TITLE PAGE

Protocol Title: 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)

Protocol Number: 206899

Short Title: Phase IIa Pharmacokinetic Study of Oral Gepotidacin (GSK2140944) in Participants With Uncomplicated Urinary Tract Infection (Acute Cystitis)

Compound Number: GSK2140944

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1. SYNOPSIS

Protocol Title: 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)

Short Title: Phase IIa Pharmacokinetic Study of Oral Gepotidacin (GSK2140944) in Participants With Uncomplicated Urinary Tract Infection (Acute Cystitis)

Rationale:

Gepotidacin (GSK2140944), a novel triazaacenaphthylene bacterial type II topoisomerase inhibitor, is being developed for the treatment of uncomplicated urinary tract infections (acute cystitis). This Phase IIa study is designed primarily to evaluate plasma and urine pharmacokinetics of gepotidacin in female participants with acute cystitis. As this pharmacokinetic (PK) study will be conducted in female participants with acute cystitis, the exploratory clinical and microbiological efficacy of gepotidacin will also be assessed.

Objectives and Endpoints:

Objectives	Endpoints
Primary • 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 • 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 and serious adverse events and change from baseline results for physical examinations, vital sign measurements, electrocardiograms, and clinical laboratory tests

Note: Exploratory objectives are described in the main protocol text.

Overall Design:

- Study 206889 is a Phase IIa single center, open-label study evaluating the PK of repeat oral doses of gepotidacin in adult female participants with clinical signs and symptoms of acute cystitis.
- All participants who meet the study entry criteria and provide informed consent will receive oral gepotidacin.
- Pretreatment and posttreatment PK collections will be performed throughout the study. Appropriate safety, efficacy, microbiological, and exploratory assessments will also be conducted throughout the study.
- Participants will be confined to the clinic from Baseline through the On-Therapy Visit. Participants will return to the clinic for the Test-of-Cure (TOC) and Follow-up Visits.
- At any time during the study, participants experiencing new or continuing signs and symptoms of acute cystitis will be assessed and treated per the investigator's judgement.

Number of Participants:

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.

Treatment Groups and Duration:

- All participants will receive oral gepotidacin 1500 mg twice daily for 5 days (total of 10 doses).
- The study duration is approximately 28 days comprising approximately 5 days of confinement at the clinic followed by 2 outpatient visits as follows:
    - 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

2. SCHEDULE OF ACTIVITIES

Table 1 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
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 (see Appendix 10).
e. Obtain a triplicate 12-lead ECG in semi-supine position at Baseline only. See Table 2 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 2 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 2 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.

3. INTRODUCTION

Gepotidacin (GSK2140944), a novel triazaacenaphthylene bacterial type II topoisomerase inhibitor, is being developed for the treatment of uncomplicated urinary tract infections (UTIs; acute cystitis). Gepotidacin is also being developed as an oral and intravenous treatment for infections caused by conventional and biothreat pathogens, including isolates resistant to existing classes of antimicrobials. The microbiological spectrum of activity of gepotidacin includes *Escherichia coli*, the key causative pathogen of acute cystitis, and *Staphylococcus saprophyticus* and *Enterococcus faecalis*.

Gepotidacin selectively inhibits bacterial DNA replication by interacting in a unique way on the GyrA subunit of bacterial DNA gyrase and the ParC subunit of bacterial topoisomerase IV. This interaction appears to be highly specific to bacterial topoisomerases as evidenced by weak in vitro inhibition of human topoisomerase IIα, supporting the selective activity of gepotidacin against the bacterial target. The novel mode of action of this new class antibacterial affords in vitro activity against most target pathogens resistant to established antibacterials, including fluoroquinolones.

3.1. Study Rationale

This Phase IIa study is designed primarily to evaluate plasma and urine pharmacokinetics of gepotidacin in female participants with acute cystitis.

This study is being conducted based on the need to identify new and effective oral antibiotic treatment options for acute cystitis, as such therapies are becoming limited due to the increase of multidrug-resistant (MDR) pathogens and extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* pathogens, which are impacting the efficacy of currently available oral antibacterial treatment options (see Section 3.2). Two Phase II studies have been conducted and the results demonstrated that gepotidacin was efficacious in the treatment of uncomplicated urogenital gonorrhea and acute bacterial skin and skin structure infections (ABSSSIs) (see Section 5.3.3 in the investigator's brochure [IB] for details).

3.2. Background

Urinary tract infections are very common, with approximately 11% of women >18 years of age experiencing at least 1 episode of acute cystitis per year [Foxman, 2000]. Of these, half will experience more than 1 recurrent episode over their lifetime [Foxman, 2000]. The peak incidence of acute cystitis occurs in young, sexually active women ages 18 to 29 years [Fihn, 2003]. The predominant uropathogen isolated in community-acquired UTIs is *E. coli* (75% to 90%) followed by *S. saprophyticus* (5% to 15%) [Stamm, 1993; Talan, 2000; Foxman, 2010]. *Klebsiella*, *Enterobacter*, and *Proteus* species and enterococci are observed in only 5% to 10% of cases [Stamm, 1993; Talan, 2000; Foxman, 2010].

Multidrug resistance, which is typically associated with nosocomial infections, has now emerged at the community level and has made treatment approaches for UTIs more difficult [Hooton, 2012; Flamm, 2014; Sanchez, 2016]. This has led to increasing patient

morbidity, increasing costs due to reassessment and retreatment, higher rates of hospitalization, and increased use of broad-spectrum antibiotics [Foxman, 2002; Gupta, 2011a; Hooton, 2012]. Furthermore, ESBL-producing *Enterobacteriaceae,* which includes *E. coli*, is recognized as a serious threat by the Centers for Disease Control and Prevention (CDC) [CDC, 2013] and drug-resistant *Enterobacteriaceae* is a critical priority pathogen for the World Health Organization (WHO) [WHO, 2017]. One reason for this serious threat level is the growing rise in the MDR *E. coli* sequence type (ST)-131 clone [Johnson, 2012; Nicolas-Chanoine, 2014]. Spread of this ST-131 clone has led to UTIs and blood stream infections caused by MDR *E. coli* worldwide [Peirano, 2010]. The availability of oral antimicrobials that are effective against ESBLs is limited and, for some outpatient infections, no oral options remain.

An in vitro evaluation of antimicrobial resistance of urinary *E. coli* isolates (n=12,253,679) among US outpatients between 2000 and 2010 was conducted using The Surveillance Network and found significant increases in the percentage of *E. coli* that were resistant to ciprofloxacin (3% to 17.1%) and trimethoprim-sulfamethoxazole (TMP-SXT) (17.9% to 24.2%), whereas there were minimal changes in the percentage of resistance to nitrofurantoin (0.8% to 1.6%) and ceftriaxone (0.2% to 2.3%) over time [Sanchez, 2012]. Another surveillance study, which looked at US susceptibility patterns and ESBL rates of *E. coli* from UTIs, showed an increase in ESBL rates from 7.8% to 18.3% ($p<0.0001$) from 2010 to 2014 [Lob, 2016]. The expansion of ESBL-producing *E. coli*, which are usually co-resistant to TMP-SXT and fluoroquinolones, is of urgent concern globally as well [Oteo, 2010]. Recent global surveillance data of *E. coli* showed high resistance rates to third-generation cephalosporins and fluoroquinolones in all 6 WHO regions [WHO, 2014]. An evaluation of the prevalence and susceptibility of acute cystitis pathogens in 9 European countries and Brazil from 2003 to 2006 showed that >10% of *E. coli* strains were MDR and 1.7% were ESBL producers [Schito, 2009]. A separate study in Brazil reported a prevalence of 7.6% ESBL-producing *Enterobacteriaceae* among pathogens from community-acquired UTIs [Abreu, 2013]. In China, the prevalence of ESBLs in urinary *E. coli* in women ranged from 5% to 10.6% depending on the age group [Ho, 2007].

Based on these resistant pathogen trends, guidelines for acute cystitis now recommend first-line antibiotic treatment with nitrofurantoin, TMP-SXT, fosfomycin, or pivmecillinam, assuming the drug is available and the patient does not have a concerning allergy history or tolerance issues [Gupta, 2011b]. Trimethoprim-sulfamethoxazole should not be used as a first-line treatment if the prevalence of resistance exceeds the 20% threshold or if TMP-SXT was used for treatment of a UTI in the previous 3 months. If any of these are concerns for a patient, then fluoroquinolones or β-lactams are recommended.

Gepotidacin is a first-in-class, novel triazaacenaphthylene antibacterial that has demonstrated in vitro activity against uropathogens including *E. coli* (see Section 4.2 of the IB for details) and provides high and sustained urine concentrations for the treatment of UTIs. With its unique ability to selectively inhibit bacterial DNA replication by a means not utilized by any currently approved human therapeutic agent, gepotidacin warrants further study as a potential opportunity to address an unmet medical need by providing a new and effective oral treatment option for acute cystitis.

This Phase IIa study is designed primarily to evaluate plasma and urine pharmacokinetics of gepotidacin in female participants with acute cystitis.

A detailed description of the chemistry, pharmacology, efficacy, and safety of gepotidacin is provided in the IB [GlaxoSmithKline Document Number CM2010/00033/05].

