TITLE PAGE

Protocol Title: A Phase III, Multicenter, Randomized, Active Reference, Double-blind, Double-dummy Study in Japanese Female Participants to Evaluate the Efficacy and Safety of Gepotidacin in the Treatment of Uncomplicated Urinary Tract Infection (Acute Cystitis)

Protocol Number: 214144/ amendment 02

Compound Number:	GSK2140944

Brief Title: A study to investigate the efficacy and safety with gepotidacin in Japanese female participants with uncomplicated urinary tract infection (acute cystitis); **Efficacy of Antibacterial Gepotidacin Evaluated in Japan (EAGLE-J)**

Study Phase: Phase III

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**Document Identifier**
Amendment 02	07-NOV-2022	TMF-15095845
Amendment 01	12-OCT-2022	TMF-15039137
Original Protocol (00)	22-AUG-2022	TMF-14785506

Amendment 02 07-NOV-2022

Overall Rationale for the Amendment: This amendment modified the requirement of high sensitivity urine pregnancy test kit provided to study sites based on the new nonclinical finding since the start of the Phase 3 program as the 12.5 mIU/mL urine pregnancy tests are more globally available than urine pregnancy tests with a sensitivity down to 6.3 mIU/mL. The name of ethical guidelines is modified. The description about a microbiology monitoring plan is deleted in Section 10.1.5.

Section # and Name	**Description of Change**	**Brief Rationale**
8.2.5. Pregnancy Testing	Modified the requirement of high sensitivity urine pregnancy test kit provided to study sites from ≤6.3 mIU/mL to ≤12.5 mIU/mL.	To update the requirement of urine pregnancy test kit based on the new nonclinical finding since the start of the Phase 3 program as the 12.5 mIU/mL urine pregnancy tests are more globally available than urine pregnancy tests with a sensitivity down to 6.3 mIU/mL.
8.6 Genetics	Modified the name of ethical guidelines	To apply the latest version of protocol template.
10.1.5. Committees Structure	Removed the description about a microbiology sample monitoring plan.	The microbiology sample monitoring plan is not prepared for this study.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase III, Multicenter, Randomized, Active Reference, Double-blind, Double-dummy Study in Japanese Female Participants to Evaluate the Efficacy and Safety of Gepotidacin in the Treatment of Uncomplicated Urinary Tract Infection (Acute Cystitis)

Brief Title: A study to investigate the efficacy and safety with gepotidacin in Japanese female participants with uncomplicated urinary tract infection (acute cystitis); **Efficacy of Antibacterial Gepotidacin Evaluated in Japan (EAGLE-J)**

Rationale:

Urinary tract infections (UTIs; acute cystitis) are very common, with approximately 11% of women (greater than 18 years of age) reporting at least 1 episode of acute uncomplicated cystitis per year. 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 *Escherichia coli* (*E. coli*; 75% to 90%) followed by *Staphylococcus saprophyticus* (5% to 15%). Multidrug resistance, which is typically associated with nosocomial infections, has emerged at the community level and has made treatment approaches for UTIs more difficult. Furthermore, extended spectrum β-Lactamase (ESBL)-producing *Enterobacteriaceae* (now recognized as *Enterobacterales*), which includes *E. coli*, is recognized as a serious threat.

In Japan, published epidemiology studies reporting the incidence of UTIs are limited [Kusama, 2021; Sako, 2021], but the disease thought to be common infectious disease [Takahashi, 2022]. Most patients suffering from acute uncomplicated cystitis are sexually active women as shown in outside of Japan [Yamamoto, 2017]. The predominant uropathogens isolated from patients with acute uncomplicated cystitis are *E coli* (approximately 70%) followed by *Klebsiella pneumoniae*, *Streptococcus agalactiae*, *S. saprophyticus*, *Enterococcus faecalis* which are observed in only 3% to 5% [Wada, 2021]. In Japan as well, the resistance rate of ESBL-producing bacteria has been increased [Hayami, 2013; Hayami, 2019; Wada, 2021], and similarly increasing global rates of MDR bacteria may elevate the likelihood of MDR associated UTI infections becoming more common [Arcilla, 2017; Hassing, 2015]. There is an unmet medical need for new therapeutic agents that exhibit strong antibacterial activity against such bacteria [Kusama, 2021; Nakagawa, 2021].

Gepotidacin is a first-in-class, novel triazaacenaphthylene bacterial type II topoisomerase inhibitor. The microbiological spectrum of activity of gepotidacin includes *E. coli*, *S. saprophyticus*, and *E. faecalis*. This Phase III study aims to assess the consistency of therapeutic response (combined per-participant microbiological and clinical response) of gepotidacin observed in this study with global studies (Studies 204989 and 212390).

Objectives and Endpoints and Estimands:

Objectives	Endpoints
Primary	
• To assess the consistency of therapeutic response of gepotidacin at the Test of cure (TOC) Visit (Day 10 to 13) in female participants with acute uncomplicated cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin in Japan, with that from global studies (Studies 204989 and 212390).	• Therapeutic response (combined per-participant microbiological and clinical response) at the TOC Visit
Secondary	
• To assess the therapeutic response of gepotidacin compared to nitrofurantoin as an active reference descriptively, at the TOC Visit, in female participants with acute uncomplicated cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin	• Therapeutic response at the TOC Visit
• To assess the clinical efficacy and microbiological efficacy of gepotidacin at the TOC Visit in female participants with acute uncomplicated cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin	• Clinical outcome and response at the TOC Visit • Microbiological outcome and response at the TOC Visit
• To assess the therapeutic response, clinical efficacy and microbiological efficacy of gepotidacin at the TOC Visit in female participants with acute uncomplicated cystitis who have qualifying uropathogen(s) resistant to two or more specific classes of antimicrobials at Baseline	• Therapeutic response at the TOC Visit • Clinical outcome and response at the TOC Visit • Microbiological outcome and response at the TOC Visit
• To assess the clinical efficacy of gepotidacin at the TOC Visit in female participants with acute uncomplicated cystitis	• Investigator assessment of clinical response at the TOC Visit

• To assess the safety and tolerability of gepotidacin in female participants with acute uncomplicated cystitis	• Occurrence of treatment-emergent adverse events (AEs), serious AEs (SAEs) and adverse events of special interest (AESIs) • Change from baseline in clinical laboratory tests • Change from baseline in electrocardiograms (ECGs) • Change from baseline in vital sign measurements
• To determine the plasma and urine PK concentrations of gepotidacin in female participants with acute uncomplicated cystitis	• Gepotidacin plasma and urine concentrations

Please refer to Section 8.1.1, 8.1.2.1 and 8.1.3.1 for the definition of therapeutic response, microbiological outcome/response and clinical outcome/response
Please refer to Section 10.8 for details of qualifying bacterial uropathogen(s)
Note: Exploratory objectives are described in the main protocol text.

Primary estimand

The primary estimand is described by the following attributes:

- Population: Japanese and non-Japanese (from Studies 204989 and 212390) female participants with acute uncomplicated cystitis who have qualifying uropathogen(s) at Baseline that all are susceptible to nitrofurantoin.
- Treatment condition: Gepotidacin 1500 mg twice daily (BID) for 5 days in this study versus gepotidacin 1500 mg BID for 5 days in the global studies (Studies 204989 and 212390) regardless of adherence.
- Variable: Therapeutic response (combined per-participant microbiological and clinical response) at the TOC Visit. Microbiological success is defined as eradication (i.e. reduction) of all qualifying bacterial uropathogens recovered at baseline to $<10^3$ colony-forming units/mL (CFU/mL) as observed on quantitative urine culture without the participant receiving other systemic antimicrobials. Clinical success is defined as resolution of signs and symptoms of acute cystitis present at Baseline (and no new signs and symptoms) without the participant receiving other systemic antimicrobials.
- Summary measure: Comparison of the proportion of Japanese participants achieving therapeutic success in this study with 10%tile of the predicted distribution for the proportion of participants achieving therapeutic success in this study derived from the global studies (Studies 204989 and 212390) under the assumption of consistency
- Intercurrent events (ICEs):
- Study treatment discontinuation (due to any reason) – treatment policy strategy (interest is in the treatment effect regardless of study treatment discontinuation)

- Use of systemic antimicrobials – composite strategy. This ICE is captured through the definitions of microbiological and clinical response (see Section 8.1.2.1 and 8.1.3.1)

The secondary estimands are provided in the Section 3.

Overall Design:

- Study 214144 is a Phase III randomized, multicentre, active reference, double-blind, double-dummy study in adolescent and adult Japanese female participants to evaluate the efficacy and safety of gepotidacin. The primary objective is to assess consistency of this study with global studies (Studies 204989 and 212390) for therapeutic response of gepotidacin.
- The study duration will be approximately 28 days with 4 visits.
- Participants will be stratified by age category (≤50 years, or >50 years) and acute uncomplicated cystitis recurrence (recurrent or nonrecurrent) and will be randomly assigned in a 3:1 ratio to receive either oral gepotidacin or oral nitrofurantoin (active reference).

Brief Summary:

The purpose of this study is to assess consistency of this study with global studies (Studies 204989 and 212390) for therapeutic response of gepotidacin at TOC Visit.

Study details include:

- Participants will receive treatment for 5 days according to their randomized treatment and assessed as follows:
    - Appropriate safety, clinical and microbiological assessments will be conducted at the Baseline (Day 1) Visit and repeated at the On-therapy (Day 2 to 4), TOC (Day 10 to 13), and Follow-up (Day 28 ± 3) Visits. CCI [redacted]
    - For the primary efficacy endpoint of therapeutic response (combined per participant microbiological and clinical response), therapeutic success refers to participants who have been deemed both a microbiological success (reduction of all qualifying bacterial uropathogens [e.g., $\geq 10^5$ colony-forming units/mL (CFU/mL)] recovered at Baseline to $<10^3$ CFU/mL as observed on quantitative urine culture without the participant receiving other systemic antimicrobials) and a clinical success (resolution of signs and symptoms of acute cystitis present at Baseline [and no new signs and symptoms] without the participant receiving other systemic antimicrobials) at the TOC Visit in the Microbiological Intent-to-Treat Nitrofurantoin-Susceptible (micro-ITT NTF-S) Population defined in Section 8.1.3, regardless of treatment discontinuation.

- PK samples will be collected in all participants for analysis at the Baseline (postdose) and the On-therapy Visits (predose and postdose).

Number of Participants:

Approximately 300 participants will be enrolled to obtain approximately 108 Japanese females (adolescent and adults) ≥12 years meeting the eligibility criteria with qualifying uropathogen(s) at Baseline that all are susceptible to nitrofurantoin (micro-ITT NTF-S Population). Enrolment will continue until the approximate target number of participants in the micro-ITT NTF-S Population has been reached. This study will be conducted at multiple sites in Japan.

Note: Enrolled means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.

