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

Title	:	Reporting and Analysis Plan for A Phase IIa Single-Center, Open-Label Study Evaluating the Pharmacokinetics of Repeat Oral Doses of Gepotidacin (GSK2140944) in Adult Female Participants With Uncomplicated Urinary Tract Infection (Acute Cystitis)
Compound Number	:	GSK2140944
Effective Date	:	14-NOV-2018

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 206899.
- 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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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: 206899.

2. SUMMARY OF KEY PROTOCOL INFORMATION

This Phase IIa study is designed primarily to evaluate plasma and urine pharmacokinetics (PK) of gepotidacin in female participants with clinical signs and symptoms of acute cystitis. As this PK study will be conducted in female participants with clinical signs and symptoms of acute cystitis, exploratory clinical and microbiological efficacy of gepotidacin will also be assessed.

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• Clinical outcome will be determined by the investigator	• In addition to investigator-determined clinical outcome, a sponsor-determined clinical outcome will be programmatically derived	• To solve the potential dilemma that a participant with record missing or unable-to-determine at Test-of-Cure (TOC) visit but free of signs and symptoms of acute cystitis at Follow-up Visit will likely be determined as "clinical success" by the investigator but falls under failure per US Food and Drug Administration (FDA) guidance [DHHS, May 2018; DHHS, June 2018].
• Clinical outcome will be determined at the On-Therapy (Days 2 through 5), TOC, and Follow-up visits by comparing the signs and symptoms of acute cystitis to those present at Baseline. Clinical response (success or failure) will be determined at the TOC and Follow-Up visits	• In addition, clinical cure, a binary result of 'Yes' or 'No' will be determined at the On-Therapy (Days 2 through 5), TOC, and Follow-Up visits. Clinical cure is defined as complete resolution of signs and symptoms of acute cystitis present at Baseline, with no new signs and symptoms, and no use of other antimicrobial therapy. Clinical cure at Follow-up visit must also meet clinical cure at TOC in addition to above criteria	• To apply a clinical criterion that is consistently focusing on complete resolution of clinical signs and symptoms through On-Therapy, TOC, and Follow-Up visits.

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

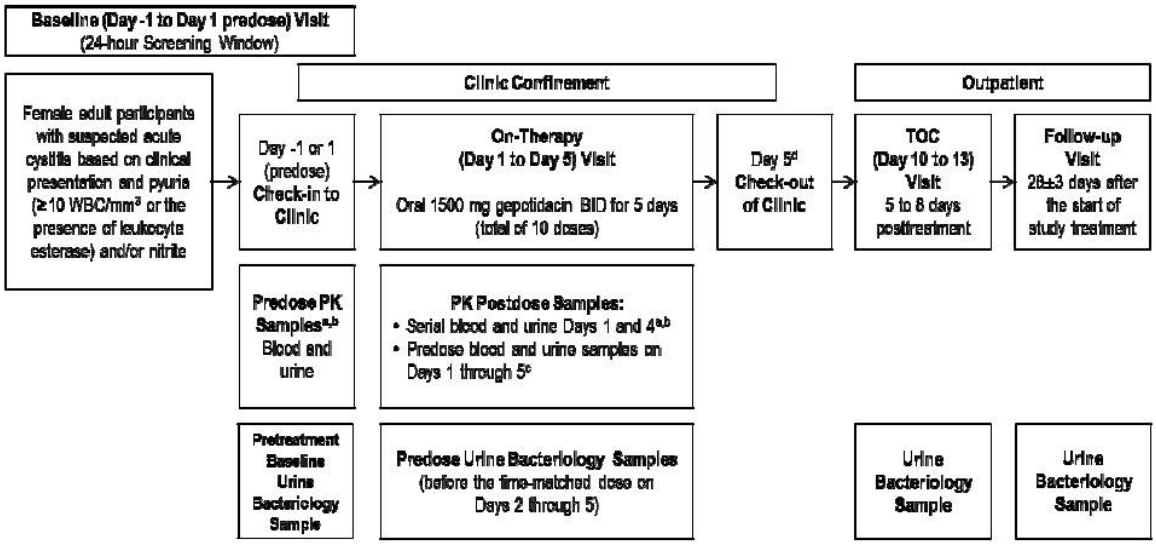
Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To determine the plasma PK parameters of gepotidacin following repeat oral doses of gepotidacin (1500 mg [2 × 750-mg tablets] twice daily [BID] for 5 days) in adult female participants with acute cystitis	• Plasma gepotidacin area under the concentration-time curve (AUC) from zero (predose) over the dosing interval (AUC[0-τ]), maximum plasma concentration (Cmax), and time of occurrence of Cmax (tmax) on Days 1 and 4 and apparent steady state clearance (CLss/F) and accumulation ratio (Ro) on Day 4 • Plasma predose concentration (Cτ) of gepotidacin on Days 1 through 5
Secondary Objectives	**Secondary Endpoints**
• To determine the urine PK parameters of gepotidacin following repeat oral doses of gepotidacin in adult female participants with acute cystitis	• Urine gepotidacin amount of drug excreted over 12 hours (Ae 12h), amount of drug excreted in urine in a time interval (Ae[t1-t2]), percentage of the given dose of drug excreted in urine (fe%), and renal clearance (CLr) of gepotidacin on Days 1 and 4 • Urine predose concentration (Cτ) on Days 1 through 5
• To assess the safety and tolerability of repeat oral doses of gepotidacin in adult female participants with acute cystitis	• Treatment-emergent adverse events (AEs) and serious AEs (SAEs) and change from baseline results for vital sign measurements, electrocardiograms (ECGs), and clinical laboratory tests
Exploratory Objectives	**Exploratory Endpoints**
• To explore the combined clinical and microbiological efficacy of gepotidacin in adult female participants with acute cystitis who have a qualifying baseline uropathogen	• Therapeutic response (combined per-participant microbiological and clinical response) at the TOC Visit
• To assess time to eradication of uropathogens in adult female participants with acute cystitis who have a qualifying baseline uropathogen	• Microbiological outcome on Days 2 through 5; Microbiological outcome and response at the TOC and Follow-up Visits
• To explore time to resolution of signs and symptoms in adult female participants with acute cystitis	• Investigator-determined clinical outcome on Days 2 through 5, TOC, and Follow-up Visits • Sponsor-determined clinical outcome on Days 2 through 5; sponsor-determined clinical outcome and response at the TOC and Follow-up Visits
• To assess the relapse rate (microbiological and clinical) of acute cystitis after treatment with gepotidacin in adult female participants with acute cystitis at the Follow-up Visit	• Therapeutic response (combined per-participant microbiological and clinical response) at the Follow-up Visit

Objectives	Endpoints
• To explore the microbiological and antimicrobial susceptibility profile of uropathogens recovered from adult female participants with acute cystitis, including subsets of isolates resistant to other antimicrobials	• Gram stain, quantitative bacteriology culture, and in vitro antimicrobial susceptibility test results at Baseline, Days 2 through 5, TOC, and Follow-up Visits
• To explore gepotidacin plasma PK/pharmacodynamic (PD) relationships in adult female participants with acute cystitis	• Relationship between gepotidacin exposure and clinical and microbiological response, if data permit
• To explore the distribution of gepotidacin in cervical, rectal, and pharyngeal tissue (swab specimens)	• Gepotidacin concentration in cervical, rectal, and pharyngeal tissues, if data permit

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; PK=pharmacokinetic; TOC=test of cure; WBC=white blood cell.

a. Serial blood PK sampling will be performed for the first dose of study treatment on Day 1 and for the time-matched dose on Day 4. Blood samples will be collected predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours postdose.
b. Serial urine PK sampling will be performed for the first dose of study treatment on Day 1 and for the time-matched dose on Day 4. Urine samples will be collected predose and at intervals of 0 to 2 hours, 2 to 4 hours, 4 to 6 hours, 6 to 8 hours, 8 to 10 hours, and 10 to 12 hours postdose.
c. Predose PK blood samples will be collected before each time-matched dose on Days 1 through 5. Predose PK urine samples will be collected 0 to 2 hours before each time-matched dose on Days 1 through 5. Only 1 sample is needed when serial and predose samples overlap.

Participants will check-out of the clinic after all study procedures have been performed, including a predose clean-catch midstream urine sample for Gram stain, quantitative bacteriology culture, and antimicrobial susceptibility testing, predose PK sample collections, and safety assessments. Participants should remain in the clinic to complete a total of 10 doses. Participants will be instructed to return for the TOC (Day 10 to 13) and Follow-up (Day 28±3) Visits

Design Features	• A Phase IIa single-center, open-label, repeat dose PK study.
	• The study duration is approximately 28 days comprising approximately 5 days of confinement at the clinic followed by 2 outpatient visits
	  ○ Clinic Confinement Visits
	  ▪ Baseline (Day -1 to Day 1 predose) Visit
	  ▪ On-Therapy (Day 1 to Day 5) Visit
	  ○ Outpatient Visits
	  ▪ TOC (Day 10 to 13) Visit
	  ▪ Follow-up (Day 28) Visit
	• Approximately 25 to 30 participants will be enrolled to achieve approximately 20 participants who complete the study assessments through Day 5 and are evaluable for the PK analyses.

