left((140 - \mathrm{age}) \times\ \mathrm{weight}\right)}{72\ \times \mathrm{Scr}} \times 0.85$$

where

- Scr is serum creatinine in (mg/dL)
- Age in years
- Weight in kg

  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)

Substance use such as smoking history, cigarettes per day, alcohol consumption, alcohol weekly use, caffeine consumption, and average caffeinated servings per day will also be summarized and listed.

The details of data displays are presented in Appendix 9

6.1.3. Prior and Concomitant Medications

Prior and concomitant medications will be coded using GSK Drug coding dictionary, summarized, and listed using generic term, verbatim text, and indication. Separate summaries of prior and concomitant medications will show the number and percentage of participants in the ITT and micro-ITT NTF-S Populations (and micro-ITT NTF-S (IA Set) Population (for concomitant medications only) if the study stops for efficacy) taking each prior and concomitant medication by corresponding Anatomical Therapeutic Chemical (ATC) classification Level 1 (Body System) information. The summary of prior medications will include a separate summary of prior antibiotic medications. The summary of concomitant medications will display separate summaries for systemic concomitant medications, non-systemic concomitant medications, systemic antibiotics taken for the disease under study (started on/after Study Day 1), systemic antibiotics taken for another disease/condition (started on/after Study Day 1), 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.

6.1.4. Medical History and Current Medical Conditions

Medical history and current medical conditions will be summarized and displayed with the number and percentage of participants for each body system for ITT and micro-ITT NTF-S Populations (and micro-ITT NTF-S (IA Set) Population if the study stops for efficacy). General medical history, previous *Clostridium 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 and micro-ITT NTF-S Populations (and micro-ITT NTF-S (IA Set) Population if the study stops for efficacy). All data will be listed.

6.1.5. Treatment Exposure

Treatment exposure will be summarized by treatment group for the Safety and micro-ITT NTF-S Populations (and micro-ITT NTF-S (IA Set) Population if the study stops for efficacy). The summary will include duration of treatment (days), the number of doses administered, number of tablets/capsules, average daily dose, cumulative actual dose, and compliance rate. The number of participants with <80%, ≥80% - <100%, and 100% compliance rate will also be summarized. Dose administration for all participants will be displayed in the listing.

Compliance rate (%) will be calculated as:

- Gepotidacin/gepotidacin placebo:

$$\frac{\text{total number of tablets taken}}{20} * 100\%$$

- Nitrofurantoin/nitrofurantoin placebo:

$$\frac{\text{total number of capsules taken}}{10} * 100\%$$

The details of data displays are presented in Appendix 9

7. EFFICACY ANALYSES

7.1. Primary Efficacy Analyses

The primary clinical question of interest is: what is the treatment effect on therapeutic success rate after 5 days treatment with gepotidacin 1500 mg twice daily compared to 5 days treatment with nitrofurantoin 100 mg twice daily in participants with acute cystitis who have a qualifying uropathogen at Baseline that is susceptible to nitrofurantoin regardless of treatment discontinuation for any reason. Receipt of systemic antimicrobials impacts the endpoint definition (see Table 6 to Table 8). Further details on the primary estimand are given in Section 2.2.1.

7.1.1. Endpoint / Variables

7.1.1.1. Therapeutic Response at TOC

The primary efficacy endpoint is therapeutic response (combined per participant microbiological and clinical response) at the Test of Cure (TOC) Visit. Therapeutic response is a dichotomous measure of overall efficacy response, either a success or failure, and will be determined programmatically. A therapeutic success refers to participants who have been deemed both a participant level "microbiological success" and a "clinical success". All other combinations will be deemed failures for therapeutic response. The detailed definitions of microbiological and clinical response are given in Table 6, Table 7, and Table 8.

7.1.1.2. Microbiological Outcome and Response at TOC

- Only those participants who have a qualifying uropathogen (Section 5.2.1) identified at Baseline will be evaluated for microbiological outcome and response by baseline qualifying uropathogen for the primary efficacy endpoint.
- The microbiological success at the uropathogen level is defined as a reduction of bacterial count to $<10^3$ CFU/mL for a specific qualifying uropathogen recovered at Baseline without the participant receiving any other systemic antimicrobials before the TOC Visit (started on/after Study Day 1). The criteria of microbiological outcome and response are shown in Table 6.
- Participant level microbiological response is a measure of the combined "by uropathogen" response(s). Per-participant level microbiological success refers to participants who have been deemed "microbiological success" for all of their qualifying baseline uropathogen(s) microbiological responses. All other combinations are deemed failures for per-participant level microbiological response. Participant-level microbiological outcome and response definitions at TOC are shown in Table 7.

Table 6 Microbiological Outcome and Response by Baseline Qualifying Uropathogen at the TOC Visit - uropathogen level

Defining Criteria	Outcome	Response
Participants considered microbiological failures at the TOC Visit will also be considered microbiological failures at the Follow-up Visit.		
A quantitative urine culture taken at the TOC Visit shows reduction of the qualifying uropathogen recovered at Baseline to $<10^3$ CFU/mL without the participant receiving other systemic antimicrobials before the TOC Visit	Microbiological eradication	Microbiological success
A quantitative urine culture taken at the TOC Visit shows that the qualifying uropathogen recovered at Baseline, and which was also shown to persist or is unable to determine at the On-therapy Visit, grows $\geq 10^3$ CFU/mL without the participant receiving other systemic antimicrobials before the TOC Visit	Microbiological persistence	Microbiological failure
A quantitative urine culture taken at the TOC Visit shows that the qualifying uropathogen recovered at Baseline, and which was also shown to be eradicated at the On-therapy Visit, grows $\geq 10^3$ CFU/mL without the participant receiving other systemic antimicrobials before the TOC Visit	Microbiological recurrence	Microbiological failure
(1) The TOC urine culture result is missing or (2) The participant received other systemic antimicrobials before the TOC Visit	Unable to determine	Microbiological failure

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

Table 7 Participant-level microbiological outcome and response at the TOC Visit

Defining Criteria	Outcome	Response
All qualifying baseline uropathogens have a microbiological outcome of eradication at TOC	Microbiological eradication	Microbiological success
At least one qualifying baseline uropathogen has an outcome of persistence at TOC	Microbiological persistence	Microbiological failure
At least one qualifying baseline uropathogen has an outcome of recurrence and none have an outcome of persistence at TOC	Microbiological recurrence	Microbiological failure
All qualifying baseline uropathogen outcomes are unable to determine at TOC	Unable to determine	Microbiological failure
TOC=Test of Cure		

7.1.1.3. Clinical Outcome and Response at TOC

- Clinical signs and symptoms of acute cystitis will be recorded by site staff based on participant interview using the following scoring system:

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

- 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. At TOC, success is defined as normal presentation of signs and symptoms with a total cumulative symptom score of zero. If the participant is missing baseline assessment, they will be considered 'Unable to determine' for outcome, and 'Clinical failure' for response at the respective visit.
- The clinical outcome and response will be programmatically determined by comparing the total scores of the signs and symptoms of acute cystitis at the TOC Visit to those present at Baseline as shown in Table 8.

Table 8 Clinical Outcome and Response at the TOC Visit

Defining Criteria	Outcome	Response
Test-of-Cure Visit		
Resolution of signs and symptoms of acute cystitis present at Baseline (and no new signs and symptoms), without the participant receiving any other systemic antimicrobials before the TOC Visit	Clinical resolution	Clinical success
Improvement in total symptom scores from Baseline, but not complete resolution, without the participant receiving other systemic antimicrobials before the TOC Visit	Clinical improvement	Clinical failure
Worsening or no change in total symptom scores from Baseline or the participant received other systemic antimicrobials for the current infection before or on the date of the TOC Visit	Clinical worsening	Clinical failure
(1) The baseline score is missing or (2) The TOC assessment is missing or (3) The participant received other systemic antimicrobials not for the current infection before the TOC Visit (unless clinical worsening outcome criteria were met)	Unable to determine	Clinical failure

TOC=Test-of-Cure.

If participant took both other systemic antimicrobials for the current infection on or before the date of the TOC Visit (started on/after Study Day 1), and other systemic antimicrobials not for the current infection before the date of the TOC Visit (started on/after Study Day 1), then participant will be derived as 'Clinical worsening'.

7.1.2. Summary Measure

Difference in the therapeutic success rate in the gepotidacin and nitrofurantoin treatment groups (gepotidacin 1500 mg BID – nitrofurantoin 100 mg BID).

7.1.3. Population of Interest

Female participants with acute cystitis with qualifying uropathogen(s) at Baseline that all are susceptible to nitrofurantoin.

7.1.4. Strategy for Intercurrent Events

There are two kinds of intercurrent events (ICE):

- Study treatment discontinuation (due to any reason) – treatment policy strategy (the occurrence of the ICE is considered irrelevant in defining the treatment effect of interest).

- Use of systemic antimicrobials - composite strategy. This intercurrent event is captured through the definitions of microbiological and clinical response (see Section 7.1.1.1 and Section 7.1.1.3) and will be counted as therapeutic failures.

If the patient experiences both of these ICE then a composite strategy (assigning therapeutic response as a failure) will be used from the point that the relevant systemic antimicrobial was taken).

7.1.5. Treatment Condition

Gepotidacin 1500 mg twice daily for 5 days versus nitrofurantoin 100 mg twice daily for 5 days regardless of adherence.

7.1.6. Statistical Analyses / Methods

7.1.6.1. Statistical Methodology Specification

The primary efficacy endpoint is the therapeutic response (combined per-participant microbiological and clinical response) at the TOC Visit. The primary analysis population is the micro-ITT NTF-S Population if the study does not stop for efficacy and micro-ITT NTF-S (IA Set) if the study stops for efficacy.

For the statistical analysis, four pooled strata will be formed according to the combinations of levels of the following categorical variables: age category (≤50 years, or >50 years) and acute cystitis recurrence (nonrecurrent infection or recurrent infection) at Baseline. If a participant is mis-stratified then the actual pooled strata collected in the eCRF will be used in the analysis instead of the randomized pooled strata, unless specified.

The Miettinen-Nurminen (score) confidence limits for the treatment difference [Miettinen, 1985] are computed (SAS PROC FREQ [SAS, 2018] uses iterative computation for this). Stratum based point estimates and variances can be estimated from these CIs. The MN estimate of the common risk difference and variance is computed by combining the point estimates and variances from the individual pooled strata using MN weights. The estimate uses inverse variance stratum weights to produce MN confidence limits for the stratum risk differences. The mathematics and algorithm of MN method can be found in the SAS procedure guide under “Summary Score Estimate of the Common Risk Difference” [SAS, 2018].

Z statistics for noninferiority are calculated by using the MN common risk difference and the variance estimator and the –10% NI margin to compare with the Z-statistics boundaries. Testing for superiority will occur if noninferiority is achieved. A one-sided *p*-value will be calculated to compare with the *p*-value boundaries.

Statistical testing will occur at the IA. If the study is not stopped for efficacy or futility, statistical testing will be repeated after the study is completed. Boundaries will be calculated at the time of the IA for both testing at the IA and at the end of study based on the actual information fraction at the time of the IA.

The point estimate of the difference in the proportion of therapeutic responders between each treatment group and its two-sided 95% CIs (using MN method adjusting for treatment and actual pooled strata) and Z statistic for noninferiority will be presented. Note: all CI are nominal without multiplicity adjustment for alpha spend at interim.

The number and proportion of participants with therapeutic success at the TOC Visit will be presented by treatment group along with the 95% Exact Clopper-Pearson CI for the success rate.

A summary of therapeutic success, failure, and reasons for failure at the TOC Visits (including receipt of non-study antibacterial therapy for uUTI) will also be presented for each treatment group at participant level.

Supportive analyses will be performed to enable the assessment of the homogeneity of the treatment difference across pooled strata used in the primary analysis. This will be conducted on the primary analysis population (micro-ITT NTF-S (IA Set) if the study stops for efficacy else the micro-ITT NTF-S Population)

The weighted least squares chi-squared statistic of Fleiss [Fleiss, 1981] will be used to test for one-way homogeneity of the treatment difference across the levels of the pooled strata used for the primary analysis. The overall test for homogeneity will use the combined strata levels constructed by cross-classification of pooled strata. Additional tests for homogeneity of the treatment difference across the levels of each pooled strata will be performed, with each pooled stratum considered separately. Following Lui and Kelly [Lui, 2000], ½ will be added to each cell in any (pooled) stratum for which the stratum-specific success rate estimates of either gepotidacin or nitrofurantoin are zero or one, and tests will be one-sided. Tests of homogeneity will be assessed at the one-sided 10% level of significance.

For each stratum, the percent of participants with therapeutic successes by treatment group and unadjusted difference in percent between treatment groups with corresponding two-sided 95% CI (using MN method adjusting for treatment only) will be reported. In addition, the *p*-value from the overall test of homogeneity will be reported, as well as the *p*-value for the additional tests of homogeneity considering each pooled strata separately.

7.1.6.2. Sensitivity Analyses

Sensitivity analyses will be performed to investigate the robustness of the primary efficacy results for the primary estimand. The following sensitivity analyses will be performed in the primary analysis population (micro-ITT NTF-S (IA Set) Population if the study stops for efficacy else micro-ITT NTF-S Population) unless otherwise specified. Z statistics for noninferiority will be compared to the boundaries used for primary efficacy testing.

1) If the study stops for efficacy, an analysis of therapeutic response at TOC adjusted for the pooled stratification factors based on the actual stratum will be performed on the micro-ITT NTF-S Population (complete trial data). Difference in the proportion of therapeutic responders between each treatment group adjusted by MN weights (using actual pooled strata) will be presented along with two-sided

95% CIs (using MN method adjusting for treatment and actual pooled strata) and Z statistics for noninferiority to provide a nominal estimate.

2) An analysis of therapeutic response at TOC unadjusted for the stratification factors. Unadjusted difference in proportions between treatment groups (gepotidacin – nitrofurantoin), Z statistic for noninferiority using the unadjusted difference, and corresponding two-sided 95% CI (using MN method adjusting for treatment only) will be presented.
   If the study stops for efficacy, this analysis will be performed on the micro-ITT NTF-S (IA Set) Population and micro-ITT NTF-S Population.
3) An analysis of therapeutic response at TOC adjusted for the stratification factors based on the randomization stratum the participant was randomized to (instead of the actual stratum the participant should be assigned to). Difference in the proportion of therapeutic responders between each treatment group adjusted by MN weights (using randomized stratification) will be presented along with two-sided 95% CIs (using MN method adjusting for treatment and pooled strata as randomized) and Z statistics for noninferiority.
   If the study stops for efficacy, this analysis will be performed on the micro-ITT NTF-S (IA Set) Population and micro-ITT NTF-S Population.
4) A sensitivity analysis for the primary endpoint will be carried out to assess the impact of missing data. If the entire TOC Visit, bacteriology samples or clinical signs and symptoms assessment were missed due to COVID-19 pandemic, then the missing value will be imputed under the MAR assumption. If the TOC bacteriology sample was taken but a result is not available for the sample for any reason, then the missed value will also be imputed under the MAR assumption. All other missing data will be considered as a failure (i.e., non-responders) in the primary analysis. Multiple imputations will be implemented with the following steps:
   - Step 1: Missing microbiology response values and clinical response values will be imputed using separate logistic regression models under a missing at random assumption in the micro-ITT NTF-S Population. The number of imputations will be 1,000 and SEED = 204989. The variables to be included in the imputation model are:
     - Age (≤50 years, or >50 years)
     - Acute cystitis recurrence (nonrecurrent infection or recurrent infection) at Baseline
     - Baseline clinical signs and symptoms total score (clinical response only)
     - Interaction term between treatment, Baseline qualifying uropathogen species/group and MIC (gepotidacin or nitrofurantoin) for randomized treatment (microbiology response only). If needed, this may be refined prior to unblinding.
       Note: Baseline uropathogen species/group will be determined by GSK microbiology prior to unblinding and will include separate holistic reviews to:
       - identify dominant uropathogen for subjects with more than one qualifying uropathogen at Baseline. This selection will be completed for all subjects with more than one qualifying uropathogen at Baseline in the micro-ITT NTF-S

Population, regardless of missing data and will be based on species and gepotidacin or nitrofurantoin MIC value and will identify the dominant uropathogen for gepotidacin and for nitrofurantoin treatment groups as these may differ. This will be documented prior to unblinding. Post unblinding, the dominant uropathogen for the randomized treatment will be used and the corresponding Baseline uropathogen species/group and MIC will be used in the analysis.

- Group similar uropathogens. This may include groupings by species and, if needed, grouping of uropathogens with smaller frequencies with other similar uropathogens. This will be documented prior to unblinding.
- Group MICs (gepotidacin or nitrofurantoin) by randomized treatment which may be based on Baseline uropathogen species/group. This will be documented prior to unblinding.

- Prior visit (On-therapy Visit) clinical outcome (clinical response only)
- Prior visit (On-therapy Visit) microbiological outcome (microbiological response only)
- Site (Sites with <10 participants in the micro-ITT NTF-S Population may be combined prior to unblinding) (clinical response only)
- Randomized treatment received

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

- Step 2: Step 1 will produce 1,000 imputed datasets with complete data. For each dataset, participants therapeutic response will then be derived using the imputed and non-missing data per Section 7.1.1.1. We will estimate the proportion of success in each treatment group and its standard error using the exact Clopper-Pearson method, and the difference in the proportion of success between the two treatment groups and its standard error using the MN method weighted on actual pooled strata as in the primary efficacy analysis for each imputed dataset separately. All estimated quantities (proportion of success in each treatment group, difference between two groups, and their associated standard errors) will be saved for step 3.
- 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 success rate in each treatment group and for the difference in the proportion of success between the two treatment groups. The 95% (Wald) CIs will be calculated for the proportions of successes in each arm as well as for the risk difference between the two treatment groups. Z statistic for noninferiority between the two treatment groups will also be calculated. Testing for superiority may occur if noninferiority is achieved. A one-sided *p*-value for superiority will be calculated to compare with the *p*-value boundary.

5) To assess the impact of failure imputation of missing data on the therapeutic response at TOC, a tipping point analysis may be performed for the primary endpoint in the micro-ITT NTF-S Population. The scope of missing data will be consistent with the multiple imputation analyses, specifically, if the entire TOC Visit, bacteriology samples or clinical signs and symptoms assessment were missed due to COVID-19 pandemic, then the missed value will be imputed under the MAR assumption. If the TOC bacteriology sample was taken but a result is not available for the sample for any reason, then the missed value will also be imputed under the MAR assumption. All other missing data will be considered as a failure (i.e., non-responders) per the primary analysis. The tipping point analysis will vary assumptions on the proportion of subjects achieving success in the two treatment groups. For each combination of assumed success rates in the two treatment groups, the number of additional subjects achieving success among subjects with missing therapeutic response will be imputed by drawing from a binomial distribution.
    - A grid of paired values will be established, ranging from 0.025 to 0.975 in steps of 0.025, establishing the assumed response rates for each treatment group in subjects with missing therapeutic response.
    - For each pair of assumed response rates corresponding to treatment group, $(\theta^{(i)}_{Gepotidacin}, \theta^{(j)}_{Nitrofurantoin})$, repeat the following steps 100 times:
        - Sample additional responders among subjects with missing responses by drawing from a binomial distribution, using the assumed response rate assigned to each treatment group. Sampling will be completed separately by treatment,
          $r^{a}_{Gepotidacin,} \sim \text{Binomial}\ (n^{miss}_{Gepotidacin}, \theta^{(i)}_{Gepotidacin})$
          $r^{a}_{Nitrofurantoin} \sim \text{Binomial}\ (n^{miss}_{Nirofurantoin}, \theta^{(j)}_{Nitrofuranotin})$
        - The proportion of success in each treatment group and the difference in the proportion of success between two treatment groups as well as the respective associated standard errors will be computed. Standard error of the risk difference estimate will be calculated using the MN method weighted on actual pooled strata.

    - Using Rubin's rules we will combine the estimated quantities (success rate in each treatment group, difference in proportions between two groups, and their respective standard errors). The calculations for pooled estimates will be implemented using SAS PROC MIANALYZE. 95% (Wald) CIs will be calculated for the proportions of successes in each arm as well as for the risk difference between the two treatment groups. Z statistic for noninferiority between the two treatment groups will also be calculated. The noninferiority conclusion will be drawn if the Z statistic is larger than the Z statistic boundary. Testing for superiority may occur if noninferiority is achieved. A one-sided *p*-value will be calculated to compare with the *p*-value boundaries.
    - The process described above will be repeated for each pair of assumed response rates, $(\theta^{(i)}_{Gepotidacin}, \theta^{(j)}_{Nitrofurantoin})$.

- Visual representations of treatment difference and noninferiority decisions will be produced using a colored heatmap illustrating the gradual change of treatment difference. Colored borders will be used to highlight the therapeutic response rates that resulted in noninferiority.

7.1.6.3. Supplementary analyses

Supplementary analysis of the primary efficacy endpoint will be performed in the micro-ITT and micro-ITT NTF-NS and in the ME-TOC/NTF-S/NTF-NS Populations on the participant level following the same layout/content contained in the original presentation of the primary analysis. MN adjusted difference using actual pooled strata and unadjusted difference in success rate will be presented along with their 95% CI (calculated using MN method).