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of gepotidacin may be found in the IB [GlaxoSmithKline Document Number CM2010/00033/05]. A summary of risk assessments is provided in Section 3.3.1.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Gepotidacin (e.g., GSK2140944)		
Cardiovascular Effects Based on nonclinical data, cardiovascular effects were reversible increase in heart rate and blood pressure (dog and monkey); reversible 10 to 21 msec (4% to 9%) increase in QTc (monkey); and at the highest dose, a reversible 2 to 3 msec (6% to 8%) increase in QRS (monkey). Based on a thorough QTc clinical study, gepotidacin may cause mild, reversible heart rate effects and QT prolongation.	In a thorough QTc study, infusion of gepotidacin at doses of 1000 and 1800 mg over 2 hours caused a mild increased heart rate effect of approximately 6 to 10 bpm and QT prolongation measured as ΔΔQTcF of 12 to 22 msec. The QT prolongation evolved during the infusion and was quickly reversed over 2 hours after the end of the infusion (see Section 5.2.6 and Section 6 of the IB). No changes in QRS or QTc of clinical concern have been seen in the clinic (Phase I studies and Phase II ABSSSI study) (see Section 6 in the IB). Cardiovascular events reported in the Phase II urogenital gonorrhea study were ECG ST segment elevation and palpitations (1 participant each) in the 1500-mg treatment group and tachycardia (1 participant) in the 3000-mg treatment group.	See Section 6.2 for excluded cardiac conditions. Close monitoring of clinical parameters and AEs (Table 1) will be conducted, and treatment monitoring and evaluation criteria (Section 8.1.2) will be utilized to mitigate cardiovascular effects. As a consequence, participants taking QT-prolonging drugs or strong CYP3A4 inhibitors and/or strong P-gp inhibitors will be excluded.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Gastrointestinal Effects Based on nonclinical data, gastrointestinal effects were mild ulceration of the nonglandular mucosa and minimal erosion and/or mural inflammation of the glandular mucosa in stomach (rat, oral study); moderate cecal ulceration and minimal colonic erosion (rat, IV study); and vomiting (dog). Lower gastrointestinal effects (soft stools, flatulence, and diarrhea) are among the most common AEs reported in gepotidacin clinical studies.	Gastrointestinal effects observed in gepotidacin clinical studies, both Phase I studies and the Phase II ABSSSI study, included diarrhea (very common, ≥10%) and flatulence (common; ≥1% and <10%); all nonserious and mild in severity (see Section 6 of the IB). In the Phase II urogenital gonorrhea study, the most frequently reported gastrointestinal AEs overall were diarrhea, flatulence, abdominal pain, and nausea. Comparing the treatment groups, the incidence of diarrhea and nausea was higher in the 3000-mg treatment group and incidence of flatulence was higher in the 1500-mg treatment group. Few occurrences of *Clostridium difficile* have been reported in clinical studies (see Section 6 of the IB). Of the 357 healthy participants in Phase I studies who have received gepotidacin, *C. difficile* was reported in 8 participants, including 2 elderly participants in association with soft stools or diarrhea. No participants in the Phase II ABSSSI or Phase II urogenital gonorrhea study received a diagnosis of *C. difficile*-associated diarrhea.	See Section 6.2 for excluded medical conditions. Close monitoring of clinical parameters and AEs (Table 1) will be conducted to mitigate and assess gastrointestinal effects. Suspected *C. difficile* infection will be managed according to a prespecified algorithm provided in the Study Reference Manual.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Acetylcholinesterase Inhibition In a mass spectrometry model performed with gepotidacin, acetylcholinesterase was inhibited with an IC_{50} of approximately 5 μg/mL (7.5 μg/mL of total drug concentration). Based on clinical data, caution should be used in participants who have a condition requiring medication that may be exacerbated by acetylcholinesterase inhibition or neuromuscular-blocking agents.	Adverse events consistent with acetylcholinesterase effects were reported infrequently in Phase I studies as single or combined AEs, including dizziness, abdominal pain, oropharyngeal discomfort, salivary hypersecretion, hot flush, diarrhea, fatigue, and nausea. In the Phase II ABSSSI study with IV or oral treatment with gepotidacin up to 10 days, AEs of diarrhea, nausea, dizziness (1 participant), salivary hypersecretion (1 participant), and hot flush (1 participant) were reported (see Section 6 of the IB). In the Phase II study of urogenital gonorrhea (oral doses: 1500 or 3000 mg), treatment-related AEs potentially associated with acetylcholinesterase inhibition included dizziness (1 and 6 participants, respectively), hyperhidrosis (1 and 6 participants, respectively), and headache (2 participants in both).	Participants who have medical conditions or require medications that may be aggravated by inhibition of acetylcholinesterase will be excluded from participation in this study. See Section 6.2 for excluded medical conditions and Section 7.7.2, Prohibited Medications and Nondrug Therapies, for prohibited medications. Close monitoring of clinical parameters and AEs will be conducted to assess effects potentially related to acetylcholinesterase inhibition (Table 1).

3.3.2. Benefit Assessment

Given gepotidacin's spectrum of activity against *E. coli*, *S. saprophyticus*, and *E. faecalis*, as well as human safety data and the pharmacokinetic (PK) profile, it is anticipated that gepotidacin will benefit participants with acute cystitis.

Overall, all participants in this study will not only receive routine medical monitoring appropriate for acute cystitis, but they will also receive heightened monitoring to ensure safety when participating in a clinical study.

The PK data from this study will be used to support the indication for gepotidacin as a potential new treatment option for acute cystitis.

3.3.3. Overall Benefit:Risk Conclusion

Together with the known preclinical data for gepotidacin against *E. coli*, *S. saprophyticus*, and *E. faecalis*, cumulative safety results from Phase I and Phase II studies with oral gepotidacin treatment, and the PK data from this study will be used to support the indication for gepotidacin as a potential new treatment option for acute cystitis.

None of the potential or identified risks seen to date in participants dosed with gepotidacin preclude further clinical development. Mitigation strategies have been implemented to promptly identify and appropriately address risks in order to protect participant safety and to better characterize the safety profile of the study treatment (Section 3.3.1), including additional 12-lead ECG assessments during the study while participants are confined. Careful safety monitoring should also identify any emerging safety issues for gepotidacin and contribute to further benefit-risk profile development.

The investigator may, at his or her discretion, discontinue the participant from study treatment at any time and initiate appropriate alternative therapy.

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with gepotidacin are justified by the anticipated benefits that may be afforded to participants with acute cystitis.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary • 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 • 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 AEs and serious AEs and change from baseline results for physical examinations, vital sign measurements, electrocardiograms (ECGs), and clinical laboratory tests
Exploratory • 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 Test-of-Cure (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	• Clinical outcome on Days 2 through 5; 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, and at the 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

5. STUDY DESIGN

5.1. Overall Design

A study design schematic is depicted in Figure 1.

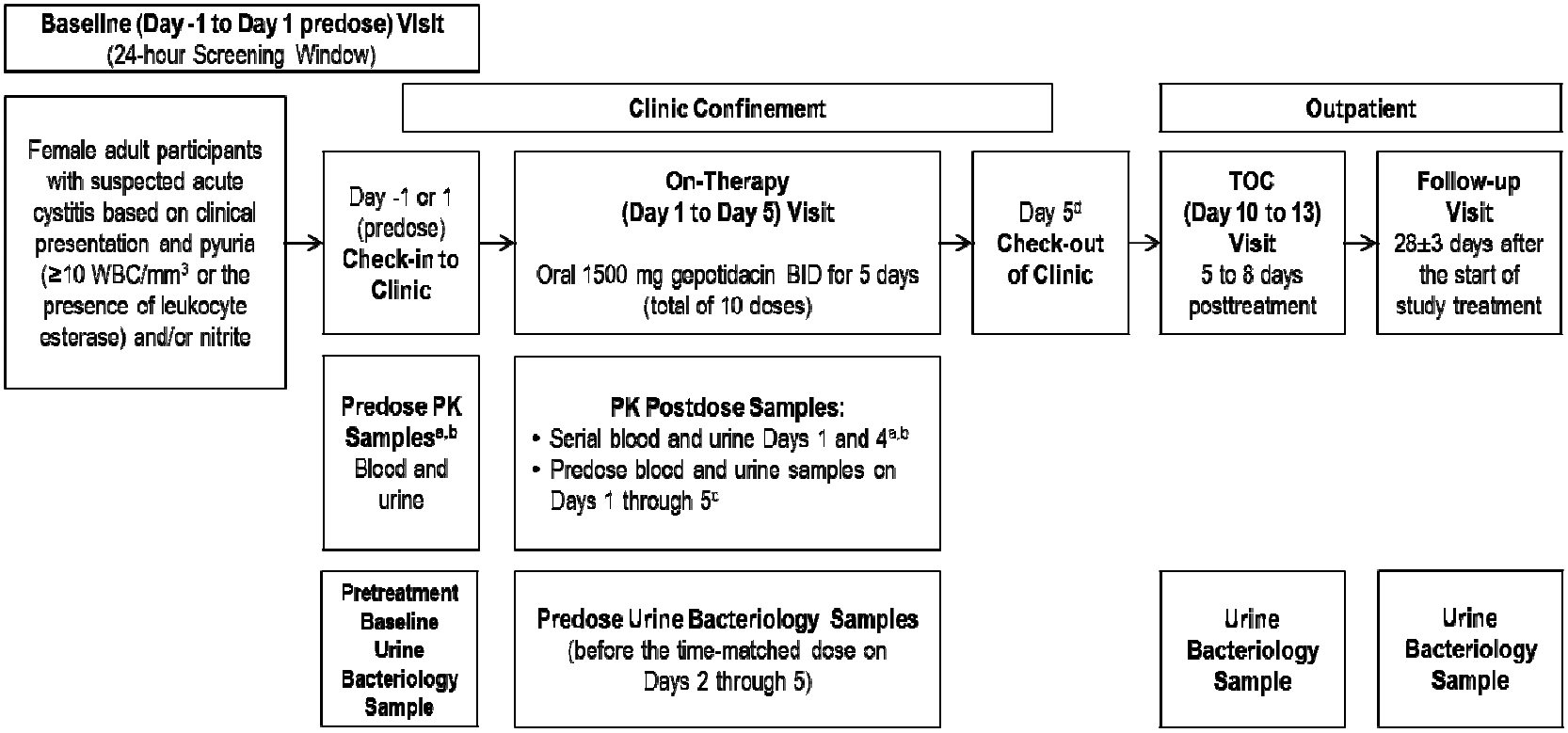
- Study 206889 is a Phase IIa single center, open-label study evaluating the PK of repeat oral doses of gepotidacin in adult female participants with clinical signs and symptoms of acute cystitis.
- All participants who meet the study entry criteria and provide informed consent will receive oral gepotidacin 1500 mg BID for 5 days (total of 10 doses).
- Pretreatment and posttreatment PK collections will be performed throughout the study. Appropriate safety, efficacy, microbiological, and exploratory assessments will also be conducted throughout the study.
- The study duration is approximately 28 days comprising approximately 5 days of confinement at the clinic followed by 2 outpatient visits as follows (see Table 1 and Section 9 for study visit details):
  - Clinic Confinement Visits
    - Baseline (Day -1 to Day 1 predose) Visit
    - On-Therapy (Day 1 to Day 5) Visit
  - Outpatient Visits
    - Test-of-Cure (TOC) (Day 10 to 13) Visit
    - Follow-up (Day 28) Visit
- Participants will be confined to the clinic from Baseline through the On-Therapy Visit. Participants will return to the clinic for the 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.

- Participants with a concomitant fungal infection can only be treated with topical antifungals per local standard of care.
- At any time during the study, participants experiencing new or continuing signs and symptoms of acute cystitis will be assessed and treated per the investigator's judgement. If a participant is switched to a different antibiotic before or during the TOC Visit, all TOC procedures should be completed before the other antibiotic is started. Any participant who discontinues from the PK portion of the study should return for the TOC and Follow up-Visits.

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.

d. 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.

5.2. Number of Participants

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.

If participants prematurely discontinue the study, additional replacement participants may be recruited at the discretion of the sponsor and in consultation with the investigator.