Intervention Groups and Duration:

Participants will be stratified by age category and acute uncomplicated cystitis recurrence (recurrent or nonrecurrent). Recurrence is defined as a confirmed infection [not including the current infection in the calculation] with at least 1 prior episode within the past 3 months, at least 2 prior episodes within the past 6 months, or at least 3 prior episodes within the past 12 months before study entry). Participants will be randomly assigned in a 3:1 ratio to receive either oral gepotidacin or oral nitrofurantoin as follows:

- Gepotidacin: 1500 mg administered orally BID for 5 days
- Nitrofurantoin: 100 mg administered orally BID for 5 days

Note: each dose of gepotidacin and nitrofurantoin should be taken after food consumption and with water.

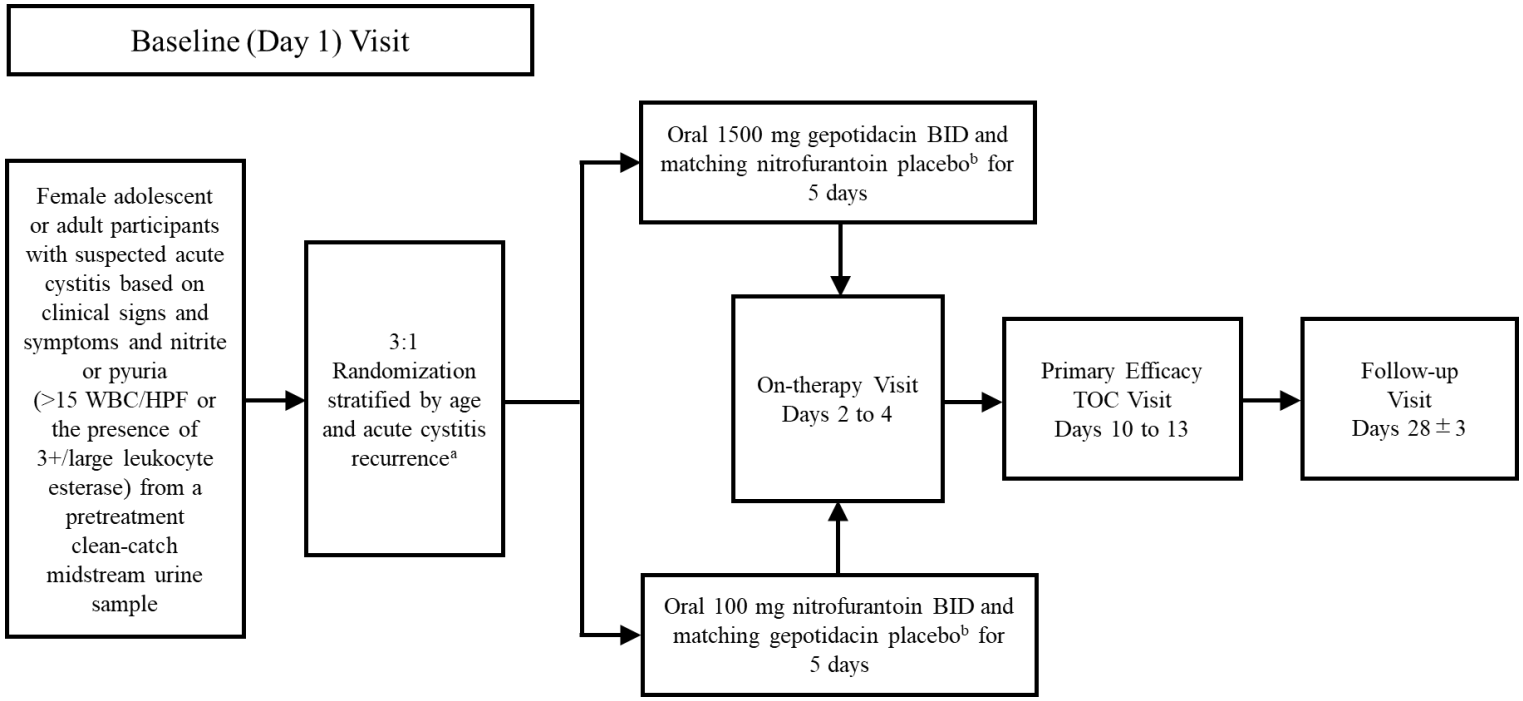
The duration of study participation is approximately 28 days with 4 planned study visits:

- Baseline (Day 1) Visit
- On-therapy (Day 2 to 4) Visit
- TOC (Day 10 to 13) Visit
- Follow-up (Day 28±3) Visit

Data Monitoring/ Other Committee: A GlaxoSmithKline Safety Review Team will monitor blinded safety data, while a Microbiology Review Team will monitor blinded microbiological data instream.

1.2. Schema

Figure 1 Study Design Schematic



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

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

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

1.3. Schedule of Activities (SoA)

Visit	Baseline		On-Therapy[a]	TOC[b]	Follow-up	Early Withdrawal	Notes
Study Day	1		2 to 4	10 to 13	28±3	NA	
Procedure	Pre-dose	Post-dose					
Written informed consent/assent	X						
IRT – Screening module	X						
Inclusion and exclusion criteria	X						
Participant demography	X						
Medical/surgical history	X						
IRT – Randomization module	X						
Randomization	X						
Schedule next visit	X		X	X	X		• On Day 1, the planned return day/time for the On-therapy, TOC, and Follow-up Visits should be scheduled before the participant leaves the study site. • Pre-visit reminder: Study site staff will contact the participant 24±4 hours before the scheduled On-therapy, TOC, and Follow-up Visits.
Assessments							
Physical examination (including height and weight at Baseline only)	X			X			At the TOC Visit, the physical examination may be symptom directed and is only required if indicated for a specific participant.
12-lead ECG	X	X	X	X			• See Section 5.2 for ECG exclusion criterion for participants aged ≥12 to <18 years. For additional details see Section 7.1.2 and Section 8.2.3. • For postdose on Day 1 and On-Therapy Visit, ECGs will be collected at approximately 2 hours postdose (i.e., expected time of maximum concentration; ECG collection should ideally be within approximately 1.5 hours postdose to 4 hours postdose). Electrocardiograms will be reviewed locally by the investigator for safety purposes.
Vital sign measurements	X		X	X			Take measurement of temperature, blood pressure, and pulse rate.
Record acute cystitis sign and symptoms	X		X	X	X	X	Individual clinical signs and symptoms scores of acute cystitis will be recorded by a study physician or otherwise appropriately medically trained staff based on participant interview and using the scoring system in 10.10. The same scorer will be used at all

Visit	Baseline		On-Therapy[a]	TOC[b]	Follow-up	Early Withdrawal	Notes
Study Day	1		2 to 4	10 to 13	28±3	NA	
Procedure	Pre-dose	Post-dose					
							assessment time points for each participant, on all occasions, whenever possible.
Investigator assessment of clinical response				X	X	X	The investigator will provide an assessment of clinical response (clinical success, clinical failure, or indeterminate, per the definitions in Section 10.11) for each participant at the TOC and Follow-up Visits, and at early withdrawal (if applicable). This assessment should be completed after the clinical signs and symptoms score is determined by the same study physician or otherwise appropriately medically trained staff who performed the clinical scoring assessment.
CCI							
Labs & blood/urine sampling							
Bacteriology samples	X		X	X	X	X	• Participants will provide a clean-catch midstream urine sample at each visit for Gram stain, quantitative bacteriology culture, and in vitro antimicrobial susceptibility testing by a designated central laboratory(ies). Refer to the laboratory manual. • A predose bacteriology urine sample will be collected at the On-therapy Visit.
Hematology, chemistry, and urinalysis	X		X	X			
Diagnosis of presumptive acute uncomplicated cystitis	X						Based on confirmation of nitrite or pyuria (>15 WBC/HPF or the presence of 3+/large leukocyte esterase) from a pretreatment clean-catch midstream urine sample per local laboratory procedures.
Urine pregnancy test	X		X	X		X	For women of childbearing potential, a negative high sensitivity urine pregnancy test is sufficient for eligibility. See Section 8.2.5 for Baseline urine test sensitivity requirements and 10.4 for associated contraception requirements. Pregnancy testing should

Visit	Baseline		On-Therapy[a]	TOC[b]	Follow-up	Early Withdrawal	Notes
Study Day	1		2 to 4	10 to 13	28±3	NA	
Procedure	Pre-dose	Post-dose					
							be performed after Dose 4 and before Dose 8, as specified in Section 8.2.5.
Serology (hepatitis B and C and HIV)	X						If serology testing was performed within 3 months prior to the first dose of study treatment and the results were positive, testing at Baseline is not required. If testing was performed within 3 months and any result was negative, testing at Baseline is required.
Drug and alcohol screen	X						
Genetic sample	X						Collect sample only if the participant has a signed consent/assent specific for this purpose. The Baseline Visit is the recommended time to collect the sample, but it can be collected at any time during the study.
PK blood sample		X	X				Sparse PK blood samples will be collected. • At the Baseline Visit, the PK blood samples will be collected at 1-2 hours post-dose as peak concentration. • At the On-therapy Visit, the PK blood samples will be collected at pre-dose as trough concentration (i.e., 12 hours post-dose, which is at the end of the dosing interval from the previous dose) and at 1-2 hours-post dose as peak concentration. (Further detailed information will be provided in the SRM.)
PK urine sample		X	X				• At the Baseline Visit, samples will be collected from pre-dose to approximately 2 hours (1 to 3 hours) post-dose as pooled urine. • At the On-therapy Visit, samples will be collected at pre-dose (i.e., 12 hours postdose as spot urine, which is at the end of the dosing interval from the previous dose) and from pre-dose to approximately 2 hours (1 to 3 hours) post-dose as pooled urine. (Further detailed information will be provided in the SRM.)
Study treatment							
Administer oral dose of study treatment		X	X				• Participants will receive oral study treatment BID for 5 days under double-blind, double-dummy conditions. The first oral dose will be administered at the study site during the Baseline Visit; participants will self-administer as outpatients thereafter, beginning with the second dose, excluding the day of On-therapy Visit (i.e., taking morning dose at study site). Each dose should

Visit	Baseline		On-Therapy[a]	TOC[b]	Follow-up	Early Withdrawal	Notes
Study Day	1		2 to 4	10 to 13	28±3	NA	
Procedure	Pre-dose	Post-dose					
							be taken after food consumption and with water. The date and time of each dose administered at the study site will be recorded in the source documents. • At the On-therapy Visit, whenever it is possible, the participant will have the pregnancy test performed at the study site. If the visit coincides with the 8th dose, the participant will take their next dose of study treatment at the study site after negative pregnancy test results are confirmed. Note: The On-therapy Visit should be scheduled to support completion of the postdose ECG within the protocol-defined window. Also, in a woman of childbearing potential, the high sensitivity pregnancy test must be performed and show negative results at the latest before Dose 8 of study treatment is taken.
Study treatment compliance			X	X			Determine study treatment compliance by performing pill count.
Safety reviews							
Serious adverse events	X[C]	X	X	X	X	X	
Adverse events		X	X	X	X	X	Record adverse events from the time of the first dose of study treatment.
Concomitant medication review	X	X	X	X	X	X	

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

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

b. For the TOC (Day 10 to 13) Visit: Participants will be instructed to return to the study site 5 to 8 days after completion of study treatment.

c. SAEs must be collected from signing of Informed Consent if considered related to study procedures or GSK concomitant medication.