Dosing	• All participants who meet the study entry criteria and provide informed consent will receive oral gepotidacin 1500 mg (2 × 750-mg tablets) BID for 5 days (total of 10 doses).
Time & Events	• Refer to Appendix 1: Schedule of Activities
Treatment Assignment	• This is a nonrandomized, open-label study. Clinic personnel will enroll the participant into the study once a participant has met all eligibility requirements.
Interim Analysis	• No interim analyses are planned for this study.

2.4. Statistical Hypotheses

A formal hypothesis will not be tested; however, an estimation approach will be taken to characterize the PK of gepotidacin in female participants with uncomplicated urinary tract infection (UTI).

3. PLANNED ANALYSES

3.1. 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 Follow-up Visit.
2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Safety	• All participants who take at least 1 dose of gepotidacin.	• Study Population • Safety
PK	• All participants in the Safety Population and have evaluable plasma, urine, or tissue concentration data for gepotidacin. A subject is considered to have evaluable PK data for gepotidacin if the subject has at least 1 measurable post-dose PK concentration value for gepotidacin that was not excluded from the analysis due to a protocol deviation. This primary analysis population will be used in the assessment and characterization of PK concentrations (summary tables, listings, and figures)	• PK Concentration
PK Parameter	• All participants in the PK Population who receive gepotidacin 1500 mg BID through the completion of all PK collections for whom valid and evaluable plasma or urine PK parameters are derived for gepotidacin. This primary analysis population will be used in the assessment and characterization of PK parameters (summary and analysis tables, listings, and figures)	• PK Parameter
Intent-To-Treat (ITT)	• All participants that met all eligibilities and were assigned to study treatment	• Study Population
Microbiological ITT (micro-ITT)	• All participants in the ITT Population, receive at least 1 dose of gepotidacin, and have a qualifying baseline uropathogen from a quantitative bacteriological culture of a pretreatment clean catch midstream urine specimen. • The algorithm of the qualifying bacterial uropathogen is presented in Appendix 4: Derived and Transformed Data, Figure 2 .	• Efficacy
PKPD	• All participants in both the PK Parameter Population and the Micro-ITT Population	• PKPD

Refer to Appendix 9: List of Data Displays.

4.1. Protocol Deviations

Significant protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised 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.

- Data will be reviewed prior to freezing the database to ensure all significant deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.

- This dataset will be the basis for the summaries and listings of 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 electronic case report form (eCRF).

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Only one treatment, oral gepotidacin 1500 mg BID will be administered in this study as the study treatment.

5.2. Baseline Definitions

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

Parameter	Study Assessments Considered as Baseline		Baseline Used in Data Display
	Day -1	Day 1 (Predose)	
Efficacy			
Acute Cystitis Signs and Symptoms	X		Day -1
Gram Stain		X	Day 1 (Predose)
Quantitative Bacteriology Culture		X	Day 1 (Predose)
In Vitro Antimicrobial Susceptibility Test		X	Day 1 (Predose)
Safety			
12-lead Electrocardiogram (ECG)	X	X	Day 1 (Predose)[1]
Vital Sign	X	X	Day 1 (Predose)[1]
Hematology	X		Day -1
Clinical Chemistry	X		Day -1
Urinalysis	X		Day -1

1. Vital sign and ECG assessments at predose on Day 1 will be only performed if the Day -1 assessment is not within 4 hours of the first dose of study treatment. If the Day 1 predose assessments are not performed, Day -1 assessments will be used as baseline in data display. Average of the triplicate ECG assessment at Day -1 will be used as the baseline if Day 1 predose assessment is not performed as described in Appendix 4: Derived and Transformed Data.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

5.3. 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
12.1	Appendix 1: Schedule of Activities
12.2	Appendix 2: Study Phases and Treatment Emergent Adverse Events
12.3	Appendix 3: Data Display Standards & Handling Conventions
12.4	Appendix 4: Derived and Transformed Data
12.5	Appendix 5: Reporting Standards for Missing Data
12.6	Appendix 6: Values of Potential Clinical Importance
12.7	Appendix 7: Division of Microbiology and Infectious Disease Adult Toxicity Tables for Adverse Event Assessment
12.8	Appendix 8: Abbreviations & Trade Marks
12.9	Appendix 9: List of Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the "ITT" population, unless otherwise specified.

Study population analyses including analyses of subject's 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 uropathogen recovery rate (including drug-resistant uropathogens), baseline clinical symptom score, current medication conditions, and exposure data will be summarized. History of uncomplicated urinary tract infection will be listed.

The details of data displays are presented in Appendix 9: List of Data Displays.

7. PHARMACOKINETIC ANALYSES

7.1. Primary Pharmacokinetic Analyses

7.1.1. Endpoint / Variables

7.1.1.1. Drug Concentration Measures

Refer to Appendix 3: Data Display Standards & Handling Conventions (Section 12.3.3 Reporting Standards for Pharmacokinetic). Only total gepotidacin plasma PK concentrations will be measured and reported in the bioanalytical data. Therefore, unbound plasma PK concentrations will be derived by multiplying the total plasma PK concentrations by 0.67, to correct for the low plasma protein binding of gepotidacin (33%) observed in previous studies.

7.1.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of Phoenix WinNonlin version 6.4 or higher. All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from the plasma and urine concentration-time data, as data permits. Table 2 provides the details of derived plasma PK parameters.

Table 2 Derived Plasma Pharmacokinetic Parameters

Parameter	Parameter Description
AUC(0-τ)	Area under the concentration-time curve (AUC) from time 0 to the 12-hour dosing interval, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid. Calculated from Days 1 and 4.
AUC(0-24)	Area under the concentration-time curve (AUC) from time 0 to the 24-hour, calculated as: $AUC(0\text{-}24) = AUC(0\text{-}\tau) \times 2$ Calculated for Day 4.
Cmax	Maximum observed concentration, determined directly from the concentration-time data. Calculated from Days 1 and 4.
Tmax	Time to first occurrence of Cmax. Calculated from Days 1 and 4.
CLss/F	Apparent steady state clearance (Day 4 only), calculated as $CLss/F = Dose/AUC(0\text{-}\tau)$
Ro	Accumulation ratio (Day 4 only), calculated as: $Ro = AUC(0\text{-}\tau)$ Day 4/$AUC(0\text{-}\tau)$ Day 1
Cτ	Observed predose (nominal time = 0) concentrations on Days 1 through 5

NOTES:

- Additional parameters may be included as required.

7.1.2. Summary Measure

Summary statistics (arithmetic mean, geometric mean, median, standard deviation (SD), minimum, maximum, and coefficient of variation [CV]) for plasma gepotidacin PK parameter values will be summarized by study day, as appropriate. The Cτ will be summarized and used to assess achievement of steady state. Gepotidacin plasma PK parameter estimates will be listed by participant and study day.

7.1.3. Population of Interest

The primary pharmacokinetic analyses will be based on the Pharmacokinetic population and Pharmacokinetic Parameter population, unless otherwise specified.

7.1.4. Statistical Analysis / Methods

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

Unless otherwise specified, endpoints / variables defined in Section 7.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.1.4.1. Statistical analysis of Pharmacokinetic Parameters

All the derived parameters described in Table 2 will be listed. For each of these parameters, except Tmax, the following summary statistics will be calculated for each active treatment group: median, maximum, minimum, arithmetic mean, SD, CV on arithmetic mean, geometric mean, CV on geometric mean, 95% confidence interval (CI) for the geometric mean, and SD of logarithmically transformed data. For tmax, tmin, and tlag, median, maximum, minimum, arithmetic mean, and SD will be calculated.

The following pharmacokinetic statistical analyses will only be performed if sufficient data is available (i.e. if participants have well defined plasma profiles).

Endpoint / Variables
• Plasma primary PK endpoints include predose concentrations (Cτ) Day 1 through Day 5
Model Specification
• To assess the achievement of steady state, Cτ concentrations between Days 1 through 5 for each treatment. A linear mixed model using Day as fixed effects and subject as a random effect on the ln-transformed pre-dose values will be performed evaluating whether steady state was achieved using Helmert transformation approach. The comparison will begin with Day 1 vs the average of Days 2, 3, 4 and 5. The ratio of geometric least square means and its 95% CI will be presented for the comparison(s).
Model Results Presentation
• Statistical analysis of steady state will be analyzed using Helmert transformation approach.

7.2. Secondary Pharmacokinetic Analyses

7.2.1. Endpoint / Variables

7.2.1.1. Drug Concentration Measures

Refer to Appendix 3: Data Display Standards & Handling Conventions (Section 12.3.3 Reporting Standards for Pharmacokinetic).

7.2.1.2. Derived Urine Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of SAS version 9.3. All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from the urine concentration-time data, as data permits.