5.3. Participant and Study Completion

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

The end of the study is defined as the date of the last visit of the last participant in the study.

5.4. Scientific Rationale for Study Design

This Phase IIa study is designed primarily to evaluate plasma and urine pharmacokinetics of gepotidacin in participants with acute cystitis. Serial sample collections will be performed on Day 1 (first dose) and on Day 4.

As this PK study will be conducted in female participants with acute cystitis, the exploratory clinical and microbiological efficacy of gepotidacin will also be assessed. The time points and success definitions were based on the Food and Drug Administration (FDA) guidance for industry for developing drug treatments for uncomplicated and complicated UTIs [DHHS, 1998; DHHS, 2015] and the European Medicines Agency (EMA) addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections [EMA, 2013].

Efficacy will be assessed daily during the On-Therapy Visit, at TOC, and at Follow-up. Clinical success is defined as the resolution of signs and symptoms of acute cystitis present at Baseline (and no new signs and symptoms) and no use of other antimicrobial therapy. Microbiological success is defined as the reduction of the qualifying bacterial uropathogen (defined in Appendix 9) recovered at Baseline to $<10^3$ colony-forming units (CFU)/mL as observed on quantitative urine culture. Therapeutic success refers to participants who have been deemed both a microbiological success and a clinical success (i.e., responders).

Adult (≥18 to ≤65 years of age) eligible female participants will be enrolled in this open-label Phase IIa PK study. This age range was selected to minimize variability in systemic exposures as well as baseline uropathogens. This study in acute cystitis is restricted to female participants per the FDA guidance [DHHS, 1998]. As described in Section 5.5, the dose of gepotidacin and the 5-day duration were selected to provide efficacious treatment for acute cystitis and is in alignment with current clinical practice.

5.5. Dose Justification

The oral gepotidacin dose in this study is 1500 mg BID (total daily dose of 3000 mg) for 5 days. A 5-day dosing duration is in alignment with current treatment guidelines for efficacious antibacterial treatment of uncomplicated acute cystitis in women, which typically ranges from 3 to 7 days [Gupta, 2011b; GOV.UK, 2017; EAU, 2017]. The safety and tolerability at this oral dose and duration have been evaluated in Phase I studies and in a Phase II study (BTZ116704) (see Section 5 of the IB for details). Furthermore, high urine concentrations of gepotidacin are expected in this study based on a Phase I study (BTZ117351) where approximately 285 mg of unchanged gepotidacin was excreted in urine after a single, oral, 1500-mg (2 × 750-mg tablets) dose of gepotidacin.

The gepotidacin dose and duration for this Phase IIa PK uncomplicated UTI study were selected based on in vitro and in vivo studies including experimental animal pyelonephritis studies that simulated human PK exposures of gepotidacin to determine the efficacy of gepotidacin against isolates of *E. coli*, including MDR strains (see Section 4.2 of the IB for further details).

Additionally, preliminary data from a recently completed in vitro study to determine the PK/PD characteristics of gepotidacin against *E. coli* (dose-fractionation and dose-ranging studies) indicate that AUC/minimum inhibitory concentration (MIC) is the primary PK/PD index predictive of gepotidacin efficacy against *E. coli*. The magnitude of the ratio of the area under the free-drug concentration-time curve to MIC over 24 hours (*f*AUC/MIC) required to achieve net bacterial stasis as well as 1- and 2-log reductions in bacterial burden from baseline across multiple *E. coli* isolates with gepotidacin MIC values ranging from 1 to 4 µg/mL, were 34.5, 41.3, and 49.7, respectively.

A set of duplicate 10-day hollow fiber infection model studies were also completed using *E. coli* isolate NCTC 13441 to determine the *f*AUC/MIC exposure of gepotidacin required to prevent the amplification of resistant subpopulation. An inverted-U shaped function described the relationship between drug resistance amplification and *f*AUC, with *f*AUC values ≥549 preventing resistance amplification to gepotidacin for *E. coli* in the hollow fiber infection model. This equates to an *f*AUC/MIC value ≥275 when applying the gepotidacin broth microdilution MIC of 2 µg/mL for *E. coli* 13441, as determined in this study.

When taking the *f*AUC/MIC target of 275 for resistance supression into consideration with the concentrations of gepotidacin in human urine measured in a Phase I study (BTZ117351, minimum *f*AUC12h=807 µg.h/mL, so *f*AUC24h=1610 µg.h/mL) and, applying an MIC value of 4 µg/mL, the minimum human urine *f*AUC/MIC achieved for the 1500 mg oral BID dose exceeds the *f*AUC/MIC resistance supression target of 275 by approximately 1.5-fold and 100% target attainment for an *f*AUC/MIC target of 275 would be expected for participants with *E. coli* isolates with gepotidacin MICs ≤4 µg/mL following 1500 mg BID oral dosing.

In conclusion, minimum urine levels of gepotidacin are anticipated to be in excess of the *f*AUC/MIC target necessary for both efficacy and resistance suppression for *E. coli* as

determined from the in vitro PK/PD models. Given that the bladder is the primary site of infection in cystitis, the use of gepotidacin urine PK data, coupled with the robust in vivo efficacy demonstrated in the human simulated PK pyelonephritis model, is appropriate for selecting the gepotidacin 1500 mg BID oral dose for 5 days for study in the treatment of participants with acute cystitis.

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Otherwise healthy participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be ≥18 to ≤65 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. The participant has 2 or more of the following clinical signs and symptoms of acute cystitis with onset ≤72 hours of the screening assessment: dysuria, frequency, urgency, or lower abdominal pain (see Appendix 10).
3. The participant has pyuria (≥10 WBC/mm^3 or the presence of leukocyte esterase) and/or nitrite from a pretreatment clean-catch midstream urine sample based on local laboratory procedures.

   Note: Repeat baseline urine samples are allowed if contamination, defined as ≥10 squamous epithelial cells, is observed under microscopic evaluation.

Sex

4. The participant is female. A female participant is eligible to participate if she is not pregnant (Appendix 6), not breastfeeding, and at least 1 of the following conditions applies:

   - Not a woman of childbearing potential (WOCBP) as defined in Appendix 6

   OR

   - A WOCBP who agrees to follow the contraceptive guidance in Appendix 6 from the Baseline Visit through completion of the TOC Visit.

Informed Consent

5. Capable of giving signed informed consent as described in Appendix 3, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. The participant resides in a nursing home or dependent care-type facility.
2. The participant has a body mass index ≥40.0 kg/m^2 or a body mass index ≥35.0 kg/m^2 with obesity-related health conditions such as high blood pressure or uncontrolled diabetes.
3. The participant has a history of sensitivity to the study treatment, or components thereof, or a history of a drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates her participation.
4. The participant is immunocompromised or has altered immune defenses that may predispose the participant to a higher risk of treatment failure and/or complications (e.g., renal transplant recipients, participants with clinically significant persistent granulocytopenia [absolute neutrophil count <1000/μL], and participants receiving immunosuppressive therapy, including corticosteroid therapy [>40 mg/day prednisolone or equivalent for >1 week or ≥20 mg/day prednisolone or equivalent for >6 weeks; or prednisolone or equivalent ≥10 mg/day for >6 weeks]). Participants with a known CD4 count of <200 cells/mm^3 should not be enrolled. **Note**: Participants with a positive test for human immunodeficiency virus are eligible for study participation.
5. The participant has uncontrolled diabetes, defined as a nonfasting glucose value >300 mg/dL or based on investigator judgment.
6. The participant has any of the following:
   - A medical condition that requires medication that may be aggravated by inhibition of acetylcholinesterase, such as:
     - Poorly controlled asthma or chronic obstructive pulmonary disease at Baseline and, in the opinion of the investigator, not stable on current therapy
     - Acute severe pain, uncontrolled with conventional medical management
     - Active peptic ulcer disease
     - Parkinson disease
     - Myasthenia gravis
     - A history of seizure disorder requiring medications for control (this does not include a history of childhood febrile seizures)

   OR

   - Any surgical or medical condition (active or chronic) that may interfere with drug absorption, distribution, metabolism, or excretion of the study drug (e.g., ileostomy or malabsorption syndrome). Participants who have had a gastric bypass or a cholecystectomy are excluded from the study.

OR

- Hemoglobin value <12 g/dL or a known uncorrected iron deficiency.

7. The participant, in the judgment of the investigator, would not be able or willing to comply with the protocol or complete study follow-up.
8. The participant has a serious underlying disease that could be imminently life threatening, or the participant is unlikely to survive for the duration of the study period.

Urinary Tract Infection/Renal/Urogenital Exclusions

9. The participant has acute cystitis that is known or suspected to be due to fungal, parasitic, or viral pathogens; or known or suspected to be due to *Pseudomonas aeruginosa* or *Enterobacteriaceae* (other than *E. coli*) as the contributing pathogen.
10. The participant has symptoms known or suspected to be caused by another disease process such as asymptomatic bacteriuria or chronic interstitial cystitis.
11. The participant has an anatomical or physiological anomaly that predisposes the participant to UTIs or may be a source of persistent bacterial colonization, including calculi, obstruction or stricture of the urinary tract, primary renal disease (e.g., polycystic renal disease), or neurogenic bladder, or the participant has a history of anatomical or functional abnormalities of the urinary tract (e.g., chronic vesico-ureteral reflux, detrusor insufficiency).
12. The participant has an indwelling catheter, nephrostomy, ureter stent, or other foreign material in the urinary tract.
13. The participant who, in the opinion of the investigator, has an otherwise complicated UTI, an active upper UTI (e.g., pyelonephritis, urosepsis), signs and symptoms onset ≥96 hours before the screening assessment, or a temperature ≥101°F, flank pain, chills, or any other manifestations suggestive of upper UTI.
14. The participant has anuria, oliguria, or significant impairment of renal function (creatinine clearance <30 mL/min or clinically significant elevated serum creatinine).
15. The participant presents with vaginal discharge at Baseline (e.g., suspected sexually transmitted disease).

Cardiac Exclusions

16. The participant has congenital long QT syndrome or known prolongation of the corrected QT (QTc) interval.
17. The participant has uncompensated heart failure, defined as New York Heart Association Class ≥III.
18. The participant has severe left ventricular hypertrophy.
19. The participant has a family history of QT prolongation or sudden death.
20. The participant has a recent history of vasovagal syncope or episodes of symptomatic bradycardia or bradyarrhythmia within the last 12 months.
21. The participant is taking QT-prolonging drugs or drugs known to increase the risk of torsades de points (TdP) per the www.crediblemeds.org “Known Risk of TdP”

category at the time of her Baseline Visit, which cannot be safely discontinued from the Baseline Visit to the TOC Visit; or the participant is taking a strong cytochrome P450 enzyme 3A4 (CYP3A4) inhibitor or a strong P-glycoprotein (P-gp) inhibitor.