2. 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 has activity versus key pathogens, including drug-resistant strains associated with a range of conventional and biothreat infections. The microbiological spectrum of activity of gepotidacin includes *Escherichia coli*, the key causative pathogen of acute uncomplicated cystitis, *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.

2.1. Study Rationale

This study is being conducted based on the need to establish new and effective oral antimicrobial treatment options for acute uncomplicated cystitis, as such therapies are becoming limited due to the increase of multidrug-resistant (MDR) pathogens and extended-spectrum β-lactamase (ESBL) producing *Enterobacterales* pathogens, which are impacting the efficacy of currently available oral antibacterial treatment options (see Section 2.2).

Two Phase II studies were conducted and the results demonstrated that gepotidacin was effective in the treatment of uncomplicated urogenital gonorrhea and acute bacterial skin and skin structure infections (ABSSSIs) (see investigator's brochure [IB] for details). In addition, a Phase IIa pharmacokinetic (PK) study (206899) was conducted in 22 female participants with acute uncomplicated cystitis that also included exploratory clinical and microbiological efficacy objectives. All 22 participants were evaluated for PK and clinical efficacy analysis. Of the 22 participants, 19 participants (86%) and 18 participants (82%) achieved symptom resolution at the Test-of-Cure (TOC) and Follow-up Visits, respectively. Eight of 22 participants (36%) who received at least 1 dose of gepotidacin had a qualifying baseline uropathogen (5 with *E. coli* isolates, 1 with a *S. saprophyticus* isolate, 1 with a *Klebsiella pneumoniae* isolate, and 1 with a *Citrobacter koseri* isolate). Of these 8 participants, 7 participants (88%) and 6 participants (75%) had a microbiological response of microbiological success ($<10^3$ colony-forming units/mL [CFU/mL]) at the TOC and Follow-up Visits, respectively. Furthermore, of these 8 participants, 6 participants (75%) and 5 participants (63%) had a therapeutic response (combined per-participant microbiological and clinical response) of success at the TOC and Follow-up Visits, respectively. Refer to the IB for PK, safety, and additional efficacy results.

Global Phase III studies (204989 and 212390) are being conducted aiming to evaluate the therapeutic response (combined microbiological and clinical efficacy per participant) of

oral gepotidacin compared to oral Nitrofurantoin for acute uncomplicated cystitis in adolescent and adult female participants.

The purpose of this Phase III study (214144) is to assess the consistency of therapeutic response (combined per-participant microbiological and clinical response) of gepotidacin observed in this study with global studies (Studies 204989 and 212390).

2.2. Background

2.2.1. Urinary Tract Infection

Urinary tract infections (UTIs) are very common, with approximately 11% of women >18 years of age experiencing at least 1 episode of acute uncomplicated 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 uncomplicated cystitis occurs in young, sexually active women ages 18 to 29 years [Fihn, 2003]. The predominant uropathogens isolated in community-acquired UTIs are *E. coli* (75% to 90%) followed by *S. saprophyticus* (5% to 15%) [Stamm, 1993; Talan, 2000; Foxman, 2010]. *Klebsiella*, *Enterobacter*, *Proteus* species, and enterococci are observed in only 5% to 10% of acute uncomplicated cystitis [Stamm, 1993; Talan, 2000; Foxman, 2010].

In Japan, published epidemiology studies reporting the incidence of UTIs are limited [Kusama, 2021; Sako, 2021], but the disease thought to be common infectious disease [Takahashi, 2022]. Most patients suffering from acute uncomplicated cystitis are sexually active women as shown in overseas [Yamamoto, 2017]. The predominant uropathogens isolated from patients with acute uncomplicated cystitis are *E. coli* (approximately 70%) followed by *Klebsiella pneumoniae*, *Streptococcus agalactiae*, *S. saprophyticus*, *Enterococcus faecalis* which are observed in only 3% to 5% [Wada, 2021].

2.2.2. Multidrug resistance in UTI

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 antimicrobials [Foxman, 2002; Gupta, 2011a; Hooton, 2012]. Furthermore, ESBL-producing *Enterobacteriaceae* (now recognized as *Enterobacterales*), which includes *E. coli*, is recognized as a serious threat by the Centers for Disease Control and Prevention (CDC) [CDC, 2019] and drug-resistant *Enterobacteriaceae* is a critical priority pathogen for the World Health Organization (WHO) [WHO, 2017]. The availability of oral antimicrobials that are effective against ESBL producers 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 uncomplicated 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 the prevalence of 7.6% ESBL-producing *Enterobacterales* 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 uncomplicated cystitis now recommend first-line antimicrobial 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 the 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.

In Japan, fluoroquinolone-resistant bacteria and ESBL-producing bacteria have been paying attention as well. In early 2000, quinolone-resistant strains were rarely isolated in acute uncomplicated cystitis, but gradually increased, and the resistance rate of *E. coli* was reported to be 15.6% in a recent study [Wada, 2021]. ESBL-producing bacteria were originally regarded as one of the pathogens of nosocomial infections, and were rarely a problem in pathological conditions such as acute uncomplicated cystitis previously, however in recent years, ESBL-producing *E. coli* could be detected at approximately 9.5% [Wada, 2021].

In Japan, the treatment recommendations of antimicrobials for acute uncomplicated cystitis differ between premenopausal and postmenopausal women. This is because the frequency of isolation of Gram-positive cocci is low and isolated *E. coli* shows a high rate of fluoroquinolone resistance in postmenopausal women, compared with premenopausal women. The Japanese therapeutic guideline recommends that fluoroquinolones should be used as the first-line treatment for acute uncomplicated cystitis in premenopausal women if tested positive by urinalysis for Gram-positive cocci, but should not be used if tested positive for Gram-negative rods [Yamamoto, 2017]. For these women, the guideline recommends using cephalosporins, or penicillins with β-Lactamase inhibitor (BLI). For postmenopausal women, on the other hand, the guideline recommends selecting cephalosporins or penicillins with BLI as the first-line treatment because of a high proportion of fluoroquinolone-resistant isolates for the major uropathogen *E. coli* in acute uncomplicated cystitis. However, when Gram-positive cocci have been detected in a urine test, fluoroquinolones are recommended. Since ESBL-producing strains are frequently resistant to fluoroquinolones, fosfomycin and faropenem

are recommended in both premenopausal and postmenopausal women if their uropathogen(s) are ESBL-producing strains [Yamamoto, 2017].

ESBL-producing *E. coli* has been spreading rapidly and worldwide, with extremely high detection rates in some areas [Doi, 2013; Flamm, 2014]. In current global society, there are no borders in the transmission of bacteria, and anyone can be a carrier of ESBL-producing bacteria and MDR bacteria [Arcilla, 2017; Hassing, 2015]. In fact, the resistance rate of ESBL-producing *E. coli* has been gradually increased in Japan [Hayami, 2013; Hayami, 2019; Wada, 2021], and similarly increasing global rates of MDR bacteria may elevate the likelihood of MDR associated UTI infections becoming more common in Japan. In addition, National action plan on Antimicrobial Resistance was established [The Government of Japan, 2016]. There is an unmet medical need for new therapeutic agents that exhibit strong antibacterial activity against such bacteria [Kusama, 2021; Nakagawa, 2021].

2.2.3. Gepotidacin in acute uncomplicated cystitis treatment

Gepotidacin is a first-in-class, novel triazaacenaphthylene antibacterial compound that has demonstrated *in vitro* activity against uropathogens including *E. coli* (see 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 uncomplicated cystitis.

A detailed description of the chemistry, pharmacology, efficacy, and safety of gepotidacin is provided in the IB.