Table 3 Derived Urine Pharmacokinetic Parameters

Parameter	Parameter Description
Ae 12h	Total unchanged drug excreted over 12 hours (total amount of drug excreted in urine), calculated by adding all the fractions of drug collected over all the allotted time intervals. Calculated from Days 1 and 4.
Ae(t1-t2)	Amount of drug excreted in urine in time intervals for predose, 0 to 2 hours, 2 to 4 hours, 4 to 6 hours, 6 to 8 hours, 8 to 10, and 10 to 12 hours postdose. Calculated from Days 1 and 4.
AUC(0-τ)	Area under the urine concentration-time curve (AUC) from time 0 to the 12-hour dosing interval, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid. Calculated from Days 1 and 4.
AUC(0-24)	Area under the urine concentration-time curve (AUC) from time 0 to the 24-hour, calculated as: $AUC(0\text{-}24) = AUC(0\text{-}\tau) \times 2$ Calculated Day 4.
fe%	Percentage of the given dose of drug excreted in urine, calculated as: fe% = (Ae 12h/Dose) × 100 Calculated for Days 1 and 4
CLr	Renal clearance of drug, calculated as: $CLr = Ae\ 12h/AUC(0\text{-}\tau)$ Calculated from Days 1 and 4.
Cτ	Observed predose (nominal time = 0) urine concentrations on Days 1 through 5.

NOTES:

- Additional parameters may be included as required.

7.2.2. Summary Measure

Summary statistics (arithmetic mean, geometric mean, median, SD, minimum, maximum, and CV) for urine gepotidacin PK parameter values will be summarized by study day, as appropriate. Gepotidacin urine PK parameter estimates will be listed by participant and study day.

7.2.3. Population of Interest

The secondary PK analyses will be based on the Pharmacokinetic population and Pharmacokinetic Parameter population, unless otherwise specified.

7.2.4. Statistical Analyses / Methods

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

Unless otherwise specified, endpoints / variables defined in Section 7.2.1 will be summarised using descriptive statistics and listed.

7.3. Exploratory Pharmacokinetic Analyses

7.3.1. Endpoint / Variables

7.3.1.1. Drug Concentration Measures

Refer to Appendix 3: Data Display Standards & Handling Conventions (Section 12.3.3 Reporting Standards for Pharmacokinetic).

7.3.1.2. Derived Pharmacokinetic Parameters

Cervical, rectal, and pharyngeal swab specimens for PK analysis of gepotidacin will be obtained Day 4 at predose and at approximately 2 hours postdose. The actual date and time of each sample collection will be recorded. Participation is optional. Participants who do not wish to participate in the tissue PK assessments may still participate in the study. Specific details to ensure a similar physical site of the pharynx is used for swab collection are provided in the Study Reference Manual (SRM) and/or laboratory manual. Collection, processing, storage, and shipping procedures for cervical, rectal, and pharyngeal swab specimens are provided in the SRM and/or laboratory manual.

Summary statistics (arithmetic mean, geometric mean, median, SD, minimum, maximum, and CV) for cervical, rectal, and pharyngeal gepotidacin PK concentration values will be summarized by collection time point, as appropriate. Gepotidacin cervical, rectal, and pharyngeal concentration estimates will be listed by participant and collection time point.

8. SAFETY ANALYSES

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

8.1. Adverse Events Analyses

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 system organ class (SOC) and preferred term (PT) will be listed. Summary tables will be provided for AEs and drug-related AEs by SOC, PT, and maximum grade. Number of subjects and occurrences with common non-serious AEs will be provided in a summary table by SOC.

In summary tables where are presented by SOC, PT, and maximum 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.

The details of data displays are presented in Appendix 9: List of Data Displays.

8.2. 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.

Summaries of change from baseline values for clinical chemistry and hematology tests will be provided in separate tables. Shift tables for clinical chemistry and hematology results with toxicity grades 2 to 4 will be provided. Urinalysis dipstick results will be summarized using categorical statistics. Clinical chemistry, hematology, and urinalysis test results with toxicity grade 2 or higher will be listed in separate listings.

The details of data displays are presented in Appendix 9: List of Data Displays.

8.3. Other Safety Analyses

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

Summary tables will be provided for ECG findings, ECGs change from baseline values, maximum post-baseline QTc values relative to baseline values, and maximum increase in post-baseline QTc values relative to baseline values, vital signs change from baseline values, and worst post-baseline vital signs results relative to baseline results.

Listings will be provided for abnormal ECG findings, ECG values of potential clinical importance, vital sign values of potential clinical importance, liver events, and clostridium difficile results.

The details of data displays are presented in Appendix 9: List of Data Displays.

9. EFFICACY ANALYSES

9.1. Exploratory Efficacy Analyses

The details of data displays being presented in Appendix 9: List of Data Displays.

9.1.1. Endpoint / Variables

- Therapeutic response (combined per-participant microbiological and clinical response) at the TOC Visit
- Microbiological outcome on Days 2 through 5
- Microbiological outcome and response at the TOC and Follow-up Visits
- Sponsor-determined clinical outcome on Days 2 through 5
- Sponsor-determined clinical outcome and response at the TOC and Follow-up Visits
- Investigator-determined clinical outcome on Days 2 through 5 and at the TOC and Follow-up Visits
- Therapeutic response (combined per-participant microbiological and clinical response) at the Follow-up Visit
- Gram stain results at Baseline, Days 2 through 5, TOC, and Follow-up Visits
- Quantitative bacteriology culture results at Baseline, Days 2 through 5, TOC, and Follow-up Visits
- In vitro antimicrobial susceptibility test results at Baseline, Days 2 through 5, TOC, and Follow-up Visits

9.1.1.1. Microbiological Outcome and Response

- The microbiological outcome and response to study treatment will be determined by prespecified programmed algorithm for each participant/qualifying uropathogen.
- The microbiological outcome is determined by comparing the baseline culture results to the culture results at each subsequent visit. The corresponding microbiological response “by qualifying uropathogen” is then assigned. The criteria of microbiological outcome and response are shown in Table 4, Table 5, and Table 6.
- Participant level microbiological success refers to participants who have been deemed a “microbiological success” for all their “qualifying baseline uropathogen” microbiological responses.
- All other combinations are deemed failures for participant level microbiological response.
- Participants who withdraw from the study prior to TOC or Follow-Up Visits will be considered not achieving success as the microbiological response. Microbiological outcome will be derived and listed at early termination visit.
- Microbiological outcome and response along with the 95% Clopper-Pearson CI for the percentage of microbiological response will be summarized for qualifying uropathogens isolated at baseline using the groups listed below at the On-therapy, TOC, and Follow-up visits using counts and percentages. Participant level microbiological response and 95% Clopper-Pearson CI will be summarized within the same table. The necessity of these categories will depend on the uropathogens that are recovered. Any additional uropathogens present in 10 or more participants will be

summarized separately. Additional uropathogens present in less than 10 participants will be grouped into the combined categories (eg, other beta-hemolytic streptococci).
    - *Escherichia coli*
        - Quinolone-resistant *E. coli*
        - Extended spectrum beta-lactamase (ESBL) producing *E. coli*
        - Multidrug-resistant (MDR) *E. coli*
    - Other gram-negative bacilli
    - *Staphylococcus aureus*
    - *Staphylococcus saprophyticus*
    - Coagulase-negative staphylococci
    - Beta-hemolytic streptococci
    - Viridans streptococci
    - *Enterococcus* spp.
    - *Gardnerella vaginalis*
    - *Aerococcus urinae*
    - Other Gram-positive uropathogens
- A participant will be counted multiple times under an uropathogen category if multiple qualifying uropathogens within that uropathogen category are isolated at baseline for the participant.
- Urine quantitative bacteriology culture results will be summarized and plotted by visit and qualifying uropathogens isolated at baseline

Table 4 Microbiological Outcome by Qualifying Uropathogen at the On-Therapy Visit

Defining Criteria	Outcome
• Any participant that receives administration of an alternative or additional antibacterial therapy during the On-Therapy visit will be assigned a microbiological outcome of "unable to determine" from that day onward.	
• A quantitative urine culture taken during the On-Therapy Visit (Days 2 through 5 only) shows that the qualifying bacterial uropathogen recovered at Baseline is reduced to $<10^3$ CFU/mL	• Microbiological eradication
• A quantitative urine culture taken during the On-Therapy Visit (Days 2 through 5 only) shows that the qualifying bacterial uropathogen recovered at Baseline grows $\geq 10^3$ CFU/mL	• Microbiological persistence
• A determination of the baseline qualifying bacterial uropathogen microbiological outcome cannot be made (e.g., no urine culture taken, sample lost, etc.)	• Unable to determine
• A new qualifying bacterial uropathogen, not identified at Baseline, is documented by quantitative urine culture during the On-Therapy Visit (Days 2 through 5 only) in a participant who is a sponsor-determined clinical failure or unable to determine	• Superinfection

Defining Criteria	Outcome
• A new qualifying bacterial uropathogen, not identified at Baseline, is documented by quantitative urine culture at the On-Therapy Visit (Days 2 through 5 only) in a participant who is a sponsor-determined clinical success	• Colonization

CFU=colony-forming units

Table 5 Microbiological Outcome and Response by Qualifying Uropathogen at the Test-of-Cure Visit