An additional supplementary analysis of participant-level therapeutic response at TOC will be provided for a modified micro-ITT NTF-S Population for EMA. Inclusion into an "EU micro-ITT NTF-S" Population for this analysis will be based on baseline susceptibility to nitrofurantoin according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints and interpretive criteria instead of CLSI. The key EU supplementary analysis population is the EU micro-ITT NTF-S Population (complete trial data) if the study does not stop for efficacy and EU micro-ITT NTF-S (IA Set) if the study stops for efficacy. If the study stops for efficacy a sensitivity to the EU supplementary analysis will be performed on the EU micro-ITT NTF-S Population (complete trial data). Unadjusted difference, MN adjusted difference using actual pooled strata, and MN adjusted difference using pooled strata as randomized in success rate will be presented along with their 95% CI (calculated using MN method) and nominal Z statistics for noninferiority. One-sided *p*-value for superiority for MN adjusted difference using actual pooled strata in success rate will also be presented. Nominal tests for noninferiority and superiority will follow the same method as the primary efficacy analysis as described in Section 7.1.6.1 using the same boundary based on the information fraction of the CLSI-based micro-ITT NTF-S. Test for homogeneity will also be conducted for primary efficacy endpoint in the key EU supplementary analysis population (EU micro-ITT NTF-S Population (complete trial data) if the study does not stop for efficacy and EU micro-ITT NTF-S (IA Set) if the study stops for efficacy).

In the event that one or more investigators/sites receive a corrective and preventative action (CAPA) that stipulates a supplementary analysis should be conducted excluding them as agreed by a multidisciplinary GSK team prior to unblinding, a supplementary analysis will be performed. A flag will be included to identify subjects enrolled by those investigators/sites. This will enable further subpopulations to be defined for the primary analysis populations (micro-ITT NTF-S if the study continues / micro-ITT NTF-S (IA Set) if the study stops for futility). The sub population will consist of all subjects in the primary analysis population except subjects from those investigative sites (e.g., micro-ITT NTF-S (CAPA)/ micro-ITT NTF-S (IA Set) (CAPA) respectively) and will be used to perform the additional supplemental analysis for the primary efficacy endpoint only. Note: this analysis is included in the IA recommendation framework per Section 5.5.

7.1.6.4. Subgroup Analyses

Subgroup analyses will be performed for the primary endpoint (therapeutic response at the TOC Visit) in the micro-ITT NTF-S Population (complete trial data). Subgroup analyses for the primary endpoint in additional populations (micro-ITT, micro-ITT NTF-NS and ME-TOC/NTF-S/NTF-NS) will also be included. See Section 5.4.2 for definition of subgroups. For qualifying uropathogen thresholds, see the corresponding Section 5.2.1. Analysis of therapeutic response at the TOC Visit by number of qualified uropathogens at Baseline will only be performed in the micro-ITT/NTF-S/NTF-NS Populations.

A summary of therapeutic success, failure, reasons for failure at the TOC Visit will also be presented by subgroup for each treatment group. The associated 95% Exact Clopper-Pearson CI for the success rate will be included for each treatment group at each level. Unadjusted difference in proportions between treatment groups and corresponding two-sided 95% CI (using MN method adjusting for treatment only) at each level will be presented.

Percent of therapeutic success at TOC overall and by qualifying uropathogen will be plotted for each treatment group for the micro-ITT NTF-S Population. Forest plot for therapeutic success rate at TOC overall and by subgroup will be plotted for micro-ITT/NTF-S/NTF-NS.

All subgroup analyses will follow the same layout/content contained in the original presentation of the primary analysis. Summary tables will be paginated by each level of the subgroup, and only the unadjusted difference in success rate will be presented.

7.2. Secondary Efficacy Analyses

The secondary clinical efficacy questions of interest are: what is the treatment effect on each of the secondary efficacy endpoints after 5 days treatment with gepotidacin 1500 mg twice daily compared to 5 days treatment with nitrofurantoin 100 mg twice daily in participants with acute cystitis (clinical endpoints) and in participants with acute cystitis with qualifying uropathogen(s) at Baseline that all are susceptible to nitrofurantoin (therapeutic, clinical, and microbiological endpoints), regardless of treatment discontinuation for any reason. Receipt of systemic antimicrobials impacts the endpoint definition (see Section 7.2.1.1, Section 7.2.1.2, and Section 7.2.1.3). Further details of the estimands for secondary efficacy endpoints are given in Section 2.2.2.

7.2.1. Endpoint / Variables

7.2.1.1. Microbiological Outcome and Response at TOC and Follow-up

The microbiological outcome and response are evaluated at participant level at the TOC and FU Visits. The criteria of uropathogen-level microbiological outcome and response are defined in Table 6 (TOC) and similarly in Table 9 (FU). The criteria of participant-level microbiological outcome and response are defined in Table 7 (TOC) and Table 10 (FU).

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

Defining Criteria	Outcome	Response
Participants considered microbiological failures at the TOC Visit will also be considered microbiological failures at the FU Visit.		
A quantitative urine culture taken at the Follow-up Visit shows reduction of the qualifying uropathogen recovered at Baseline to $<10^3$ CFU/mL following microbiological eradication at the TOC Visit, without the participant receiving other systemic antimicrobials before the Follow-up Visit	Sustained microbiological eradication	Microbiological success
A quantitative urine culture taken at the Follow-up Visit shows that the qualifying uropathogen recovered at Baseline grows $\geq 10^3$ CFU/mL following microbiological eradication at the TOC Visit, without the participant receiving other systemic antimicrobials before the Follow-up Visit	Microbiological recurrence	Microbiological failure
A quantitative urine culture taken at the Follow-up Visit shows that the qualifying uropathogen recovered at Baseline grows $\geq 10^3$ CFU/mL, and also did not achieve an outcome of microbiological eradication at the TOC Visit, without the participant receiving other systemic antimicrobials before the Follow-up Visit	Microbiological persistence	Microbiological failure
A quantitative urine culture taken at the Follow-up Visit shows reduction of the qualifying uropathogen recovered at Baseline to $<10^3$ CFU/mL, and also did not achieve an outcome of microbiological eradication at the TOC Visit, without the participant receiving other systemic antimicrobials before the Follow-up Visit	Delayed microbiological eradication	Microbiological failure
1) The FU urine culture result is missing or 2) The participant received other systemic antimicrobials before the FU Visit	Unable to determine	Microbiological failure

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

Table 10 Participant-Level Microbiological Outcome and Response at the Follow-Up Visit

Defining Criteria at FU Visit	Outcome	Response
All qualifying baseline uropathogens have a microbiological outcome of sustained eradication at Follow-up	Sustained Microbiological eradication	Microbiological Success
At least one qualifying baseline uropathogen has an outcome of recurrence and none have an outcome of persistence at Follow-up	Microbiological recurrence	Microbiological Failure
At least one qualifying baseline uropathogen has an outcome of persistence at Follow-up	Microbiological persistence	Microbiological Failure
At least one qualifying baseline uropathogen has an outcome of delayed eradication and none have an outcome of persistence or recurrence at Follow-up	Delayed microbiological eradication	Microbiological Failure
All qualifying baseline uropathogen outcomes are unable to determine at Follow-up	Unable to determine	Microbiological Failure

7.2.1.2. Clinical Outcome and Response at TOC and Follow-Up

Clinical outcome and response are evaluated at participant level at the TOC and FU Visits. The criteria for clinical outcome and response are defined in Table 8 (TOC) and similarly in Table 11(FU).

Table 11 Clinical Outcome and Response at the Follow-Up Visit

Defining Criteria	Outcome	Response
Participants who withdraw from the study prior to the FU Visit will be considered not achieving success (imputed as failure) as the clinical response at FU.		
Resolution of signs and symptoms of acute cystitis demonstrated at the TOC Visit persist at the FU Visit (and no new signs and symptoms), without the participant receiving other systemic antimicrobials before the FU Visit.	Sustained clinical resolution	Clinical success
Resolution of signs and symptoms of acute cystitis present at Baseline (and no new signs or symptoms), after clinical failure at TOC, without the participant receiving other systemic antimicrobials before the FU Visit.	Delayed clinical resolution	Clinical failure
Improvement in total symptom scores from Baseline, but not complete resolution, without the participant receiving other systemic antimicrobials before the FU Visit.	Clinical improvement	Clinical failure
Worsening or no change in total symptom scores at FU compared to Baseline after clinical failure at TOC or the participant received other systemic antimicrobials for the current infection before or on the date of the FU Visit	Clinical worsening	Clinical failure
Signs and symptoms of acute cystitis reoccur at the FU Visit assessment after clinical success at the TOC Visit	Clinical recurrence	Clinical failure
1) The baseline score is missing or 2) The FU assessment is missing or 3) The participant received other systemic antimicrobials not for the current infection before the FU Visit (unless clinical worsening or recurrence outcome criteria were met)	Unable to determine	Clinical failure

TOC=Test-of-Cure. FU=Follow-up.

If participant took both other systemic antimicrobials for the current infection on or before the date of the FU Visit, and other systemic antimicrobials not for the current infection before the date of the FU Visit, then participant outcome will be derived as 'Clinical worsening'.

7.2.1.3. Therapeutic Response at Follow-up

A therapeutic success at Follow-up refers to participants who have been deemed both a "microbiological success" and a "clinical success" at the Follow-up Visit. All other combinations will be deemed failures for therapeutic response.

7.2.2. Summary Measure

For details of the estimand summary measure see Table 1 in Section 2.2.2.

7.2.3. Population of Interest

For details of the estimand population see Table 1 in Section 2.2.2.

7.2.4. Strategy for Intercurrent Events

For details of the estimand strategy for intercurrent events see Table 1 in Section 2.2.2.

7.2.5. Treatment Condition

For details of the estimand treatment condition see Table 1 in Section 2.2.2.

7.2.6. Statistical Analyses / Methods

7.2.6.1. Statistical Methodology Specification

There will be no multiplicity adjustment for the testing of the secondary endpoints. No formal hypothesis testing will be performed.

Secondary efficacy endpoint for clinical outcome and response at the TOC and FU Visits will be summarized using the ITT and micro-ITT NTF-S Populations. In addition, if the study stops for efficacy, a summary of clinical outcome and response at the TOC visit will be performed on the micro-ITT NTF-S (IA Set) Population.

Secondary efficacy endpoints for participant-level microbiological outcome and response at the TOC and FU Visits, as well as therapeutic response at the FU Visit, will be summarized using the micro-ITT NTF-S Population. In addition, if the study stops for efficacy a summary of participant-level microbiological outcome and response at the TOC visit will be performed on the micro-ITT NTF-S (IA Set) Population.

The 95% Exact Clopper-Pearson CI for microbiological, clinical, and therapeutic success rate will be included by treatment group. For participant level response, the MN weighted success rate difference (via actual stratification) will be calculated along with the 95% CI (using MN method adjusting for treatment and actual pooled strata). Reasons for failure (including receipt of non-study antibacterial therapy for uUTI) will be summarized for each treatment group for all participants that are failures.

Supportive analyses to assess the homogeneity of the treatment difference across analysis strata will be implemented as in the primary efficacy analysis. This will also include the components of the primary composite endpoint of clinical response and micro response at TOC for the primary population (micro-ITT NTF-S (IA Set) if the study stops for efficacy else the micro-ITT NTF-S Population).

Separately, percent of clinical outcomes by visit will be plotted for the ITT Population, and percent of participant level microbiological outcomes by visit will be plotted for the micro-ITT/NTF-S/NTF-NS Populations.

7.2.6.2. Sensitivity Analyses

Sensitivity analyses will be performed to investigate the robustness of the secondary estimands for microbiological response at TOC and FU, clinical response at TOC and FU, as well as therapeutic response at FU in their corresponding analysis populations defined in Section 7.2.6.1. Success rate between treatment groups (gepotidacin – nitrofurantoin) will be analyzed using unadjusted difference and corresponding two-sided 95% CI (using MN method adjusting for treatment only) will also be presented.

7.2.6.3. Supplementary Analyses

Supplementary analyses will be performed on secondary endpoints including:

An analysis of therapeutic response at FU will be performed in the micro-ITT and micro-ITT NTF-NS and in the ME-FU/NTF-S/NTF-NS Populations.

An analysis of clinical outcome and response by visit will be performed in the CE-TOC, CE-FU, micro-ITT, and micro-ITT NTF-NS Populations.

An analysis of microbiological outcome and response by visit will be performed in the micro-ITT, micro-ITT NTF-NS, ME-TOC/NTF-S/NTF-NS, and ME-FU/NTF-S/NTF-NS Populations.

Success rate between treatment groups (gepotidacin – nitrofurantoin) will be analyzed using unadjusted difference and corresponding two-sided 95% CI (using MN method adjusting for treatment only) will also be presented. Reasons for failure (including receipt of non-study antibacterial therapy for acute cystitis) will be summarized for each treatment group for all participants that are failures.

7.2.6.4. Subgroup Analyses

Subgroup analyses of each secondary endpoint (participant-level therapeutic response, participant-level clinical outcome / response, and participant-level & uropathogen-level microbiological outcome / response, at the relevant visit) will be performed as listed in Table 12. See Section 5.4.2 for the definition of subgroups. For qualifying uropathogen thresholds, see Section 7.3.2. All subgroup analyses will follow the same layout/content contained in the original presentation of the main analyses. The population will include complete trial data (i.e., including participants in the IA Set and overrun if the study stops early for efficacy). Summary tables will be paginated by each subgroup level, and only the unadjusted difference and its 95% CI (using MN method adjusting for treatment only) in success rate will be presented.

Table 12 Subgroup and Uropathogen Level Analyses

Analysis/Endpoint Description: Therapeutic Response **Visit: FU**	
Population	**Subgroup**
micro-ITT	Qualifying uropathogen species/group (including phenotypic and genotypic subcategories), by age category (<18, ≥18 to 50, >50), acute cystitis recurrence (nonrecurrent infection, recurrent infection), stratification combinations (age group and acute cystitis recurrence), region, race, ethnicity, baseline clinical symptom score, menopausal status, number of qualified uropathogens at Baseline
micro-ITT NTF-S	Qualifying uropathogen species/group (including phenotypic and genotypic subcategories), by age category (<18, ≥18 to 50, >50), acute cystitis recurrence (nonrecurrent infection, recurrent infection), stratification combinations (age group and acute cystitis recurrence), region, race, ethnicity, baseline clinical symptom score, menopausal status, number of qualified uropathogens at Baseline
micro-ITT NTF-NS	Qualifying uropathogen species/group (including phenotypic and genotypic subcategories), by age category (<18, ≥18 to 50, >50), acute cystitis recurrence (nonrecurrent infection, recurrent infection), stratification combinations (age group and acute cystitis recurrence), region, race, ethnicity, baseline clinical symptom score, menopausal status, number of qualified uropathogens at Baseline
ME-FU	Qualifying uropathogen species/group (including phenotypic and genotypic subcategories), by age category (<18, ≥18 to 50, >50), acute cystitis recurrence (nonrecurrent infection, recurrent infection), stratification combinations (age group and acute cystitis recurrence), region, race, ethnicity, baseline clinical symptom score, menopausal status
ME-FU NTF-S	Qualifying uropathogen species/group (including phenotypic and genotypic subcategories), by age category (<18, ≥18 to 50, >50), acute cystitis recurrence (nonrecurrent infection, recurrent infection), stratification combinations (age group and acute cystitis recurrence), region, race, ethnicity, baseline clinical symptom score, menopausal status
ME-FU NTF-NS	Qualifying uropathogen species/group (including phenotypic and genotypic subcategories), by age category (<18, ≥18 to 50, >50), acute cystitis recurrence (nonrecurrent infection, recurrent infection), stratification combinations (age group and acute cystitis recurrence), region, race, ethnicity, baseline clinical symptom score, menopausal status

Analysis/Endpoint Description: Clinical outcome and response **Visit: TOC/FU**	
ITT	Age category (<18, ≥18 to 50, >50), acute cystitis recurrence (nonrecurrent infection, recurrent infection), stratification combinations (age group and acute cystitis recurrence), region, race, ethnicity, baseline clinical symptom score, menopausal status
CE-TOC CE-FU	Age category (<18, ≥18 to 50, >50), acute cystitis recurrence (nonrecurrent infection, recurrent infection), stratification combinations (age group and acute cystitis recurrence), region, race, ethnicity, baseline clinical symptom score, menopausal status
micro-ITT	Qualifying uropathogen species/group (including phenotypic and genotypic subcategories)
micro-ITT NTF-S	Age category (<18, ≥18 to 50, >50), acute cystitis recurrence (nonrecurrent infection, recurrent infection), stratification combinations (age group and acute cystitis recurrence), region, race, ethnicity, baseline clinical symptom score, menopausal status, qualifying uropathogen species/group (including phenotypic and genotypic subcategories)
micro-ITT NTF-NS	Qualifying uropathogen species/group (including phenotypic and genotypic subcategories)
Analysis/Endpoint Description: Participant-level Microbiological outcome and response **Visit: TOC/FU**	
micro-ITT NTF-S	Age category (<18, ≥18 to 50, >50), acute cystitis recurrence (nonrecurrent infection, recurrent infection), stratification combinations (age group and acute cystitis recurrence), region, race, ethnicity, baseline clinical symptom score, menopausal status,
Analysis/Endpoint Description: Uropathogen-level Microbiological outcome and response **Visit: TOC/FU**	
micro-ITT	All qualifying uropathogens and by qualifying uropathogen species/group (including phenotypic and genotypic subcategories)
micro-ITT NTF-S	All qualifying uropathogens and by qualifying uropathogen species/group (including phenotypic and genotypic subcategories)
micro-ITT NTF-NS	All qualifying uropathogens and by qualifying uropathogen species/group (including phenotypic and genotypic subcategories)

ME-TOC ME-FU	All qualifying uropathogens and by qualifying uropathogen species/group (including phenotypic and genotypic subcategories)
ME-TOC NTF-S ME-FU NTF-S	All qualifying uropathogens and by qualifying uropathogen species/group (including phenotypic and genotypic subcategories)
ME-TOC NTF-NS ME-FU NTF-NS	All qualifying uropathogens and by qualifying uropathogen species/group (including phenotypic and genotypic subcategories)

Percent of therapeutic success at FU overall and by qualifying uropathogen by visit will also be plotted for each treatment group for the micro-ITT NTF-S Population.

Forest plot for therapeutic success rate at FU overall and by subgroup will be plotted for micro-ITT/NTF-S/NTF-NS Populations.

Forest plot for clinical success rate at each visit (TOC, FU) overall and by qualifying baseline uropathogen and uropathogen phenotypic and genotypic subcategories for the micro-ITT/NTF-S/NTF-NS Populations. Stacked bars of clinical outcome at each visit (OT, TOC, FU) will be plotted for ITT Population.

Forest plot for participant level microbiological success rate and uropathogen level microbiological success rate by qualifying baseline uropathogen and uropathogen phenotypic and genotypic subcategories will be plotted for the micro-ITT/NTF-S/NTF-NS Populations at each visit (TOC, FU). Stacked bars of participant level microbiological outcome and uropathogen level microbiological outcome by qualifying baseline uropathogen at each visit (OT, TOC, FU) will be plotted for micro-ITT/NTF-S/NTF-NS Populations.