2.3. 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. And those of nitorofrantoin may be found in the package insert.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Gepotidacin (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 the IB for details). In Phase I studies, concentration-dependent QT prolongation has been observed during clinical trials with gepotidacin; however, this increase has not translated into clinically significant QTc values or changes from baseline (change from baseline >60 msec or QTcF >500 msec) or cardiovascular AEs. In Phase I and II studies, gepotidacin did not have a clinically relevant effect on cardiac conduction (PR and QRS intervals). Although there appears to be a trend to higher gepotidacin systemic exposure in healthy Japanese compared to Western subjects, the higher systemic exposure of gepotidacin observed in Japanese subjects is currently considered to be within the tolerable range and not associated with any cardiovascular safety concerns.	See Section 5.2 for excluded cardiac conditions. Close monitoring of clinical parameters and AEs (Section 1.3) will be conducted, and treatment monitoring and evaluation criteria (Section 7.1.2) will be utilized to mitigate cardiovascular effects. Participants taking medications known to increase QT or potent CYP3A4 inhibitors will be excluded (see Section 6.8.2). See also the Renal and Hepatic sections within this table below.
Gastrointestinal Effects Based on nonclinical data, gastrointestinal effects were mild ulceration of the nonglandular mucosa and minimal erosion and/or mural inflammation of	See also the Acetylcholinesterase Inhibition section within this table below.	See Section 5.2 for excluded medical conditions. Close monitoring of clinical parameters and AEs (Section 1.3) will be conducted to mitigate and assess gastrointestinal effects.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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. Nausea and vomiting AEs have also been commonly observed in gepotidacin clinical studies.	*Clostridioides difficile* and *C. difficile*-associated diarrhea has been observed in clinical trials with gepotidacin.	Suspected *C. difficile* infection will be managed according to a prespecified algorithm provided in 10.7.
Acetylcholinesterase Inhibition In vitro testing showed gepotidacin to be a rapidly reversible inhibitor of acetylcholinesterase in the clinical plasma concentration range. Based on clinical data, caution should be used in participants who have a condition requiring treatment with anticholinergic medications or who have certain medical conditions that may be exacerbated by the acetylcholinesterase inhibition activity of gepotidacin.	Increased cholinergic effects can potentially be associated with more severe symptoms including atrioventricular block, seizure/convulsions, bronchospasm, and vasovagal syncope. No causal relationship between these events and the use of gepotidacin has been established during clinical trials to date. Adverse events consistent with acetylcholinesterase inhibition, including diarrhea, nausea, vomiting, gastrointestinal cramping and pain, dyspnea, bradycardia, lacrimation, salivation, dysarthria, and diaphoresis/sweating have been reported during clinical trials with gepotidacin. Mild and transient non-gastrointestinal AEs have been associated with Cmax levels higher than this dosing regimen.	Participants who have medical conditions or require medications that may be impacted by inhibition of acetylcholinesterase will be excluded from participation in this study. See Section 5.2 for excluded medical conditions and Section 6.8.2, 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 (Section 1.3).
Hepatic Effects In preclinical studies, increases in ALT, GLDH, alkaline phosphatase, and total bilirubin were observed in some rat studies of varying exposure.	Elevations in ALT have occurred in a few participants with pre-existing hepatitis C infection, but none were felt related to study treatment. The type and pattern of elevation in liver transaminases observed has not been suggestive of an adverse effect of gepotidacin and none were considered related to study treatment.	Participants with severe hepatic impairment are excluded from Phase III trials. See Section 5.2 for excluded medical conditions. Monitoring and stopping criteria liver events have been implemented.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	A substantial increase in Cmax and AUC and decrease in clearance was observed in volunteer participants with severe hepatic impairment.	
Renal Effects In preclinical trials, mild to moderate tubular degeneration was noted in the rat and proteinuria in the dog. Proteinuria was also observed in humans.	No clinical evidence of renal toxicity has been seen in clinical trials to date. A substantial increase in Cmax and AUC and decrease in clearance was observed in severe renal impairment/ESRD participants not on hemodialysis and in ESRD participants requiring hemodialysis (note: gepotidacin may have been administered at any time other than when receiving dialysis).	Participants with severe renal impairment/ESRD (including those who may require dialysis) are excluded from Phase III trials. See Section 5.2 for excluded medical conditions. Monitoring criteria have been implemented.
Reproductive System Effects Preclinical studies demonstrated that gepotidacin was not genotoxic and no drug related malformations were observed. Although positive in vitro findings for clastogenicity, consistent with a mechanism related to mammalian topoisomerase II inhibition were found, in vivo data from rat micronucleus and COMET assays suggest that gepotidacin does not pose a genotoxic hazard to humans. Gepotidacin effects on embryofetal development were limited to decreased fetal weights for male and female fetuses in rats and decreased fetal weights and increased fetal resorptions (fetal deaths) in mice, both at maternally toxic doses.These occurred at clinically relevant exposure (65 µg.h/mL in rat and 35µg.h/mL in mouse).	There are no data on the use of gepotidacin in pregnant women.	Gepotidacin is not recommended in pregnant or nursing mothers. Pregnancy testing requirements in this study minimize the risk of exposure to a fetus. See 10.4 for contraceptive measures and Section 8.2.5 for required pregnancy testing.
Other		
Nitrofurantoin	The most frequent AEs possibly or probably related to oral nitrofurantoin treatment are nausea (8%),	Close monitoring of clinical parameters and AEs (Section 1.3) will be conducted, and treatment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	headache (6%), and flatulence (1.5%). As with gepotidacin, there is also a need to monitor for *C. difficile*-associated diarrhea during nitrofurantoin treatment. Nitrofurantoin is contraindicated for patients with anuria, oliguria, or significant impairment of renal function; pregnant patients at term (38 to 42 weeks' gestation), during labor and delivery, or when the onset of labor is imminent; neonates under 1 month of age; and patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with nitrofurantoin. Rare adverse reactions that generally occur in patients receiving treatment for 6 months or longer are acute, subacute, or chronic pulmonary reactions, with potential insidious development of chronic pulmonary reactions (diffuse interstitial pneumonitis or pulmonary fibrosis, or both). Peripheral neuropathy has occurred, which may be enhanced for patients with renal impairment, anemia, diabetes mellitus, electrolyte imbalance, vitamin B deficiency, and debilitating disease. Nitrofurantoin has induced the occurrence of hemolytic anemia of the primaquine sensitivity type, which appear to be linked to a glucose-6-phosphate dehydrogenase deficiency in the red blood cells of the affected patients.	monitoring and evaluation criteria (Section 7.1.1) will be utilized to mitigate hepatic effects. Because planned treatment in this study is only 5 days, the probability for adverse reactions associated with long-term use is low. The exclusion criteria for this study include contraindications to nitrofurantoin use and exclude participants at risk for nitrofurantoin adverse reactions, including acute porphyria as an example of a rare genetic risk (see Section 5.2). Participants with a history of sensitivity to nitrofurantoin, or components thereof, will not be allowed to enroll in the study (Section 5.2). Participant's medical history will be carefully evaluated for history of hypersensitivity. Participants must agree not to use antacid preparations containing magnesium trisilicate or uricosuric drugs during study treatment (see Section 5.2). Suspected *C. difficile* infection will be managed according to a prespecified algorithm provided in 10.7. Precautions related to nitrofurantoin are summarized in detail in the Study Reference Manual.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Hepatic reactions, including hepatitis, cholestatic jaundice, chronic active hepatitis, and hepatic necrosis, occur rarely. Concomitant administration of nitrofurantoin with antacids containing magnesium trisilicate reduces both the rate and extent of absorption, and uricosuric drugs, such as probenecid and sulfinpyrazone, can inhibit renal tubular secretion of nitrofurantoin.	Participants with a known glucose-6-phosphate dehydrogenase deficiency will not be allowed to enroll in the study (Section 5.2)

bpm=beats per minute; AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; AUC=area under the drug concentration-curve; Cmax=maximum concentration; CYP3A4=cytochrome P450 enzyme 3A4; ESRD=end-stage renal disease; GLDH=glutamate dehydrogenase; IB=investigator's brochure; IV=intravenous; ΔΔQTcF=placebo-corrected change from-baseline in corrected QT interval using the Fridericia formula; QTc=corrected QT interval; QTcF=interval corrected for heart rate according to Fridericia's formula.

2.3.2. Benefit Assessment

Acute uncomplicated cystitis is among the most common indications for which antimicrobials are prescribed for otherwise healthy women [Gupta, 2011b]. The increase in antimicrobial resistance among pathogens causing community-acquired UTIs over the past 2 decades has made treatment approaches for UTIs more difficult. Rising incidences of Anti-microbial Resistance and MDR represent a pressing and growing public health issue in both Japan and the rest of the world. There are limited options currently available for treating infections with MDR organisms. Merely a few antimicrobials with new mechanisms and no cross resistance to other antimicrobials are in clinical development at this time.

Gepotidacin is active in vitro and in vivo against the key causative pathogen in acute uncomplicated cystitis, *E. coli*, including most isolates resistant to other antibacterial treatments. Given gepotidacin's spectrum of activity against *E. coli*, *S. saprophyticus*, and *E. faecalis*, as well as human safety data and the PK profile, it is anticipated that gepotidacin will benefit participants with acute uncomplicated cystitis.

The active reference in this study is nitrofurantoin, a marketed antimicrobial in several global markets including the US and EU for the treatment of acute uncomplicated UTIs (acute cystitis) caused by susceptible strains of *E. coli* or *S. saprophyticus* as a first-line therapy with high efficacy and good tolerability dosed for 5 days or longer. Although nitrofurantoin is not approved in Japan, it was a marketed antimicrobial in Japan until 1990 and has shown efficacy in Japanese patients with acute uncomplicated cystitis and had no clinically significant safety issues [Tsunoda, 1970; Ookita, 1970; Tofukuji,1970]. Participants randomly assigned to this treatment group are also expected to experience treatment benefits.

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

2.3.3. Overall Benefit: Risk Conclusion

Antimicrobial resistance among uropathogens causing acute uncomplicated cystitis has increased in the past decades [Gupta, 2011b; Sanchez, 2016]. However, despite of increasing drug resistance to existing agents, few new antimicrobials with novel mechanisms of action are being developed. Gepotidacin selectively inhibits bacterial DNA replication by a means not utilized by any currently approved human therapeutic agent. Based on the known preclinical data for gepotidacin against *E. coli*, *S. saprophyticus*, and *E. faecalis*, the Phase II results showing the effective treatment of uncomplicated urogenital gonorrhea and ABSSSIs, Phase IIa results indicating efficacy in acute uncomplicated cystitis, and the cumulative safety results from Phase I and Phase II studies with oral gepotidacin treatment, this study will assess the consistency of this study with global studies (Studies 204989 and 212390) for the therapeutic response (combined microbiological and clinical efficacy per participant) of oral gepotidacin.

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 to protect participant safety and to better characterize the safety profile of the study treatments (Section 2.3.1). Furthermore, a GlaxoSmithKline (GSK) Safety Review Team (SRT) will monitor blinded safety data in stream (see 10.1). Careful safety monitoring should also identify any emerging safety issues for gepotidacin and nitrofurantoin.

The investigator may also, 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 and nitrofurantoin are justified by the anticipated benefits that may be afforded to participants with acute uncomplicated cystitis.

3. OBJECTIVES AND ENDPOINTS AND/OR ESTIMANDS

Objectives	Endpoints
Primary	
• To assess the consistency of therapeutic response of gepotidacin at the Test of cure (TOC) Visit (Day 10 to 13) in female participants with acute uncomplicated cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin in Japan, with that from global studies (Studies 204989 and 212390).	• Therapeutic response (combined per-participant microbiological and clinical response) at the TOC Visit
Secondary	
• To assess the therapeutic response of gepotidacin compared to nitrofurantoin as an active reference descriptively, at the TOC Visit, in female participants with acute uncomplicated cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin	• Therapeutic response at the TOC Visit
• To assess the clinical efficacy and microbiological efficacy of gepotidacin at the TOC Visit in female participants with acute uncomplicated cystitis with qualifying	• Clinical outcome and response at the TOC Visit • Microbiological outcome and response at the TOC Visit

bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin	
• To assess the therapeutic response, clinical efficacy and microbiological efficacy of gepotidacin at the TOC Visit in female participants with acute uncomplicated cystitis who have qualifying uropathogen(s) resistant to two or more specific classes of antimicrobials at Baseline	• Therapeutic response at the TOC Visit • Clinical outcome and response at the TOC Visit • Microbiological outcome and response at the TOC Visit
• To assess the clinical efficacy of gepotidacin at the TOC Visit in female participants with acute uncomplicated cystitis	• Investigator assessment of clinical response at the TOC Visit
• To assess the safety and tolerability of gepotidacin in female participants with acute uncomplicated cystitis	• Occurrence of treatment-emergent adverse events (AEs), serious AEs (SAEs) and adverse events of special interest (AESIs) • Change from baseline in clinical laboratory tests • Change from baseline in electrocardiograms (ECGs) • Change from baseline in vital sign measurements
• To determine the plasma and urine PK concentrations of gepotidacin in female participants with acute uncomplicated cystitis	• Gepotidacin plasma and urine concentrations
Exploratory	

CCI

[redacted]

Please refer to Section 8.1.1, 8.1.2.1 and 8.1.3.1 for the definition of therapeutic response, microbiological outcome/response and clinical outcome/response
Please refer to Section 10.8 for details of "qualify bacterial uropathogen(s)

Primary estimand

The primary clinical question of interest is: Whether the therapeutic response at the TOC visit in female participants with acute uncomplicated cystitis who have qualified uropathogen(s) at Baseline that all are susceptible to nitrofurantoin in this study is consistent with that from the global studies, regardless of intervention discontinuation for any reason. Receipt of systemic antimicrobials will impact the endpoint definition (see Section 8.1.2.1 and 8.1.3.1).