Cardiac ECG Exclusion

22. The participant has a QTc >450 msec or a QTc >480 msec for participants with bundle-branch block. **Note**: The QTc is the QT interval corrected for heart rate according to either Bazett or Fridericia formula, machine, or manual overread.

Hepatic Exclusions

23. The participant has a known alanine transferase (ALT) value >2 × upper limit of normal (ULN).
24. The participant has a known bilirubin value >1.5 × ULN (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
25. The participant has a current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones), including symptomatic viral hepatitis or moderate-to-severe liver insufficiency (Child Pugh class B or C). **Note**: Participants with asymptomatic viral hepatitis are eligible for study participation.

Prior Antibiotic/Antifungal Use Exclusion

26. The participant has received treatment with other systemic antimicrobials or systemic antifungals within 1 week before study entry.

Concomitant Medication Use Exclusion

27. The participant must agree not to use the medications or nondrug therapies from the Baseline Visit through the TOC Visit as detailed in Section 7.7.2.

Prior/Concurrent Clinical Study Experience

28. The participant has been previously enrolled in this study or has previously been treated with gepotidacin.
29. The participant has participated in a clinical trial and has received an investigational product within 30 days or 5 half-lives, whichever is longer.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

- Standard meals will be provided during the study dosing period at specified times that do not interfere with study procedures.
- Study treatment will be taken with food (a meal or a snack) (see Section 7.1).
- Participants will refrain from consumption of Seville oranges, grapefruit, or grapefruit juice (and/or pummelos, exotic citrus fruits, or grapefruit hybrids) from the Baseline Visit through collection of the final PK sample.

6.3.2. Caffeine and Alcohol

- Participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) from the Baseline Visit through collection of the final PK sample.
- Participants will abstain from alcohol from the Baseline Visit through collection of the final PK sample.

6.3.3. Activity

- Participants will abstain from strenuous exercise for 48 hours prior to each blood collection for clinical laboratory tests during the On-Therapy Visit; participants may engage in light recreational activities during the study (e.g., watch television, read).
- 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). Postdose compliance with a semi-supine position will be recorded in the source documents.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious AEs (SAEs).

Participants who are screen failures are not allowed to be rescreened for the same infection episode; however, participants who were screen failures for an earlier infection episode may be newly screened for a later infection episode and participate in the study if they meet all of the inclusion and exclusion criteria.

7. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

7.1. Treatments Administered

Participants will receive oral study treatment (gepotidacin 1500 mg [2 × 750-mg tablets]) BID for 5 days (10 total doses). All doses of study treatment will be administered under site staff supervision in the clinic and all doses will be administered with food (i.e., standardized meals or snacks as applicable). The first dose will be administered at the clinic by 2 PM on Day 1 (for practical reasons and participant convenience) and subsequent doses will be administered approximately every 12 hours. Participants should remain in the clinic to complete a total of 10 doses.

Study Treatment Name:	**Gepotidacin**
Dosage Formulation:	Tablets containing gepotidacin and inactive formulation excipients
Unit Dose Strengths/Dosage Levels:	750 mg per tablet/1500 mg per dose (2 × 750-mg tablets)
Route of Administration:	Oral
Dosing Instructions:	Administer twice daily for 5 days: 1500 mg – 2 × 750-mg tablets (3000 mg total daily dose) Each dose should be taken after food consumption and with water.
Packaging and Labeling:	Gepotidacin tablets will be provided in bottles. Each bottle will be labeled as required per country requirement.
Manufacturer:	GlaxoSmithKline

7.2. Dose Modification

The study design does not allow for dose modifications.

7.3. Method of 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.

7.4. Blinding

This will be an open-label study.

7.5. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual (SRM).

- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

7.6. Treatment Compliance

- Participants will receive study treatment in the clinic directly from the investigator or designee, under medical supervision. The date and time of each dose will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment. Study site personnel will examine each participant's mouth to ensure that the study treatment was ingested.

7.7. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7.7.1. Permitted Medications and Nondrug Therapies

The use of H_1 antihistaminics not associated with QT prolongation is allowed (e.g., loratadine, cetirizine, ebastine, and fexofenadine). The use of topical, nonsystemic antibacterials and topical, nonsystemic antifungals is allowed throughout the study.

7.7.2. Prohibited Medications and Nondrug Therapies

At the time of enrollment and/or during the study from the Baseline Visit through the TOC Visit, the participant is prohibited from use of the following medications and nondrug therapies:

- An investigational product within 30 days or 5 half-lives, whichever is longer, of the Baseline Visit.
- Treatment with other systemic antimicrobials or systemic antifungals within 1 week before study entry. Treatment with systemic fluconazole or other systemic antifungals per local standard of care is only allowed after all TOC Visit procedures have been completed.

- Immunosuppressive therapy, including corticosteroid therapy (>40 mg/day prednisolone or equivalent for >1 week or ≥20 mg/day prednisolone or equivalent for >6 weeks; or prednisolone or equivalent ≥10 mg/day for >6 weeks).
- QT-prolonging drugs or drugs with known TdP risk, per the www.crediblemeds.org "Known Risk of TdP" category, at the time of their Baseline Visit, which cannot be safely discontinued from the Baseline Visit to the TOC Visit. Details regarding website access are provided in the SRM.

  Note: Crediblemeds.org categorizes drugs into 4 categories. The only category for exclusion in this study is the "Known Risk of TdP" category; participants taking drugs that meet criteria of other categories are NOT excluded from participation.
- Strong CYP3A4 inhibitors (a list of strong CYP3A4 inhibitors is provided in the SRM).
- Strong P-gp inhibitors (a list of strong P-gp inhibitors is provided in the SRM).
- St John's wort is not permitted from 14 days before study entry through the TOC Visit.
- Prescription, nonprescription, or supplements that may impact UTI clinical or microbiological efficacy outcomes including, but not limited to, *Uva ursi*, cranberry tablets, phenazopyridine, nonsteroidal anti-inflammatory drugs including cyclooxygenase 2 inhibitors, uricosuric drugs (such as probenecid and sulfinpyrazone).
- Antacids administration is not permitted within 2 hours before or after study treatment administration.

Due to the gepotidacin's property of acetylcholinesterase inhibition, the concomitant use of succinylcholine or other nondepolarizing paralytic agents is also prohibited. Caution should be used in participants who have a condition requiring medication that may be exacerbated by acetylcholinesterase inhibition or neuromuscular blocking agents.

7.8. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after they discontinue or complete the study (i.e., after the Follow-up Visit). Participants experiencing signs and symptoms suggestive of infection recurrence or relapse at the Follow-up Visit will be assessed and treated per the investigator's judgement.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Participants may voluntarily discontinue study treatment at any time. The investigator may also, at his or her discretion, discontinue the participant from study treatment at any time and initiate appropriate alternative therapy. Reasons for study treatment discontinuation may include the following:

- Adverse event

- Protocol deviation
- Termination of the study by GSK
- Investigator discretion
- Lack of efficacy

Note: Pathogen identification or in vitro resistance of recovered uropathogens is not a reason for study treatment discontinuation.

The reason for study treatment discontinuation will be recorded in the electronic case report form (eCRF). Participants who discontinue study treatment for the reasons above will not be considered withdrawn from the study and should attend the TOC and Follow-up Visits as applicable.

If a participant discontinues during the on-treatment confinement period, Day 5 assessments (Table 1) will be completed before the participant is discharged. The participant will be instructed to return for the TOC and Follow-up Visits.

8.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Discontinuation of study treatment for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in Figure 2 and Figure 3.

OR

- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study treatment discontinuation is in the best interest of the participant.

Figure 2 Liver Chemistry Stopping and Increased Monitoring Algorithm

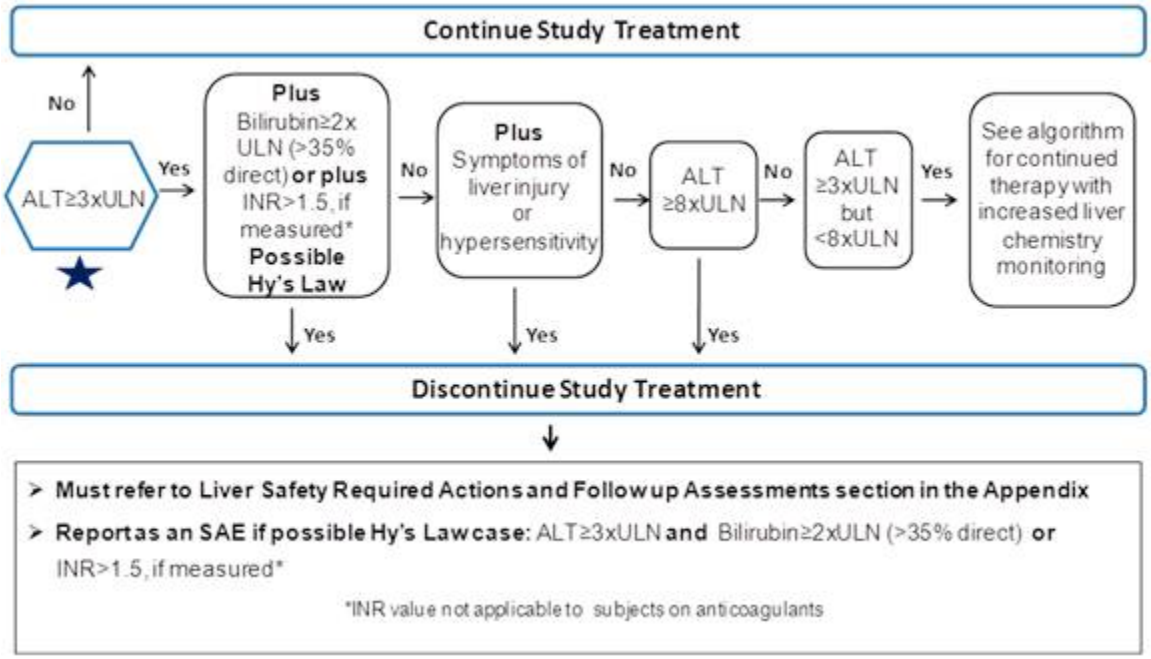
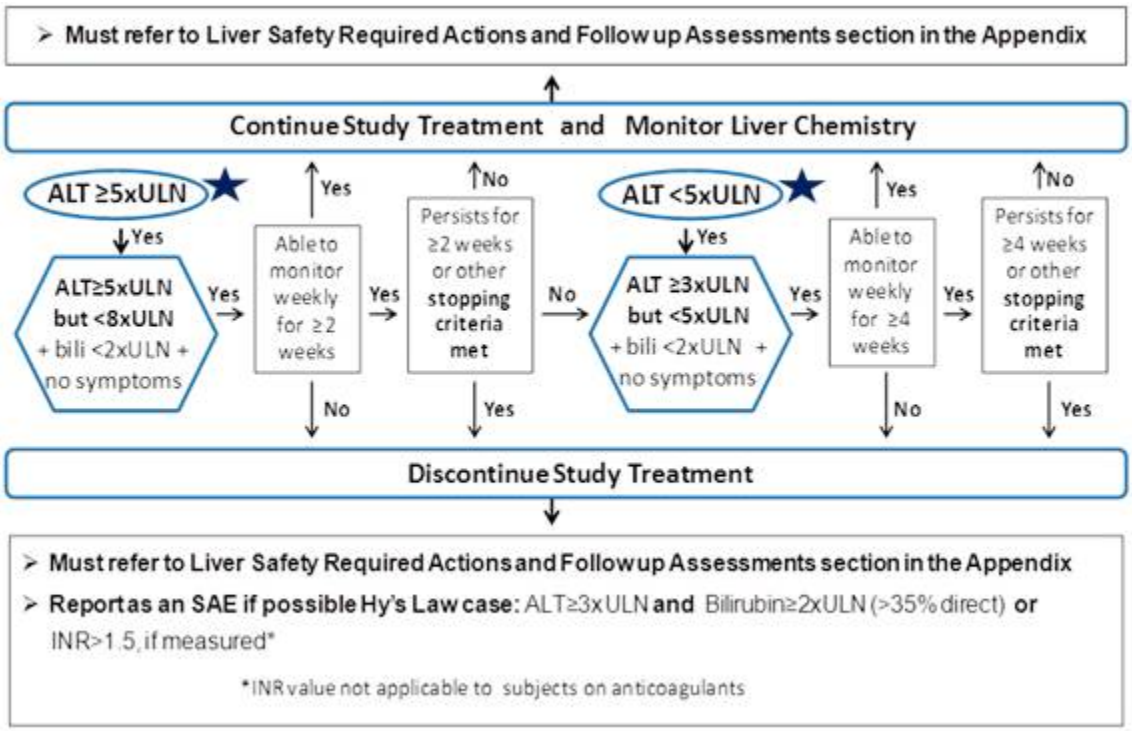