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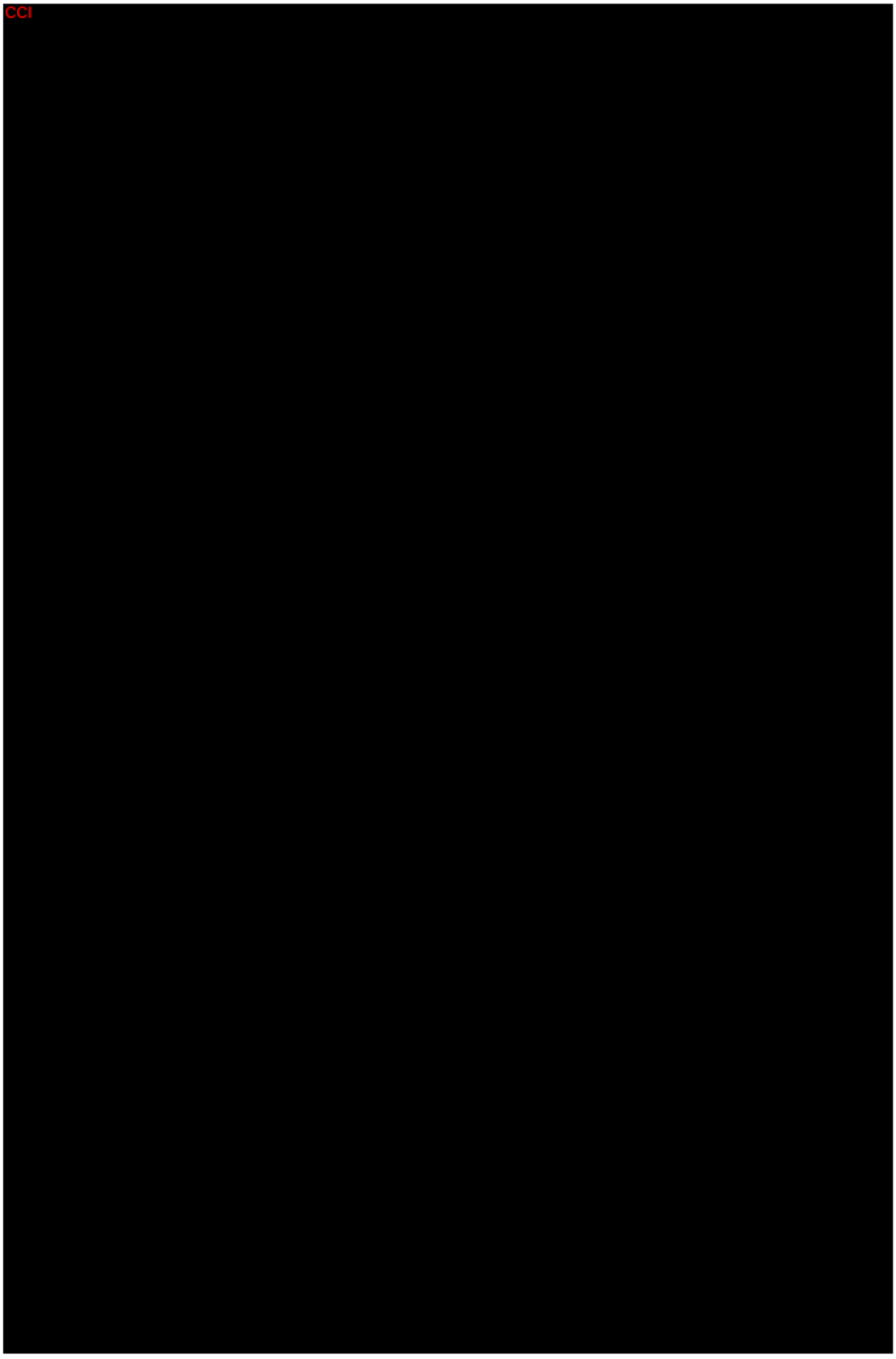

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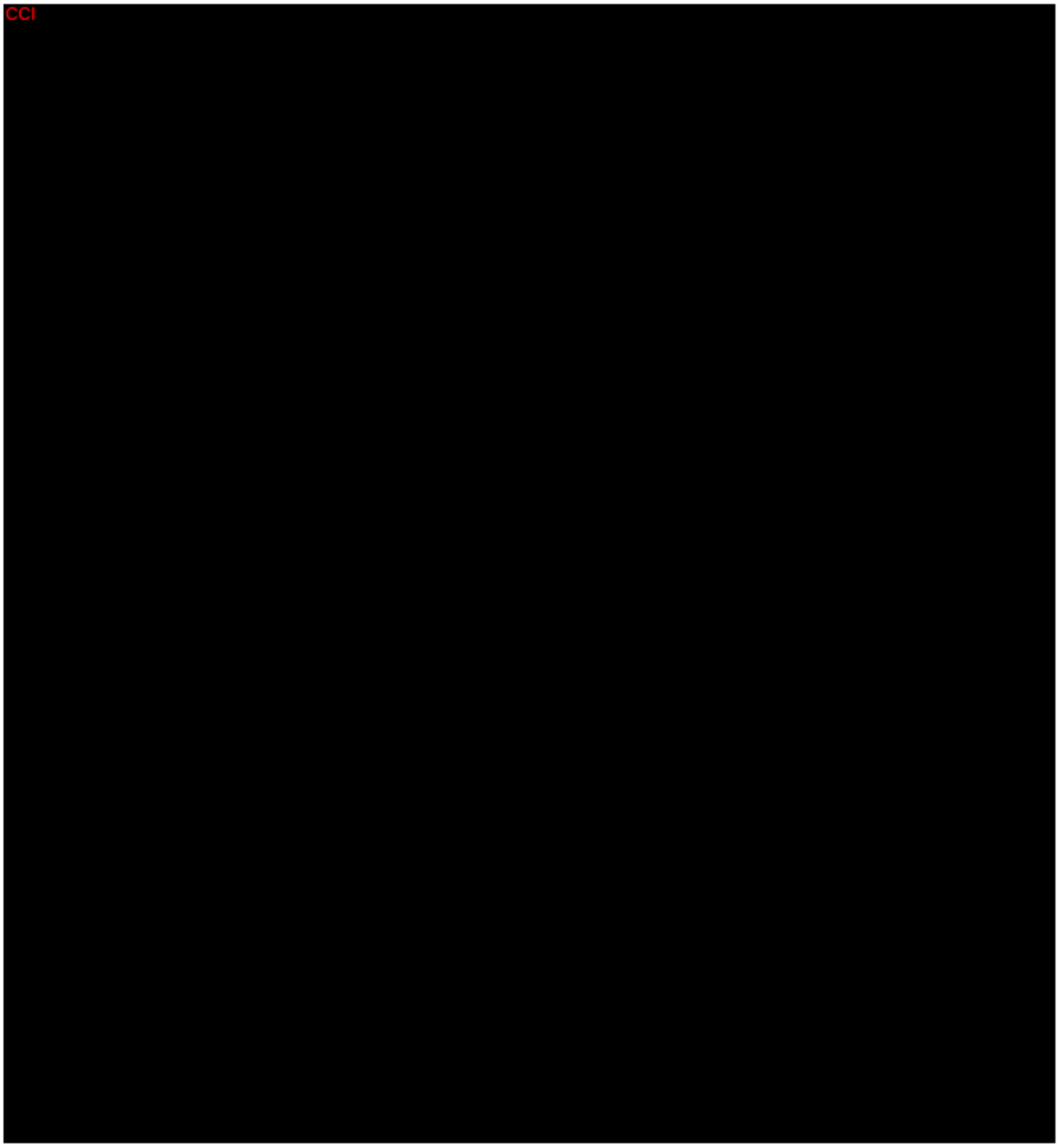

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8. SAFETY ANALYSES

The safety analyses will be based on the "Safety" Population.

8.1. Adverse Events Analyses

The severity of AEs and SAEs will be determined by the investigator according to the US National Institute of Allergy and Infectious Diseases Division of Microbiology and Infectious Diseases (DMID, 2007a) criteria for adult toxicity assessment, except for serum creatinine adolescent (adolescent participants over 12 years of age and less than 18 years of age) laboratory data, which will be assessed using DMID pediatric toxicity criteria (DMID, 2007b). All reported AEs will be coded using MedDRA and summarized by system organ class (SOC) and preferred term (PT).

A treatment emergent AE (TEAE) is defined as an AE with start date/time after the first dose date/time of the study treatment. If the time part is missing, only dates will be considered. The number and percentage of TEAEs, study treatment-related AEs, SAEs, and AEs leading to study treatment or study withdrawal will be collected. Only TEAEs will be included in summary tables, but all AEs will be displayed in detailed subject listings.

Adverse event severity is classified as mild (grade = 1), moderate (grade = 2), severe (grade = 3), potentially life threatening (grade = 4) or resulting in death (grade = 5). 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 severity will be used in the corresponding severity summaries.

Relationship to study treatment, as indicated by the investigator, is classified as "not related" or "related". Adverse events with a missing relationship to study treatment will be regarded 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 study treatment will be used in the corresponding relationship summaries.

An overall summary of AEs will present the total number of adverse events reported and the number of participants in each treatment group who experienced at least one AE, AE by maximum severity grade, drug-related AE, non-serious AE, SAE, AE leading to discontinuation of study treatment, AE leading to withdrawal from study, and AEs of special interest (AESI).

Adverse events analyses including the analysis of AEs, SAEs and other significant AEs will be based on GSK Core Data Standards. All AEs, study drug related AEs, SAEs, and AEs leading to discontinuation of study treatment or withdrawal from study will be provided in separate listings. The relationship between SOC and PT will be listed. Summary tables will be provided by SOC, PT, and maximum severity grade.

In summary tables where AEs are presented by SOC, PT, and maximum severity grade, SOCs will be sorted in descending order of the total incidence then alphabetically, 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 5.

In addition, a summary of the number and percentage of participants with common AEs, defined as AEs with ≥1% incidence (before rounding) in any treatment group, will be presented in descending order of total incidence by PT. The incidence of common AEs with relative risk and associated 95% CIs will also be presented graphically for each treatment group. AE summaries will also be presented for age subgroups (as recorded in the eCRF):

- Age: <18, 18-64, 65-74, ≥75

8.2. Adverse Events of Special Interest Analyses (AESI)

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

8.2.1. *Clostridium difficile* AESIs

C. difficile AESIs (PTs *Clostridium difficile* infection and *Clostridium difficile* colitis) will be included in the overall summary of AEs. *C. difficile* laboratory testing results are collected and recorded on distinct eCRF pages, which will be presented in a separate subject listing.

8.2.2. Cardiovascular and Gastrointestinal AESIs

GI AESIs are defined as AEs with a gastrointestinal SOC. Cardiovascular AESIs are defined as AEs with PTs that match the terms listed in Section 12.4.2.

For CV and GI AESIs, the number and percentage of participants with an event will be summarized by PT and the maximum grade. In addition, the incidence of AEs of GI effects and time to the first occurrence will be summarized. Graphical presentation of the cumulative distribution of time to the first GI event occurrence will be provided (participants with no occurrence will be regarded as censored at the last day of their participation in the study). The details of data displays are presented in Appendix 9

8.2.3. Potential Acetylcholinesterase-Inhibition AESIs

Any reported AE listed in the table below with a start time no later than 12 hours after the latest dose administered, as evaluated by the investigator as per the DMID grading criteria provided in protocol Section 12.13 Appendix 13: Division of Microbiology and Infectious Disease Adult Toxicity Tables for Adverse Event Assessment, will be included in the programmatic identification of a potential Acetylcholinesterase-Inhibition (AChE-I) AESI.

List of preferred terms for programming to be considered potentially due to AChE-I is provided in Appendix 4: (Section 12.4.2).

Cumulative grade score of potential AChE-I events will be calculated as the sum of the grade of each reported AE. This enables the number of AEs and the severity of each AE to be taken into account. The grading scale is defined in Table 21.

Table 21 AChE-I Cumulative Grade Score Scale

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

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

AChE-I AESIs will be listed and tabulated by SOC, PT, and maximum severity grade. Non-GI AChE-I events will also be summarized. Separate tables will summarize AChE-I AESI by number of events and unique PT. 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 subject listings.

Graphical presentation via a stacked bar charts of percentage of subjects in each AChE-I cumulative grade will be produced for All AChE-I events and non-GI AChE-I events separately. In addition, forest plots of the relative risk of AChE-I events between two treatment groups and the associated 95% CI for each event will also be constructed and displayed.

The details of the planned displays are provided in Appendix 9

8.3. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of chemistry laboratory tests, hematology laboratory tests, urinalysis, and liver function tests will be based on GSK Core Data Standards.

For adults, laboratory abnormalities will be graded according to the modified DMID criteria [DMID, 2007a]. For adolescent participants over 12 years of age and less than 18 years of age, the adult DMID will be applied for all laboratory parameters with the exception of serum creatinine, which will be programmatically graded according to the modified DMID criteria for pediatric participants [DMID, 2007b].

Summaries of change from baseline values over time for clinical chemistry and hematology tests will be provided in separate tables.

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.

Maximum post baseline total bilirubin vs maximum post-baseline ALT will be plotted as well as participant profile for liver function tests.

Urinalysis results will be summarized using descriptive statistics.

Clinical chemistry, hematology, and urinalysis test results with toxicity grade 3 or higher will be listed in separate listings.

The severity of renal impairment will be evaluated and presented according to the method previously described in Section 6.1.2.

The details of data displays are presented in Appendix 9

8.4. Vital Signs and Electrocardiogram (ECG)

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified.

Summary tables will be provided for vital signs change from baseline values, and worst post-baseline vital signs results relative to baseline results. Subjects with missing baseline

values are assumed to have within range baseline values. A subject listing will be provided for vital sign values of potential clinical importance defined in Appendix 6

The arithmetic mean of the three recorded ECG measurements will be employed in all subject 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 by Bazett's formula:

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

and by Fridericia's formula:

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

depending on the availability of other measurements. ECGs may be collected after start of treatment when medically warranted.

Listings will be provided for baseline abnormal ECG findings, and ECG values of potential clinical importance. Potentially clinically important values are defined in Appendix 6.

The details of data displays are presented in Appendix 9.

8.5. Physical Examinations

A physical examination (PE) will be performed at the baseline and TOC Visits, which will include assessments of the respiratory, cardiovascular, abdominal, gastrointestinal, neurological, and urogenital systems. Height and weight will only be measured and recorded before dosing at the Baseline Visit. Clinically significant changes from baseline or clinically significant new clinical signs will be reported as AEs. Since all significant data obtained from PEs will be recorded in AE eCRFs and reported within AE tables/listings, separate (stand-alone) PE tables/listings will not be generated.

9. PHARMACOKINETIC ANALYSES

9.1. Primary Pharmacokinetic Analyses

9.1.1. Endpoint / Variables

9.1.1.1. Drug Concentration Measures

Refer to Appendix 3 (Section 12.3.3). Pharmacokinetic blood and urine samples will be collected at the Baseline Visit (Day 1) 1 to 2 hours postdose. PK collections at the On-Therapy Visit (Day 2 to 4) will be taken predose (i.e., 12 hours postdose, which is at the end of the dosing interval from the previous dose [Cτ]). As per Protocol Amendment 1 and Protocol Amendment 2, PK blood and urine samples will only be collected at the On-Therapy Visit (Day 2 to 5) if at all possible, 1 to 2 hours after the most recent dose is taken. Gepotidacin PK concentrations will be measured in plasma and urine. Plasma and urine concentration data units will be converted, as applicable, and presented as µg/mL in the PK TLF outputs.

9.1.2. Summary Measure

Pharmacokinetic parameters are not calculable based on the sampling scheme and average PK concentrations will be used. All calculations of PK concentrations will be based on actual sampling times that fall within the set PK windows described below.

Summary statistics (n, arithmetic mean, geometric mean, median, standard deviation, minimum, maximum, 95% CI of the arithmetic and geometric means, and between-participant coefficient of variation [%CV and %CVb]) for plasma and urine gepotidacin concentrations will be provided by the sampling windows described in Table 22 as appropriate.

Table 22 PK Summary by sampling windows

Visit	Parameter	PK Window
Baseline Study Day 1	$C_{day1, 0\text{-}2h}$	Average concentration post-dose 0 to ≤ 2 hours
	$C_{day1, >2h}$	Average concentration post-dose >2 hours
On-Therapy Study Day 2	$C_{day2am, 0\text{-}6h}$	Average concentration post morning dose 0 to ≤ 6 hours
	$C_{day2am, 6\text{-}8h}$	Average concentration post morning dose > 6 to ≤ 8 hours
	$C_{day2am, 8\text{-}10h}$	Average concentration post morning dose > 8 to ≤ 10 hours
	$C_{day2am, 10\text{-}12h}$	Average concentration post morning dose >10 to ≤ 12 hours

Visit	Parameter	PK Window
	$C_{day2pm, 0-2h}$	Average concentration post evening dose 0 to ≤ 2 hours
On-Therapy Study Day 3 to 5	$C_{day3-5, 0-6h}$	Average concentration post-dose 0 to ≤ 6 hours
	$C_{day3-5, 6-8h}$	Average concentration post-dose > 6 to ≤ 8 hours
	$C_{day3-5, 8-10h}$	Average concentration post-dose > 8 to ≤ 10 hours
	$C_{day3-5, 10-12h}$	Average concentration post-dose >10 to ≤ 12 hours

am = morning dose; pm=evening dose

9.1.3. Population of Interest

The primary PK analyses will be based on the PK Population, unless otherwise specified.

9.1.4. Strategy for Intercurrent Events

Study treatment discontinuation (due to any reason) will follow while-on-treatment strategy (treatment phase defined as from first dose to OT Visit). Pharmacokinetic samples are planned to be collected at OT Visit.

9.1.5. Statistical Analysis / Methods

PK samples collected outside of the treatment phase will only be listed with a flag. If the PK sampling at OT Visit is collected for more than 12 hours after the latest dose taken, that PK sample will not be included in tables but only listed with a flag.

Details of the planned displays are provided in Appendix 9 and will be based on GSK Data Standards and statistical principles.

10. ADDITIONAL ANALYSES DUE TO THE COVID-19 PANDEMIC

10.1. Study Population

10.1.1. Subject Disposition

A summary of recruitment by country and site, relative to COVID-19 Pandemic measures will be produced. For the definition of the phases of the COVID-19 pandemic measures see Section 12.2.1.2.

A country level listing of the dates of the COVID-19 Pandemic measures will be produced.

10.1.2. Protocol Deviations

An optional subject listing of important protocol deviations related to COVID-19 may be produced, however, these deviations will already be captured in the listing of all important protocol deviations.

Visits and assessments missed due to the COVID-19 pandemic, together with visits conducted remotely, will be summarized in both a table and listed by subject.

10.2. Safety

COVID-19 assessments and symptoms for subjects with COVID-19 adverse events will be provided in a detailed subject listing.

11. REFERENCES

Clinical Laboratory Standards Institute (CLSI) M100; Latest edition Performance Standards for Antimicrobial Susceptibility Testing

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12. APPENDICES

12.1. Appendix 1: Schedule of Activities

Visit[a]	Baseline		On-Therapy[b]	TOC[b]	Follow-up	Early Withdrawal
Study Day	1					
Procedure	Predose	Postdose	2 to 4	10 to 13	28±3	NA
Written informed consent/assent	X					
IRT – Screening module	X					
Inclusion and exclusion criteria	X					
Participant demography	X					
Physical examination (including height and weight at Baseline only)	X			X[c]		
Record acute cystitis signs and symptoms[d]	X		X	X	X	X
CCI						
Medical/surgical history	X					
Diagnosis of presumptive acute cystitis[f]	X					
Bacteriology samples[g]	X		X[h]	X	X	X
Randomization	X					
12-lead electrocardiogram[i]	X					
Vital sign measurements[j]	X		X	X		
Hematology, chemistry, and urinalysis	X		X	X		
Serology (hepatitis B and C and HIV)[k]	X					
Urine pregnancy test[l]	X[l]		X[l]	X		X
Drug and alcohol screen	X					
CCI						
IRT – Randomization module	X					
Administer oral dose of study treatment[n]		X	X[o]			
Serious adverse events[p]	X	X	X	X	X	X

Adverse events[q]		X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X
PK blood sample			X[r]			
PK urine sample			X[r]			
Study treatment compliance[s]			X	X		
Schedule next visit	X[t]		X[u]	X[u]	X[u]	
Genetic sample[v]	X					

HIV=human immunodeficiency virus; HPF=high-power field; IRT=interactive response technology; NA=not applicable; PK=pharmacokinetic; TOC=Test-of-Cure; UTI=urinary tract infection; WBC=white blood cell.

Note: To reduce participant on-site visits or if unforeseen issues impact clinic visits, and participants are unable to attend a site visit, home healthcare (home visits and telemedicine visits) may be used to conduct procedures as detailed in the Study Reference Manual. Home healthcare will only be utilized where applicable country and local regulations and infrastructure allow.

a. For all study visits, to minimize the amount of time that participants spend at the clinic, eConsent may be utilized and remote collection of study-related data may be obtained as described in the Study Reference Manual. Thus, some visit data may be collected through a combination of telemedicine and on-site visits. Collection of information via telemedicine will be performed only where local regulations permit. Prescreening activities may also be conducted, including a prescreening informed consent and urine testing, as detailed in Section 9 of the protocol and the Study Reference Manual.

b. For the On-therapy (Day 2 to 4) Visit: Participants will be instructed to return to the study site within 1 to 3 days postrandomization. Each treatment day will be assessed over 24 hours starting with the first dose of study treatment, as further detailed in the Study Reference Manual. For the TOC (Day 10 to 13) Visit: Participants will be instructed to return to the study site 5 to 8 days after completion of study treatment.

c. At the TOC Visit, the physical examination may be symptom directed and is only required if indicated for a specific participant.

d. Individual clinical signs and symptoms scores of acute cystitis will be recorded by a study physician or otherwise appropriately medically trained staff based on participant interview and using the scoring system in Appendix 6 of the protocol. The same scorer will be used at all assessment time points for each participant, on all occasions, whenever possible.

CCI

f. Based on confirmation of nitrite or pyuria (>15 WBC/HPF or the presence of 3+/large leukocyte esterase) from a pretreatment clean-catch midstream urine sample per local laboratory procedures.

g. Participants will provide a clean-catch midstream urine sample at each visit for Gram stain, quantitative bacteriology culture, and in vitro antimicrobial susceptibility testing by a designated laboratory(ies). Refer to the laboratory manual.

CCI [redacted]

i. See Section 6.2 of the protocol for electrocardiogram exclusion criterion for participants aged ≥12 to <18 years. For additional details see Section 8.1.2 and Section 9.4.3 of the protocol.

j. Take measurement of temperature, blood pressure, and pulse rate.

k. If serology testing was performed within 3 months prior to the first dose of study treatment and the results were **positive**, testing at Baseline **is not required**. If testing was performed within 3 months and any result was **negative**, testing at Baseline **is required**.

l. For women of childbearing potential, a negative high sensitivity urine pregnancy test is sufficient for eligibility. See Appendix 2 of the protocol for Baseline urine test sensitivity requirements and associated contraception requirements. Pregnancy testing should also be performed after Dose 4 and before Dose 8 as specified in Appendix 2 of the protocol.