The estimand is described by the following attributes:

- Population: Japanese and non-Japanese (from Studies 204989 and 212390) female participants with acute uncomplicated cystitis who have qualifying uropathogen(s) at Baseline that all are susceptible to nitrofurantoin.
- Treatment condition: Gepotidacin 1500 mg BID for 5 days in this study versus gepotidacin 1500 mg BID for 5 days in the global studies (Studies 204989 and 212390) regardless of adherence.
- Variable: Therapeutic response (combined per-participant microbiological and clinical response) at the TOC Visit. Microbiological success is defined as eradication (i.e. reduction) of all qualifying bacterial uropathogens recovered at baseline to $<10^3$

colony-forming units/mL (CFU/mL) as observed on quantitative urine culture without the participant receiving other systemic antimicrobials. Clinical success is defined as resolution of signs and symptoms of acute cystitis present at Baseline (and no new signs and symptoms) without the participant receiving other systemic antimicrobials.

- Summary measure: Comparison of the proportion of Japanese participants achieving therapeutic success in this study with 10%tile of the predicted distribution for the proportion of participants achieving therapeutic success in this study derived from the global studies (Studies 204989 and 212390) under the assumption of consistency.
- Intercurrent events (ICEs):
  - Study treatment discontinuation (due to any reason) – treatment policy strategy (interest is in the treatment effect regardless of study treatment discontinuation)
  - Use of systemic antimicrobials – composite strategy. This ICE is captured through the definitions of microbiological and clinical response (see Section 8.1.2.1 and 8.1.3.1

Rationale for estimand:

Interest in this study lies in whether the efficacy of this study is consistent with the global studies.

The clinical question of interest in this study and the global studies (Studies 204989 and 212390) lies in the treatment effect regardless of whether the full course of 5 days of treatment was taken or not, which reflects how patients may be treated in clinical practice. Hence, a treatment policy strategy is appropriate for treatment withdrawal before completing 5 days of treatment. Use of other systemic antimicrobials may confound the bacterial culture results; thus, the microbiological response will be considered failure. For clinical data, the use of a systemic antimicrobial for acute uncomplicated cystitis is a sign of treatment failure and use of a systemic antimicrobial for another infection cannot be considered a success as it confounds the assessment of efficacy. Therefore, the definition of a successful therapeutic response precludes the use of other systemic antimicrobials.

Table 1 Estimand for the Other Secondary Endpoints

Secondary objective	Population	Treatment Condition	Variable	Summary Measure	Intercurrent Event
To assess the therapeutic response of gepotidacin compared to nitrofurantoin as an active reference descriptively, at the TOC Visit, in female participants with acute uncomplicated cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin	Japanese female participants with acute uncomplicated cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin	Gepotidacin 1500 mg BID for 5 days versus nitrofurantoin 100 mg BID for 5 days, regardless of adherence	Therapeutic response at the TOC Visit	Difference in proportions of participants achieving therapeutic success in the gepotidacin and nitrofurantoin treatment groups	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antimicrobials on or prior to the visit of interest – composite strategy
To assess the clinical efficacy and microbiological efficacy of gepotidacin at the TOC Visit in female participants with acute uncomplicated cystitis with qualifying bacterial uropathogen(s) at	Japanese female participants with acute uncomplicated cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin	Gepotidacin 1500 mg BID for 5 days, regardless of adherence	Clinical response at the TOC Visit	Proportion of participants achieving clinical success in the gepotidacin group	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antimicrobials on or prior to the visit of interest – composite strategy

Secondary objective	Population	Treatment Condition	Variable	Summary Measure	Intercurrent Event
Baseline that all are susceptible to nitrofurantoin			Clinical outcome at the TOC Visit	Proportion of participants in each outcome category in the gepotidacin arm	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antimicrobials on or prior to the visit of interest – composite strategy
			Microbiological response at TOC Visit	Proportion of participants achieving microbioglocal success in the gepotidacin group	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antimicrobials on or prior to the visit of interest – composite strategy

Secondary objective	Population	Treatment Condition	Variable	Summary Measure	Intercurrent Event
			Microbiological outcome at TOC Visit	Proportion of participants in each outcome category in the gepotidacin arm	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antimicrobials on or prior to the visit of interest – composite strategy
To assess therapeutic response, clinical efficacy and microbiological efficacy of gepotidacin at the TOC Visit in female participants with acute uncomplicated cystitis who have qualifying	Japanese female participants with acute uncomplicated cystitis who have qualifying uropathogen(s) resistance to two or more specific classes of antimicrobials at Baseline	Gepotidacin 1500 mg BID for 5 days	Therapeutic response (combined per-participant microbiological and clinical response) at the TOC Visit	Proportion of participants achieving therapeutic success in the gepotidacin group	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antimicrobials on or prior to the visit of interest – composite strategy

Secondary objective	Population	Treatment Condition	Variable	Summary Measure	Intercurrent Event
uropathogen(s) resistant to two or more specific classes of antimicrobials at Baseline			Clinical response at the TOC Visit	Proportion of participants achieving clinical success in the gepotidacin group	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antimicrobials on or prior to the visit of interest – composite strategy
			Clinical outcome at the TOC Visit	Proportion of participants in each outcome category in the gepotidacin arm	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antimicrobials on or prior to the visit of interest – composite strategy

Secondary objective	Population	Treatment Condition	Variable	Summary Measure	Intercurrent Event
			Microbiological response at the TOC Visit	Proportion of participants achieving microbiological success in the gepotidacin group	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antimicrobials on or prior to the visit of interest – composite strategy
			Microbiological outcome at the TOC Visit	Proportion of participants in each outcome category in the gepotidacin arm	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antimicrobials on or prior to the visit of interest – composite strategy

Secondary objective	Population	Treatment Condition	Variable	Summary Measure	Intercurrent Event
To assess the clinical efficacy of gepotidacin at the TOC Visit in female participants with acute uncomplicated cystitis	Japanese female participants with acute uncomplicated cystitis	Gepotidacin 1500 mg BID for 5 days, regardless of adherence	Investigator assessment of clinical response at the TOC Visit	Proportion of participants with investigator assessed clinical response of success, failure and indeterminate/missing on the gepotidacin arm	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antimicrobials on or prior to the visit of interest – composite strategy
To assess the safety and tolerability of gepotidacin in female participants with acute uncomplicated cystitis	Japanese female participants with acute uncomplicated cystitis	Gepotidacin 1500 mg BID for 5 days, regardless of adherence	TEAEs, AESI, SAEs, as well as change from baseline results for clinical laboratory tests, electrocardiograms (ECGs) and vital sign measurements	Summary statistics in the gepotidacin arm Incident rate for TEAE, AESI and SAE Mean change from baseline for clinical laboratory tests, ECGs and vital sign measurements.	Study treatment discontinuation (due to any reason) – treatment policy

Secondary objective	Population	Treatment Condition	Variable	Summary Measure	Intercurrent Event
Pharmacokinetic	Japanese female participants with acute uncomplicated cystitis	Gepotidacin 1500 mg BID for 5 days	Gepotidacin plasma and urine concentrations	Summary statistics (appropriate for each type of endpoint) in the gepotidacin arm	Study treatment discontinuation (due to any reason) – while on treatment strategy (treatment phase defined as from first dose to On-therapy Visit)

4. STUDY DESIGN

4.1. Overall Design

- Study 214144 is a Phase III, randomized, multicenter, active reference, parallel-group, double-blind, double-dummy study in adolescent and adult female participants to assess consistency of therapeutic response of gepotidacin at the TOC Visit in female participants with acute uncomplicated cystitis observed in this study with global studies (Studies 204989 and 212390). In addition, the efficacy (therapeutic response) of gepotidacin compared to active reference (nitrofurantoin) descriptively will also be evaluated for therapeutic response at the TOC Visit. Participants will be stratified by age category (≤50 years, or >50 years) and acute uncomplicated cystitis recurrence (nonrecurrent infection or recurrent infection, defined as a confirmed infection [not including the current infection in the calculation] with at least 1 prior episode within the past 3 months, at least 2 prior episodes within the past 6 months, or at least 3 prior episodes within the past 12 months before study entry) and will be randomly assigned in a 3:1 ratio to receive 1 of the following study treatments:
  - Gepotidacin: 1500 mg administered orally twice daily (BID) for 5 days
  - Nitrofurantoin: 100 mg administered orally BID for 5 days

  Note: Each dose of gepotidacin or nitrofurantoin should be taken after food consumption and with water.

- Appropriate safety, clinical and microbiological assessments will be conducted at the Baseline (Day 1) Visit and repeated at the On-therapy (Day 2 to 4), TOC (Day 10 to 13), and Follow-up (Day 28±3) Visits. CCI [redacted] Each treatment day will be assessed over 24 hours starting with the first dose of study treatment, as further detailed in the Study Reference Manual (SRM).
- For the primary efficacy endpoint of therapeutic response (combined per-participant microbiological and clinical response), therapeutic success refers to participants who have been deemed both a microbiological success (reduction of all qualifying bacterial uropathogens [e.g., ≥10^5 CFU/mL; defined in 10.8] recovered at Baseline to <10^3 CFU/mL as observed on quantitative urine culture without the participant receiving other systemic antimicrobials) and a clinical success (resolution of signs and symptoms of acute cystitis present at Baseline [and no new signs and symptoms] without the participant receiving other systemic antimicrobials) at the TOC Visit in the Microbiological Intent-to-Treat Nitrofurantoin-Susceptible (micro ITT NTF-S) Population, regardless of treatment discontinuation.
- PK samples will be collected in all participants for analysis at the Baseline (postdose) and the On-therapy Visits (predose and postdose).
- Participants may return to the study site at any time due to AEs or if they are experiencing new or continuing signs and symptoms of acute uncomplicated cystitis.

Participants will be assessed and treated per the investigator's judgement. If a participant is switched to a different antimicrobial before or during the TOC Visit, all TOC procedures should be completed before the other antimicrobial is started.

- Participants with a concomitant fungal infection can only be treated with topical antifungals per local standard of care.
- Participants will return to the study site on Day 28 (±3) for a Follow-up Visit. Participants experiencing signs and symptoms suggestive of infection recurrence or relapse will be assessed and treated per the investigator's judgement.
- The study duration is approximately 28 days with 4 planned study visits (see Section 8 for study visit details):
  - Baseline (Day 1) Visit
  - On-therapy (Day 2 to 4) Visit
  - TOC (Day 10 to 13) Visit
  - Follow-up (Day 28±3) Visit

A study design schematic is depicted in Figure 1. The Schedule of Activities (SoA) is provided in Section 1.3.