Defining Criteria	Outcome	Response
• Any participant that receives administration of an alternative or additional antibacterial therapy before the TOC Visit will be assigned a microbiological outcome of "unable to determine" and a response of "microbiological failure". • Participants considered microbiological failures at the TOC Visit will also be considered microbiological failures at the Follow-up Visit.		
• A quantitative urine culture taken at the TOC Visit shows reduction of the qualifying bacterial uropathogen recovered at Baseline to $<10^3$ CFU/mL	• Microbiological eradication	• Microbiological success
• A quantitative urine culture taken at the TOC Visit shows that the qualifying bacterial uropathogen recovered at Baseline, and which was also shown to persist at the On-Therapy Visit, grows $\geq 10^3$ CFU/mL	• Microbiological persistence	• Microbiological failure
• A quantitative urine culture taken at the TOC Visit shows that the qualifying bacterial uropathogen recovered at Baseline, and which was also shown to be eradicated at the On-Therapy Visit, grows $\geq 10^3$ CFU/mL	• Microbiological recurrence	• Microbiological failure
• A determination of the baseline qualifying bacterial uropathogen microbiological response cannot be made (e.g., no urine culture taken, sample lost, etc.)	• Unable to determine	• Microbiological failure
• A new qualifying bacterial uropathogen, not identified at Baseline, is documented by quantitative urine culture at the TOC Visit in a participant who is a sponsor-determined clinical failure	• New infection	• Microbiological failure
• A new qualifying bacterial uropathogen, not identified at Baseline, is documented by quantitative urine culture at the TOC Visit in a participant who is a sponsor-determined clinical success	• Colonization	• Microbiological success

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

Table 6 Microbiological Outcome and Response by Qualifying Uropathogen at the Follow-Up Visit

Defining Criteria	Outcome	Response
• Any participant that receives administration of an alternative or additional antibacterial therapy before the Follow-up Visit will be assigned a microbiological outcome of "unable to determine" and a response of "microbiological failure". • Participants considered microbiological failures at the TOC Visit will also be considered microbiological failures at the Follow-up Visit.		
• A quantitative urine culture taken at the Follow-up Visit shows reduction of the qualifying bacterial uropathogen recovered at Baseline to $<10^3$ CFU/mL	• Sustained microbiological eradication	• Microbiological success
• A quantitative urine culture taken at the Follow-up Visit shows that the qualifying bacterial uropathogen recovered at Baseline grows $\geq 10^3$ CFU/mL	• Microbiological recurrence	• Microbiological failure
• A determination of the baseline qualifying bacterial uropathogen microbiological response cannot be made (e.g., no urine culture taken, sample lost, etc.)	• Unable to determine	• Microbiological failure
• A new qualifying bacterial uropathogen, not identified at Baseline, is documented by quantitative urine culture at the Follow-up Visit in a participant who is a sponsor-determined clinical failure	• New infection	• Microbiological failure
• A new qualifying bacterial uropathogen, not identified at Baseline, is documented by quantitative urine culture at the Follow-up Visit in a participant who is a sponsor-determined clinical success	• Colonization	• Microbiological success

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

9.1.1.2. Susceptibility

- Results and interpretations of susceptibility testing for all uropathogens against gepotidacin and other antimicrobials will be summarized by uropathogen, visit, and antimicrobials tested. For summaries, a participant will be counted multiple times under an uropathogen category if multiple uropathogens within that uropathogen category are isolated at baseline for the participant.
- The overall frequency distribution of minimum inhibitory concentrations (MICs) and the minimum, maximum, median (MIC_{50}), and 90^{th} percentile (MIC_{90}) MIC will be presented. Percent susceptibility (susceptible, intermediate, or resistant) will be summarized where available.
- Reduction in susceptibility to gepotidacin will be evaluated by comparing the baseline gepotidacin MIC value for uropathogens with the value obtained post-baseline. Post-baseline uropathogens of the same species and from the same participant with a confirmed $\geq$ 4-fold increase in gepotidacin MIC are considered to have developed a reduction in susceptibility to gepotidacin.

- The number and percentage of participants who demonstrate a reduction in susceptibility to GSK 2140944 will be summarized by visit and uropathogen. A participant will be counted multiple times under an uropathogen category if multiple uropathogens within that uropathogen category are isolated at baseline for the participant.

9.1.1.3. Clinical Outcome and Response

- Clinical signs and symptoms of acute cystitis will be recorded by site staff based on participant interview using the scoring system.
- The clinical signs and symptoms include at least dysuria, frequency, urgency, and lower abdominal or suprapubic pain. The clinical 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. At TOC, success is recorded as normal presentation of signs and symptoms with a total cumulative symptom score of zero and no new signs and symptoms of the infection under study.
- The investigator will determine the clinical outcome by comparing the signs and symptoms of acute cystitis at the On-Therapy (Days 2 through 5 only), TOC, and Follow-up Visits to those present at Baseline. The clinical response based on investigator-determined clinical outcome will be programmatically derived using the criteria in Table 7.
- The sponsor-determined clinical outcome and response will be programmatically determined by comparing the scores of the signs and symptoms of acute cystitis at the On-Therapy (Days 2 through 5 only), TOC, and Follow-up Visits to those present at Baseline as shown in Table 7.
- Participants who withdraw from the study prior to TOC or Follow-Up Visits will be considered not achieving success as the clinical response at TOC or Follow-Up Visits. The investigator- and sponsor-determined clinical response and outcome at Early Termination visit will only be listed.
- Clinical response (success or failure) will be determined at TOC or Follow-Up visits for each participant. A “success” clinical response is defined as if the clinical outcome for all qualifying uropathogens is “clinical success” for the visit, otherwise a “failure” clinical response will be assigned.
- Clinical cure is defined in Table 8 and will be programmatically derived at the On Therapy (Days 2 through 5), TOC, and Follow-up Visits. If a participant does not meet clinical cure at TOC visit, the participant will not be considered as clinical cure at Follow-up visit.
- The investigator- and sponsor-determined clinical outcome and response will be summarized for qualifying uropathogens isolated at baseline at the On-therapy, TOC, and Follow-up visits using counts and percentages. A participant will be counted multiple times under an uropathogen category if multiple qualifying uropathogens within that uropathogen category are isolated at baseline for the participant. In addition, participant level of clinical outcome will be summarized in the same table. The 95% Clopper-Pearson CI will be presented for the proportion clinical response at each visit.

- Clinical cure will be summarized for qualifying uropathogens isolated at baseline at the On-therapy, TOC, and Follow-up visits using counts and percentages. A participant will be counted multiple times under an uropathogen category if multiple qualifying uropathogens within that uropathogen category are isolated at baseline for the participant. The 95% Clopper-Pearson CI will be presented for the proportion clinical cure at each visit.
- Percent of clinical cure and microbiological eradication over time will be plotted. A participant with multiple qualifying uropathogens within an uropathogen category will be counted multiple times.
- The mean clinical symptom scores and boxplots of total score over time will be overlaid within one figure for the ITT population.

Table 7 Sponsor-Determined Clinical Outcome and Response

Defining Criteria	Outcome	Response
On-Therapy visit (Days 2 through 5 only)		
• Resolution of or improvement in signs and symptoms of acute cystitis present at Baseline (and no new signs and symptoms) • Improvement is based on investigator-evaluated score and is defined as no increase of scores in each sign and symptom of acute cystitis present at Baseline and no new signs and symptoms of acute cystitis and no use of other antimicrobial therapy for the current infection	• Clinical success	• Not applicable
• Increase of scores in any of signs and symptoms of acute cystitis present at Baseline or new signs and symptoms of acute cystitis or use of other antimicrobial therapy for the current infection	• Clinical failure	• Not applicable
• Refusal to consent to a clinical examination or failure to attend the On-Therapy visit (Days 2 through 5 only)	• Unable to Determine	• Not applicable
Test-of-Cure Visit		
• Resolution of signs and symptoms of acute cystitis (total cumulative score is zero) present at Baseline (and no new signs or symptoms) and no use of other antimicrobial therapy	• Clinical success	• Success
• Persistence of signs and symptoms of infection (total cumulative score is >0), reappearance of signs and symptoms, or use of other antimicrobial therapy for the current infection	• Clinical failure	• Failure
• Refusal to consent to a clinical examination of failed to attend the TOC Visit	• Unable to determine	• Failure

Follow-up Visit		
• Resolution of signs and symptoms of acute cystitis demonstrated at the TOC Visit persist at the Follow-up Visit (total cumulative score is zero) (and no new signs and symptoms) and no use of other antimicrobial therapy	• Sustained clinical success	• Success
• Resolution of signs and symptoms of acute cystitis at the Follow-up Visit (total cumulative score is zero) and no use of other antimicrobial therapy, but lack of clinical success at the TOC Visit	• Delayed clinical success	• Failure
• Persistence of signs and symptoms of infection (total cumulative score is >0), reappearance of signs and symptoms, or use of other antimicrobial therapy for the current infection	• Clinical failure	• Failure
• Signs and symptoms of acute cystitis absent at the TOC Visit re-occur at the Follow-up Visit and no use of other antimicrobial therapy	• Clinical recurrence	• Failure
• Refusal to consent to a clinical examination or failed to attend the Follow-up Visit	• Unable to determine	• Failure

TOC=Test-of-Cure.