CCI [redacted]

n. Participants will receive oral study treatment twice daily for 5 days under double-blind, double-dummy conditions. The first oral dose will be administered at the study site during the Baseline Visit; participants will self-administer as outpatients thereafter. Each dose should be taken after food consumption and with water.

o. Participants should continue taking study treatment per their planned dosing schedule. If at all possible, the appointment time of the On-therapy Visit should be approximately 1 to 2 hours after the participant's most recent dose is expected to be taken. See the Study Reference Manual for additional details.

p. Record serious adverse events from the time of consent/assent in order to fulfill international regulatory requirements.

q. Record adverse events from the time of the first dose of study treatment.

r. At the On-therapy Visit, PK samples will be collected, as further detailed in Section 9 of the protocol and the Study Reference Manual.

s. Determine study treatment compliance by performing pill count.

t. Confirm return day/time for the On-therapy, TOC, and Follow-up Visits. Refer to footnote o for scheduling the On-therapy Visit.

u. Previsit reminder: Study site staff will contact the participant 24±4 hours before the scheduled On-therapy, TOC, and Follow-up Visits.

v. Collect sample only if the participant has a signed consent/assent specific for this purpose. The Baseline Visit is the recommended time to collect the sample, but it can be collected at any time during the study.

12.2. Appendix 2: Study Phases and Treatment Emergent Adverse Events

12.2.1. Study Phases

Assessments and events will be classified according to the time of occurrence relative to the start and end date of study treatment.

Study Phase	Definition
Pre-Treatment	Date and Time < Study Treatment Start Date and Time
On-Treatment	Study Treatment Start Date and Time ≤ Date and Time ≤ Study Treatment Stop Date and Time
Post-Treatment	Date and Time > Study Treatment Stop Date and Time

12.2.1.1. Study Phases for Concomitant Medication

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

1. **NOTES:**

- Please refer to Appendix 5 for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.
- If a single medication taken on the same date as the first dose date, time will be used to determine if it's prior or concomitant. If time is missing, it will be considered concomitant.

12.2.1.2. Phases of COVID-19 Pandemic Measures

Pandemic measures began in different countries at different times. A dataset containing the date when pandemic measures began, as determined by the GSK country Issue Management Teams will be used to determine the start date of pandemic measures within each country. A copy of this dataset will be taken at the time of database freeze (DBF).

12.2.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• If AE onset date/time is on or after treatment start date/time. That is, study treatment start date/time ≤ AE start date/time. If time is missing, only date will be compared.

NOTES:

- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

12.2.3. Participant and Study Completion

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

12.3. Appendix 3: Data Display Standards & Handling Conventions

12.3.1. 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 3.2 & ADaM IG Version 1.1). • 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 RAP.

12.3.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics
• Do not include participant level listings in the main body of the GSK Clinical Study Report. All participant level listings should be located in the modular appendices as ICH or non-ICH listings

Formats
• GSK IDSL Statistical Principles (5.03, 6.06.3, & 6.09) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the participant's listings.

Unscheduled Visits	
• Unscheduled visits may be included in summary tables and/or figures as described in Section 5.6 on Analysis Visits and analyses such as “all post baseline”, “worst case post baseline”, and “max post baseline” etc.. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

12.3.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics and summarized graphical displays only.

12.4. Appendix 4: Derived and Transformed Data

12.4.1. General

Multiple Measurements at One Analysis Time Point
• The arithmetic mean of the three recorded ECG measurements will be employed as described in Section 8.4. Analysis visits will be created based on visit windows as described in Section 5.6. All assessments (including unscheduled and early termination visits) will be presented in subject listings. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from First Dose Date (or Randomization Date if not dosed):
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Date ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

12.4.2. Study Population

Age
Age is derived using the date of first dose. When first dose date is missing, the informed consent date is used. Only year of birth is collected so Day and Month of birth are imputed as 30 June. Formula for deriving age is the integer component of: • (First Dose Date – 30 Jun of collected birth year +1)/365.25

12.4.3. Safety

Adverse Events
AEs of Special Interest
• *Clostridium difficile* events • Cardiovascular events • Gastrointestinal events • Acetylcholinesterase inhibition events

List of Cardiovascular AESIs Preferred Terms	
Pulmonary oil microembolism	Atrioventricular node dispersion
Peripheral revascularization	Cardiac arrest
Supraventricular extrasystoles	Holiday heart syndrome
Rebound tachycardia	Anomalous atrioventricular excitation
Cardio-respiratory arrest neonatal	Bundle branch block
Atrial conduction time prolongation	Adams-Stokes syndrome
Cardiac death	Atrioventricular dissociation
Paroxysmal arrhythmia	Atrial flutter
Cardiac flutter	Prosthetic cardiac valve thrombosis
Neonatal sinus bradycardia	Heart valve incompetence
Neonatal bradyarrhythmia	Cardiac valve disease
Sinus bradycardia	Metastatic pulmonary embolism
Bradycardia foetal	Renal revascularisation surgery
Junctional ectopic tachycardia	Angina unstable
Ventricular fibrillation	Ventricular extrasystoles
Accessory cardiac pathway	Lenegre's disease
Sinoatrial block	Atrioventricular block
Pulseless electrical activity	Nodal arrhythmia
Ventricular parasystole	Rhythm idioventricular
Paroxysmal atrioventricular block	Nonreassuring foetal heart rate pattern
Ogden syndrome	Ventricular asystole
Nodal rhythm	Defect conduction intraventricular
Bundle branch block left	Atrial fibrillation
Heart valve stenosis	Tachycardia foetal
Acute myocardial infarction	Atrioventricular block first degree
ECG signs of myocardial infarction	Foetal arrhythmia
Embolism arterial	Neonatal tachycardia
Pulmonary embolism	Carcinoid heart disease
Central bradycardia	Cardiac valve replacement complication
Sinus arrest	Degenerative multivalvular disease
Cardiac fibrillation	Cardiac valve sclerosis
Trifascicular block	Cardiac valve abscess
Ventricular tachycardia	Newborn persistent pulmonary hypertension
Accelerated idioventricular rhythm	Deep vein thrombosis postoperative
Bundle branch block bilateral	Carotid revascularization
Bundle branch block right	Transmyocardial revascularization
Bezold-Jarisch reflex	Ventricular tachyarrhythmia
Chronotropic incompetence	Tachycardia
Arrhythmia neonatal	Torsade de pointes
Inherited cardiac conduction disorder	Lown-Ganong-Levine syndrome
Baseline foetal heart rate variability disorder	Conduction disorder
Ventricular flutter	Congenital supraventricular tachycardia
Lambl's excrescences	Pacemaker generated arrhythmia
Periprocedural myocardial infarction	Wolff-Parkinson-White syndrome
Congenital pulmonary hypertension	Long QT syndrome
Portopulmonary hypertension	Parasystole
Deep vein thrombosis	Cardiac arrest neonatal
Revascularisation procedure	Neonatal sinus tachycardia
Cardiac failure congestive	Foetal tachyarrhythmia
Atrioventricular node dysfunction	Cerebrovascular disorder
Ventricular pre-excitation	Pulmonary arterial hypertension
Supraventricular tachyarrhythmia	Post procedural pulmonary embolism
Arrhythmia	Pulmonary microemboli

List of Cardiovascular AESIs Preferred Terms	
Timothy syndrome	Sinusoidal foetal heart rate pattern
Heart alternation	Bradyarrhythmia
Reperfusion arrhythmia	Tachycardia paroxysmal
Foetal heart rate disorder	Sinus tachycardia
Atrial parasystole	Wandering pacemaker
Atrial tachycardia	Withdrawal arrhythmia
Bifascicular block	Foetal heart rate acceleration abnormality
Atrioventricular block complete	Pacemaker syndrome
Sudden cardiac death	Structural valve deterioration
Sinus node dysfunction	Cardiac valve thickening
Sudden death	Post procedural myocardial infarction
Cardio-respiratory arrest	Pulmonary hypertension
Arrhythmia supraventricular	Obstetrical pulmonary embolism
Neonatal tachyarrhythmia	Heart block congenital
Bradycardia	Atrioventricular block second degree
Congenital heart valve incompetence	Extrasystoles
Cardiac valve rupture	Brugada syndrome
Heart valve calcification	Wolff-Parkinson-White syndrome congenital
Cardiac valve discolouration	BRASH syndrome
Cardiac valve vegetation	Ventricular arrhythmia
Congenital heart valve disorder	Foetal heart rate deceleration abnormality
Myocardial infarction	Long QT syndrome congenital
Silent myocardial infarction	Agonal rhythm
Septic pulmonary embolism	Frederick's syndrome
Coronary revascularization	Bradycardia neonatal
Atrioventricular conduction time shortened	Shone complex
Sinus arrhythmia	Transient ischaemic attack
Tachyarrhythmia	Cerebrovascular accident
Postural orthostatic tachycardia syndrome	
List of Acetylcholinesterase Inhibition AESIs Preferred Terms	

List of Cardiovascular AESIs Preferred Terms

Abdominal discomfort	Generalised non-convulsive epilepsy
Abdominal pain	Generalised tonic-clonic seizure
Abdominal pain lower	Heart rate decreased
Abdominal pain upper	Hyperhidrosis
Abdominal symptom	Hyperkinesia
Abdominal tenderness	Hypocalcaemic seizure
Asthma	Hypoglycaemic seizure
Atonic seizures	Hyponatraemic seizure
Atypical benign partial epilepsy	Idiopathic generalised epilepsy
Autonomic seizure	Idiopathic partial epilepsy
Bradyarrhythmia	Irregular breathing
Bradycardia	Lacrimation increased
Bronchial hyperreactivity	Lafora's myoclonic epilepsy
Bronchospasm	Lennox-Gastaut syndrome
Clonic convulsion	Myoclonic epilepsy
Cold sweat	Nausea
Convulsions local	Night sweats
Convulsive threshold lowered	Partial seizures
Defaecation urgency	Partial seizures with secondary generalisation
Diarrhoea	Petit mal epilepsy
Drooling	Psychomotor hyperactivity
Dyspnoea	Retching
Dyspnoea at rest	Salivary hypersecretion
Dyspnoea exertional	Seizure
Epigastric discomfort	Seizure cluster
Epilepsy	Simple partial seizures
Epilepsy with myoclonic-atonic seizures	Status asthmaticus
Faeces soft	Status epilepticus
Febrile convulsion	Sweat gland disorder
Febrile infection-related epilepsy syndrome	Syncope
Flatulence	
Focal dyscognitive seizures	Tonic clonic movements
Frequent bowel movements	Tonic convulsion
Frontal lobe epilepsy	Unilateral bronchospasm
Gastrointestinal disorder	Vomiting
Gastrointestinal pain	Vomiting projectile
Gastrointestinal tract irritation	Wheezing

Adverse Events with Missing Relationship or Missing Serious Indicator

- If the relationship to study treatment is missing for a treatment-emergent AE (TEAE), then the TEAE will be considered related to the study treatment.
- If the serious indicator “Was event serious?” is missing, the AE will be considered as SAE.
- Adverse events with missing relationship or missing serious indicator will be presented as it is in listings but will be treated as related AEs or SAEs in summary tables.

12.4.4. Efficacy

Microbiology Procedures

- Microbiology data will be received from below sources:
  - GSK microbiologists
  - Central laboratory

Microbiology Procedures

- 3rd party laboratory
- CCI [redacted]

- All gram-negative uropathogens will be tested by broth microdilution (MIC) to determine production of extended spectrum beta-lactamases (ESBLs). In accordance with the Clinical and Laboratory Standards Institute (CLSI) M100 guidelines (Table3A), ESBL production may be indicated by a MIC result of >1 mcg/mL for ceftriaxone, ceftazidime, cefotaxime or aztreonam for *E. coli, K. pneumoniae or K. oxytoca* or a MIC result of >1 mcg/mL for ceftazidime, cefotaxime or cefpodoxime for *P. mirabilis*.
- Gradient diffusion results (MIC) on all uropathogens for susceptibility to gepotidacin
- Gradient Diffusion MICs and Interpretation
  - Gradient diffusion strips generate MIC values from a continuous scale and can give results in-between conventional two-fold dilutions i.e. half dilutions. A gradient diffusion MIC value which falls between standard two-fold dilutions must be rounded up to the next upper two-fold value before categorization.
    - As an example, a gradient diffusion MIC of 1 ug/mL is reported as intermediate (I) while 1.5 is rounded up to 2 ug/mL and the category reported as resistant (R).
    - When growth occurs along the entire strip i.e. no inhibition ellipse is seen, report the MIC as >= the highest value on the MIC scale. When the inhibition ellipse is below the strip (does not intersect the strip), report the MIC < the lowest value on the MIC scale.
- MIC Reporting Concentrations

Microbiology Procedures

- When serial two-fold dilution MICs are being prepared and tested, the actual dilution scheme is, e.g.: 16, 8, 4, 2, 1, 0.5, 0.25, 0.125, 0.0625, 0.03125, 0.015625, 0.0078125 ug/ml, etc.
- For convenience only, it was decided to use the following values for reporting purpose (reporting format):16, 8, 4, 2, 1, 0.5, 0.25, 0.12, 0.06, 0.03, 0.016, 0.008, 0.004, 0.002 ug/mL, etc. The values that appear in the tables are equivalent to the actual values tested, e.g., 0.12 ug/mL = 0.125 ug/mL; 0.016 ug/ml = 0.015625 ug/ml.
- Any values containing '<', '<=', '>=', '>' will be counted in its separate categories. However, when calculating the minimum, maximum, MIC_{50}, MIC_{90}, a small amount will be added or subtracted in order to impute the corresponding numeric value for calculation. For example,
  - '<0.06' will be imputed as 0.06-0.001;
  - '>256' will be imputed as 256+0.001.
  - '>=32' will be imputed as 32.
- But for reporting, they will still be presented in original format if they happen to be those summary statistics.

- Disk Diffusion results (mm) will be conducted on uropathogens as follows. CLSI interpretive criteria are applied with the exceptions of nitroxoline and cefadroxil where EUCAST interpretive criteria are applied.

Compound	Organisms
Gepotidacin[a]	All uropathogens
Nitroxoline [b]	All uropathogens
Nitrofurantoin	All uropathogens
Mecillinam [c,d]	Gram-negative uropathogens
Cefadroxil [b]	Gram-negative uropathogens
Penicillin	Staphylococci (*S. aureus* and *S. saprophyticus*) and enterococci uropathogens
Cefoxitin [b]	Staphylococci uropathogen isolates (*S. aureus* and *S. saprophyticus*)

a. Two manufacturers (Becton Dickinson and MAST)
b. To be tested by disk diffusion (surrogate test or no MIC QC ranges)
c. To be tested by disk diffusion (broth method not approved and gradient diffusion is not available)
d. Tested to predict the activity of pivmecillinam

- The 3rd party laboratory will conduct confirmatory nitrofurantoin susceptibility testing, agar dilution testing for fosfomycin and genetic characterization of selected isolates as described directly below.
  - Uropathogens exhibiting intermediate or resistant (with the exception of species considered intrinsically resistant to nitrofurantoin per CLSI M100 guidelines) nitrofurantoin MIC results at the central laboratory will be submitted to the 3rd party laboratory for confirmatory susceptibility testing of nitrofurantoin (dilution range of 2–256 µg/mL) by reference broth microdilution. Broth microdilution nitrofurantoin MIC from JMI Laboratories (if available) will take precedence over global central laboratory (GCL) nitrofurantoin MIC result for determining susceptibility to nitrofurantoin.
  - All uropathogens will be submitted for susceptibility testing of fosfomycin (dilution range of 0.12–256 mcg/mL) by reference agar dilution methodology.


CCI

Microbiology Procedures

Microbiological Data Procedures

- PPD global central laboratory (GCL) will identify the uropathogen classification and phenotype via GSK source documents regarding qualified uropathogen flagging and uropathogen resistance flagging (Uropathogen and qualifying uropathogen decision tree_112119_GSK final.docx and GSK Uropathogen resistance decision trees_112119_final.docx).
- JMI laboratories genotype data is derived from isolate whole genome sequencing and other genomic assays as requested by GSK and will be performed by JMI when a minimum of 20 isolates are available but not more frequent on a monthly basis (testing may be conducted more frequently near the end of the study). Genotype data therefore will be available no sooner than 1-2 months from isolate recovery.
- JMI isolate genotype data will be sent to PPD GCL and included in PPD GCL data transfers to PPD clinical and therefore available for PPD Biostatistics and PPD clinical programming for inclusion in analysis database.
- Data from the GSK study microbiologist/or clinical scientist will include clarification of which uropathogen species should be reported separately and which should be grouped for display, classification of uropathogens as Gram-positive or Gram-negative, determination of the phenotype and genotype subcategories and a determination of whether the susceptibility results for identically labelled uropathogens from the same participant at the same visit differ enough to classify the uropathogens as separate ("keepers").

"Keepers" process

- Includes all cases within the central laboratory dataset where two or more uropathogens of the same genus and species for the same participant at the same visit will be identified.
- An excel file containing a list of these uropathogens and the associated quantitative bacterial counts, MIC results and CLSI interpretations for each isolate will be provided to the microbiologist.
    - The microbiologist will review the list and determine if the isolates are the same or different strains of the identified uropathogen based on a predefined algorithm:
        - For example, if two uropathogens of the same genus and species have a ≥4-fold difference in MIC (or ≥6 mm difference in zone diameter for antibiotics only tested by disk) to three or more antibiotic classes, they will be considered two different strains and both uropathogen isolates will be analyzed.
- If none of the criteria for determining the isolates as different are met, the uropathogen isolates will be considered to be of the same strain and only one isolate will be retained for analysis based on a pre-defined algorithm.

Microbiology Procedures

- The microbiologist will add a flag to the list to indicate which of the duplicate records to keep (flag = >0; e.g. 1, 2). All duplicate records will be kept in the SDTM datasets, and those records that are deemed to be duplicates (flag = 0) will not be included in any analyses.

Microbiological outcome and response in instances of 2 baseline qualifying uropathogens

- If two baseline qualifying uropathogens are recovered that are of two different genus and species (e.g. a *K. pneumoniae* and *E. coli*), each baseline uropathogen will be considered separately for microbiological outcome and response.
- If more than one baseline qualifying uropathogen is recovered that are of the same genus and species (e.g. two morphotypes of *E. coli*) and if the same genus and species is recovered from a post-baseline visit, the microbiological outcome and response will not be linked to the baseline uropathogen (i.e., genetic relatedness of the baseline and post-baseline isolates will not be considered for determination of microbiological outcome/response). For these cases, the microbiological outcomes will be either persistence, recurrence or unable to determine (e.g. if other antibiotic therapy started before TOC) and the microbiological response will be failure for both baseline qualifying uropathogens of the same species.

Uropathogen species/groups; Gram-positive/-negative classification; phenotype and genotype sub-categories flagging:

- A summary for the number of isolates in each distinct uropathogen species (by decoded uropathogen code, phenotypic and genotypic data) for uropathogens at Baseline will be produced for the microbiologist.
- The microbiologist and clinical scientist will review that summary to flag those uropathogen species/groups, Gram-positive/-negative classifications, and phenotype and genotype uropathogen subcategories(s) which are to be reported in the TLFs.

Invalid and non-evaluable results

- In rare cases of concern about the integrity of a subject(s) urine sample, the microbiologist or clinical scientist may determine that all microbiological assessments done on that urine sample are invalid and non-evaluable. Potential reasons include evidence of sample mishandling and cross-contamination.
- CCI [redacted]
- These invalid records will be kept in the SDTM dataset but not ADaM dataset and will not be included in any analyses.
- The microbiologist will document the rationale for invalid results and store in a similar manner along with the rationale for the keepers analyses.

Out of stability (OOS)

- GCL will include an out of stability (OOS) flag for urine samples that are received OOS. OOS urine samples are those where receipt date is more than 4 days from the specimen collection date for urine specimens sent refrigerated, and those where receipt date is more than 2 days from the specimen collection date for urine specimens sent ambient. Samples received frozen are marked as 'unable to perform' and are not tested. All microbiological assessments done on the OOS urine sample are invalid and non-evaluable.

These OOS samples will be kept in SDTM dataset but not ADaM dataset and will not be included in any analyses.

Microbiology Procedures

Fold Change

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

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

MIC Range, MIC50 and MIC90

MIC50 and MIC90 are defined as the 50th and 90th percentile of the MIC values. They will only be reported if sample size is larger or equal to 10. For an even number of samples, the MIC50 is the next one above the median. Similar algorithm applies to MIC90.