Figure 3 Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥3 x ULN but <8 x ULN



For details of the required assessments if a participant meets the above criterion, refer to Appendix 8.

8.1.2. QTc Stopping Criteria

A participant who meets the following bulleted criteria based on the average of triplicate ECG readings will be withdrawn from study treatment:

- QTc >500 msec OR uncorrected QT >600 msec
- Change from baseline of QTc >60 msec

For participants with underlying bundle-branch block, follow the discontinuation criteria listed below:

Baseline QTc with Bundle-Branch Block	Discontinuation QTc with Bundle-Branch Block
<450 msec	>500 msec
450 to 480 msec	≥530 msec

- The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.
  - For example, if a participant is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual participant as well.
  - Once the QT correction formula has been chosen for a participant's eligibility, the same formula must continue to be used for that participant *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTc should be based on averaged QTc values of triplicate ECGs obtained over a brief (e.g., 5- to 10-minute) recording period.

See Table 1 for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

8.1.3. Temporary Discontinuation

Temporary discontinuation of study treatment is not allowed. Participants who discontinue study treatment will not be considered withdrawn from the study and should attend the TOC and Follow-up Visits.

8.1.4. Rechallenge

8.1.4.1. Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- Reasons for study withdrawal include:
  - Participant lost to follow-up
  - Participant withdrew consent
  - Termination of the study by GSK
  - Investigator discretion
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to Table 1 for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in Table 1 and Table 2.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in Table 1 and Table 2, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in Table 1.
- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:

  1. 12-lead ECG
  2. Vital signs
  3. Pharmacokinetic and bacteriology urine specimen collection
  4. Pharmacokinetic and safety blood draws

  Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Participants will be confined to the clinic from Baseline through the On-Therapy Visit. Participants will return to the clinic for the 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 study will comprise the following visits and clinical procedures:

Clinic Confinement Visits

- **Baseline (Day -1 to Day 1 predose) Visit:** The Baseline Visit includes a screening window of up to 24 hours from the time of informed consent to the first dose of study treatment. Baseline assessments performed during the screening window do not need to be repeated before study treatment is started unless indicated as a Day 1 predose assessment in Table 1.

  Baseline assessments will be performed, including the following (see Table 1):

  - Participants will provide a pretreatment clean-catch midstream urine sample for confirmation of pyuria (≥10 WBC/mm^3 or the presence of leukocyte esterase) and/or nitrite per local laboratory procedures.

    Note: Repeat baseline urine samples are allowed if contamination, defined as ≥10 squamous epithelial cells, is observed under microscopic evaluation.

  - Site staff will record clinical signs and symptoms of acute cystitis (Appendix 10), clinical laboratory samples will be collected, vital signs will be measured, and a triplicate 12-lead ECG and complete physical examination will be performed.

  - Participants who meet the eligibility criteria in time to support the first dose of study treatment by 2 PM will be admitted to the clinic on Day 1 and On-Therapy procedures will begin. Participants who meet the eligibility criteria past the first dose time limit of 2 PM may be admitted that same day (Day -1) or the next morning (Day 1); dosing will start on the morning of Day 1.

  Day 1 predose assessments will be performed (see Table 1 and Table 2), including the following:

  - An ECG will be performed and vital signs will be measured if the baseline assessment was not within 4 hours of the first dose of study treatment.

  - Participants will provide a pretreatment clean-catch midstream urine sample for Gram stain, quantitative bacteriology culture, and antimicrobial susceptibility testing.

  - Predose blood and urine PK samples will be collected.

  - A stool microbiome specimen will be obtained from participants who consent to provide such specimens.

  - Vaginal and pharyngeal swab microbiome specimens will be obtained from participants who consent to provide such specimens.

- **On-Therapy (Day 1 to Day 5) Visit:** Participants will be confined to the clinic during the 5-day On-Therapy Visit period, and will receive oral gepotidacin 1500 mg BID for 5 days (total of 10 doses) starting with the first dose on Day 1. 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).

- The first dose of gepotidacin must be administered by 2 PM on Day 1 and subsequent doses will be administered approximately every 12 hours.
- Only if medically appropriate per the investigator's judgement, for participants who are enrolled after 2 PM, the first dose of study treatment will be postponed until the next morning; nonexclusionary pain medication will be allowed for these participants before study treatment is started.
- Study assessments and PK collections on Days 1 through 5 will be performed relative to the time-matched dose as determined by the first dose of study treatment (e.g., if the first dose is at 11 AM on Day 1 for a participant, then their time-matched dose on subsequent days will be at 11 AM; or, if the first dose is at 1 PM on Day 1 for a participant, then their time-matched dose on subsequent days will be at 1 PM).
- On Day 1, a single 12-lead ECG will be performed at 2 hours after the first dose of study treatment. On Day 4, a single 12-lead ECG will be performed at predose and 2 hours postdose (at the same ECG time points as on Day 1) (see Table 2).
- Vital sign measurements will be taken daily from Days 2 through 5.
- On Days 2 through 5, before the time-matched dose, clinical signs and symptoms of acute cystitis will be recorded (Appendix 10) and participants will provide a clean-catch midstream urine sample for Gram stain, quantitative bacteriology culture, and antimicrobial susceptibility testing.
- Blood and urine PK collection (see Table 1, Table 2, and Section 9.5.1).
- On Day 3, clinical laboratory samples will be collected for hematology, chemistry, and urinalysis.
- On Day 4, at predose and at approximately 2 hours postdose, cervical, rectal, and pharyngeal swab PK specimens will be obtained from participants who consent to provide such specimens.
- On Day 5, a stool microbiome specimen will be obtained from participants who consent to provide such specimens.
- On Day 5, vaginal and pharyngeal swab microbiome specimens will be obtained from participants who consent to provide such specimens.
- On Day 5, 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 will be discharged from the clinic. 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.

- At any time during the study, participants experiencing new or continuing signs and symptoms of acute cystitis will be assessed and treated per the investigator's judgement. If a participant is switched to a different antibiotic before or during the TOC Visit, all TOC procedures should be completed before the other antibiotic is started. Any participant who discontinues from the PK portion of the study should return for the TOC and Follow-up Visits.

Outpatient Visits

- **TOC (Day 10 to 13) Visit:** Participants will return for the TOC Visit 5 to 8 days after completion of study treatment. Clinical signs and symptoms of acute cystitis will be recorded (Appendix 10) and samples for Gram stain, quantitative bacteriology culture, and antimicrobial susceptibility testing will be collected. Safety assessments will be performed and AEs and concomitant medication use will be recorded.
- **Follow-up (Day 28) Visit:** Participants will return for the Follow-up Visit 28 (±3) days after the start of study treatment. Clinical signs and symptoms of acute cystitis will be recorded (Appendix 10) and samples for Gram stain, quantitative bacteriology culture, and antimicrobial susceptibility testing will be collected. Adverse events and concomitant medication use will be recorded. A stool microbiome specimen will be obtained from participants who consent to provide such specimens. Vaginal and pharyngeal swab microbiome specimens will be obtained from participants who consent to provide such specimens.

9.1. Efficacy Assessments

Efficacy is an exploratory assessment in this study. Please refer to Section 9.5 for the primary PK assessments.

9.1.1. Therapeutic Response Evaluation

Therapeutic response (success/failure) is a measure of the overall efficacy response. A therapeutic success refers to participants who have been deemed both a "microbiological success" (see Section 9.1.2.1) and a "clinical success" (i.e., "responders") (see Section 9.1.3). All other combinations (other than clinical success + microbiological success) will be deemed failures for therapeutic response.

Therapeutic response will be determined by statistical programming for TOC and Follow-up Visits.

9.1.2. Bacteriology Samples

At the Baseline Visit (predose on Day 1), a pretreatment, clean-catch midstream urine sample must be obtained from all participants for Gram stain, quantitative bacteriological culture, and in vitro antimicrobial susceptibility testing. For inclusion in the micro-ITT Population (Section 10.2), a baseline qualifying bacterial uropathogen (defined in Appendix 9) is required. At the On-Therapy (Days 2 through 5 only), TOC, and Follow-up Visits, a clean-catch midstream urine sample will be obtained and sent to a

central laboratory for Gram stain, quantitative bacteriological culture, and in vitro antimicrobial susceptibility testing. Identification and susceptibility testing of isolates recovered from urine specimens at all visits will also be conducted at a designated laboratory. Additional tests, as needed, to further characterize recovered isolates will also be performed by a designated laboratory. Instructions for sample collection, processing, and shipment are provided in the SRM and the laboratory manual. The study site should follow the Microbiology Procedures section of the laboratory manual to minimize potential contamination of the specimens.