Table 8 Clinical Cure

Defining Criteria	Clinical Cure (Yes/No)
On-Therapy visit (Days 2 through 5 only), Test-of-Cure visit, and Follow-up visit	
• Complete resolution of signs and symptoms of acute cystitis present at Baseline, with no new signs and symptoms, and no use of other antimicrobial therapy. Clinical Cure at Follow-up must also meet Clinical Cure at Test-of-Cure in addition to above criteria.	• Yes

9.1.1.4. Therapeutic Response

- A measure of overall efficacy response, success, or failure.
- A therapeutic success refers to participants who have been deemed both a 'microbiological success' (refer to 'Microbiological Outcome and Response') and a 'clinical success' (i.e., 'responders')
- All other combinations will be deemed failures for therapeutic response.
- Programmatically derived for TOC and Follow-up Visits
- Number of participants achieving therapeutic success at the TOC and Follow-up visits along with the 95% Clopper-Pearson CI will be summarized by per-participant microbiological response and clinical response by qualifying uropathogens isolated at baseline. A participant will be counted multiple times under an uropathogen category if multiple qualifying uropathogens within that uropathogen category are isolated at baseline for the participant.
- Percent of clinical success and microbiological eradication over time will be plotted.

9.1.2. Summary Measure

This study only has one treatment group; thus, treatment comparison is not applicable.

9.1.3. Population of Interest

The exploratory efficacy analyses will be based on the “micro-ITT” population, unless otherwise specified.

10. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

Relationships between the ratio of Day 4 free plasma and urine PK parameters to baseline MIC (free plasma AUC(0-24)/MIC, free plasma Cmax/MIC, urine AUC(0-24)/MIC and urine Ctau/MIC) and PD measures (therapeutic response) will be explored in tabular and graphical format.

Summary statistics (arithmetic mean, geometric mean, median, SD, minimum, maximum, and CV) for free plasma and urine PK parameters to baseline MIC values will be summarized by uropathogen and therapeutic response, as appropriate. Free plasma and urine PK parameters to baseline MIC values will be listed by uropathogen and therapeutic response for individual participants.

10.1. Population of Interest

The exploratory analyses will be based on the PKPD population, unless otherwise specified.

11. REFERENCES

GlaxoSmithKline Document Number 2017N317982_00 (Original 10-MAY-2018): A Phase IIa Single-Center, Open-Label Study Evaluating the Pharmacokinetics of Repeat Oral Doses of Gepotidacin (GSK2140944) in Adult Female Participants With Uncomplicated Urinary Tract Infection (Acute Cystitis).

US Department of Health and Human Services, DHHS, Food and Drug Administration, Center for Drug Evaluation and Research, Clinical/Antimicrobial. Draft guidance for industry. Uncomplicated urinary tract infections: developing drugs for treatment. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm607095.pdf. Last updated May 2018. Accessed 20-Jun-2018.

US Department of Health and Human Services, DHHS, Food and Drug Administration, Center for Drug Evaluation and Research, Clinical/Antimicrobial. Guidance for industry. Complicated urinary tract infections: developing drugs for treatment. https://www.fda.gov/downloads/Drugs/.../Guidances/ucm070981.pdf. Last updated June 2018. Accessed 20-Jun-2018.

US National Institute for Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases. Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table. Draft. https://www.niaid.nih.gov/sites/default/files/dmidadulttox.pdf. Last updated November 2007. Accessed 20-Jun-2018.

12. APPENDICES

12.1. Appendix 1: Schedule of Activities

12.1.1. Protocol Defined Schedule of Events

Table 9 Schedule of Activities

Visit	Baseline (includes a screening window of up to 24 hours before the first dose of study treatment)		On-Therapy				Test-of-Cure	Follow-up
Study Day	**-1**	**1**	**2**	**3**	**4**	**5[a]**	**10 to 13**	**28±3**
Procedure		**Predose** / **Postdose**						
Written informed consent	X							
Inclusion and exclusion criteria	X							
Admission to clinic	X							
Participant demography	X							
Physical examination (including height and weight at Baseline only)	X					X	X	
Medical/surgical history	X							
Diagnosis of presumptive acute cystitis[b]	X							
Bacteriology samples[c]		X	X	X	X	X	X	X
Record acute cystitis signs and symptoms[d]	X		X	X	X	X	X	X
12-lead ECG[e]	X	X[f] / X			X			
Vital sign measurements[g]	X	X[f]	X	X	X	X	X	
Hematology, chemistry, and urinalysis	X			X		X	X	
Serology (hepatitis B and C and HIV)[h]	X							
Pregnancy test[i]	X					X	X	
Administer study treatment[j]		X[j] / X	X	X	X	X[j]		
Blood and urine PK sampling[k]		X / X	X	X	X	X		
Cervical, rectal, and pharyngeal PK sampling (optional)[l]					X			
Genetic sample (optional)		X[m]						
Stool microbiome collection (optional)[n]		X				X		X
Vaginal and pharyngeal microbiome collection (optional)[n]		X				X		X

Visit	Baseline (includes a screening window of up to 24 hours before the first dose of study treatment)		On-Therapy					Test-of-Cure	Follow-up
Serious adverse events[o,p]	X	X	X	X	X	X	X	X	X
Adverse events[p]			X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Discharge from clinic							X[a,j]		
Schedule/Reminder for next outpatient visit							X[q]	X[r]	X[r]

ECG=electrocardiogram; HIV=human immunodeficiency virus; PK=pharmacokinetic; TOC=Test-of-Cure; WBC=white blood cell.

a. If a participant discontinues during the on-treatment confinement period, Day 5 assessments will be completed before the participant is discharged, with the exception of study treatment administration.
b. Based on confirmation of pyuria (≥10 WBC/mm^3 or the presence of leukocyte esterase) and/or nitrite from a pretreatment clean-catch midstream urine sample per local laboratory procedures. Note: Repeat baseline urine samples are allowed if contamination, defined as ≥10 squamous epithelial cells, is observed under microscopic evaluation.
c. Participants will provide a clean-catch midstream urine sample pretreatment at Baseline (predose on Day 1), predose on Days 2 through 5 (i.e., before the time-matched dose); and at the TOC and Follow-up Visits for Gram stain, quantitative bacteriology culture, and in vitro antimicrobial susceptibility testing.
d. Site staff will record clinical signs and symptoms of acute cystitis based on participant interview.
e. Obtain a triplicate 12-lead ECG in semi-supine position at Baseline only. See Table 10 for single 12-lead ECG predose and postdose assessment time points on Days 1 and 4.
f. Only repeat the ECG and vital sign assessments at predose on Day 1 if the baseline assessment was not within 4 hours of the first dose of study treatment.
g. Take measurement of temperature, blood pressure, and pulse rate in semi-supine position.
h. If serology testing was performed within 3 months prior to the first dose of study treatment and 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.
i. For women of childbearing potential, a negative serum pregnancy test is needed for eligibility at Baseline. A urine pregnancy test may be performed on Day 5 and at the TOC Visit.
j. The first dose on Day 1 will only be administered after all baseline procedures have been completed. All doses of study treatment will be administered under site staff supervision and all doses will be administered with food (i.e., standardized meals or snacks as applicable). Participants should remain in the clinic to complete a total of 10 doses.
k. See Table 10 for serial collection time points. Predose PK blood samples will be collected before each time-matched dose on Days 1 through 5. Predose PK urine samples will be collected 0 to 2 hours before each time-matched dose on Days 1 through 5. Only 1 sample is needed when serial and predose samples overlap. If a participant is switched to a different antibiotic before the end of study treatment, a final blood and urine PK sample should be collected prior to administration of the different antibiotic.
l. Collection of cervical, rectal, and pharyngeal swab PK specimens is optional. Specimens will be collected on Day 4 at predose and at approximately 2 hours postdose. The 2-hour postdose collection should be as close as possible to the 2-hour postdose blood PK draw time on Day 4.
m. Collect sample only if the participant has a signed consent specific for this purpose. Baseline (predose on Day 1) is the recommended time to collect the sample, but it can be collected at any time during the study.
n. Collection of stool, vaginal, and pharyngeal microbiome specimens is optional. The pretreatment specimens may be collected any time from Day -1 to Day 1 predose. The posttreatment specimens on Day 5 and at Follow-up may be collected at any time. Posttreatment stool, vaginal, and pharyngeal microbiome specimens should only be collected from participants who had a corresponding baseline specimen collected for each specimen type.
o. Record serious adverse events from the time of consent.

p. Record adverse events from the time of the first dose of study treatment.
q. Confirm return day/time for the TOC and Follow-up Visits.
r. Pre-visit reminder: Site staff will contact the participant 24±4 hours before the scheduled TOC and Follow-up Visits.

Note:

At the discretion of the investigator, for emergency purposes only, participants may temporarily leave the clinic on study days without serial PK collections and only at times that do not interfere with required study assessments. Participants will be instructed to follow the protocol restrictions. The investigator will ensure the participant is eligible to continue in the study upon return to the clinic. All doses of study treatment will be administered under site staff supervision in the clinic.

The timing and number of planned study assessments, including PK assessments may be altered during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring. Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The institutional review board will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the informed consent form.