- MIC ranges to be tested in this protocol (in ug/mL):

Gepotidacin	<=0.03; 0.06; 0.12; 0.25; 0.5; 1; 2; 4; 8; 16; 32; 64; >64
Ciprofloxacin	<=0.002; 0.004; 0.008; 0.015; 0.03; 0.06; 0.12; 0.25; 0.5; 1; 2; 4; >4
Levofloxacin	<=0.004; 0.008; 0.015; 0.03; 0.06; 0.12; 0.25; 0.5; 1; 2; 4; 8; >8
Sulfisoxazole	<=4; 8; 16; 32; 64; 128; 256; 512; >512
Trimethoprim	<=0.015; 0.03; 0.06; 0.12; 0.25; 0.5; 1; 2; 4; 8; 16; 32; >32
Trimethoprim / Sulfamethoxazole	<=0.015; 0.03; 0.06; 0.12; 0.25; 0.5; 1; 2; 4; 8; >8
Ampicillin	<=0.25; 0.5; 1; 2; 4; 8; 16; 32; 64; >64
Vancomycin	<=0.25; 0.5; 1; 2; 4; 8; 16; 32; >32
Nitrofurantoin	<=0.5; 1; 2; 4; 8; 16; 32; 64; 128; 256; >256
Ceftolozane / Tazobactam	<=0.015; 0.03; 0.06; 0.12; 0.25; 0.5; 1; 2; 4; 8; 16; 32; >32
Ceftazidime / Avibactam	<=0.015; 0.03; 0.06; 0.12; 0.25; 0.5; 1; 2; 4; 8; 16; 32; >32
Piperacillin / Tazobactam	<=0.12; 0.25; 0.5; 1; 2; 4; 8; 16; 32; 64; 128; >128
Amoxicillin / Clavulanic Acid	<=0.25; 0.5; 1; 2; 4; 8; 16; 32; >32
Ceftriaxone	<=0.015; 0.03; 0.06; 0.12; 0.25; 0.5; 1; 2; 4; >4
Cefazolin	<=0.25; 0.5; 1; 2; 4; 8; 16; 32; >32
Meropenem	<=0.004; 0.008; 0.015; 0.03; 0.06; 0.12; 0.25; 0.5; 1; 2; 4; 8; >8
Gentamicin	<=0.06; 0.12; 0.25; 0.5; 1; 2; 4; 8; 16; >16
Amikacin	<=0.25; 0.5; 1; 2; 4; 8; 16; 32; 64; >64
Aztreonam	<=1; >1
Ceftazidime	<=1; >1
Cefotaxime	<=1; >1
Cefpodoxime	<=1; >1
Fosfomycin (JMI)	<=0.12; 0.25; 0.5; 1; 2; 4; 8; 16; 32; 64; 128; 256; >256
Nitrofurantoin (JMI)	<=0.5; 1; 2; 4; 8; 16; 32; 64; 128; 256; >256
Gepotidacin Gradient Strip	<0.015; 0.03; 0.06; 0.12; 0.25; 0.5; 1; 2; 4; 8; 16; 32; 64; 128; 256; >=256

Susceptibility Interpretations
• Susceptibility interpretations will be calculated and reported by the central laboratory and will be based on the CLSI M100 and EUCAST guidelines in effect at that time the bacterial isolate is tested. • Since CLSI breakpoints for certain drug/bug combinations can change in new yearly editions of M100 guidelines, as GSK and/or the central laboratory become aware of relevant breakpoint changes, the central laboratory will identify any reports which would qualify as needing a change in interpretation (e.g. a MIC value that was originally reported as susceptible, and would now be considered resistant based on the new breakpoint), and will issue amended reports. Of note, for piperacillin/tazobactam against Enterobacterales species/groups, susceptible-dose dependent (SDD) may be presented as intermediate. • The final clinical database will report interpretations according to the most recent CLSI M100 and EUCAST interpretations regardless of what the breakpoints were at the time the isolate was initially tested. • For specific drugs (e.g. nitroxoline, cefadroxil) which do not have approved FDA or CLSI breakpoints, susceptibility interpretations will be determined using EUCAST guidelines.
Bacterial Nomenclature
• Whilst the scientific formatting requirements for bacterial nomenclature is for genus and species names to be italicized, with first letter of genus upper case, and rest of the genus and species name in lower case, GSK system limitations have resulted in the lack of italicization in TFL outputs.
CCI [redacted]
Quantitative Bacterial Counts

- The central laboratory will quantitatively determine the growth of uropathogens from culture of participant urine samples.
- The central laboratory will report the following quantification results
  - If there is no growth on the culture plates for a urine sample:
    - No growth ($<10^3$)
  - If there is growth on the urine culture plates for a urine sample, each uropathogen will receive an associated colony count:
    - 10^3-$<10^4$
    - 10^4-$<10^5$
    - $\geq 10^5$
- At subsequent visits, determination of 'no growth' for individual uropathogens will need to be derived from an overall urine culture result of no growth (meaning there was no growth on the urine culture plates) or no identification/quantification being reported for that specific uropathogen (assuming that a urine sample was taken and that results were reported).
- If the bacterial sample at a subsequent visit is not collected, then it's considered as "unable to determine" for the uropathogens identified at Baseline.

12.5. Appendix 5: Reporting Standards for Missing Data

12.5.1. Premature Withdrawals

Element	Reporting Detail
General	• Participant study treatment completion is defined as if the participant has taken all doses of the study treatment and completed the TOC Visit. Participants who discontinue study treatment will not be considered withdrawn from the study and should attend the TOC and Follow-up Visits as applicable. • Participant study completion (i.e. as specified in the protocol) is defined as if the 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 data will be included in summary tables and figures as described in Section 5.6 on Analysis Visits.

12.5.2. 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: o These data will be indicated by the use of 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. 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). For Investigator-Assessed Clinical Response, handling of missing data is described in Section 7.3.1.13.
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.

12.5.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) 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: o Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment and treatment emergent as per Appendix 2. o Missing Start Time: Midnight 0:00:00 will be used for AEs with missing start time to determine if it's AChE-I.

Element	Reporting Detail
	○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. • Adverse events with entirely missing or unknown start dates will be assumed to be on-treatment and also treatment emergent for reporting.
Concomitant Medications/ Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If the partial date is a start date, a '01'" will be used for the day and 'Jan'" will be used for the month ○ If the partial date is a stop date, a '28'/29/30/31' will be used for the day (dependent on the month and year) and 'Dec'" will be used for the month. • The recorded partial date will be displayed in listings.

12.6. Appendix 6: Values of Potential Clinical Importance

12.6.1. ECG

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

12.6.2. Vital Signs

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

12.7. Appendix 7: Division of Microbiology and Infectious Diseases Adult Toxicity Tables for Adverse Event Assessment

12.7.1. Laboratory Values

12.7.1.1. Adults

For adults, laboratory abnormalities will be graded according to the modified US National institute of Allergy and Infectious Diseases Division of Microbiology and Infectious Diseases (DMID) criteria [DMID, 2007a]. Laboratory results are converted to SI units.

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

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

CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to 135 mEq/L	123 to 129 mEq/L	116 to 122 mEq/L	<116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146 to 150 mEq/L	151 to 157 mEq/L	158 to 165 mEq/L	>165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 to 3.4 mEq/L	2.5 to 2.9 mEq/L	2.0 to 2.4 mEq/L or intensive replacement therapy of hospitalization required	<2.0 mEq/L or abnormal potassium *with* paresis, ileus, or life-threatening arrhythmia
Hyperkalemia	5.6 to 6.0 mEq/L	6.1 to 6.5 mEq/L	6.6 to 7.0 mEq/L	>7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55 to 64 mg/dL	40 to 54 mg/dL	30 to 39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 to 160 mg/dL	161 to 250 mg/dL	251 to 500 mg/dL	>500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 to 7.8 mg/dL	7.7 to 7.0 mg/dL	6.9 to 6.1 mg/dL	<6.1 mg/dL or abnormal calcium *with* life-threatening arrhythmia or tetany
Hypercalcemia (corrected for albumin)	10.6 to 11.5 mg/dL	11.6 to 12.5 mg/dL	12.6 to 13.5 mg/dL	>13.5 mg/dL or abnormal calcium *with* life-threatening arrhythmia
Hypomagnesemia	1.4 to 1.2 mEq/L	1.1 to 0.9 mEq/L	0.8 to 0.6 mEq/L	<0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 to 2.4 mg/dL	1.5 to 1.9 mg/dL or replacement Rx required	1.0 to 1.4 mg/dL intensive therapy or hospitalization required	<1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when	1.1 to <1.25 × ULN	1.25 to <1.5 × ULN	1.5 to 1.75 × ULN	>1.75 × ULN

CHEMISTRIES				
accompanied by any increase in other liver function test)				
Hyperbilirubinemia (when other liver function tests are in the normal range)	1.1 to <1.5 × ULN	1.5 to <2.0 × ULN	2.0 to 3.0 × ULN	>3.0 × ULN
Blood urea nitrogen	1.25 to 2.5 × ULN	2.6 to 5 × ULN	5.1 to 10 × ULN	>10 × ULN
Hyperuricemia (uric acid)	7.5 to 10.0 mg/dL	10.1 to 12.0 mg/dL	12.1 to 15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1 to 1.5 × ULN	1.6 to 3.0 × ULN	3.1 to 6.0 × ULN	>6 × ULN or dialysis required

Rx=therapy; ULN=upper limit of normal.

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

ULN=upper limit of normal.

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

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

12.7.1.2. Adolescent Participants

For adolescent participants over 12 years of age and less than 18 years of age, the adult DMID will be applied for all parameters with the exception of serum creatinine which will be graded programmatically according to the modified DMID pediatric toxicity criteria [DMID, 2007b]. Laboratory results are converted to SI units.

CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Creatinine	1.0 to 1.7 x ULN	1.8 to 2.4 x ULN	2.5 to 3.5 x ULN	>3.5 x ULN

ULN=upper limit of normal.

12.8. Appendix 8: Abbreviations & Trademarks

12.8.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AChE-I	Acetylcholinesterase Inhibition
AE	Adverse Event
AESI	Adverse Event of Special Interest
BID	Twice Daily
BL	Baseline
CE	Clinically Evaluable
CFU	Colony-Forming Units
CI	Confidence Interval
CLSI	Clinical and Laboratory Standards Institute
CV	Cardiovascular
DBF	Database Freeze
DMID	Division of Microbiology and Infectious Diseases
DP	Decimal Places
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FU	Follow-up
GCL	Global Central Laboratory
GI	Gastrointestinal
GSK	GlaxoSmithKline
ICH	International Conference on Harmonization
ICE	Intercurrent Event
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
ITT	Intent-To-Treat
MAR	Missing at Random
MDR	Multidrug-resistant
ME	Microbiologically Evaluable
m-ITT	Microbiological ITT
MI	Multiple Imputation
Micro-ITT	Microbiological ITT
MIC	Minimum Inhibitory Concentration
MLST	Multi-Locus Sequence Typing
MN	Miettinen-Nurminen
NTF-NS	Not Susceptible to nitrofurantoin
NTF-R	Resistant to nitrofurantoin
NTF-S	Susceptible to nitrofurantoin
OOS	Out of stability
OT	On-therapy
PD	Pharmacodynamic
PK	Pharmacokinetic

Abbreviation	Description
RAP	Reporting and Analysis Plan
SAC	Statistical Analysis Complete
SAE	Serious AE
SDTM	Study Data Tabulation Model
TEAE	Treatment-Emergent Adverse Event
TOC	Test-of-Cure
UTI	Urinary Tract Infection
uUTI	Uncomplicated Urinary Tract Infection

12.8.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
GSKDrug

Trademarks not owned by the GlaxoSmithKline Group of Companies
MedDRA
SAS

12.9. Appendix 9: List of Data Displays

12.9.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.19	1.1 to 1.2
Efficacy	2.1 to 2.81	2.1 to 2.15
Safety	3.0 to 3.32	3.1 to 3.9
Pharmacokinetic	4.1 to 4.2	4.1 to 4.4
Section	**Listings**	
ICH Listings	1 to 54	

12.9.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in each tables, listings, and figures shells.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

12.9.3. Deliverable, Priority and Conditional Column

Delivery	Description
HDL	Headline results
SAC	Statistical Analysis Complete
AAC	All Analysis Complete – All Output to support the writing of the CSR and disclosures

12.9.4. Footnotes

The footnotes will follow the general wording conventions and labels:

12.9.4.1. Analyses Footnotes

When analyses were not calculated include the footnote:

"NC=Not calculated"

12.9.5. Study Population Tables

Study Population Tables						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
Participant Disposition						
1.101	Intent-to-Treat	ES1	Summary of Subject Disposition		SAC	SAC
1.102	Micro-ITT NTF-S	ES1	Summary of Subject Disposition		SAC	SAC
1.103	Micro-ITT NTF-S (IA Set)	ES1	Summary of Subject Disposition (IA Set)	Produce only if the study stops early for efficacy at the IA.	SAC	Not produced
1.201	Intent-to-Treat	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment		SAC	SAC
1.202	Micro-ITT NTF-S	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment		SAC	SAC
1.203	Micro-ITT NTF-S (IA Set)	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment (IA Set)	Produce only if the study stops early for efficacy at the IA.	SAC	Not produced
1.3	Intent-to-Treat	NS1	Summary of Number of Subjects Enrolled by Country and Site ID		SAC	SAC
1.4	Screened	ES6	Summary of Reasons for Screening Failures		SAC	SAC
1.5	Screened	SP1	Summary of Study Populations		HDL	HDL
1.6	Intent-to-Treat	SP2	Summary of Exclusions from Study Population		SAC	SAC
Protocol Deviation						
1.7	Intent-to-Treat	DV1	Summary of Important Protocol Deviations		SAC	SAC

Study Population Tables						
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**	
					If study stops	**If study continues**
Demographic and Baseline Characteristics						
1.801	Intent-to-Treat	DM1	Summary of Demographic and Other Baseline Characteristics		SAC	SAC
1.802	Micro-ITT-NTF-S	DM1	Summary of Demographic and Other Baseline Characteristics		SAC	HDL
1.803	CE-TOC	DM1	Summary of Demographic and Other Baseline Characteristics		SAC	SAC
1.804	ME-TOC-NTF-S	DM1	Summary of Demographic and Other Baseline Characteristics		SAC	SAC
1.805	Micro-ITT NTF-S (IA Set)	DM1	Summary of Demographic and Other Baseline Characteristics (IA Set)	Produce only if the study stops early for efficacy at the IA.	HDL	Not produced
1.9	Intent-to-Treat	DM5	Summary of Race and Racial Combinations		SAC	SAC
1.10	Intent-to-Treat	DM11	Summary of Age Ranges		SAC	SAC
1.1101	Intent-to-Treat	POP_T1	Summary of Disease Characteristics at Baseline		SAC	SAC
1.1102	Micro-ITT	POP_T1	Summary of Disease Characteristics at Baseline		SAC	SAC
1.1103	Micro-ITT NTF-S	POP_T1	Summary of Disease Characteristics at Baseline		SAC	HDL
1.1104	Micro-ITT NTF-NS	POP_T1	Summary of Disease Characteristics at Baseline		SAC	SAC
1.1105	CE-TOC	POP_T1	Summary of Disease Characteristics at Baseline		SAC	SAC

Study Population Tables						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
1.1106	ME-TOC	POP_T1	Summary of Disease Characteristics at Baseline		SAC	SAC
1.1107	ME-TOC NTF-S	POP_T1	Summary of Disease Characteristics at Baseline		SAC	SAC
1.1108	ME-TOC NTF-NS	POP_T1	Summary of Disease Characteristics at Baseline		SAC	SAC
1.1109	ME-FU	POP_T1	Summary of Disease Characteristics at Baseline		SAC	SAC
1.1110	ME-FU NTF-S	POP_T1	Summary of Disease Characteristics at Baseline		SAC	SAC
1.1111	ME-FU NTF-NS	POP_T1	Summary of Disease Characteristics at Baseline		SAC	SAC
1.1112	Micro-ITT NTF-S (IA Set)	POP_T1	Summary of Disease Characteristics at Baseline (IA Set)		HDL	Not produced
1.1121	Intent-to-Treat		Summary of Baseline Uropathogens		SAC	SAC
1.1122	Micro-ITT		Summary of Baseline Uropathogens		SAC	SAC
1.1123	Micro-ITT NTF-S		Summary of Baseline Uropathogens		SAC	SAC
1.1124	Micro-ITT NTF-NS		Summary of Baseline Uropathogens		SAC	SAC
1.1125	ME-TOC		Summary of Baseline Uropathogens		SAC	SAC
1.1126	ME-TOC NTF-S		Summary of Baseline Uropathogens		SAC	SAC
1.1127	ME-TOC NTF-NS		Summary of Baseline Uropathogens		SAC	SAC

Study Population Tables						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
1.1128	ME-FU		Summary of Baseline Uropathogens		SAC	SAC
1.1129	ME-FU NTF-S		Summary of Baseline Uropathogens		SAC	SAC
1.1130	ME-FU NTF-NS		Summary of Baseline Uropathogens		SAC	SAC
1.1131	Micro-ITT/NTF-S/NTF-NS		Summary of Baseline Qualifying Uropathogens and Uropathogen Groups	Include separate columns for the three populations included	SAC	SAC
1.1132	ME-TOC/NTF-S/NTF-NS		Summary of Baseline Qualifying Uropathogens and Uropathogen Groups	Include separate columns for the three populations included	SAC	SAC
1.1133	ME-FU/NTF-S/NTF-NS		Summary of Baseline Qualifying Uropathogens and Uropathogen Groups	Include separate columns for the three populations included	SAC	SAC
1.12	Intent-to-Treat	MH4	Summary of Past and Current Medical Conditions		SAC	SAC
1.1201	Micro-ITT NTF-S	MH4	Summary of Past and Current Medical Conditions		SAC	SAC
1.1202	Micro-ITT NTF-S (IA Set)	MH4	Summary of Past and Current Medical Conditions (IA Set)	Produce only if the study stops early for efficacy at the IA.	SAC	Not produced
1.1301	Intent-to-Treat		Summary of History of Uncomplicated Urinary Tract Infection and Pre-existing Conditions with Similar Symptoms		SAC	SAC
1.1302	Micro-ITT NTF-S		Summary of History of Uncomplicated Urinary Tract Infection and Pre-existing Conditions with Similar Symptoms		SAC	SAC

Study Population Tables						
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**	
					If study stops	**If study continues**
1.1303	Micro-ITT NTF-S (IA Set)		Summary of History of Uncomplicated Urinary Tract Infection and Pre-existing Conditions with Similar Symptoms (IA Set)	Produce only if the study stops early for efficacy at the IA.	SAC	Not produced
1.1401	Intent-to-Treat		Summary of Prior Medications		SAC	SAC
1.1402	Micro-ITT NTF-S		Summary of Prior Medications		SAC	SAC
1.1501	Intent-to-Treat		Summary of Concomitant Medications		SAC	SAC
1.1502	Micro-ITT NTF-S		Summary of Concomitant Medications		SAC	SAC
1.1503	Micro-ITT NTF-S (IA Set)		Summary of Concomitant Medications (IA Set)	Produce only if the study stops early for efficacy at the IA.	SAC	Not produced
Exposure						
1.1601	Safety	EX1	Summary of Exposure to Study Treatments		SAC	SAC
1.1602	Micro-ITT NTF-S	EX1	Summary of Exposure to Study Treatments		SAC	SAC
1.1603	Micro-ITT NTF-S (IA Set)		Summary of Exposure to Study Treatments (IA Set)	Produce only if the study stops early for efficacy at the IA.	SAC	Not produced
Other						
1.17	Intent-to-Treat	SU1	Summary of Substance Use		SAC	SAC
1.19	Intent-to-Treat	PAN4	Summary of COVID-19 Pandemic Visit Impacts		SAC	SAC

12.9.6. Study Population Figures

Study Population: Figures						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
1.1	Intent-to-Treat		Bar Plot of Baseline Total and Individual Component Clinical Symptom Score		AAC	AAC
1.201	Micro-ITT		Bar Plot of Number and Percent of Baseline Qualifying Uropathogens Isolated		AAC	AAC
1.202	Micro-ITT NTF-S		Bar Plot of Number and Percent of Baseline Qualifying Uropathogens Isolated		AAC	AAC
1.203	Micro-ITT NTF-NS		Bar Plot of Number and Percent of Baseline Qualifying Uropathogens Isolated		AAC	AAC

12.9.7. Efficacy Tables

Efficacy: Tables						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
Therapeutic Response						
2.1	Micro-ITT NTF-S or Micro-ITT NTF-S (IA Set) (see notes)	EFF_T1	Analysis of Therapeutic Response at the TOC Visit (Primary)	just Micro-ITT NTF-S and Subject level. This will be produced for the primary analysis set (i.e. the IA Set if the study is stopped early for efficacy)	HDL	HDL
2.2	Micro-ITT NTF-S or Micro-ITT NTF-S (IA Set) (see notes)	EFF_T1	Treatment by Strata Tests of Homogeneity for Percent of Subjects with Therapeutic Response at the TOC Visit	just Micro-ITT NTF-S and Subject level. This will be produced for the primary analysis set (i.e. the IA Set if the study is stopped early for efficacy)	SAC	SAC
2.2001	Micro-ITT NTF-S or Micro-ITT NTF-S (IA Set) (see notes)	EFF_T1	Treatment by Strata Tests of Homogeneity for Percent of Subjects with Clinical Response at the TOC Visit	This will be produced for the primary analysis set (i.e. the IA Set if the study is stopped early for efficacy)	SAC	SAC
2.2002	Micro-ITT NTF-S or Micro-ITT NTF-S (IA Set) (see notes)	EFF_T1	Treatment by Strata Tests of Homogeneity for Percent of Subjects with Microbiological Response at the TOC Visit	This will be produced for the primary analysis set (i.e. the IA Set if the study is stopped early for efficacy)	SAC	SAC
2.2003	EU Micro-ITT NTF-S or EU Micro-ITT NTF-S (IA Set) (see notes)		Treatment by Strata Tests of Homogeneity for Percent of Subjects with Therapeutic Response at the TOC Visit	This will be produced for the key EU supplementary analysis set (i.e. the IA Set if the study is stopped early for efficacy)	SAC	SAC