9.1.2.1. Microbiological Outcome and Response

Only those participants who have a qualifying bacterial uropathogen (defined in Appendix 9) identified at Baseline will be evaluated for microbiological outcome and response. The microbiological outcome and response to study treatment will be determined by prespecified programmed algorithm for each participant/pathogen.

The microbiological outcome is determined by comparing the baseline culture results to the culture results at each subsequent visit (see Table 3, Table 4, and Table 5). The corresponding microbiological response (success or failure) “by pathogen” is then assigned, as shown in Table 4 and Table 5. Participant level microbiological response is a measure of the combined “by pathogen” response(s). Participant level microbiological success refers to participants who have been deemed a “microbiological success” for all of their “by pathogen” microbiological responses. All other combinations (other than all “microbiological successes”) are deemed failures for participant level microbiological response. Participant level microbiological response will be determined by statistical programming.

Table 3 Microbiological Outcome by Pathogen 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 clinical failure or unable to determine	Superinfection
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 clinical success	Colonization

CFU=colony-forming units.

Table 4 Microbiological Outcome and Response by Pathogen 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 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 clinical success	Colonization	Microbiological success

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

Table 5 Microbiological Outcome and Response by Pathogen 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 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 clinical success	Colonization	Microbiological success

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

9.1.3. Clinical Evaluation

Clinical signs and symptoms of acute cystitis will be recorded by site staff based on participant interview per the Schedule of Activities table (Table 1) using the scoring system in Appendix 10. 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. Clinical response (success or failure) will be determined at the TOC and Follow-up Visits, as summarized in Table 6. Clinical success at the On-Therapy (Days 2 through 5 only), TOC, and Follow-up Visits is defined as resolution of signs and symptoms of acute cystitis present at Baseline (and no new signs and symptoms) and no use of other antimicrobial therapy. For participants who

are clinical failures, additional questions may be asked regarding their acute cystitis signs and symptoms.

Table 6 Clinical Outcome and Response at the On-Therapy, Test-of-Cure, and Follow-Up Visits

Defining Criteria	Outcome (Investigator-Determined)[a]	Response
On-Therapy Visit (Days 2 through 5 only)[b]		
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 judgement and is defined as no worsening in signs and symptoms 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
Worsening 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 failed 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 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, reappearance of signs and symptoms, or use of other antimicrobial therapy for the current infection *Participants considered clinical failures at the TOC Visit will also be considered clinical failures at the Follow-up Visit.*	Clinical failure	Failure
Refusal to consent to a clinical examination or failed to attend the TOC Visit	Unable to determine	Failure

Defining Criteria	Outcome (Investigator-Determined)[a]	Response
Follow-up Visit		
Resolution of signs and symptoms of acute cystitis demonstrated at the TOC Visit persist at the Follow-up Visit (and no new signs and symptoms) and no use of other antimicrobial therapy	Sustained clinical success	Success
Persistence of signs and symptoms of infection, 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.

a. 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.

b. A participant showing some improvement at the On-Therapy Visit (Days 2 through 5 only) but less than what would be considered a clinical success should remain on study treatment per protocol, but study treatment may be discontinued per predefined criteria (see Section 8.1) or if there has been no clinical improvement; study treatment may be replaced by a different antibiotic, at the discretion of the investigator.

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment or from the study (see Section 8).

9.2.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the signing of the ICF until the Follow-up Visit at the time points specified in Table 1.
- All AEs will be collected from the start of treatment until the Follow-up Visit at the time points specified in Table 1.
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section.

- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and nonserious AEs of special interest (as defined in Section 9.2.5), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review board (IRB), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB, if appropriate according to local requirements.

9.2.5. Adverse Events of Special Interest

Predefined AEs of special interest for this study are cardiovascular (CV) events and gastrointestinal events (see Section 3.3.1), which will be identified by a prespecified list of coded terms.

9.2.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular and Death sections of the eCRF will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-CV death.

The CV CRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific CV section of the eCRF within 1 week of receipt of a CV Event data query prompting its completion.

The Death eCRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within 1 week of when the death is reported.

9.2.7. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment and through the Follow-up Visit.
- If a pregnancy is reported, the investigator should inform GSK/PPD within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 6.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

9.3. Treatment of Overdose

There is no specific antidote for overdose with a bacterial topoisomerase inhibitor. In the event of a suspected overdose, it is recommended that the appropriate supportive clinical care should be instituted, as dictated by the participant's clinical status.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for AEs/SAEs and laboratory abnormalities until study treatment can no longer be detected systemically (at least 72 hours).
3. Obtain a plasma sample for PK analysis within 24 hours from the date of the last dose of study treatment if requested by the medical monitor (determined on a case-by-case basis).

4. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

9.4. Safety Assessments

Planned time points for all safety assessments are provided in Table 1.

9.4.1. Physical Examinations

- Physical examinations will be performed at the time points indicated in Table 1.
- The physical examination will include assessments of the respiratory, CV, abdominal, gastrointestinal, neurological, and urogenital systems. Height and weight will only be measured and recorded at Baseline.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Clinically significant changes from baseline or clinically significant new clinical signs will be reported as AEs.

9.4.2. Vital Signs

- Vital signs will be measured at the time points indicated in Table 1.
- Vital signs will be measured in a semi-supine position and will include temperature, systolic and diastolic blood pressure, and pulse rate.
- Vital sign measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Vital sign measurements should be obtained before any blood draws scheduled on the same assessment day.
- Clinically significant changes from baseline will be reported as AEs.

9.4.3. Electrocardiograms

- Triplicate 12-lead ECGs will be performed at Baseline and single 12-lead ECGs will be performed at other time points as indicated in Table 1 and Table 2 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 8.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- Electrocardiograms will be obtained in semi-supine position.

- Electrocardiograms should be obtained before any vital sign measurements or blood draws scheduled on the same assessment day.
- For triplicate ECGs, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.
- If additional ECGs are performed, clinically significant changes occurring during the study will be reported as AEs.
- Refer to Section 8.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

9.4.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to Table 1 for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and Table 1.

9.5. Pharmacokinetics

9.5.1. Blood and Urine Samples

- Blood and urine samples for PK analysis of gepotidacin will be collected at the time points indicated in Table 1 and Table 2. The actual date and time of each sample collection will be recorded. The volume of blood required for each PK sample is approximately 3 mL.
- During the On-Therapy Visit, when the predose urine PK collection coincides with the predose urine bacteriology sample collection, a single urine sample of adequate volume may be collected and split into separate samples for PK and microbiological purposes. **Note:** The date and time of the last dose taken before the predose PK collection will be recorded.
- 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. The actual date and time of each sample collection will be recorded.

- Collection, processing, storage, and shipping procedures for blood and urine PK samples are provided in the SRM and/or laboratory manual.
- Plasma PK parameters for gepotidacin will include AUC(0-τ), Cmax, tmax, CLss/F, Ro, and Cτ. Urine PK parameters for gepotidacin will include Ae 12h, Ae(t1-t2), fe%, CLr, and Cτ.

9.5.2. Cervical, Rectal, and Pharyngeal Swab Specimens

- Cervical, rectal, and pharyngeal swab specimens for PK analysis of gepotidacin will be obtained at the time points shown in Table 1. 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 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.

9.6. Pharmacodynamics

9.6.1. Pharmacokinetics/Pharmacodynamics

Minimum inhibitory concentration values will be included for PK/PD analyses examining the potential relationship between gepotidacin exposure and clinical and microbiological outcome and/or response at the On-Therapy, TOC, and Follow-up Visits, if data permit.

9.6.2. Microbiome Assessments

- Stool specimens for potential microbiome assessment will be obtained at the time points shown in Table 1. The actual date and time of each sample collection will be recorded. Participation is optional. Participants who do not wish to participate in this microbiome assessment may still participate in the study.
- Vaginal and pharyngeal swab specimens for potential microbiome assessment will be obtained at the time points shown in Table 1. The actual date and time of each sample collection will be recorded. Participation is optional. Participants who do not wish to participate in this microbiome assessment may still participate in the study.
- Posttreatment stool, vaginal, and pharyngeal microbiome specimens should only be collected from participants who had a corresponding baseline specimen collected for each specimen type.
- Collection, processing, storage, and shipping procedures for microbiome specimens are provided in the SRM and/or laboratory manual.

9.7. Genetics

A 6-mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

Details on processes for collection and shipment and destruction of these samples can be found in Appendix 7.

9.8. Biomarkers

Biomarkers are not evaluated in this study.

9.9. Health Economics or Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics endpoints are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

Full details of all data handling conventions and statistical analyses conducted for this study will be provided in the reporting and analysis plan (RAP).

Hypothesis

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 UTI.

10.1. Sample Size Determination

The target sample size is approximately 20 participants who complete the study assessments through Day 5. The sample size for this study was based on feasibility; however, justification has been considered. Gepotidacin 1500 mg BID PK parameter estimates are available from a healthy volunteer study with repeat dosing for 14 days. For this dose of gepotidacin, the coefficient of variations for AUC(0-τ) and Cmax were 21.9% and 40.3%, respectively, after the initial dose, and 29.6% and 31.1%, respectively, at steady state. The upper limit of the 95% confidence interval for the mean of the PK parameters on both Days 1 and 4 for AUC(0-τ) and Cmax will be approximately within 15% and 20%, respectively, above the point estimate of the corresponding PK parameter.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
PK Population	Participants who receive at least 1 dose of gepotidacin and have evaluable plasma, urine, or tissue concentration data for gepotidacin. This primary analysis population will be used in the assessment and characterization of PK concentrations (summary tables and figures).
PK Parameter Population	All participants in the PK Population who received 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 and figures).
Intent-to-Treat (ITT) Population	All participants assigned to study treatment.
Microbiological ITT (micro-ITT) Population	All participants assigned to study treatment who receive at least 1 dose of gepotidacin have a qualifying baseline uropathogen (as defined in Appendix 9) from a quantitative bacteriological culture of a pretreatment clean catch midstream urine specimen.
Safety	All participants who take at least 1 dose of gepotidacin.