Table 10 Blood and Urine Pharmacokinetic Collections and Electrocardiogram Assessments on Days 1 and 4

	Time point (hours)											
Procedure[a]	**Predose**	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**10**	**12**
12-lead electrocardiogram[b]	X[c]					X						
Administer study treatment[d]		X										X[e]
Blood collection for pharmacokinetics[f]	X		X	X	X	X	X	X	X	X		X
Urine collection for pharmacokinetics[g]	X	X				X		X	X	X	X	

a. Assessments scheduled at the same nominal time should occur in the following order: electrocardiogram, urine collection, blood collection. The timing of the assessments should allow the blood draw to occur at the exact nominal time.
b. Obtain single 12-lead electrocardiogram in semi-supine position at predose and 2 hours postdose on Days 1 and 4. The predose and postdose electrocardiogram time points should be the same on both days.
c. Only repeat the electrocardiogram assessment at predose on Day 1 if it was not performed within 4 hours of the baseline assessment.
d. Study treatment will be administered under site staff supervision and with food (i.e., standardized meals or snacks as applicable). On Days 1 and 4, for the dose associated with serial PK collections, participants should be in a semi-supine position for approximately 3 hours after study treatment administration with only minor exceptions (e.g., urine PK collections).
e. Collection of the PK samples should occur before this dose is administered.
f. Blood PK samples will be collected at predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours postdose for the first dose of study treatment on Day 1 and for the time-matched dose on Day 4.
g. Urine PK samples will be collected predose and at intervals of 0 to 2 hours, 2 to 4 hours, 4 to 6 hours, 6 to 8 hours, 8 to 10 hours, and 10 to 12 hours postdose for the first dose of study treatment on Day 1 and for the time-matched dose on Day 4.

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 end date is not missing and is before participant enrollment
Concomitant	Any medication that is not a prior

NOTES:

- Please refer to Appendix 5: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

12.2.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• If AE onset date is on or after treatment start date & on or before the treatment stop date + 2 days. • Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 2 days.

NOTES:

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

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 1.0) • 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 subject level listings in the main body of the GSK Clinical Study Report. All subject 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) 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:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • 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 subject's listings.

Unscheduled Visits	
• Unscheduled visits will not be included in summary tables and/or figures except for determining baseline or determining the worst-case values. • 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	
PC Windows Non-Linear (WNL) File	PC WNL file (xpt format) for the non compartmental analysis will be created according to SOP 314000(2.0). Note: Concentration values will be imputed as per GUI_51487
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/analysis and summarized graphical displays only.
Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by Programmer	The following plasma PK parameters will be derived by the Programmer: Ro, $C\tau$ The following urine PK parameters will be derived by the Programmer: Ae 12h, Ae(t1-t2), Fe%, CLr, $C\tau$
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes, refer to [Standards for Handling NQ Impacted PK Parameters].
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards.

12.4. Appendix 4: Derived and Transformed Data

12.4.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • The worst finding/interpretation associated with multiple measurements as the finding/interpretation for that time point. • 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:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

12.4.2. Study Population

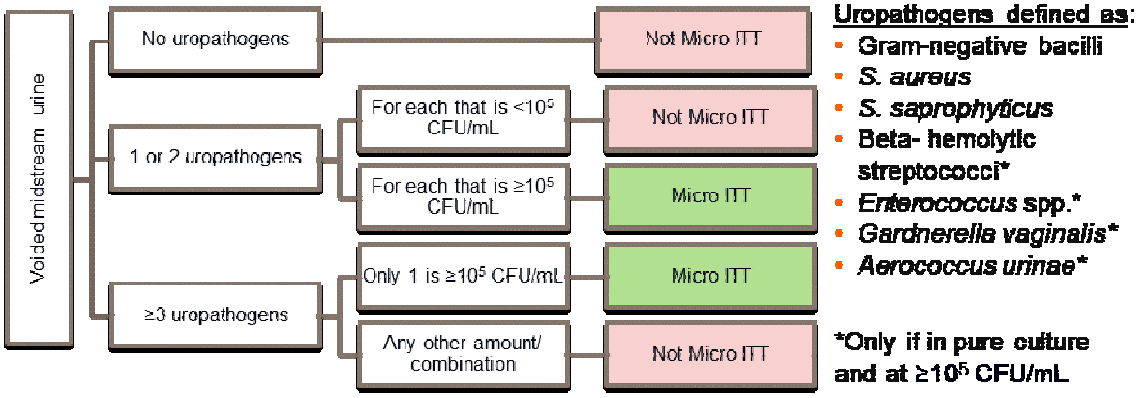
Age

• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  ○ Any subject with a missing day will have this imputed as day '15'.
  ○ Any subject with a missing day and month will have this imputed as '30th June'.
• Birth date will be presented in listings as 'YYYY'.

Body Mass Index (BMI)
• Calculated as Weight (kg) / Height $(m)^2$

Micro-ITT Population
• Micro-ITT population include participants who receive at least 1 dose of gepotidacin and have a qualifying bacterial uropathogen at Baseline from a quantitative bacteriology culture of a pretreatment clean-catch midstream urine specimen. • The algorithm of the qualifying bacterial uropathogen is presented in Figure 2. If there're 2 uropathogens identified at baseline for a participant, the participant will be included in the micro-ITT population if at least 1 of the 2 uropathogens is $\geq 10^5$ CFU/mL.

Figure 2 Baseline Algorithm for the Microbiological intent-to-Treat Population



CFU=colony-forming units; micro-ITT=Microbiological Intent-to-Treat.

12.4.3. Safety

Adverse Events
AE'S of Special Interest
• Cardiovascular (CV) events • Gastrointestinal events • A comprehensive list of Medical Dictionary for Regulatory Activities (MedDRA) terms based on clinical review will be used to identify each type of event.
Adverse Events with Missing Relationship or Missing Serious Indicator
• If the relationship to study treatment is missing for a treatment-emergent AE, it'll be considered as 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 two sources
  - Central laboratory
  - Excel spreadsheets from the study microbiologist and/or clinical scientist
- The central laboratory will analyse the bacteriology urine samples by conducting a Gram stain, quantifying and identifying uropathogens and will perform susceptibility testing as listed below.
  - Broth microdilution results (MIC) on all gram-positive uropathogens for gepotidacin, ampicillin, trimethoprim-sulfamethoxazole, trimethoprim, sulfisoxazole, ciprofloxacin, levofloxacin, nitrofurantoin and vancomycin.
  - Broth microdilution results (MIC) on all gram-negative uropathogens for gepotidacin, ampicillin, amoxicillin/clavulanic acid, ceftolozatone/tazobactam, ceftazidime/avibactam, piperacillin/tazobactam, cefazolin, ceftriaxone, meropenem, amikacin, gentamicin, trimethoprim-sulfamethoxazole, trimethoprim, sulfisoxazole, ciprofloxacin, levofloxacin, nitrofurantoin and vancomycin
    - Amoxicillin/clavulanic acid is tested in the ratio of 2:1, concentrations for amoxicillin/clavulanic acid will be expressed as the amoxicillin concentration. Piperacillin/tazobactam and ceftolozane/tazobactam are tested with the concentration of tazobactam fixed at 4 mg/L, concentrations for piperacillin/tazobactam and ceftolozane/tazobactam will be expressed as the piperacillin and ceftolozane concentration, respectively. Ceftazidime/avibactam is tested with the concentration of avibactam fixed at 4 mg/L, concentrations for ceftazidime/avibactam will be expressed as the ceftazidime concentration. Trimethoprim-sulfamethoxazole is tested in the ratio 1:19, concentrations for trimethoprim-sulfamethoxazole will be expressed as the trimethoprim concentration.
  - Gradient diffusion results (MIC) on all gram-negative and gram-positive uropathogens for:fosfomycin
  - All gram-negative uropathogens will be also be tested by broth microdilution (MIC) to determine indicate 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.*
- The data from the study microbiologist and/or clinical scientist will include clarification of which isolates should be labelled as uropathogens and qualifying uropathogens 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.

Microbiological Data Procedures

• Statistics and Programming will identify all cases within the central laboratory dataset where two or more uropathogens of the same genus and species have been identified for the same participant at the same visit.
• An excel file containing a list of these uropathogens and the associated quantitative bacterial counts and MIC results 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 the susceptibility data patterns.
  • If there is a ≥ 4-fold difference in MIC to one member of two or more antibiotic classes, then the two isolates will be considered two different strains and both will be used in the analysis.
  • Otherwise, only one isolate will be kept for analysis based on a pre-defined algorithm.
• The microbiologist will add a flag to the list to indicate which of the duplicate records to keep. All records will be kept in the SDTM datasets, and those records that are deemed to be duplicates will be removed from the final Analysis Data Model (ADaM) dataset.
• For participants whom the microbiologist has indicated that both sets of uropathogen records should be maintained, Statistics and Programming will provide all central laboratory data from all visits for the particular uropathogens to the microbiologist.
• Should the same uropathogen be presented at additional visits, the microbiologist, with the use of the MIC result, will make a determination as to which of the baseline uropathogens has been isolated at this new visit.
• Statistics and Programming will also provide a list of all distinct isolates (by participant, visit, identification, and quantitative bacterial count) from the central laboratory to the microbiologist and clinical scientist.
• The microbiologist and clinical scientist will provide an excel spreadsheet containing a list of decoded uropathogen codes and a flag to indicate which items within the code list are uropathogens and qualifying uropathogens for this protocol. This flag will then be merged into the SDTM dataset.

Fold Change
• Fold change will be used to describe how much the MIC for gepotidacin 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.
Susceptibility Interpretations
• Susceptibility interpretations will be calculated and reported by the central laboratory and will be based on the CLSI M100 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. • The final clinical database will report interpretations according to the most recent CLSI M100 interpretations regardless of what the breakpoints were at the time the isolate was initially tested.