Efficacy: Tables						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
2.3	Micro-ITT/NTF-S/NTF-NS	EFF_T1	Summary of Therapeutic Response at the TOC Visit	include 6 columns with Micro-ITT, Micro-ITT NTF-S, Micro-ITT NTF-NS	HDL	HDL
2.3001	Micro-ITT NTF-S (IA Set)		Summary of Therapeutic Response at the TOC Visit (IA Set)	Note: this table includes reasons for failure and will be produced if the study is stopped early for efficacy. Refer to the IDMC Table 14 mock shell	HDL	Not produced
2.3002	Micro-ITT NTF-S or Micro-ITT NTF-S (IA Set) (see notes)		Sensitivity Analysis of Therapeutic Response at the TOC Visit with Multiple Imputation	This will be produced for the primary analysis set (i.e. the IA Set if the study is stopped early for efficacy)	SAC	SAC
2.3003	Micro-ITT NTF-S or Micro-ITT NTF-S (IA Set) (see notes)		Sensitivity Analysis: Multiple Imputation Tipping Point Analysis of Therapeutic Success at the TOC Visit	This will be produced for the primary analysis set (i.e. the IA Set if the study is stopped early for efficacy)	SAC	SAC
2.3004	Micro-ITT NTF-S (CAPA)/ Micro-ITT NTF-S (IA Set) (CAPA) (see notes)		Supplementary Analysis of Therapeutic Response at the TOC Visit (Excluding Sites with CAPA Exclusion Requirements)	This will be produced for the primary analysis set (i.e. the IA Set if the study is stopped early for efficacy) subset to exclude Sites with CAPA Exclusion Requirements	SAC	SAC
2.3005	EU Micro-ITT NTF-S		Summary of Therapeutic Response at the TOC Visit		SAC	HDL
2.3006	EU Micro-ITT		Summary of Therapeutic Response at	This table will be produced if the	SAC	Not

Efficacy: Tables						
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**	
					If study stops	**If study continues**
	NTF-S (IA Set)		the TOC Visit (EU IA Set)	study is stopped early for efficacy.		produced
2.4	Micro-ITT	EFF_T1	Summary of Therapeutic Response at the TOC Visit by Actual Strata	Subgroup for rand strata (age/recurrent/age*recurrence); include 6 columns with Micro-ITT, Micro-ITT NTF-S, Micro-ITT NTF-NS	SAC	SAC
2.5	Micro-ITT	EFF_T1	Summary of Therapeutic Response at the TOC Visit by Other Subgroups	Subgroup for Other Subgroups (region/race/ethnicity/baseline clinical symptom score/menopausal status); include 6 columns with Micro-ITT, Micro-ITT NTF-S, Micro-ITT NTF-NS	SAC	SAC
2.6	Micro-ITT/NTF-S/NTF-NS	EFF_T1	Summary of Therapeutic Response by Visit and Number of Qualified Uropathogens at Baseline	include 6 columns with Micro-ITT, Micro-ITT NTF-S, Micro-ITT NTF-NS; paginate by visit (TOC/FU)	SAC	SAC
2.7	ME	EFF_T1	Summary of Therapeutic Response at the TOC Visit	include 6 columns with ME-TOC, ME-TOC NTF-S, ME-TOC NTF-NS	SAC	SAC
2.8	ME	EFF_T1	Summary of Therapeutic Response at the TOC Visit by Actual Strata	Subgroup for rand strata (age/recurrent/age*recurrence); include 6 columns with ME-TOC, ME-TOC NTF-S, ME-TOC NTF-NS	SAC	SAC
2.9	ME	EFF_T1	Summary of Therapeutic Response at the TOC Visit by Other Subgroups	Subgroup for Other Subgroup (region/race/ethnicity/baseline clinical symptom score/menopausal status); include 6 columns with ME-TOC, ME-TOC NTF-S, ME-TOC NTF-NS	SAC	SAC

Efficacy: Tables						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
2.10	Micro-ITT	EFF_T1	Summary of Therapeutic Response at the Follow Up Visit	include 6 columns with Micro-ITT, Micro-ITT NTF-S, Micro-ITT NTF-NS	HDL	HDL
2.11	Micro-ITT	EFF_T1	Summary of Therapeutic Response at the Follow Up Visit by Actual Strata	Subgroup for actual strata (age/recurrent/age*recurrence); include 6 columns with Micro-ITT, Micro-ITT NTF-S, Micro-ITT NTF-NS	SAC	SAC
2.12	Micro-ITT	EFF_T1	Summary of Therapeutic Response at the Follow Up Visit by Other Subgroups	Subgroup for Other Subgroup (region/race/ethnicity/baseline clinical symptom score/menopausal status) include 6 columns with Micro-ITT, Micro-ITT NTF-S, Micro-ITT NTF-NS	SAC	SAC
2.13	ME	EFF_T1	Summary of Therapeutic Response at the Follow Up Visit	include 6 columns with ME-FU, ME-FU NTF-S, ME-FU NTF-NS	SAC	SAC
2.14	ME	EFF_T1	Summary of Therapeutic Response at the Follow Up Visit by Actual Strata	Subgroup for actual strata (age/recurrent/age*recurrence); include 6 columns with ME-FU, ME-FU NTF-S, ME-FU NTF-NS	SAC	SAC
2.15	ME	EFF_T1	Summary of Therapeutic Response at the Follow Up Visit by Other Subgroups	Subgroup for Other Subgroup (region/race/ethnicity/baseline clinical symptom score/menopausal status); include 6 columns with ME-FU, ME-FU NTF-S, ME-FU NTF-NS	SAC	SAC
2.1601	Intent-to-Treat	EFF_T6	Summary of Clinical Outcome and Response by Visit, Overall and by	by visit (OT/TOC/FU), Subgroup for actual strata	SAC	SAC

Efficacy: Tables						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
			Actual Strata	(age/recurrent/age*recurrence)		
2.1602	Micro-ITT NTF-S	EFF_T6	Summary of Clinical Outcome and Response by Visit, Overall and by Actual Strata	by visit (OT/TOC/FU), Subgroup for actual strata (age/recurrent/age*recurrence)	SAC	SAC
2.1603	Micro-ITT NTF-S (IA Set)		Summary of Clinical Outcome and Response at TOC Visit (IA Set)	Produced for the primary analysis set (i.e. the IA Set if the study is stopped early for efficacy). Refer to IDMC Table 15 mock shell.	HDL	Not produced
2.1604	Micro-ITT NTF-S		Summary of Microbiological Outcome and Response by Visit, Overall and by Actual Strata	Participant level Microbiological outcome/response by visit (OT/TOC/FU), Subgroup for actual strata (age/recurrent/age*recurrence)	SAC	SAC
2.1701	Intent-to-Treat	EFF_T6	Summary of Clinical Outcome and Response by Visit and Other Subgroups	by visit (OT/TOC/FU), Subgroup for Other Subgroup (region/race/ethnicity/baseline clinical symptom score/menopausal status)	SAC	SAC
2.1702	Micro-ITT NTF-S	EFF_T6	Summary of Clinical Outcome and Response by Visit and Other Subgroups	by visit (OT/TOC/FU), Subgroup for Other Subgroup (region/race/ethnicity/baseline clinical symptom score/menopausal status)	SAC	SAC
2.1703	Micro-ITT NTF-S		Summary of Microbiological Outcome and Response by Visit and Other Subgroup	Participant level Microbiological outcome/response by visit (OT/TOC/FU), Subgroup for Other Subgroup	SAC	SAC

Efficacy: Tables						
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**	
					If study stops	**If study continues**
				(region/race/ethnicity/baseline clinical symptom score/menopausal status)		
2.18	Clinically Evaluable	EFF_T6	Summary of Clinical Outcome and Response by Visit, Overall and by Actual Strata	by visit (OT/TOC/FU), Subgroup for actual strata (age/recurrent/age*recurrence)	SAC	SAC
2.19	Clinically Evaluable	EFF_T6	Summary of Clinical Outcome and Response by Visit and Other Subgroups	by visit (OT/TOC/FU), Subgroup for Other Subgroup (region/race/ethnicity/baseline clinical symptom score/menopausal status)	SAC	SAC
2.20	Micro-ITT	EFF_T6	Summary of Clinical Outcome and Response by Visit, Overall and by Qualifying Uropathogen Isolated at Baseline	by visit (OT/TOC/FU)	SAC	SAC
2.21	Micro-ITT NTF-S	EFF_T6	Summary of Clinical Outcome and Response by Visit, Overall and by Qualifying Uropathogen Isolated at Baseline	by visit (OT/TOC/FU)	SAC	HDL
2.22	Micro-ITT NTF-NS	EFF_T6	Summary of Clinical Outcome and Response by Visit, Overall and by Qualifying Uropathogen Isolated at Baseline	by visit (OT/TOC/FU)	SAC	SAC
Microbiological Outcome and Response						
2.23	Micro-ITT		Summary of Microbiological Outcome and Response by Visit, Overall and	by visit (OT/TOC/FU)	SAC	SAC

Efficacy: Tables						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
			by Qualifying Uropathogen Isolated at Baseline			
2.24	Micro-ITT NTF-S		Summary of Microbiological Outcome and Response by Visit, Overall and by Qualifying Uropathogen Isolated at Baseline	by visit (OT/TOC/FU)	SAC	HDL
2.25	Micro-ITT NTF-S (IA Set)		Summary of Microbiological Outcome and Response at TOC Visit (IA Set)	Produced for the primary analysis set (i.e. the IA Set if the study is stopped early for efficacy). Refer to IDMC Table 16 mock shell.	HDL	Not produced
2.26	Micro-ITT NTF-NS		Summary of Microbiological Outcome and Response by Visit, Overall and by Qualifying Uropathogen Isolated at Baseline	by visit (OT/TOC/FU)	SAC	SAC
2.27	ME		Summary of Microbiological Outcome and Response by Visit, Overall and by Qualifying Uropathogen Isolated at Baseline	by visit (OT/TOC/FU) for ME-OT/ME-TOC/ME-FU population as applicable	SAC	SAC
2.28	ME NTF-S		Summary of Microbiological Outcome and Response by Visit, Overall and by Qualifying Uropathogen Isolated at Baseline	by visit (OT/TOC/FU) for ME-OT/ME-TOC/ME-FU population derivative as applicable	SAC	SAC
2.30	ME NTF-NS		Summary of Microbiological Outcome and Response by Visit, Overall and	by visit (OT/TOC/FU) for ME-OT/ME-TOC/ME-FU population derivative as	SAC	SAC

Efficacy: Tables						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
			by Qualifying Uropathogen Isolated at Baseline	applicable		
CCI [redacted]						

Efficacy: Tables						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
CCI [redacted]						

Efficacy: Tables						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
CCI [redacted]						

Efficacy: Tables						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
CCI [redacted]						

Efficacy: Tables						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
CCI [redacted]						

Efficacy: Tables						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
CCI [redacted]						

Efficacy: Tables						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
CCI [redacted]						

Efficacy: Tables						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
CCI [redacted]						

12.9.8. Efficacy Figures

Efficacy: Figures						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
2.1	Micro-ITT NTF-S	EFF_F1	Percent of Therapeutic Success by Visit, Overall and by Qualifying Uropathogen Isolated at Baseline	by uropathogen	AAC	AAC
2.2	Micro-ITT		Forest Plot for Therapeutic Success Rate Overall and by Subgroup		AAC	AAC
2.3	Micro-ITT NTF-S		Forest Plot for Therapeutic Success Rate Overall and by Subgroup	If the studies stop early for efficacy, please include a row on the micro-ITT NTF-S (IA Set) as this will be the primary analysis	AAC	AAC
2.4	Micro-ITT NTF-NS		Forest Plot for Therapeutic Success Rate Overall and by Subgroup		AAC	AAC
2.5	Micro-ITT/NTF-S/NTF-NS		Forest Plot for Therapeutic Success Rate by Qualifying Baseline Uropathogen and Uropathogen Phenotypic and Genotypic Subcategories	by population (Micro-ITT, Micro-ITT-NTF-S, Micro-ITT NTF-NS) and visit (TOC/FU)	AAC	AAC
2.6	Micro-ITT/NTF-S/NTF-NS		Forest Plot for Clinical Success Rate by Qualifying Baseline Uropathogen and Uropathogen Phenotypic and Genotypic Subcategories	by population (Micro-ITT, Micro-ITT-NTF-S, Micro-ITT NTF-NS) and visit (TOC/FU)	AAC	AAC
2.7	Micro-ITT/NTF-S/NTF-NS		Forest Plot for Microbiological Success Rate by Qualifying Baseline Uropathogen and Uropathogen Phenotypic and Genotypic Subcategories	by population (Micro-ITT, Micro-ITT-NTF-S, Micro-ITT NTF-NS) and visit (TOC/FU)	AAC	AAC
2.8	Micro-ITT NTF-S		Tipping Point Analysis of Therapeutic Response at TOC	This will be produced for the primary analysis set (i.e. the	SAC	SAC

Efficacy: Figures						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
				IA Set if the study is stopped early for efficacy)		
2.11	Intent-to-Treat	EFF_F3	Boxplot of Individual Clinical Symptom Score and Total Score by Visit		AAC	AAC
2.1101	Intent-to-Treat	EFF_F3	Boxplot of Change from Baseline Individual Clinical Symptom Score and Total Score by Visit		AAC	AAC
2.12	Intent-to-Treat	EFF_F1	Percent of Clinical Outcome by Visit		AAC	AAC
2.1301	Micro-ITT	EFF_F1	Percent of Microbiological Outcome by Visit, Overall and by Qualifying Uropathogen Isolated at Baseline	by visit (TOC/FU)	AAC	AAC
2.1302	Micro-ITT NTF-S	EFF_F1	Percent of Microbiological Outcome by Visit, Overall and by Qualifying Uropathogen Isolated at Baseline	by visit (TOC/FU)	AAC	AAC
2.1303	Micro-ITT NTF-NS	EFF_F1	Percent of Microbiological Outcome by Visit, Overall and by Qualifying Uropathogen Isolated at Baseline	by visit (TOC/FU)	AAC	AAC
CCI [redacted]						

12.9.9. Safety Tables

Safety: Tables						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
Adverse Events (AEs)						
3.0	Safety		Overall Summary of Adverse Events		HDL	HDL
3.1	Safety	AE5B	Summary of Adverse Events by System Organ Class and Preferred Term and Maximum Grade		HDL	HDL
3.2	Safety	AE5B	Summary of Adverse Events by System Organ Class and Preferred Term and Maximum Grade and Age	subgroup age group	SAC	SAC
3.3	Safety	AE5B	Summary of Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Grade		SAC	SAC
3.4	Safety	AE3	Summary of Common (>=1%) Adverse Events by Preferred Term		SAC	SAC
3.5	Safety	AE3	Summary of Common (>=1%) Adverse Events by Preferred Term and Age	subgroup age group	SAC	SAC
3.6	Safety	AE15	Summary of Common (>=1%) Non-Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)		SAC	SAC
3.7	Safety	AE3	Summary of Common (>=1%) Grade 2-5 Adverse Events by Preferred Term		SAC	SAC

Safety: Tables						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
3.9	Safety	E16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC	SAC
3.10	Safety	AE5B	Summary of Serious Adverse Events by System Organ Class and Preferred Term and Maximum Grade		SAC	SAC
3.11	Safety	AE5B	Summary of Serious Adverse Events by System Organ Class and Preferred Term and Maximum Grade and Age	subgroup age group	SAC	SAC
3.12	Safety	AE5B	Summary of Drug-Related Serious Adverse Events by System Organ Class and Preferred Term and Maximum Grade		SAC	SAC
3.13	Safety	AE3	Summary of Non-Fatal Serious Adverse Events		SAC	SAC
3.14	Safety	AE3	Summary of Drug-Related Non-Fatal Serious Adverse Events		SAC	SAC
3.15	Safety	AE5B	Summary of Cardiovascular and Gastrointestinal Adverse Events of Special Interest by System Organ Class and Preferred Term and Maximum Grade		SAC	SAC
3.17	Safety	AE5B	Summary of Acetylcholinesterase-Inhibition Adverse Events of Special Interest by System Organ Class and Preferred Term and Maximum Grade		SAC	SAC

Safety: Tables						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
3.19	Safety	AE5B	Summary of Acetylcholinesterase-Inhibition Adverse Events of Special Interest by Number of Events and Unique Preferred Term	a table to summarize the number and % of patients experiencing 1, 2, 3, 4, 5 or more events and 1,2,3,4,>=5 or more distinct PTs. See mock up on slides 8	SAC	SAC
3.20	Safety	AE5B	Summary of Acetylcholinesterase-Inhibition Adverse Events of Special Interest by Number of Events and Unique Preferred Term and Age	subgroup age group	SAC	SAC
3.21	Safety		Summary of Onset, Duration and Lag Time of AChE-I Event	a summary table to present the statistics (mean, median, max, min) of time to first event, duration, and lag time since last dose for AchEI, non-GI AchEI, and GI AchEI events	SAC	SAC
3.22	Safety		Summary of Onset, Duration and Lag Time of AChE-I Event by Age	subgroup age group	SAC	SAC
3.23	Safety	AE5B	Summary of Adverse Events Leading to Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term and Maximum Grade		SAC	SAC
3.2301	Safety	AE5B	Summary of Adverse Events Leading to Discontinuation of Study Treatment by System Organ Class and Preferred Term and Maximum Grade		SAC	SAC

Safety: Tables						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
Laboratory						
3.24	Safety	LB1	Summary of Clinical Chemistry Values Change from Baseline		SAC	SAC
3.25	Safety	LB2	Summary of Emergent Chemistry Laboratory Results by Maximum Grade Increase from Baseline		SAC	SAC
3.26	Safety	LB1	Summary of Hematology Change from Baseline		SAC	SAC
3.27	Safety	LB2	Summary of Emergent Hematology Laboratory Results by Maximum Grade Increase from Baseline		SAC	SAC
3.28	Safety	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting		SAC	SAC
3.29	Safety	UR3	Summary of Urinalysis Results		SAC	SAC
3.30	Safety	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities		SAC	SAC

Safety: Tables						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
Vital Signs						
3.31	Safety	VS3	Summary of Worst-Case Vital Signs Results Relative to Potential Clinical Importance Criteria Post-Baseline Relative to Baseline		SAC	SAC
3.32	Safety	VS1	Summary of Change from Baseline in Vital Signs		SAC	SAC
Family History						
3.34	Safety	FH1	Summary of Family History of Cardiovascular Risk Factors		SAC	SAC

12.9.10. Safety Figures

Safety: Figures						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
3.1	Safety	AE10	Plot of Common (>=1%) Adverse Events and Relative Risk		AAC	AAC
3.2	Safety	AE11	Cumulative Distribution of Time to First Gastrointestinal Event		AAC	AAC
3.3	Safety		Stacked Bar Chart of AChE-I Cumulative Grades		AAC	AAC
3.4	Safety		Stacked Bar Chart of non-GI AChE-I Cumulative Grade		AAC	AAC
3.5	Safety		Bar Chart of GI Events by Grade in Percentage of Subjects over Time		AAC	AAC
3.6	Safety		Plot for AChE-I Events and Relative Risk		AAC	AAC
3.7	Safety		Plot of Maximum Post-Baseline vs Baseline for ALT		AAC	AAC
3.8	Safety		Plot of Maximum Post-Baseline Total Bilirubin vs Maximum Post-Baseline ALT		AAC	AAC
3.9	Safety		Liver Function Tests Patient Profiles		AAC	AAC

12.9.11. Pharmacokinetic Tables

Pharmacokinetic: Tables						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
Pharmacokinetic Concentrations						
4.1.	PK	PKCT1	Summary of Gepotidacin Plasma Pharmacokinetic Concentration Actual Time Data (ug/mL)	By study day and sampling window	SAC	SAC
4.2.	PK	PKCT1	Summary of Gepotidacin Urine Pharmacokinetic Concentration Actual Time Data (ug/mL)	By study day and sampling window	SAC	SAC

12.9.12. ICH and Non-ICH Listings

Listings						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
Participant Disposition						
1	Intent-to-Treat	ES2	Listing of Reasons for Study Withdrawal	ICH Listing	AAC	AAC
2	Intent-to-Treat	SD2	Listing of Reasons for Study Treatment Discontinuation	ICH Listing	AAC	AAC
3	Intent-to-Treat	SP3	Listing of Subjects Excluded from Any Population	ICH Listing	AAC	AAC
Protocol Deviations						
4	Intent-to-Treat	DV2	Listing of Important Protocol Deviations	ICH Listing	AAC	AAC
5	Screened	ES7	Listing of Reasons for Screen Failure	Non-ICH Listing	AAC	AAC
6	Intent-to-Treat	BL1	Listing of Subjects for Whom the Treatment Blind was Broken During the Study	ICH Listing	AAC	AAC
7	Intent-to-Treat	TA1	Listing of Randomized and Actual Treatments	Non-ICH Listing	pre-HDL (2 days post unblinding)	pre-HDL (2 days post unblinding)
8	Intent-to-Treat	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	ICH Listing	AAC	AAC
Demographic and Baseline Characteristics						
9	Intent-to-Treat	DM2	Listing of Demographic Characteristics	ICH Listing	AAC	AAC
10	Intent-to-Treat	DM9	Listing of Race	ICH Listing	AAC	AAC
11	Intent-to-Treat	SAFE_L1	Listing of History of Uncomplicated Urinary Tract Infection and Pre-Existing Conditions with Similar Symptoms	ICH Listing	AAC	AAC