10.3. Statistical Analyses

10.3.1. Pharmacokinetic Analyses

Endpoint	Statistical Analysis Methods
Primary	• The primary endpoints of this study are PK-related. The analysis for the primary PK endpoints will be performed for the PK Parameter Population. Plasma concentrations of gepotidacin will be subjected to PK analyses using noncompartmental methods. • Based on the individual concentration-time data the following plasma parameters will be estimated: – Day 1 (first dose): AUC(0-τ), Cmax, and tmax – Day 4 (repeat dose): AUC(0-τ), Cmax, tmax, CLss/F, and Ro – Days 1 through 5 (predose): Cτ • Summary statistics (arithmetic mean, geometric mean, median, standard deviation, minimum, maximum, and coefficient of variation) for plasma

Endpoint	Statistical Analysis Methods
	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. Individual plasma gepotidacin PK parameter estimates will be plotted by day on linear scales.
Secondary	• The analysis for the secondary PK endpoints will be performed for the PK Parameter Population. Urine concentrations of gepotidacin will be subjected to PK analyses using noncompartmental methods. • Based on the individual concentration-time data the following urine parameters will be estimated: – Day 1 (first dose): Ae 12h, Ae(t1-t2), fe%, and CLr – Day 4 (repeat dose): Ae 12h, Ae(t1-t2), fe%, and CLr – Days 1 through 5 (predose): Cτ • Summary statistics (arithmetic mean, geometric mean, median, standard deviation, minimum, maximum, and coefficient of variation) for urine 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 urine PK parameter estimates will be listed by participant and study day. Individual urine gepotidacin PK parameter estimates will be plotted by day on linear scales

10.3.2. Safety Analyses

All safety analyses will be performed on the Safety Population. The severity of AEs and SAEs will be determined by the investigator according to the US National Institute of Allergy and Infectious Diseases Division of Microbiology and Infectious Diseases (DMID) criteria for adult toxicity assessment [DMID, 2007] (Appendix 5). All reported AEs will be coded using MedDRA and summarized by system organ class and preferred terms.

Endpoint	Statistical Analysis Methods
Secondary	• The number and percentage of treatment-emergent AEs, study treatment-related AEs, deaths, SAEs, and AEs leading to study treatment or study withdrawal will be provided. • Treatment-emergent AEs will be summarized by severity. • Change from baseline over time in laboratory parameters, vital signs, and ECGs will be summarized with descriptive statistics. • The frequency of laboratory abnormality events along with the shift from baseline to the worst-case postbaseline value will be provided. Abnormal liver chemistry results will be determined using both change from baseline values and increases above the upper limit of normal.

Endpoint	Statistical Analysis Methods
	• The severity of specified AEs and laboratory abnormalities will be graded according to the modified DMID toxicity grading system (Appendix 5). Data will be tabulated and reported by absolute grade for Grade 2/4 and shift tables, as appropriate.

10.3.3. Exploratory Analyses

Endpoint	Statistical Analysis Methods
Exploratory	• Therapeutic response (number and percentage of participants with combined per-participant microbiological and clinical response) will be summarized by pathogen at the TOC Visit for the micro-ITT Population. • The microbiological outcome and response (number and percentage of participants with microbiological success) will be summarized by pathogen group on Days 2 through 5 (outcome only) and at the TOC and Follow-up Visits for the micro-ITT Population. • The clinical outcome and response (number and percentage of participants with resolution of signs and symptoms) will be summarized by pathogen group on Days 2 through 5 (outcome only) and at the TOC and Follow-up Visits for the micro-ITT Population. • Therapeutic response (number and percentage of participants with combined per-participant microbiological and clinical response) at the Follow-up Visit for the micro-ITT Population. • Gram stain, quantitative bacteriology culture, and in vitro antibacterial susceptibility testing results for urine specimens will be summarized at the Baseline Visit (predose on Day 1), on Days 2 through 5, and at the TOC and Follow-up Visits for the micro-ITT Population. • The PK/PD relationship between gepotidacin exposure and microbiological and clinical outcome and/or response at the On-Therapy, TOC, and Follow-up Visits may be explored, if data permit. This may include assessment of gepotidacin exposures correlated with baseline minimum inhibitory concentrations and/or decreases in the baseline pathogen CFU/mL. • Gepotidacin concentrations in cervical, rectal, and pharyngeal tissues will be summarized, if data permit.

The PK/PD exploratory analyses will be described in the RAP and may be presented separately from the main clinical study report.

Stool, vaginal, and pharyngeal microbiome specimens may be analyzed to assess the number and proportion of relevant bacterial populations and metabolomics, as data permit. This analysis may be presented separately from the main clinical study report.

10.3.4. Interim Analyses

No interim analyses are planned for this study.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

ABSSSI	acute bacterial skin and skin structure infection
AE	adverse event
Ae 12h	amount of drug excreted over 12 hours
Ae(t1-t2)	amount drug excreted in urine in a time interval
ALT	alanine aminotransferase
AUC	area under the concentration-time curve
AUC(0-τ)	area under the concentration-time curve from zero (predose) over the dosing interval
BID	twice daily
CDC	Centers for Disease Control and Prevention
CFU	colony-forming units
CLr	renal clearance
CLss/F	apparent steady state clearance
Cmax	maximum plasma concentration
Cτ	predose concentration (trough)
CV	cardiovascular
CYP3A4	cytochrome P450 enzyme 3A4
DMID	Division of Microbiology and Infectious Diseases
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
ESBL	extended-spectrum β-lactamase
F	Fahrenheit
*f*AUC/MIC	ratio of the area under the free-drug concentration-time curve to minimum inhibitory concentration over 24 hours
FDA	Food and Drug Administration
fe%	percentage of the given dose of drug excreted in urine
GSK	GlaxoSmithKline
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
INR	international normalized ratio
IRB	institutional review board
ITT	Intent-to-Treat
kg	kilogram
m	meter
MDR	multidrug-resistant
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MIC	minimum inhibitory concentration
micro-ITT	Microbiological Intent-to-Treat
min	minute

mL	milliliter
mm	millimeter
msec	millisecond
P-gp	P-glycoprotein
PD	pharmacodynamic
PK	pharmacokinetic
QTc	corrected QT interval
QTcB	QT interval corrected for heart rate according to Bazett
QTcF	QT interval corrected for heart rate according to Fridericia
RAP	reporting and analysis plan
Ro	accumulation ratio
SAE	serious adverse event
SRM	Study Reference Manual
ST	sequence type
TdP	torsades de points
tmax	time of occurrence of Cmax
TOC	Test-of-Cure
TMP-SXT	trimethoprim-sulfamethoxazole
µg	microgram
ULN	upper limit of normal
UTI	urinary tract infection
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman of childbearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
None

Trademarks not owned by the GlaxoSmithKline group of companies
MedDRA

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 7 will be performed by the designated laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 7 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet count RBC count Hemoglobin Hematocrit	RBC Indices: MCV MCH	WBC Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[a]	Blood urea nitrogen	Potassium	AST/SGOT	Total and direct bilirubin
	Creatinine	Sodium	ALT/SGPT	Total protein
	Glucose nonfasting	Calcium	Alkaline phosphatase	Albumin
	Chloride			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, nitrite, and leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			

Laboratory Assessments	Parameters
Other Screening Tests	• A serum or urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines) • Serum hCG pregnancy test (as needed for women of childbearing potential)[b] • Serology (HBsAg, hepatitis C virus antibody, and HIV). 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. The results of each test must be entered into the eCRF.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; eCRF=electronic case report form; HBsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; WBC=while blood cell.

a. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1.1 and Appendix 8. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as a serious adverse event.

b. 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 Test-of-Cure Visit.

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB of an SAE or other significant safety findings as required by IRB procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of

informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

Committees Structure

To protect the safety interests of participants, a GlaxoSmithKline (GSK) Safety Review Team will review safety data in real time on a regular basis throughout study conduct. Data reviews will include but are not limited to the following participants: medical monitor, safety team lead, statistician, clinical team lead, and data quality lead.

Any written documentation regarding key decisions made by the review teams will be promptly distributed to participating investigator and IRB.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as

individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK policy.
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed case report form (CRF) or electronic CRF (eCRF) unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered into the eCRF.
- The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the

sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Study Reference Manual.

Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's

condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

Recording AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
• The severity of AEs and SAEs will be determined by the investigator according to the US National Institute of Allergy and Infectious Diseases Division of Microbiology and Infectious Diseases criteria for adult toxicity assessment [DMID, 2007] and (Appendix 5). An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The investigator will also consult the investigator's brochure (IB) and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has

minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the study site can report this information to the medical monitor or SAE coordinator by telephone.
- Contacts for SAE reporting can be found in SRM.

12.5. Appendix 5: Division of Microbiology and Infectious Diseases Adult Toxicity Tables for Adverse Event Assessment

ESTIMATING SEVERITY GRADE: For abnormalities NOT found elsewhere in the Toxicity Tables, use the scale below to estimate grade of severity:

GRADE 1	**Mild**	Transient or mild discomfort (<48 hours); no medical intervention/therapy required
GRADE 2	**Moderate**	Mild to moderate limitation in activity – some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	**Severe**	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4	**Life-threatening**	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

SERIOUS OR LIFE-THREATENING AEs: ANY clinical event deemed by the investigator to be serious or life-threatening should be considered a grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, and severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, National Cancer Institute's Common Toxicity Criteria, and World Health Organization) have been adapted for use by the Division of Microbiology and Infectious Diseases (DAIDS) and modified to better meet the needs of participants in Division of Microbiology and Infectious Diseases (DMID) trials.
- For parameters not included in the following Toxicity Tables, study sites should refer to the "Guide for Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.

Some protocols may have additional protocol specific grading criteria, which will supersede the use of these tables for specified criteria.

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.

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac rhythm	N/A	Asymptomatic, transient signs, no Rx required	Recurrent/persistent; symptomatic Rx required	Unstable dysrhythmia; hospitalization and treatment required
Hypertension	Transient increase >20 mm/Hg; no treatment	Recurrent, chronic increase >20 mm/Hg; treatment required	Acute treatment required; outpatient treatment or hospitalization possible	End organ damage or hospitalization required
Hypotension	Transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mmHg systolic BP. No treatment required	Symptoms due to orthostatic hypotension or BP decreased by <20 mmHg systolic; correctable with oral fluid treatment	Requires IV fluids; no hospitalization required	Mean arterial pressure <60 mmHg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	Minimal effusion	Mild/moderate asymptomatic effusion, no treatment	Symptomatic effusion; pain; EKG changes	Tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	Microscopic/occult	Mild, no transfusion	Gross blood loss; 1 to 2 units transfused	Massive blood loss; >3 units transfused

BP=blood pressure; IV=intravenous; EKG=electrocardiogram; N/A=not applicable; Rx=therapy.

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cough	Transient; no treatment	Persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	N/A
Bronchospasm, Acute	Transient; no treatment; FEV_1 70 to 80% of peak flow	Requires treatment; normalizes with bronchodilator; FEV_1 50 to 70% of peak flow	No normalization with bronchodilator; FEV_1 25 to 50% of peak flow; or retractions present	Cyanosis: FEV_1 <25% of peak flow; or intubation necessary
Dyspnea	Dyspnea on exertion	Dyspnea with normal activity	Dyspnea at rest	Dyspnea requiring oxygen therapy

FEV_1=forced expiratory volume in 1 second; N/A=not applicable.