Quantitative Bacterial Counts

• The central laboratory will quantitatively determine the growth of bacterial 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
  ▪ >/-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	• Subject 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. • Subject 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. • Withdrawn subjects may be replaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data except for efficacy will be included in summary tables and figures, unless otherwise specified.

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: ○ These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
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 subject 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: ○ 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 as per Appendix 3: Study Phases and Treatment Emergent Adverse Events. ○ 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 for reporting.
Concomitant Medications/	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:

Element	Reporting Detail
Medical History	○ 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	> 450[1]	
		> 450[2]	≤ 479[2]
		≥ 480[2]	≤ 499[2]
		≥ 500[2]	
Absolute PR Interval	msec	< 110[1]	> 220[1]
Absolute QRS Interval	msec	< 75[1]	> 110[1]
Change from Baseline			
Increase from Baseline QTc	msec	> 30[1]	
		> 30[2]	≤ 59[2]
		≥ 60[2]	

NOTES:

1. Represent standard ECG values of PCI for HV studies.
2. Represent further subdivisions of ECG values for analysis.

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 Disease Adult Toxicity Tables for Adverse Event Assessment

12.7.1. Laboratory Values

Laboratory abnormalities will be graded according to the modified US National institute of Allergy and Infectious Disease Division of Microbiology and Infectious Diseases (DMID) criteria [DMID, 2007]. Laboratory results are converted to use 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	13,000 to 15,000 /mm^3	15,000 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 accompanied by any increase in other liver function test)	1.1 to <1.25 × ULN	1.25 to <1.5 × ULN	1.5 to 1.75 × ULN	>1.75 × ULN
Hyperbilirubinemia (when other liver function tests are in the normal range)	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.

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.

12.8. Appendix 8: Abbreviations & Trade Marks

12.8.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
Ae[t1-t2]	Amount of Drug Excreted in Urine in a Time Interval
Ae 12h	Amount of Drug Excreted over 12 Hours
AIC	Akaike's Information Criteria
AUC	Area under the Concentration-Time Curve
AUC(0-τ)	AUC from Zero over the Dosing Interval
BID	Twice Daily
CDISC	Clinical Data Interchange Standards Consortium
CFU	Colony-Forming Units
CI	Confidence Interval
CLr	Renal Clearance
CLSI	Clinical and Laboratory Standards Institute
CLss/F	Apparent Steady State Clearance
Cmax	Maximum Plasma Concentration
CV	Coefficient of Variation
Cτ	Predose Concentration
DBF	Database Freeze
DBR	Database Release
DMID	Division of Microbiology and Infectious Disease
DP	Decimal Places
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
FDA	Food and Drug Administration
fe%	Percentage of the Given Dose of Drug Excreted in Urine
GSK	GlaxoSmithKline
ICH	International Conference on Harmonization
IDSL	Integrated Data Standards Library
ITT	Intent-To-Treat
MIC	Minimum Inhibitory Concentration
PD	Pharmacodynamic
PK	Pharmacokinetic
RAP	Reporting & Analysis Plan
Ro	Accumulation Ratio
SAC	Statistical Analysis Complete
SAE	Serious AE
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
SRM	Study Reference Manual
tmax	Time of Occurrence of Cmax

Abbreviation	Description
TOC	Test-of-Cure
UTI	Urinary Tract Infection

12.8.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
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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 1.9	
Efficacy	2.1 to 2.9	2.1 to 2.3
Safety	3.1 to 3.12	
Pharmacokinetic	4.1 to 4.6	4.1 to 4.10
Pharmacokinetic / Pharmacodynamic	5.1	5.1
Section	**Listings**	
ICH Listings	1 to 36	
Non-ICH Listings	37 to 42	

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
Pharmacokinetic / Pharmacodynamic	PKPD_Fn	PKPD_Tn	PKPD_Ln

NOTES:

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

12.9.3. Deliverables

Delivery	Description
DS	During Study
SAC	Final Statistical Analysis Complete

NOTE:

- A dry run will be performed during the study (DS).

12.9.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.1.	Intent-to-Treat	ES1	Summary of Subject Disposition		DS, SAC
1.2.	Intent-to-Treat	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment		DS, SAC
Protocol Deviation					
1.3.	Intent-to-Treat	DV1	Summary of Significant Protocol Deviations		DS, SAC
Demographic and Baseline Characteristics					
1.4.	Intent-to-Treat	DM1	Summary of Demographic Characteristics		DS, SAC
1.5.	Intent-to-Treat	DM5	Summary of Race and Racial Combinations		DS, SAC
1.6.	Intent-to-Treat	DM11	Summary of Age Ranges		DS, SAC
1.7.	Intent-to-Treat	POP_T1	Summary of Disease Characteristics at Baseline		DS, SAC
1.8.	Intent-to-Treat	MH4	Summary of Past and Current Medication Conditions		DS, SAC
Exposure					
1.9.	Intent-to-Treat	EX1	Summary of Exposure to Study Treatments		DS, SAC

12.9.5. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Bacteriology Assessments and Microbiological Outcome and Response					
2.1.	Micro-ITT	EFF_T1	Summary of Microbiological Outcome and Response by Visit and Qualifying Uropathogen Isolated at Baseline		DS, SAC
2.2.	Micro-ITT	EFF_T2	Summary of Urine Quantitative Bacteriology Culture Results by Qualifying Uropahtogen and Visit		DS, SAC
2.3.	Micro-ITT	EFF_T3	Summary of MIC and Susceptibility Results of Qualifying Uropathogens	Summarize only qualifying uropathogens (flagged by study microbiologist and/or clinical scientist), including those no present at baseline but emerging later	DS, SAC
2.4.	Micro-ITT	EFF_T4	Distribution of MIC Results of Qualifying Uropathogens by Drug	Summarize only qualifying uropathogens (flagged by study microbiologist and/or clinical scientist), including those no present at baseline but emerging later	DS, SAC
2.5.	ITT	EFF_T5	Summary of Reduction in Susceptibility to Gepotidacin	Summarize all uropathogens regardless of counts	DS, SAC
Clinical Outcome and Response, Therapeutic Response					
2.6.	Intent-to-Treat	EFF_T6	Summary of Investigator-Determined and Sponsor-Determined Clinical Outcome and Response by Uropathogen Isolated at Baseline		DS, SAC
2.7.	Micro-ITT	EFF_T7	Summary of Therapeutic Response		DS, SAC
2.8.	ITT	EFF_T8	Summary of Clinical Symptom Score by Visit		DS, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.9.	ITT	EFF_T9	Summary of Clinical Cure by Qualifying Uropathogen Isolated at Baseline		DS, SAC

12.9.6. Efficacy Figures

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.1.	Micro-ITT	EFF_F1	Percent of Clinical Cure and Microbiological Eradication Over Time by Uropathogen Isolated at Baseline		DS, SAC
2.2.	Micro-ITT	EFF_F2	Quantitative Bacterial Counts (CFU/mL) by Qualifying Baseline Uropathogen Over Time		DS, SAC
2.3.	Micro-ITT	EFF_F3	Individual Clinical Symptom Score and Boxplot of Total Score Over Time		DS, SAC

12.9.7. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events (AEs)					
3.1.	Safety	AE5B	Summary of Adverse Events by System Organ Class and Preferred Term and Maximum Grade		DS, SAC
3.2.	Safety	AE5B	Summary of Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Grade		DS, SAC
3.3.	Safety	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		DS, SAC
Laboratory					
3.4.	Safety	LB1	Summary of Clinical Chemistry Values Change from Baseline		DS, SAC
3.5.	Safety	LB1	Summary of Hematology Change from Baseline		DS, SAC
3.6.	Safety	UR3	Summary of Urinalysis Dipstick Results		DS, SAC
ECG					
3.7.	Safety	EG1	Summary of ECG Findings		DS, SAC
3.8.	Safety	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category		DS, SAC
3.9.	Safety	EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category		DS, SAC
3.10.	Safety	EG2	Summary of Change from Baseline in ECG Values		DS, SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Vital Signs					
3.11.	Safety	VS3	Summary of Worst Case Vital Signs Results Relative to Potential Clinical Importance Criteria Post-Baseline Relative to Baseline		DS, SAC
3.12.	Safety	VS1	Summary of Change from Baseline in Vital Signs		DS, SAC

12.9.8. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Pharmacokinetic Concentrations					
4.1.	PK Concentration	PKCT1	Summary of Gepotidacin Plasma Pharmacokinetic Concentration-Time Data (units)		SAC
4.2.	PK Concentration	PKCT1	Summary of Gepotidacin Urine Pharmacokinetic Concentration-Time Data (units)		SAC
4.3.	PK Concentration	PKCT1	Summary of Gepotidacin Cervical, Rectal, and Pharyngeal Pharmacokinetic Concentration-Time Data (units)		SAC
Pharmacokinetic Parameters					
4.4.	PK Parameter	PKPT4	Summary Statistics of Derived Gepotidacin Plasma Pharmacokinetic Parameters	Free and total PK Parameters include: AUC(0-tau) (units), AUC(0-24) (units), Cmax (units), Tmax (units), CLss/F (units), Ro (units), Ctau (units). Do not ln-transform Tmax. Ctau will have values for Day 1 through 5	SAC
4.5.	PK Parameter	PKPT4	Summary Statistics of Derived Gepotidacin Urine Pharmacokinetic Parameters	Parameters include: Ae12h (units), A(t1-t2) (units), %fe (units), CLr (units), Ctau (units), AUC(0-tau) (units), and AUC(0-24) (units) for all subjects; Ae(t1-t2) include Ae(0-2) (units), Ae(2-4) (units), Ae(4-6) units), Ae(6-8) (units), Ae(8-10) and Ae(10-12) (units). Ctau has values on Day 1 through Day 5	SAC
4.6.	PK Parameter	PK_T1	Statistical Analysis of Gepotidacin Plasma Predose	Ctau values of day 1 through 5	SAC