Listings						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
12	Intent-to-Treat	MH2	Listing of Medical Conditions	ICH Listing	AAC	AAC
12.1	Intent-to-Treat	MH2	Listing of Findings of Medical History	ICH Listing	AAC	AAC

Listings						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
Prior and Concomitant Medications						
13	Intent-to-Treat	CM3	Listing of Prior and Concomitant Medications	Non-ICH Listing	AAC	AAC
14	Intent-to-Treat	CM3	Listing of Prior and Concomitant Antibiotic Medications for uUTI	Non-ICH Listing	AAC	AAC
Exposure and Treatment Compliance						
15	Intent-to-Treat	EX3	Listing of Exposure Data	ICH Listing	AAC	AAC
Efficacy						
16	Micro-ITT		Listing of Microbiological Outcome and Response, Clinical Outcome and Response, and Therapeutic Response by Subject ID and Baseline Qualifying Uropathogen	Non-ICH Listing	AAC	AAC
17	Intent-to-Treat	EFF_L1	Listing of Clinical Outcome and Response	Non-ICH Listing	AAC	AAC
CCI						
20	Intent-to-treat	EFF_L3	Listing of Susceptibility Results	Non-ICH Listing	AAC	AAC
21	Micro-ITT	EFF_L4	Listing of Clinical Response, Microbiological Outcome and Response, Therapeutic Response, Study Drug MIC and Zone Diameter Results by Qualifying Baseline Uropathogen	Non-ICH Listing	AAC	AAC

Listings						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
22	Intent-to-Treat	EFF_L4	Listing of Clinical Response, Microbiological Outcome and Response, Therapeutic Response, MIC and Zone Diameter Results for Uropathogens with a 4-fold Increase in Study Treatment MIC	Non-ICH Listing	AAC	AAC
CCI						
24	Intent-to-treat		Listing of Genetic Characterization Results	Non-ICH Listing	AAC	AAC
25	Intent-to-treat		Listing of New Qualifying Uropathogens	Non-ICH Listing	AAC	AAC
26	Micro-ITT		Listing of Sequence Typing and Phenotypic Subcategories for Qualifying Uropathogens from Microbiological Failures	Non-ICH Listing	AAC	AAC
Adverse Events						
27	Safety	AE2	Listing of Relationship Between System Organ Class and Verbatim Text	Non-ICH Listing	AAC	AAC
28	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH Listing	AAC	AAC
29	Safety	AE8CP	Listing of All Adverse Events	ICH Listing	AAC	AAC
Serious and Other Significant Adverse Events						
30	Safety	AE8CP	Listing of Study Drug Related Adverse Events	ICH Listing	AAC	AAC
31	Safety	SAFE_L2	Listing of Serious Adverse Events (Fatal & Non-Fatal)	ICH Listing	HDL	HDL
31.1	Safety		Listing of Fatal Serious Adverse Events	ICH Listing	AAC	AAC
32	Safety	AE8CP	Listing of Adverse Events Leading to Discontinuation of Study Treatment or Withdrawal from Study	ICH Listing	AAC	AAC

Listings						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
33	Safety	AE8CP	Listing of Cardiovascular and Gastrointestinal Adverse Events of Special Interest	ICH Listing	AAC	AAC
34	Safety	AE8CP	Listing of Acetylcholinesterase-Inhibition Adverse Events of Special Interest	ICH Listing	AAC	AAC
35	Safety	AE8CP	Listing of Non-Gastrointestinal Acetylcholinesterase-Inhibition Adverse Events of Special Interest	ICH Listing	AAC	AAC
All Laboratory						
36	Safety	LB5A	Listing of Clinical Chemistry Toxicities of Grade 3 or Higher	ICH Listing	AAC	AAC
37	Safety	LB5A	Listing of All Clinical Chemistry Data for Subjects with Toxicities of Grade 3 or Higher	ICH Listing	AAC	AAC
38	Safety	LB5A	Listing of Hematology Toxicities of Grade 3 or Higher	ICH Listing	AAC	AAC
39	Safety	LB5A	Listing of Hematology Data for Subjects with Toxicities of Grade 3 or Higher	ICH Listing	AAC	AAC
40	Safety	UR2A	Listing of Urinalysis Data	ICH Listing	AAC	AAC
ECG						
41	Safety	EG5	Listing of All ECG Findings for Subjects with an Abnormal Finding	Non-ICH Listing	AAC	AAC
42	Safety	EG3	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance	Non-ICH Listing	SAC	SAC
Vital Signs						
43	Safety	VS4	Listing of All Vital Signs for Subjects with Potential Clinical Importance Values	Non-ICH Listing	AAC	AAC

Listings						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
Liver Events and Other Safety Endpoints						
44	Safety	SAFE_L3	Listing of Clostridium Difficile Testing Results	Non-ICH Listing	AAC	AAC
45	Safety	SU2	Listing of Alcohol Intake at Onset of Liver Event	Non-ICH Listing	AAC	AAC
46	Safety	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting	Non-ICH Listing	AAC	AAC
47	Safety	LIVER7	Listing of Liver Biopsy Details	Non-ICH Listing	AAC	AAC
48	Safety	LIVER8	Listing of Liver Imaging Details	Non-ICH Listing	AAC	AAC
Pharmacokinetic Concentrations						
49	PK	PKCL1P	Listing of Gepotidacin Plasma Concentrations (ug/mL)	Non-ICH Listing	AAC	AAC
50	PK	PKUL1P	Listing of Gepotidacin Urine Concentrations (ug/mL)	Non-ICH Listing	AAC	AAC
COVID-19						
51	Intent-to-Treat		Listing of Substance Use	Non-ICH Listing	AAC	AAC
52	Intent-to-Treat	PAN5A	Country Level Listing of Start Dates of Waves of COVID-19 Pandemic Measures	Non-ICH Listing	AAC	AAC
53	Intent-to-Treat	PAN7	Listing of All Subjects with Visits and Assessments Impacted by COVID-19 Pandemic	Non-ICH Listing	AAC	AAC
54	Safety	PAN12	Listing of COVID-19 Assessments and Symptom Assessments for Subjects with COVID-19 Adverse Events	Non-ICH Listing	AAC	AAC
55	Intent-to-Treat	PREG1	Listing of Subjects Who Became Pregnant During the Study	Non-ICH Listing	AAC	AAC

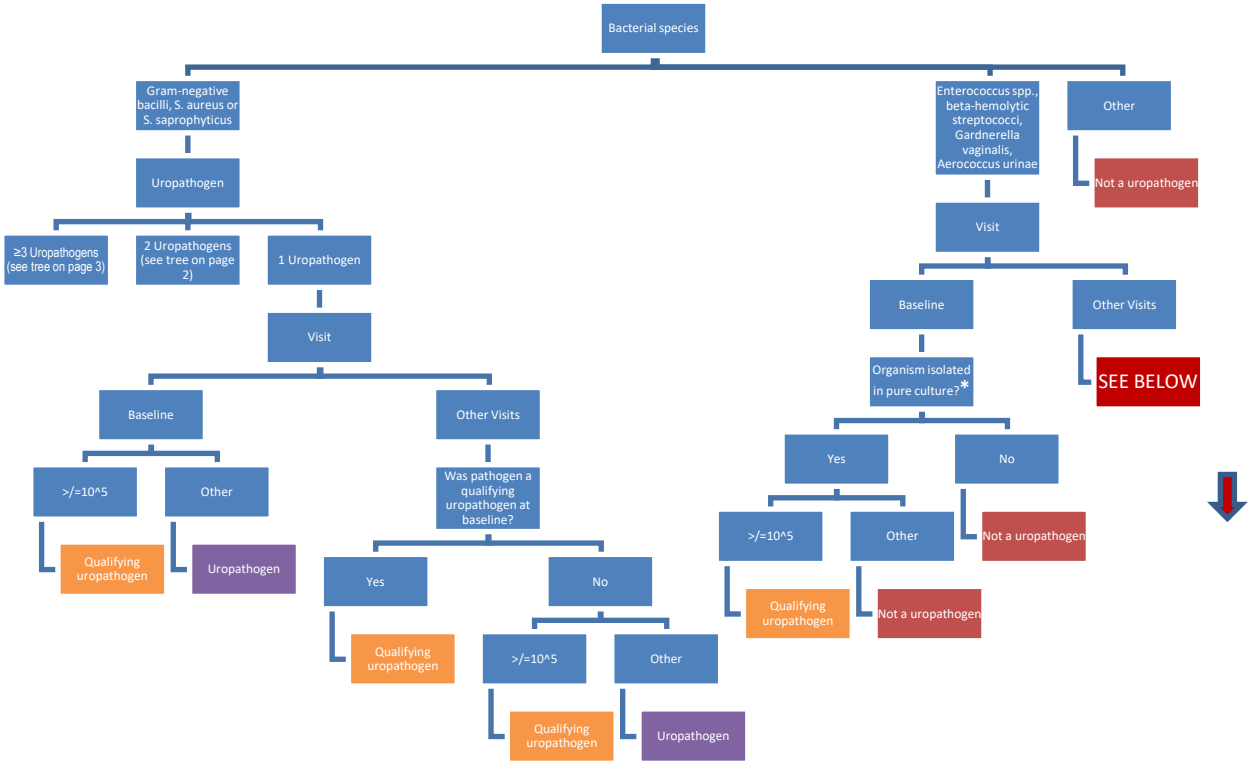
Listings						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
56	Intent-to-Treat	LIVER15	Liver Stopping Event Profile	Non-ICH Listing Conditional output that will only be produced if participant have corresponding event	AAC	AAC
57	Intent-to-Treat	ARR1	Patient Profile for Arrythmias	Non-ICH Listing Conditional output that will only be produced if participant have corresponding event	AAC	AAC
58	Intent-to-Treat	CHF1	Patient Profile for Congestive Heart Failure	Non-ICH Listing Conditional output that will only be produced if participant have corresponding event	AAC	AAC
59	Intent-to-Treat	CVATIA1	Patient Profile for Cerebrovascular Events, Stroke and Transient Ischemic Attack	Non-ICH Listing Conditional output that will only be produced if participant have corresponding event	AAC	AAC

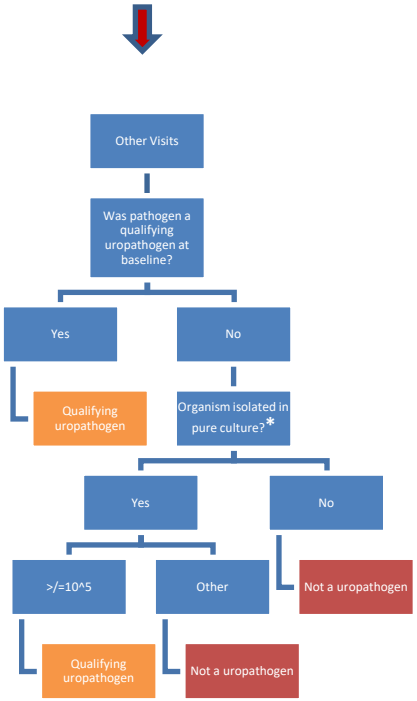
Listings						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
60	Intent-to-Treat	DVT1	Patient Profile for Deep Vein Thrombosis/Pulmonary Embolism	Non-ICH Listing Conditional output that will only be produced if participant have corresponding event	AAC	AAC
61	Intent-to-Treat	MI1	Patient Profile for Myocardial Infarction	Non-ICH Listing Conditional output that will only be produced if participant have corresponding event	AAC	AAC
62	Intent-to-Treat	PATE1	Patient Profile for Peripheral Arterial Thromboembolism	Non-ICH Listing Conditional output that will only be produced if participant have corresponding event	AAC	AAC
63	Intent-to-Treat	PUL1	Patient Profile for Pulmonary Hypertension	Non-ICH Listing Conditional output that will only be produced if participant have corresponding event	AAC	AAC

Listings						
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable	
					If study stops	If study continues
64	Intent-to-Treat	REV1	Patient Profile for Revascularisation	Non-ICH Listing Conditional output that will only be produced if participant have corresponding event	AAC	AAC
65	Intent-to-Treat	VAL1	Patient Profile for Valvulopathy	Non-ICH Listing Conditional output that will only be produced if participant have corresponding event	AAC	AAC
66	Intent-to-Treat	DD3	Subject Profile for Death	Non-ICH Listing Conditional output that will only be produced if participant have corresponding event	AAC	AAC

12.10. Appendix 10: Qualifying Uropathogen Algorithm

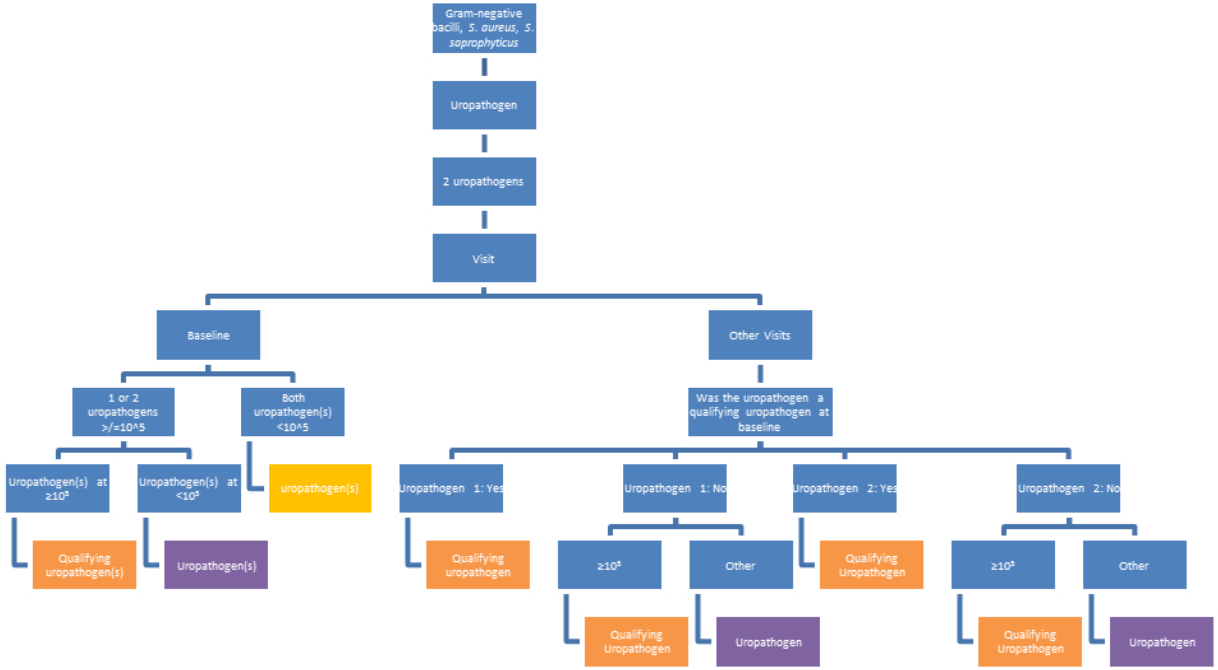
Qualifying Uropathogen Decision Tree: Single Uropathogen


Bacterial species
Gram-negative bacilli, S. aureus or S. saprophyticus
Enterococcus spp., beta-hemolytic streptococci, Gardnerella vaginalis, Aerococcus urinae
Other
Not a uropathogen
Uropathogen
≥3 Uropathogens (see tree on page 3)
2 Uropathogens (see tree on page 2)
1 Uropathogen
Visit
Baseline
Other Visits
SEE BELOW
Organism isolated in pure culture?*
Yes
No
>/=10^5
Other
Qualifying uropathogen
Uropathogen
Not a uropathogen
Was pathogen a qualifying uropathogen at baseline?
Yes
No
>/=10^5
Other
Qualifying uropathogen
Uropathogen
Not a uropathogen



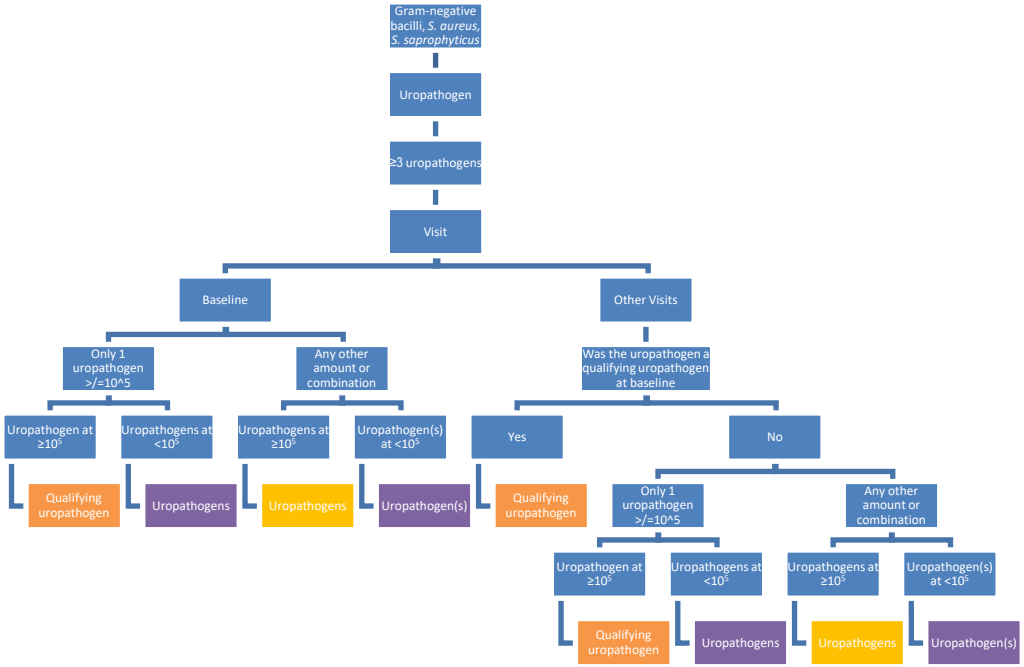
*Pure culture: a culture containing the growth of a single strain of organism free from other pathogens or normal flora.