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Nausea	Mild or transient; maintains reasonable intake	Moderate discomfort; intake decreased significantly; some activity limited	No significant intake; requires IV fluids	Hospitalization required
Vomiting	1 episode in 24 hours	2 to 5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	Physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	Requiring stool softener or dietary modification	Requiring laxatives	Obstipation requiring manual evacuation or enema	Obstruction or toxic megacolon
Diarrhea	Mild or transient; 3 to 4 loose stools/day or mild diarrhea lasting <1 week	Moderate or persistent; 5 to 7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	Hypotensive shock or physiologic consequences requiring hospitalization
Oral discomfort/ Dysphagia	Mild discomfort; no difficulty swallowing	Some limits on eating/drinking	Eating/talking very limited; unable to swallow solid foods	Unable to drink fluids; requires IV fluids

IV=intravenous.

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Neuro-Cerebellar	Slight incoordination dysdiadochokinesis	Intention tremor, dysmetria, slurred speech; nystagmus	Locomotor ataxia	Incapacitated
Psychiatric	Mild anxiety or depression	Moderate anxiety or depression; therapy required; change in normal routine	Severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	Acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle strength	Subjective weakness; no objective symptoms/signs	Mild objective signs/symptoms; no decrease in function	Objective weakness; function limited	Paralysis
Paresthesia (burning, tingling, etc.)	Mild discomfort; no treatment required	Moderate discomfort; non- narcotic analgesia required	Severe discomfort; or narcotic analgesia required with symptomatic improvement	Incapacitating; or not responsive to narcotic analgesia
Neurosensory	Mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision, and/or hearing	Moderate impairment (moderately decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	Severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least moderate degree in multiple different body areas (i.e., upper and lower extremities)	Sensory loss involves limbs and trunk; paralysis; or seizures

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia (joint pain)	Mild pain not interfering with function	Moderate pain, analgesics and/or pain interfering with function but not with ADL	Severe paid; pain and/or analgesics interfering with ADL	Disabling pain
Arthritis	Mild pain with inflammation, erythema or joint swelling, but not interfering with function	Moderate pain with inflammation, erythema or joint swelling; interfering with function but not with ADL	Severe pain with inflammation, erythema or joint swelling, and interfering with ADL	Permanent and/or disabling joint destruction
Myalgia	Myalgia with no limitation of activity	Muscle tenderness (at other than injection site) or with moderate impairment of activity	Severe muscle tenderness with marked impairment of activity	Frank myonecrosis

ADL=activities of daily living.

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mucocutaneous	Erythema; pruritus	Diffuse, maculo-papular rash, dry desquamation	Vesiculation or moist desquamation or ulceration	Exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	<15 mm	15 to 30 mm	>30 mm	N/A
Erythema	<15 mm	15 to 30 mm	>30 mm	N/A
Edema	<15 mm	15 to 30 mm	>30 mm	N/A
Rash at injection site	<15 mm	15 to 30 mm	>30 mm	N/A
Pruritus	Slight itching at injection site	Moderate itching at injection extremity	Itching over entire body	N/A

N/A=not applicable.

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Allergic reaction	Pruritus without rash	Localized urticarial	Generalized urticarial; angioedema	Anaphylaxis
Headache	Mild, no treatment required	Transient, moderate; treatment required	Severe; responds to initial narcotic therapy	Intractable; requires repeated narcotic therapy
Fever: oral	37.7 to 38.5°C or 100.0 to 101.5°F	38.6 to 39.5°C or 101.6 to 102.9°F	39.6 to 40.5°C or 103 to 105°F	>40°C or >105°F
Fatigue	Normal activity reduced <48 hours	Normal activity decreased 25 to 50%; >48 hours	Normal activity decreased >50%; cannot work	Unable to care for self

12.6. Appendix 6: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 8 in addition to using a male condom during intercourse.

Table 8 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

WOCBP=woman of childbearing potential.

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case 2 highly effective methods of contraception should be utilized during the treatment period and through the Test-of-Cure (Day 10 to 13) Visit.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test
- Additional pregnancy testing will be performed on Day 5 and at the Test-of-Cure (Day 10 to 13) Visit, 5 to 8 days after the last dose of study treatment and as required locally
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
- Pregnancy testing, with a sensitivity of 25 mIU/mL, will be performed using the test kit provided by the designated laboratory

Collection of Pregnancy Information

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GlaxoSmithKline (GSK)/PPD within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating will discontinue study treatment.

12.7. Appendix 7: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity, and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and institutional review board allow, a blood sample will be collected for DNA analysis.
- DNA samples will be used for research related to gepotidacin or uncomplicated urinary tract infections and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to and uncomplicated urinary tract infections. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate)
- DNA samples will be analyzed if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to gepotidacin or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on gepotidacin (or study treatments of this class) or uncomplicated urinary tract infections continues but no longer than 15 years after the last participant last visit or other period as per local requirements.

12.8. Appendix 8: Liver Safety: Required Actions and Follow-up Assessments

Phase IIa liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Phase IIa liver chemistry stopping criteria and required follow-up assessments

Liver Chemistry Stopping Criteria	
ALT Absolute	ALT ≥8 x ULN
ALT Increase	ALT ≥5 x ULN but <8 x ULN persists for ≥2 weeks ALT ≥3 x ULN but <5 x ULN persists for ≥4 weeks
Bilirubin[a,b]	ALT ≥3 x ULN **and** bilirubin ≥2 x ULN (>35% direct bilirubin)
INR[b]	ALT ≥3 x ULN **and** INR >1.5, if INR measured
Cannot Monitor	ALT ≥5 x ULN but <8 x ULN and cannot be monitored weekly for ≥2 weeks ALT ≥3 x ULN but <5 x ULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[c]	ALT ≥3 x ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow-up Assessments	
Actions	**Follow-up Assessments**
• Immediately discontinue study treatment • Report the event to GSK/PPD **within 24 hours** • Complete the liver event eCRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[b] • Perform liver event follow-up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** participant with study treatment • If restart/rechallenge **not allowed or not granted**, permanently discontinue study treatment and continue participant in the	• Viral hepatitis serology[d] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen), quantitative hepatitis B DNA, and hepatitis delta antibody[e] • Obtain blood sample for PK analysis, within 24 hours after last dose[f] • Serum creatine phosphokinase and lactate dehydrogenase • Fractionate bilirubin, if total bilirubin

study for any protocol-specified follow-up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within **24 hours** • Monitor participants twice weekly until liver chemistries resolve, stabilize, or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within **24 to 72 hours** • Monitor participants weekly until liver chemistries resolve, stabilize, or return to within baseline	≥2 x ULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake eCRF page **<u>For bilirubin or INR criteria:</u>** • Antinuclear antibody, antismooth muscle antibody, type 1 antiliver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computed tomography) and/or liver biopsy to evaluate liver disease; complete liver imaging and/or liver biopsy eCRFs.

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; eCRF=electronic case report form; GSK=GlaxoSmithKline; HPLC=high-performance liquid chromatography; IgM=immunoglobulin M; INR=international normalized ratio; PK=pharmacokinetic; SAE=serious adverse event; ULN=upper limit of normal.

a. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥3 x ULN and bilirubin ≥2 x ULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.

b. All events of ALT ≥3 x ULN and bilirubin ≥2 x ULN (>35% direct bilirubin) or ALT ≥3 x ULN and INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants.

c. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).
d. Includes: hepatitis A IgM antibody; hepatitis B surface antigen and hepatitis B core antibody (IgM); hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); hepatitis E IgM antibody.
e. If hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction of hepatitis D RNA virus (where needed) [Le Gal, 2005].
f. The PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to PK blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Study Reference Manual.

Phase III liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5 x ULN and <8 x ULN **and** bilirubin <2 x ULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3 x ULN and <5 x ULN **and** bilirubin <2 x ULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK/PPD medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize, or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5 x ULN and <8 x ULN to ≥3 x ULN but <5 x ULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3 x ULN and bilirubin <2 x ULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GSK=GlaxoSmithKline; ULN=upper limit of normal.

References

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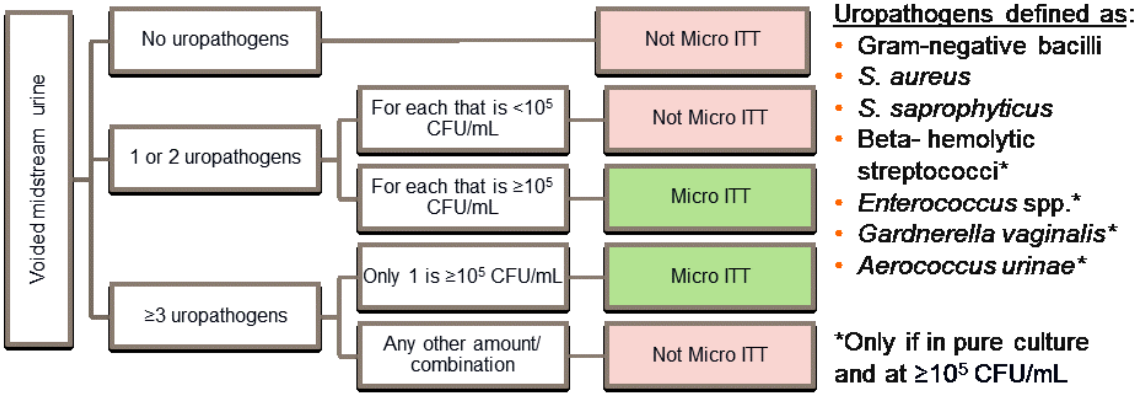
12.9. Appendix 9: Algorithm for the Microbiological Intent-to-Treat Population

Participants will be included in the Microbiological Intent-to-Treat Population if they receive at least 1 dose of gepotidacin and have a qualifying bacterial uropathogen (defined in Figure 4) at Baseline (predose on Day 1) from a quantitative bacteriology culture of a pretreatment clean-catch midstream urine specimen.

The algorithm for determining microbiological evaluable participants based on microbiology laboratory quantitative culture results is provided in Figure 4.

Figure 4 Baseline Algorithm for the Microbiological Intent-to-Treat Population



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

References

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12.10. Appendix 10: Clinical Signs and Symptoms Scoring for Acute Cystitis

Acute cystitis clinical signs and symptoms will be scored as follows:

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

Scores will be recorded by the investigator or a qualified designee. When possible, the same scorer will be used at all assessment time points.