Refer to 10.9 for details regarding allowed revisions to study conduct and/or monitoring due to coronavirus disease (COVID-19). For all study visits, to minimize the amount of time that participants spend at the clinic, eConsent may be utilized and remote collection of study-related data may be obtained as described in the SRM. Thus, some visit data may be collected through a combination of telemedicine and on-site visits. Collection of information via telemedicine will be performed only where local regulations permit.

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

4.1.1. Safety Review Team/Microbiology Review Team

There will be a GlaxoSmithKline Safety Review Team to monitor blinded safety data, and a Microbiology Review Team to monitor blinded microbiological data instream (see Section 10.1.5).

4.2. Scientific Rationale for Study Design

The study design of global Phase III studies (Studies 204989 and 212390) was based on the Food and Drug Administration (FDA) guidance for industry for developing drug treatments for uncomplicated and complicated UTIs [DHHS, 2019; DHHS, 2018], the European Medicines Agency (EMA) addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections [EMA, 2013], and feedback from the FDA and EMA. This study is designed in consideration of bridging to assess the consistency between this study and the global Phase III studies based on the

feedback from the Pharmaceuticals and Medical Devices Agency (PMDA) at the consultation meeting.

The primary efficacy endpoint will be the therapeutic response (combined per-participant microbiological and clinical response) at the TOC Visit in participants who have a qualifying bacterial uropathogen at Baseline that all are susceptible to nitrofurantoin. Although the guidance differs in their criteria for defining qualifying uropathogens, this study has been designed with the qualifying uropathogen criteria defined in 10.8 and microbiological success defined as reduction of all qualifying bacterial uropathogens recovered at Baseline to $<10^3$ CFU/mL as observed on quantitative urine culture without the participant receiving other systemic antimicrobials. Clinical success at the TOC Visit is defined as the resolution of signs and symptoms of acute cystitis present at Baseline (and no new signs and symptoms) without the participant receiving other systemic antimicrobials. Therapeutic success refers to participants who have been deemed both a microbiological success and a clinical success (i.e., responders). The primary objective of this study is to assess consistency of this study with global studies (Studies 204989 and 212390) for therapeutic response of gepotidacin at the TOC Visit.

Nitrofurantoin has been selected as the active reference in this study. Nitrofurantoin is globally available as the indication for the treatment of acute uncomplicated UTI (acute cystitis) caused by susceptible strains of *E. coli* or *S. saprophyticus* in most regions except for Japan and is a recommended oral first-line treatment for acute uncomplicated cystitis per current US and European Association of Urology guidelines [Gupta, 2011b; EAU, 2019]. Although nitrofurantoin is not approved in Japan, nitrofurantoin was a marketed antimicrobial in Japan until 1990 and showed efficacy in Japanese patients with acute uncomplicated cystitis and had no clinically significant safety issues [Tsunoda, 1970; Ookita, 1970; Tofukuji, 1970]. Both gepotidacin and nitrofurantoin will be administered BID for a treatment duration of 5 days. As described in Section 4.3, the dose of each study treatment and the 5-day duration were selected to provide efficacious treatment for acute uncomplicated cystitis. Having the same dose regimen will also support double-blind dose administration.

Both adult and adolescent (≥12 to <18 years of age) eligible female participants will be enrolled in this double-blinded study. The study is restricted to female participants since this study is conducted as bridging-like study to assess the consistency between this study and the global studies, which was planned per FDA guidance [DHHS, 2019]. Adolescent participants will only be enrolled at study sites where investigators have experience in this population and if allowed per the study site's institutional ethics committees and enrollment will be contingent upon such approvals. Adolescent assent forms and adult consent forms will be developed with oversight from local governing institutional review boards (IRBs)/independent ethics committees (IECs) (see 10.1). There is no upper age limit for study participants; however, participants are excluded if they reside in a nursing home or dependent care type-facility, or if they have any comorbidities associated with complicated UTI. Thus, any participants >75 years of age will only be eligible for the study if they are residing independently.

In order to maximize the efficiency of this study while minimizing discomfort and inconvenience to participants consenting to this protocol, a GSK SRT will monitor

blinded safety data in stream, while a Microbiology Review Team will monitor blinded uropathogen identification and susceptibility data in stream, including the enrollment rate of participants with a qualifying bacterial uropathogen at Baseline and the resistance profile of uropathogens. For details on these review teams, refer to 10.1.

4.2.1. Participant Input into Design

Interview of patients with acute uncomplicated cystitis was conducted during the design of this protocol. The findings confirmed that the study design is acceptable. A record of insights from the patients into the design and implementation is maintained in the Trial Master File.

4.3. Justification for Dose

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 acute uncomplicated cystitis in women, which typically ranges from 3 to 7 days [Gupta, 2011b;; EAU, 2019;Yamamoto, 2017]. The safety and tolerability at this oral dose and duration have been evaluated in Phase I studies and in Phase II studies (BTZ116704 and 206899) (see IB for details). Furthermore, high urine concentrations of gepotidacin are expected in this study based on a healthy volunteer Phase I study (BTZ117351) and a Phase IIa study in participants with acute uncomplicated cystitis (206899). In BTZ117351, approximately 287 mg of unchanged gepotidacin was excreted in urine after a single oral 1500-mg (2 × 750-mg tablets) dose of gepotidacin (minimum urine area under drug concentration-time curve over 12 hours [AUC12h]=807 µg.h/mL). In the Phase IIa study, 206899, in participants with acute uncomplicated cystitis, approximately 460 mg of unchanged gepotidacin was excreted in urine over the steady-state dosing interval of 12 hours after repeat BID oral dosing of 1500 mg (2 × 750-mg tablets) gepotidacin (minimum steady-state urine AUC12h=2256 µg.h/mL).

For the global phase III studies (Studies 204989 and 212390), the gepotidacin dose and duration 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 the IB for further details). Based on GSK assessment of the limitations of the current acute cystitis efficacy model in rodents, the pyelonephritis model is considered to allow evaluation of antibacterial efficacy in a more robust UTI.

Additionally, an in vitro study to determine the PK/pharmacodynamic (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 free-drug AUC 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 was also completed using *E. coli* isolate NCTC 13441 to determine the *f*AUC/MIC exposure of gepotidacin required to prevent the amplification of a 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 for 10 days. This equates to an *f*AUC/MIC value ≥275 when applying the gepotidacin broth microdilution MIC of 2 µg/mL for *E. coli* NCTC 13441.

When taking the *f*AUC/MIC target of 275 for resistance suppression into consideration with the concentrations of gepotidacin in human urine measured in BTZ117351 (minimum urine AUC12h=807 µg.h/mL; thus, minimum urine AUC over 24 hours [AUC 24 h]=1614 µg.h/mL) and applying an MIC value of 4 µg/mL, the minimum human urine AUC/MIC achieved for the 1500 mg oral BID dose exceeds the *f*AUC/MIC resistance suppression target of 275 by approximately 1.5-fold and 100% target attainment for a urine 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.

When applying the higher concentrations of gepotidacin in human urine measured in the Phase IIa study (206899; minimum urine AUC 12 h=2256 µg.h/mL; thus, AUC 24 h=4512 µg.h/mL) and applying a MIC value of 4 µg/mL, the minimum human urine AUC/MIC achieved for the 1500 mg oral BID dose further exceeds the *f*AUC/MIC resistance suppression target of 275 by approximately 4 fold and 100% target attainment for a urine AUC/MIC target of 275 would also be expected for participants with *E. coli* isolates with gepotidacin MICs ≤4 µg/mL following 1500 mg BID oral dosing.

Additionally, in the Phase IIa study (206899), for 4 participants with available urine AUC24h steady-state PK parameters and qualifying *Enterobacterales* uropathogens who were microbiological successes at TOC, the plasma *f*AUC24h/MIC values ranged from 7 to 90.5 and urine AUC24h/MIC ratios ranged from 1292 to 121,698. The participant with the lowest plasma *f*AUC/MIC (7.0) and urine AUC/MIC (1292) had a *K. pneumoniae* uropathogen with a gepotidacin MIC of 4 µg/mL. No participants had an outcome of microbiological persistence at TOC.

Based on results from Phase I study (213678), following a 1500 mg single gepotidacin dose and twice 3000 mg gepotidacin doses under fed conditions, there was a trend to higher geometric mean gepotidacin Cmax (7% to 30%) in Japanese participants compared to Western Caucasian participants, while total plasma exposures (AUC) were generally similar. Following the administration of 1500 mg single dose of gepotidacin to Japanese participants in the fed state, the mean trough concentration in the urine obtained in the 8- to 12-hour window was 53.7 µg/mL, which exceeds the gepotidacin MIC90 of 4 µg/mL for drug-resistant subsets of *E. coli*. Geometric mean gepotidacin urine AUC (0-24) and AUC (0-τ) was slightly lower in Japanese participants compared to Western (Caucasian) participants.

To investigate the possibility that the dosage and administration of gepotidacin (1500 mg orally BID for 5 days) specified in global phase III studies (Studies 204989 and 212390) may affect the dosage regimen in Japanese patients, a PK-PD study was conducted from the viewpoints of efficacy evaluation and safety evaluation. From the viewpoint of

efficacy evaluation, the overall probability of target attainment in Japanese subjects considering the percentage of actual MICs is as high as 99.9% for *f*AUC0-24hr/MIC = 41.3 in urine and 96.1% for *f*AUC0-24hr/MIC = 275 in urine (related to resistance suppression), which is also expected to be effective in Japanese subjects. From the viewpoint of safety evaluation, the predicted plasma concentration after twice-daily administration of gepotidacin 1500 mg to Japanese subjects is below the concentration associated with mild transient adverse events (such as salivation, blurred vision, and slurred speech) in previous studies, and the predicted ΔΔΔ QTcF in the Japanese population is below the value observed in previous intravenous and oral studies in which clinically relevant QTc changes were reported. Therefore, it is considered safe in Japanese subjects. Based on the above, it is appropriate to apply the dosage and administration of gepotidacin (1500 mg orally BID for 5 days) used in global phase III studies (Studies 204989 and 212390) to the Japanese study (Study 214144).

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 Phase IIa acute uncomplicated cystitis study and 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 uncomplicated cystitis.

In addition, a PK evaluation (Study 209611) in healthy adult and adolescent participants has been completed (see the IB for further details). Overall, plasma Cmax values were 27% higher in adolescents; however, the range of Cmax values were similar, and AUC(0-∞) values were similar for adults and adolescents following a 1500-mg single gepotidacin dose. Following the first of two 3000 mg gepotidacin doses 6 hours apart, Cmax values were 29% higher in adolescents; however, the ranges of Cmax values were similar, and following the second dose for adults and adolescents Cmax values were similar. The AUC(0-τ) was approximately 35% higher in adolescents following both doses compared to adults. The total amount of gepotidacin excreted in urine was similar in adult and adolescent participants following a 1500-mg single gepotidacin dose. Following two 3000 mg gepotidacin doses given 6 hours apart, the total amount excreted was approximately 35% higher in adolescents compared to adults. The maximum dose of gepotidacin evaluated in adolescents was 3000 mg given as 2 doses 6 hours apart. Across the age groups, the safety-risk profile was similar.