Qualifying Uropathogen Decision Tree: 2 Uropathogens



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

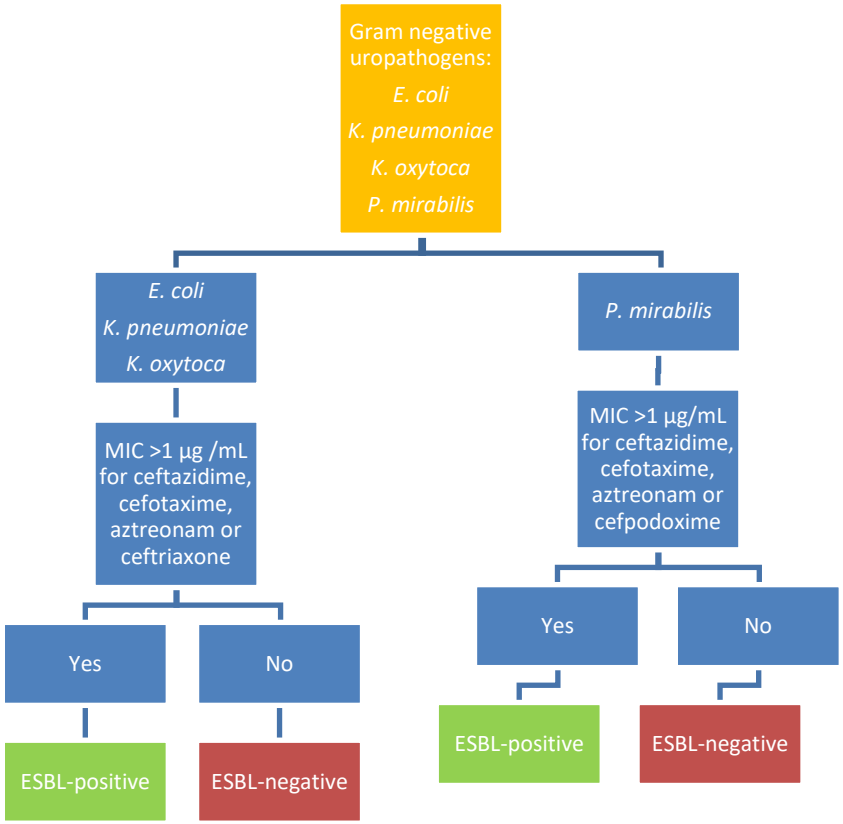
Qualifying Uropathogen Decision Tree: ≥3 Uropathogens



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

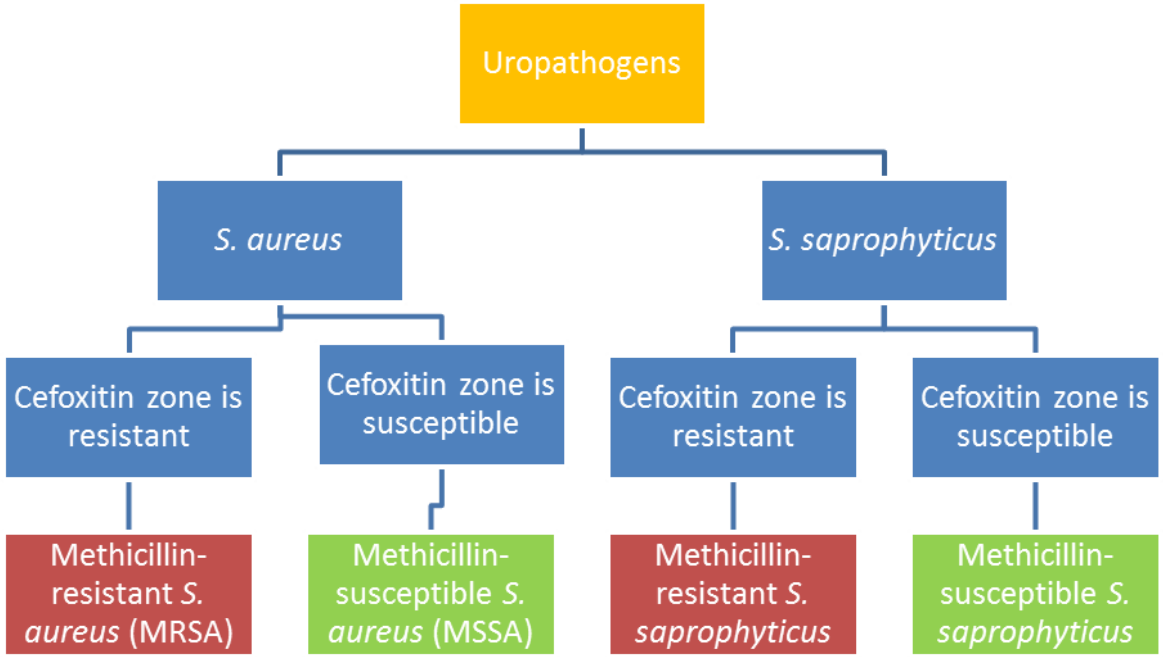
12.11. Appendix 11: Uropathogen Phenotype Algorithm

ESBL Decision Tree



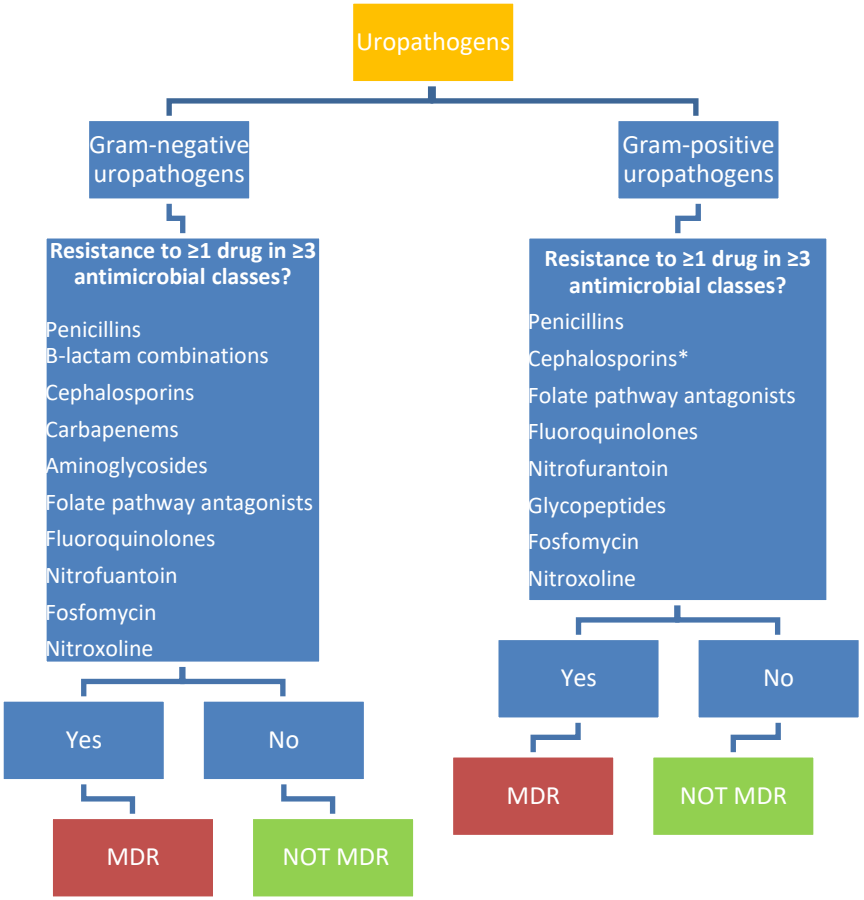
Note: ESBL not determined for other Gram-negative organisms.

Methicillin* Decision Tree



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

Multi-drug Resistance (MDR) Decision Tree



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

Antimicrobial Resistant Phenotypes

Antimicrobial class	Antimicrobial	Drug relevant to Gram-negatives	Drug relevant to Gram-positives	Resistant phenotype to be reported if interpretation is resistant*
Penicillin	Ampicillin	X	X	AMP-R
	Mecillinam	X		MEC-R
	Penicillin		X	PEN-R
B-lactam combination	Amoxicillin/clavulanic acid	X		AUG2-R
	Ceftolozane/tazobactam	X		C/T-R
	Ceftazidime/avibactam	X		CZA-R
	Piperacillin/tazobactam	X		P/T4-R
Cephalosporin	Cefazolin	X		FAZ-R
	Ceftriaxone	X		AXO-R
	Cefadroxil	X		CFR-R
	Cefoxitin**		X	See methicillin resistance tree
Carbapenem	Meropenem	X		MERO-R
Aminoglycoside	Amikacin	X		AMI-R
	Gentamicin	X		GEN-R

Antimicrobial class	Antimicrobial	Drug relevant to Gram-negatives	Drug relevant to Gram-positives	Resistant phenotype to be reported if interpretation is resistant*
Folate Pathway Antagonist	Trimethoprim-sulfamethoxazole	X	X	SXT-R
	Trimethoprim	X	X	TMP-R
	Sulfisoxazole	X	X	SFX-R
Fluoroquinolone	Ciprofloxacin	X	X	CIP-R
	Levofloxacin	X	X	LEV-R
Nitrofuran	Nitrofurantoin	X	X	NIT-R
Glycopeptide	Vancomycin		X	VAN-R
Fosfomycin	Fosfomycin	X	X	FOF-R
Nitroxoline	Nitroxoline	X	X	NOX-R

*resistant phenotype based on CLSI M100 interpretations with the exception of nitroxoline and cefadroxil which are based on EUCAST interpretations

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

R=resistant

12.12. Appendix 12: Uropathogen Genotype Algorithm

Gepotidacin Study 204989 – Genotype Analysis

Genotype Description	Details	When Performed	Example Reporting Values
Whole Genome Sequencing			
Screen for beta-lactamase genes	1. Beta-lactamase screening 2. Extended-spectrum beta-lactamases (ESBL) 3. Original-spectrum beta-lactamases 4. Plasmid-mediated AmpC beta-lactamases 5. Extended spectrum AmpC 6. carbapenemases 7. uncategorized spectrum beta-lactamase 8. Chromosomal AmpC	Enterobacterales isolates (except *P. mirabilis*) with MIC results of ≥2 µg/mL for ceftriaxone and/or ceftazidime and/or cefotaxime, and/or aztreonam *P. mirabilis* with MIC results of ≥2 µg/mL for cefpodoxime and/or ceftazidime and/or cefotaxime Enterobacterales isolates with MIC results of ≥2 µg/mL for meropenem	1. pos/neg 2. CTX-M-15* 3. TEM-1* 4. CMY-2* 5. EC-6* 6. KPC-3* 7. SHV-35* 8. PDC-30*
Screen for plasmid-mediated fluoroquinolone resistance (FQ-R) genes	• Genes from the *gnr* family 1. FQ screening 2. Aminoglycosides	• Isolates resistant to FQs (levofloxacin or ciprofloxacin) • *E. coli* isolates with gepotidacin MICs ≥8 mcg/mL	1. pos/neg 2. aac(6')-Ib-cr, gnrB, oqxA*
Screen for gene mutations of the quinolone (FQ) resistant determining region (QRDR)	• Mutations in the FQ binding region GyrA	• Isolates resistant to FQs (levofloxacin or ciprofloxacin) • *E. coli* isolates with gepotidacin MICs ≥8 mcg/mL	"wildtype" or S81F, delS81F, S81Fins
	• Mutations in the FQ binding region GyrB		"wildtype" or G425E, delG425, G425ins
	• Mutations in the FQ binding region grlA		"wildtype" or S80F, delS80, S80ins
	• Mutations in the FQ binding region grlB		"wildtype" or D432N, delD432, D432ins
	• Mutations in the FQ binding region parC		"wildtype" or S79F, dels79, S79ins

Genotype Description	Details	When Performed	Example Reporting Values
	• Mutations in the FQ binding region parE		"wildtype" or V90A, delV90, V90ins
MLST (multi-locus sequence typing)	• 7 housekeeping genes sequenced	Enterobacterales isolates (except *P. mirabilis*) with MIC results of ≥2 µg/mL for ceftriaxone and/or ceftazidime and/or cefotaxime, and/or aztreonam *P. mirabilis* with MIC results of ≥2 µg/mL for cefpodoxime and/or ceftazidime and/or cefotaxime Enterobacterales isolates with MIC results of ≥2 µg/mL for meropenem *E. coli* isolates with gepotidacin MICs ≥8 mcg/mL	ST131*
O:H serotyping	• Typing of the lipopolysaccharide (LPS) (O antigen) and the flagellar (H) antigens of *E. coli*	*E. coli* isolates with MIC results of ≥2 µg/mL for ceftriaxone and/or ceftazidime and/or cefotaxime, and/or aztreonam *E. coli* isolates with MIC results of ≥2 µg/mL for meropenem	O157:H7*
fimH typing	• *fimH* is a bacterial cell surface component that facilitates adhesion to other cells	*E. coli* isolates designated as MLST131	*fimH*27*
Clonal assessment of microbiological failures (by MLST or PFGE)	• See MLST description above • PFGE (pulse field gel electrophoresis): assessment of isolate genetic relatedness (*performed only if MLST typing is unavailable*) 1. PFGE_type	• all isolates from patients who were a microbiological failure	• MLST: same as above • PFGE: allowed values: 1. alpha/numeric (eg, "A1") 2. allowed values: any percentage (eg, 99.5%)

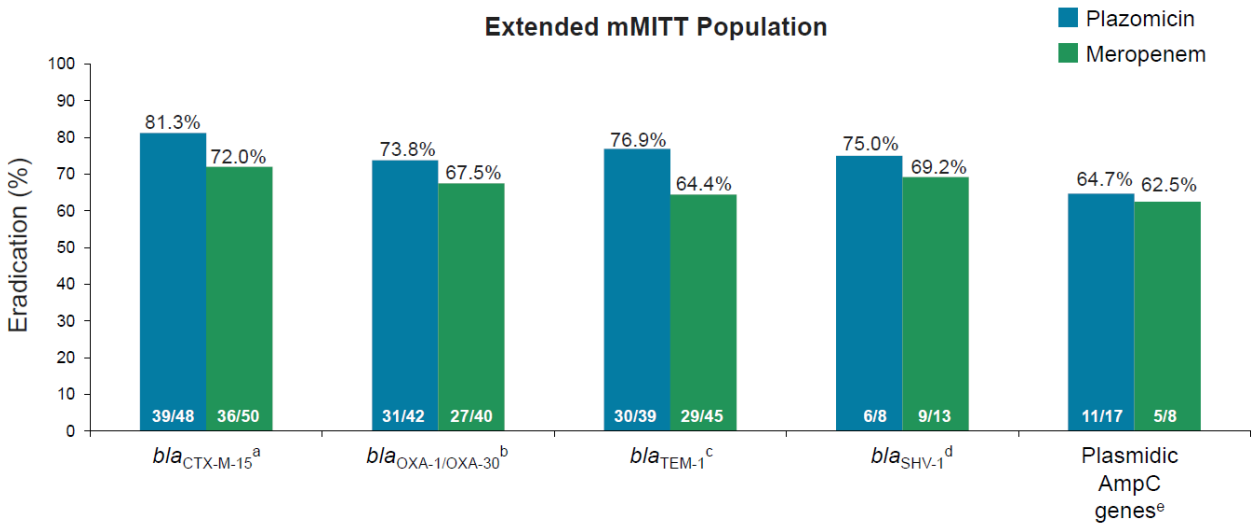
Genotype Description	Details	When Performed	Example Reporting Values
	2. PFGE_similarity 3. PFGE_interpretation		3. allowed values: baseline, identical to baseline, related to baseline, or unrelated to baseline
Expression Analysis			
Expression of AmpC (chromosomally encoded)	• gene expression from clinical isolates will be compared to expression from reference strains 1. AmpC expression value 2. AmpC expression interpretation	• For the following isolates in which no beta-lactamases were detected • Enterobacterales isolates (except *P. mirabilis*) with MIC results of ≥2 µg/mL for ceftriaxone and/or ceftazidime and/or cefotaxime, and/or aztreonam • *P. mirabilis* with MIC results of ≥2 µg/mL for cefpodoxime and/or ceftazidime and/or cefotaxime • Enterobacterales isolates with MIC results of ≥2 µg/mL for meropenem	1. numeric RQ value (eg 0.845766776)* 2. allowed values: a. similar to baseline (0 to <5) b. moderate expression (5 to <10) c. overexpression (>/=10)
Expression of AcrAB (efflux pump)	• same as for AmpC	• FQ-resistant *E. coli* isolates for which no QRDR or plasmid mutations were detected • *E. coli* isolates with gepotidacin MICs ≥8 mcg/mL	• same as for AmpC

*Numerous results are possible for these test codes.

Example outputs from published studies:

Microbiological Eradication at TOC by β-Lactamase Genotype of Uropathogens

High rates of eradication were achieved across pathogens with β-lactamase genes



[a]Includes *bla*$_{CTX-M-15}$-like.
[b]Includes *bla*$_{OXA-1/OXA-30}$-like.
[c]Includes *bla*$_{TEM}$-like.
[d]Includes *bla*$_{SHV-1}$-like.
[e]Includes all variants of *bla*$_{ACT}$, *bla*$_{CMY}$ and *bla*$_{DHA}$.

14

Table 1. Per-Pathogen Microbiological Eradication at TOC[a] by Resistance Phenotype and Resistance Mechanism (Extended mMITT Population)

Pathogen	PLZ (N = 202) n/N1 (%)	MEM (N = 205) n/N1 (%)	Difference PLZ Minus MEM (95% CI)
Overall	191/215 (88.8)	164/222 (73.9)	15.0 (7.4 to 22.4)
Enterobacteriaceae	189/213 (88.7)	161/217 (74.2)	14.5 (6.9 to 22.0)
AG-NS phenotype[b]	46/60 (76.7)	37/58 (63.8)	12.9 (-4.8 to 29.6)
ESBL phenotype[c]	47/59 (79.7)	47/67 (70.1)	9.5 (-6.9 to 25.0)
AME-gene positive[d]	51/67 (76.1)	49/75 (65.3)	10.8 (-5.3 to 25.9)
aac(6`)Ib-cr	29/38 (76.3)	29/41 (70.7)	5.6 (-15.5 to 25.8)
aac(3)-IIa	18/25 (72.0)	21/31 (67.7)	4.3 (-22.0 to 28.7)
β-Lactamase-gene positive[d]	62/80 (77.5)	53/81 (65.4)	12.1 (-2.8 to 26.2)
$bla_{CTX\text{-}M\text{-}15}$	39/48 (81.3)	36/50 (72.0)	9.3 (-9.0 to 26.7)
$bla_{OXA\text{-}1/OXA\text{-}30}$	31/42 (73.8)	27/40 (67.5)	6.3 (-14.7 to 26.8)

[a]Microbiological eradication defined as a reduction in baseline pathogen from $\geq 10^5$ CFU to $<10^4$ CFU in urine culture.
[b]AG-NS defined as nonsusceptible interpretation (intermediate or resistant) to any of amikacin, gentamicin, or tobramycin based on central laboratory MIC testing and Clinical and Laboratory Standards Institute 2016 breakpoints.
[c]ESBL phenotype defined as MIC ≥2 µg/mL to any of ceftazidime, aztreonam, or ceftriaxone based on central laboratory testing.
[d]All isolates with AG-NS and ESBL phenotypes were sequenced for both AME and ESBL genes.
N, number of patients in the specified population; N1, number of uropathogens in the specified category at baseline; n, number of uropathogens eradicated in the specified category.
CFU, colony forming units; CI, confidence interval; ESBL, extended-spectrum β-lactamase; MIC, minimum inhibitory concentration; $MIC_{50/90}$, minimum inhibitory concentration required to inhibit the growth of 50%/90% of organisms; mMITT, microbiological modified intent-to-treat; NS, nonsusceptible; TOC, test of cure.

<u>Note:</u> Uropathogen genotypic subcategories may be reported individually (e.g. *bla*$_{CTX\text{-}M\text{-}15}$) or grouped together (e.g. ESBL-gene positive) for reporting, dependent on numbers recovered and epidemiological significance. See examples above. The potential individual and group categories will be monitored in stream during the study and provided by the GSK microbiology team.

12.13. Appendix 13: Uropathogen Grouping and Order Example

The following uropathogen grouping and display order examples are for information only. The lists will be updated at the appropriate study milestones, and will be finalized for use prior to unblinding of the database.

12.13.1. Uropathogen Grouping and Gram Positive/Negative Example

Uropathogens	Display Group	GRAMPNO
Acinetobacter baumanni	Gram-negative non-fermenters	Negative
Aerococcus urinae	NA (non regulatory approved uropathogen)	Positive
Alcaligenes faecalis	Other Enterobacterales	Negative
Citrobacter amalonaticus	Other Enterobacterales	Negative
Citrobacter freundii	Other Enterobacterales	Negative
Citrobacter koseri	Other Enterobacterales	Negative
Enterobacter aerogenes	Other Enterobacterales	Negative
Enterobacter cloacae	Other Enterobacterales	Negative
Enterobacter cloacae complex	*Enterobacter cloacae* complex	Negative
Enterococcus faecalis	*Enterococcus faecalis*	Positive
Escherichia coli	*Escherichia coli*	Negative
Klebsiella aerogenes	Other *Klebsiella* spp.	Negative
Klebsiella oxytoca	Other *Klebsiella* spp.	Negative
Klebsiella pneumoniae	*Klebsiella pneumoniae*	Negative
Klebsiella variicola	Other *Klebsiella* spp.	Negative
Morganella morganii	Other Enterobacterales	Negative
Proteus mirabilis	*Proteus mirabilis*	Negative
Providencia rettgeri	Other Enterobacterales	Negative
Providencia stuartii	Other Enterobacterales	Negative
Pseudomonas aeruginosa	Gram-negative non-fermenters	Negative
Serratia marcescens	Other Enterobacterales	Negative
Staphylococcus aureus	NA (non regulatory approved uropathogen)	Positive

Staphylococcus saprophyticus	*Staphylococcus saprophyticus*	Positive
Stenotrophomona maltophilia	Gram-negative non-fermenters	Negative
Streptococcus agalactiae	NA (non regulatory approved uropathogen)	Positive

12.13.2. Qualifying Uropathogen Grouping Example

Uropathogens	Display Group
Acinetobacter baumanni	Gram-negative non fermenters
Aerococcus urinae	NA (non regulatory approved uropathogen)
Citrobacter freundii	Other Enterobacterales
Citrobacter koseri	Other Enterobacterales
Enterobacter aerogenes	Other Enterobacterales
Enterobacter cloacae	Other Enterobacterales
Enterobacter cloacae complex	*Enterobacter cloacae* complex
Enterococcus faecalis	*Enterococcus faecalis*
Escherichia coli	*Escherichia coli*
Klebsiella oxytoca	Other *Klebsiella* spp.
Klebsiella pneumoniae	*Klebsiella pneumoniae*
Klebsiella variicola	Other *Klebsiella* spp.
Morganella morganii	Other Enterobacterales
Proteus mirabilis	*Proteus mirabilis*
Providencia rettgeri	Other Enterobacterales
Staphylococcus aureus	NA (non regulatory approved uropathogen)
Staphylococcus saprophyticus	*Staphylococcus saprophyticus*
Streptococcus agalactiae	NA (non regulatory approved uropathogen)

12.13.3. Display Order Example

Display Group	Display Order
Escherichia coli	1
Proteus mirabilis	2

Klebsiella pneumoniae	3
Other *Klebsiella* spp.	4
Enterobacter cloacae complex	5
Other Enterobacterales	6
Gram-negative non-fermenters	7
Enterococcus faecalis	8
Staphylococcus saprophyticus	9
NA (non regulatory approved uropathogen)	10