12.9.9. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Pharmacokinetic Concentrations					
4.1.	PK Concentration	PKCF1P	Individual Gepotidacin Plasma Concentration-Time Plots (Linear and Semi-Logarithmic)		SAC
4.2.	PK Concentration	PKCF1P	Individual Gepotidacin Ctau Plasma Concentration-Time Plots (Linear and Semi-Logarithmic)		SAC
4.3.	PK Concentration	PKCF1P	Individual Gepotidacin Urine Concentration-Time Plots (Linear and Semi-Logarithmic)		SAC
4.4.	PK Concentration	PKCF1P	Individual Gepotidacin Ctau Urine Concentration-Time Plots (Linear and Semi-Logarithmic)		SAC
4.5.	PK Concentration	PKCF2	Mean Gepotidacin Plasma Concentration-Time Plots (Linear and Semi-Logarithmic)		SAC
4.6.	PK Concentration	PKCF2	Mean Gepotidacin Ctau Plasma Concentration-Time Plots (Linear and Semi-Logarithmic)		SAC
4.7.	PK Concentration	PKCF2	Mean Gepotidacin Urine Concentration-Time Plots (Linear and Semi-Logarithmic)		SAC
4.8.	PK Concentration	PKCF2	Median Gepotidacin Plasma Concentration-Time Plots (Linear and Semi-Logarithmic)		SAC
4.9.	PK Concentration	PKCF2	Median Gepotidacin Ctau Plasma Concentration-Time Plots (Linear and Semi-Logarithmic)		SAC
4.10.	PK Concentration	PKCF2	Median Gepotidacin Urine Concentration-Time Plots (Linear and Semi-Logarithmic)		SAC

12.9.10. Pharmacokinetic / Pharmacodynamic Tables

Pharmacokinetic / Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Pharmacokinetic/Pharmacodynamic Relationship					
5.1.	Micro-ITT	PKPD_T1	Summary of Response by Qualifying Baseline Uropathogen for Gepotidacin Free Plasma and Urine PKPD Parameters	Summary of Free plasma AUC/MIC, Cmax/MIC and urine AUC(0-24)/MIC and Ctau/MIC vs clinical, microbiological and therapeutic success and failure by qualifying baseline uropathogen.	SAC

12.9.11. Pharmacokinetic / Pharmacodynamic Figures

Pharmacokinetic / Pharmacodynamic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Pharmacokinetic/Pharmacodynamic Relationship					
5.1.	Micro-ITT	PKPD_F1	Plot of Response by Qualifying Baseline Uropathogen for Gepotidacin Free Plasma and Urine PKPD Parameters	Plot of ind free plasma AUC(0-24)/MIC, Cmax/MIC and urine AUC(0-24)/MIC, Ctau/MIC vs clinical, microbiological and therapeutic success and failure by qualifying baseline uropathogen .	SAC

12.9.12. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.	Intent-to-Treat	ES2	Listing of Reasons for Study Withdrawal		DS, SAC
2.	Intent-to-Treat	SD2	Listing of Reasons for Study Treatment Discontinuation		DS, SAC
3.	Intent-to-Treat	SP3	Listing of Subjects Excluded from Any Population		DS, SAC
Protocol Deviations					
4.	Intent-to-Treat	DV2	Listing of Significant Protocol Deviations		DS, SAC
5.	Intent-to-Treat	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		DS, SAC
Demographic and Baseline Characteristics					
6.	Intent-to-Treat	DM2	Listing of Demographic Characteristics		DS, SAC
7.	Intent-to-Treat	DM9	Listing of Race		DS, SAC
8.	Intent-to-Treat	SAFE_L1	Listing of History of Uncomplicated Urinary Tract Infection		DS, SAC
9.	Intent-to-Treat	MH2	Listing of Medical Conditions		DS, SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Prior and Concomitant Medications					
10.	Intent-to-Treat	CM3	Listing of Prior and Concomitant Medications		DS, SAC
Exposure and Treatment Compliance					
11.	Intent-to-Treat	EX3	Listing of Exposure Data		DS, SAC
Efficacy					
12.	Intent-to-Treat	EFF_L1	Listing of Clinical Outcome and Response		DS, SAC
13.	ITT	EFF_L2	Listing of Urine Specimen Gram Stain Results		DS, SAC
14.	ITT	EFF_L2	Listing of Urine Quantitative Bacteriology Culture Results		DS, SAC
15.	ITT	EFF_L3	Listing of Susceptibility Results		DS, SAC
16.	Intent-to-treat	EFF_L4	Listing of Gepotidacin MIC Result, Sponsor-Determined Clinical Response, Microbiological Outcome and Response, and Therapeutic Response by Uropathogen Isolated at Baseline	Page by participants in micro-ITT population and participants not in micro-ITT population	DS, SAC
Adverse Events					
17.	Safety	AE2	Listing of Relationship Between System Organ Class and Verbatim Text		DS, SAC
18.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events		DS, SAC
19.	Safety	AE8CP	Listing of All Adverse events		DS, SAC
Serious and Other Significant Adverse Events					
20.	Safety	AE8CP	Listing of Study Drug Related Adverse Events		DS, SAC
21.	Safety	SAFE_L2	Listing of Serious Adverse Events (Fatal & Non-Fatal)		DS, SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
22.	Safety	AE8CP	Listing of Adverse Events Leading to Discontinuation of Study Treatment or Withdrawal from Study		DS, SAC
All Laboratory					
23.	Safety	LB5A	Listing of Clinical Chemistry Toxicities of Grade 2 or Higher		DS, SAC
24.	Safety	LB5A	Listing of All Clinical Chemistry Data for Subjects with Toxicities of Grade 2 or Higher		DS, SAC
25.	Safety	LB5A	Listing of Hematology Toxicities of Grade 2 or Higher		DS, SAC
26.	Safety	LB5A	Listing of Hematology Data for Subjects with Toxicities of Grade 2 or Higher		DS, SAC
27.	Safety	UR2A	Listing of Urinalysis Data	Include all urinalysis data for all participants	DS, SAC
ECG					
28.	Safety	EG5	Listing of All ECG Findings for Subjects with an Abnormal Finding	Flag abnormal ECG findings	DS, SAC
29.	Safety	EG3	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance	Flag ECG values of PCI	DS, SAC
Vital Signs					
30.	Safety	VS4	Listing of All Vital Signs for Subjects with Potential Clinical Importance Values	Flag vital sings of PCI	DS, SAC
Liver Events and Other Safety Endpoints					
31.	Safety	SAFE_L3	Listing of Clostridium Difficile Results		DS, SAC
32.	Safety	SU2	Listing of Alcohol Intake at Onset of Liver Event	Conditional Display	DS, SAC
33.	Safety	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting	Conditional Display	DS, SAC
34.	Safety	LIVER6	Listing of Liver Stopping Event Information for RUCAM Score	Conditional Display	DS, SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
35.	Safety	LIVER7	Listing of Liver Biopsy Details	Conditional Display	DS, SAC
36.	Safety	LIVER8	Listing of Liver Imaging Details	Conditional Display	DS, SAC

12.9.13. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Pharmacokinetic Concentrations					
37.	PK	PKCL1P	Listing of Gepotidacin Plasma Concentrations (units)		SAC
38.	PK	PKUL1P	Listing of Gepotidacin Urine Concentrations (units)		SAC
39.	PK	PKCL1P	Listing of Gepotidacin Free Plasma, Cervical, Rectal and Pharyngeal Concentrations (units)		SAC
Pharmacokinetic Parameters					
40.	PK Parameter	PKPL1P	Listing of Gepotidacin Plasma Pharmacokinetic Parameters	Parameters include: AUC(0-tau) (units), AUC(0-24) (units), Cmax (units), Tmax (units), CLss/F (units), Ro (units), Ctau (units). Do not ln-transform Tmax. Ctau will have values for Day 1 through 5, Total and free PK parameters	SAC
41.	PK Parameter	PKPL1P	Listing of Gepotidacin Urine Pharmacokinetic Parameters	Parameters unclude: Ae12h (units), AUC(0-24) (units), A(t1-t2) (units), %fe (units), CLr (units), Ctau (units) for all subjects; Ae(t1-t2) include Ae(0-2) (units), Ae(2-4) (units), Ae(4-6) units), Ae(6-8) (units), Ae(8-10) and Ae(10-12) (units). Ctau has values on Day 1 through Day 5	SAC
42.	Micro-ITT	EFF_L5	Listing of Qualifying Baseline Uropathogen for Gepotidacin Free Plasma and Urine PKPD Parameters	Free plasma AUC/MIC, Cmax/MIC and urine AUC(0-24)/MIC, Ctau/MIC	SAC