The oral nitrofurantoin dose in this study is 100 mg BID (total daily dose of 200 mg) for 5 days. Nitrofurantoin is commonly available as 2 formulations (macrocrystals and a monohydrate) and the most common commercial products globally are nitrofurantoin monohydrate/macrocrystals (Macrobid) and nitrofurantoin macrocrystals (Macrodantin, Furandantin) [Gupta, 2011b]. Adequate clinical response and safety profiles have been reported with nitrofurantoin treatment in acute uncomplicated cystitis and similar PK, safety, and efficacy profiles were reported between the 2 formulations: 100 mg BID nitrofurantoin monohydrate/macrocrystals and 50 mg QID nitrofurantoin macrocrystals [Pelletier, 1992; Ten Doesschate, 2019; Wijma, 2020; Macrobid, 2020]. The previously recommended dosing of nitrofurantoin (macrocrystals) in Japan was 100 mg, QID (total

daily dose of 400 mg). The oral dose, duration, and formulation of nitrofurantoin (monohydrate/macrocrystals) in this study is within the prescribed recommendations globally, which is 100 mg BID for up to 7 days for adults and paediatric patients over 12 years of age [Gupta, 2011b]. In this study, the monohydrate/macrocrystal nitrofurantoin formulation (Macrobid) is used, which is same formulation used in the global Phase III studies (Studies 204989 and 212390). The labeled 7 days dosing duration of nitrofurantoin was based on clinical registration studies from several decades ago. More recently, a 5-day dosing duration of nitrofurantoin was shown to be efficacious for the treatment of acute uncomplicated cystitis in women [Gupta, 2007] and a treatment duration of <7 days for nitrofurantoin is in alignment with current treatment guidelines [Gupta, 2011b; EAU, 2019].

4.4. End of Study Definition

A participant is considered to have completed study treatment if she has taken all doses of the randomly assigned study treatment and completed the TOC Visit. The end of the study is defined as the date of the last visit of the last participant in the study.

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

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

Age

1. The participant must be ≥12 years of age inclusive, at the time of signing the informed consent/assent and has a body weight ≥40 kg.

   Note: Although participants as young as 12 years may enrol in the study, study sites must follow their institutional ethics committee and enrollment will be contingent upon such approvals regarding the allowed lower age limit for clinical study participants.

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 <96 hours prior to study entry: dysuria, frequency, urgency, or lower abdominal pain (see Section 10.10).
3. The participant has nitrite or pyuria (>15 WBC/HPF or the presence of 3+/large leukocyte esterase) from a pretreatment clean-catch midstream urine sample based on local laboratory procedures.

Sex and Contraceptive/Barrier Requirements

4. The participant is female

Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

- A female participant is eligible to participate if she is a woman of childbearing potential (WOCBP) who is not pregnant as confirmed by a high sensitivity urine pregnancy test at Baseline (Day 1) regardless of current or prior contraception use or abstinence, is not breastfeeding, or is not a WOCBP.

  Note: Pregnancy testing requirements, contraceptive guidance, and WOCBP definitions are provided in Section 10.4 and requirements for pregnancy testing during and after study treatment are located in Section 8.2.5.

- Additional requirements for pregnancy testing during and after study treatment are located in in section 8.2.5.

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

5. The participant is capable of giving signed informed consent/assent as described in Section 10.1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) /assent form and in this protocol.

5.2. 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 and is experiencing obesity-related health conditions such as uncontrolled high blood pressure or uncontrolled diabetes.
3. 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., uncontrolled diabetes, 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, ≥20 mg/day prednisolone or equivalent for >2 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.
4. The participant has any of the following:
   - Medical condition that requires medication that may be impacted 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

- Known acute porphyria
- Any surgical or medical condition (active or chronic) that may interfere with drug absorption, distribution, metabolism, or excretion of the study treatment (e.g., ileostomy or malabsorption syndrome)

5. The participant has a known glucose-6-phosphate dehydrogenase deficiency.
6. The participant, in the judgment of the investigator, would not be able or willing to comply with the protocol or complete study follow-up.
7. 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.
8. The participant has acute uncomplicated 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 Enterobacterales (other than *E. coli*) as the contributing pathogen.
9. The participant has symptoms known or suspected to be caused by another disease process, such as asymptomatic bacteriuria, overactive bladder, chronic incontinence, or chronic interstitial cystitis, that may interfere with the clinical efficacy assessments or preclude complete resolution of acute cystitis symptoms.
10. 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).
11. The participant has an indwelling catheter, nephrostomy, ureter stent, or other foreign material in the urinary tract.
12. The participant who, in the opinion of the investigator, has an otherwise complicated UTI, an active upper UTI (e.g., pyelonephritis, urosepsis), signs and symptom onset ≥96 hours before study entry, or a temperature ≥38°C, flank pain, chills, or any other manifestations suggestive of upper UTI.

13. The participant has known anuria, oliguria, or significant impairment of renal function (creatinine clearance <60 mL/min or clinically significant elevated serum creatinine as determined by the investigator).
14. The participant presents with vaginal discharge at Baseline (e.g., suspected sexually transmitted disease).
15. The participant has congenital long QT syndrome or known prolongation of the corrected QT (QTc) interval.
16. The participant has uncompensated heart failure.
17. The participant has severe left ventricular hypertrophy.
18. The participant has a family history of QT prolongation or sudden death.
19. The participant has a recent history of vasovagal syncope or episodes of symptomatic bradycardia or brady arrhythmia within the last 12 months.
20. The participant is taking QT-prolonging drugs or drugs known to increase the risk of torsades de pointes (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.
21. For any participant ≥12 to <18 years of age, the participant has an abnormal ECG reading at Baseline.
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's formula (QTcB), or Fridericia's (QTcF) formula, and/or another method. It is either machine read or manually overread.
    - The specific formula used to determine eligibility and discontinuation for an individual participant should be determined prior to initiation of the study. In other words, several different formulas cannot be used to calculate the QTc for an individual participant and then the lowest QTc value used to include or discontinue the participant from the trial.
23. The participant has a documented or recent history of uncorrected hypokalemia within the past 3 months.
24. The participant has a known alanine aminotransferase (ALT) value >2 × upper limit of normal (ULN).
25. The participant has a known total bilirubin value >1.5 × ULN (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
26. The participant has cirrhosis or current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice.

Note: Stable noncirrhotic chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B or C [e.g., presence of hepatitis B surface antigen or positive hepatitis C antibody test result]) is acceptable if the participant otherwise meets entry criteria.

27. The participant has a previous history of cholestatic jaundice/hepatic dysfunction associated with nitrofurantoin.

Prior/Concomitant Therapy

28. The participant has received treatment with other systemic antimicrobials or systemic antifungals within 1 week before study entry.
29. The participant who are expected to be non-compliant with restrictions on medications or nondrug therapies prior to the study or during the study as detailed in Section 6.8.2.

Prior/Concurrent Clinical Study Experience

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

Diagnostic Assessments

32. The participant has a positive human immunodeficiency virus (HIV) antibody test

Other Exclusions

33. Current drug or alcohol abuse or dependence, or history of drug or alcohol abuse or dependence within 12 months prior to randomisation
34. The participant has a history of sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates participation in the study.

5.3. Lifestyle Considerations

Participants must abstain from sexual activity from the Baseline Visit through the TOC Visit to prevent possible re-infection.

5.3.1. Meals and Dietary Restrictions

Study treatment should be taken after food consumption (a meal or a snack) and with water (see Section 6.1).

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomized. 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 (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any protocol deviations and any serious adverse events (SAEs).

Participants who are screen failures are allowed to be rescreened once with the agreement of the Medical Monitor for the same infection episode or a subsequent infection episode and participate in the study if they meet all the inclusion and do not meet all the exclusion criteria.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1. Study Intervention(s) Administered

- All doses of study treatment should always be taken after food consumption and with water. Participants will receive oral study treatment (gepotidacin [2 tablets] + nitrofurantoin matching placebo [1 capsule] or nitrofurantoin [1 capsule] + gepotidacin matching placebo [2 tablets]) BID (approximately every 12 hours) for 5 days.
- The first oral dose will be administered at the study site during the Baseline Visit; participants will self-administer subsequent doses as outpatients thereafter, excluding the day of On-therapy Visit.
- At the On-therapy Visit, participants will go to the study site before taking the morning dose, have the PK sample collection performed, and then take the morning dose, while aiming to keep the time of dosing as close as possible to 12 hours after the previous evening dose was taken.
- At the On-therapy Visit, whenever it is possible, the participant will have the pregnancy test performed at the study site. If the visit coincides with the 8th dose, the participant will take their next dose of study treatment at the study site after negative pregnancy test results are confirmed.
- Before the On-therapy Visit, if the requirement for the single pregnancy test to be done between dose 4 and dose 8 cannot be done at the study site due to availability of open clinic hours and the investigator considers the participant reliable to accurately perform the study-provided pregnancy test at home will be instructed to do so. If the pregnancy test is negative, those participants will be instructed to take their next dose of study treatment at home via text or by study site staff before going to the study site for their On-therapy Visit.

Note: The On-therapy Visit should be scheduled to support completion of the postdose PK sample collection and ECG within the protocol-defined window. Also, in WOCBP, the high sensitivity pregnancy test must be performed and show negative results at the latest before Dose 8 of study treatment is taken.

Table 2 Study Intervention(s) Administered

Intervention Label	Gepotidacin	Placebo (Matched to Nitrofurantoin)	Nitrofurantoin	Placebo (Matched to Gepotidacin)
Intervention on Label	Gepotidacin (GSK2140944)	Placebo (Matched to Nitrofurantoin)	Nitrofurantoin	Placebo (Matched to Gepotidacin)
Intervention Description	Tablet for BID dosing	Capsule for BID dosing	Capsule for BID dosing	Tablet for BID dosing
Type	Drug	Drug	Drug	Drug
Dose Formulation	Tablets containing gepotidacin and inactive formulation excipients	Over-encapsulated unit-dose nitrofurantoin placebo to match capsule	Over-encapsulated capsules containing nitrofurantoin (25 mg nitrofurantoin macrocrystals and 75 mg nitrofurantoin monohydrate) and inactive formulation excipients	Unit-dose gepotidacin placebo-to-match tablet
Unit Dose Strength(s)	2 x 750-mg tablets	Not applicable	1 x 100-mg capsule	Not applicable
Dosage Level(s)	1500 mg, BID	BID	100 mg, BID	BID
Route of Administration	Oral	Oral	Oral	Oral
Use	Experimental	Placebo matched to Nitrofurantoin for blinding	Active reference	Placebo matched to Gepotidacin for blinding
IMP and NIMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Dosing Instructions	Administer BID for 5 days: 1500 mg – 2 tablets	Administer BID for 5 days: 1 capsule	Administer BID for 5 days: 100 mg – 1 capsule	Administer BID for 5 days: 2 tablets

	(3000 mg total daily dose) Each dose should be taken after food consumption and with water.	Each dose should be taken after food consumption and with water.	(200 mg total daily dose) Each dose should be taken after food consumption and with water.	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.	Placebo-to-match nitrofurantoin capsules will be over-encapsulated and provided in bottles. Each bottle will be labeled as required per country requirement.	Nitrofurantoin capsules will be over-encapsulated and provided in bottles. Each bottle will be labeled as required per country requirement.	Placebo-to-match gepotidacin tablets will be provided in bottles. Each bottle will be labeled as required per country requirement.

Table 3 Study Arm(s)

Arm Title	Gepotidacin	Nitrofurantoin
Arm Type	Experimental	Active reference
Arm Description	Participants will receive Gepotidacin 1500 mg (with placebo matched to Nitrofurantoin) BID for 5 days	Participants will receive Nitrofurantoin 100 mg (with placebo matched to Gepotidacin) BID for 5 days
Associated Intervention Labels	Gepotidacin tablets and Placebo-to-match nitrofurantoin capsules will be provided in bottles. Each bottle will be labeled as required per country requirement.	Nitrofurantoin capsules and Placebo-to-match gepotidacin tablets will be provided in bottles. Each bottle will be labeled as required per country requirement.

6.2. Preparation, Handling, Storage and Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions 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 intervention 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 intervention are provided in the Study Reference Manual.

Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff.

A Material Safety Data Sheet (MSDS)/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.

6.3. Measures to Minimize Bias: Randomization and Blinding

Participants will be stratified by age category (≤50 years, or >50 years) and acute uncomplicated cystitis recurrence (nonrecurrent infection or recurrent infection, defined as a confirmed infection [not including the current infection in the calculation] with at least 1 prior episode within the past 3 months, at least 2 prior episodes within the past 6 months, or at least 3 prior episodes within the past 12 months before study entry). Participants will be centrally randomized in a 3:1 ratio to either gepotidacin + matching nitrofurantoin placebo or nitrofurantoin + matching gepotidacin placebo. All participants will be centrally randomized using interactive response technology (IRT). Before the study is initiated, information and directions for the IRT will be provided to each study site.

Study treatment will be dispensed at the study visits summarized in Section 1.3.

Returned study treatment should not be re-dispensed to other participants.

This is a double-blind, double-dummy study. The study treatment taken during the study will be double-blind. Neither the participant nor study personnel (i.e., investigators, GSK) will know which study treatment the participant is receiving. In order to maintain study treatment blinding, participants will receive, in addition to their randomized active treatment (gepotidacin or nitrofurantoin), a matching placebo form of the active treatment to which they were not assigned. The matching placebos will look identical to the active form.

Designated independent representative(s), that is a few selected GSK CP-M&S, SDTM Unblinding Programmer, Biostatistics and appropriate service provider (when it is possible) members, may be unblinded for performing population PK and PKPD dataset preparation and draft PK and PKPD model development using scrambled (random reassignment of subject identification numbers) PK and PKPD unblinded datasets, including baseline demographic characteristics.

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact GSK prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. If a participant's treatment assignment is unblinded GSK must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

A participant may continue in the study if that participant's treatment is unblinded provided that there are no safety concerns for the participant per the investigator's judgement.

The GSK SRT, which will monitor safety data in stream, will remain blinded to participant treatment assignment throughout the study (see Section 10.3). A Microbiology Review Team will monitor blinded pathogen identification and susceptibility data in stream as well as the number of participants eligible for the micro ITT Population. Blinded monitoring of pathogens will be conducted, to determine whether end-of-study targets are likely to be achieved.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.4. Study Intervention Compliance

- When participants are dosed at the site during the Baseline and On-therapy Visits, they will take their study intervention when directed by the investigator or designee, under medical supervision. The date and time of each dose administered in the study site will be recorded in the source documents. The dose of study intervention 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 intervention.
- When participants self-administer study intervention(s) at home, compliance with gepotidacin, nitrofurantoin placebo, nitrofurantoin, and gepotidacin placebo will be assessed by direct questioning during the site visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded.
- A record of the quantity of gepotidacin and gepotidacin placebo tablets and nitrofurantoin and nitrofurantoin placebo capsules dispensed to and returned by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays will also be recorded.

6.5. Dose Modification

The study design does not allow for dose modifications.

6.6. Continued Access to Study Intervention 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.

6.7. Treatment of Overdose

For this study, any dose of Gepotidacin or Nitrofurantoin greater than 3000 mg or 200 mg within a 24-hour time period, respectively, will be considered an overdose, as further detailed in the SRM.

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.

Occasional incidents of acute overdosage of nitrofurantoin have not resulted in any specific symptoms other than vomiting (refer to the package insert). Induction of emesis is recommended. There is no specific antidote, but a high fluid intake should be maintained to promote urinary excretion of the drug.

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 intervention 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 intervention 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 CRF.

Decisions regarding dose interruptions will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

6.8. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving within 30 days prior to the Baseline Visit or receives during the study must be recorded in the eCRF. In addition, any antimicrobial use within 6 months prior to the Baseline Visit or during the study must be recorded in the eCRF. The concomitant therapy name must be recorded in the eCRF along with the following:

- 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.

6.8.1. 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 (e.g., topical clindamycin, fradiomycin or polymyxin) and topical, nonsystemic antifungals (e.g., topical clotrimazole, tolnaftate, or ketoconazole) is allowed throughout the study.

Acetaminophen use is permitted throughout the study as it does not mask symptoms of the disease under study. Low-dose aspirin (≤100 mg/day) is permitted for the prevention of cardiovascular (CV) disease events.

6.8.2. Prohibited Medications and Nondrug Therapies

At the time of enrollment and/or during the study from the Baseline Visit through the Follow-up Visit, the participant is prohibited from use of the following medications.

- Treatment with other systemic antimicrobials (e.g., oral ciprofloxacin, amoxicillin/clavulanate, cephalexin, or doxycycline) within 1 week before study entry, unless other systemic antimicrobials are needed as additional therapy for the infection under study (acute uncomplicated cystitis), including recurrence of the infection or new infection.

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 systemic antifungals (e.g., oral fluconazole, itraconazole, or terbinafine) within 1 week before study entry.
- Immunosuppressive therapy, including corticosteroid therapy (>40 mg/day prednisolone or equivalent for >1 week, ≥20 mg/day prednisolone or equivalent for >2 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. Of note, ondansetron is not allowed from the Baseline Visit to the TOC Visit due to its known TdP risk.

  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.
- St John's wort or other strong CYP3A4 inducers are 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, D-mannose, cranberry tablets, nonsteroidal anti-inflammatory drugs including ibuprofen and cyclooxygenase-2 inhibitors, and uricosuric drugs (e.g., probenecid). Aspirin (doses >100 mg/day) is not permitted.

In addition, antacid preparations containing magnesium trisilicate are prohibited from the start of study treatment at the Baseline Visit throughout the completion of the dosing period (i.e., until all 10 doses of study treatment have been received).

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Section 10.1.

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety and efficacy. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

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 eCRF. Participants who discontinue study treatment for the reasons above will not be considered withdrawn from the study and should attend all subsequent study visits (see Section 1.3).

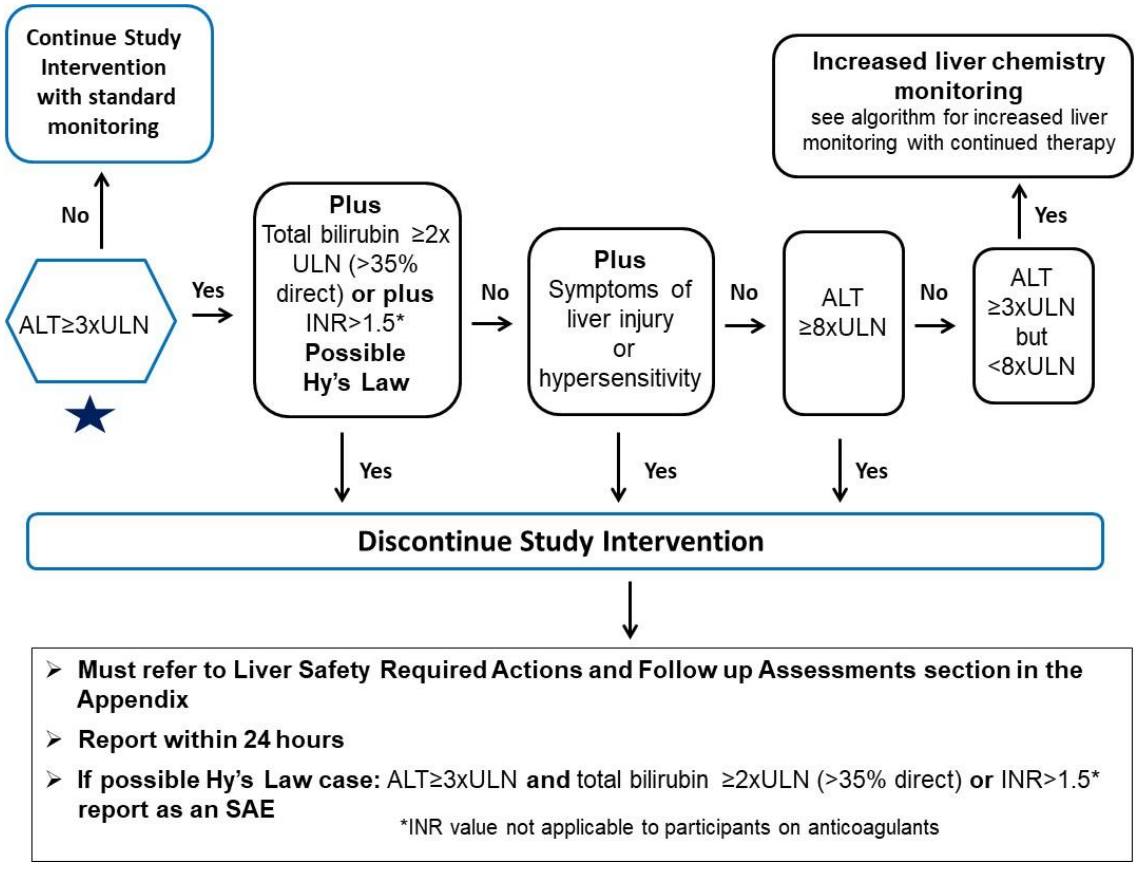
7.1.1. Liver Chemistry Stopping Criteria

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

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

- a participant meets one of the conditions outlined Algorithm A or Algorithm B or
- in the presence of abnormal liver chemistry not meeting protocol-specified stopping rules, if the investigator believes that it is in the best interest of the participant.

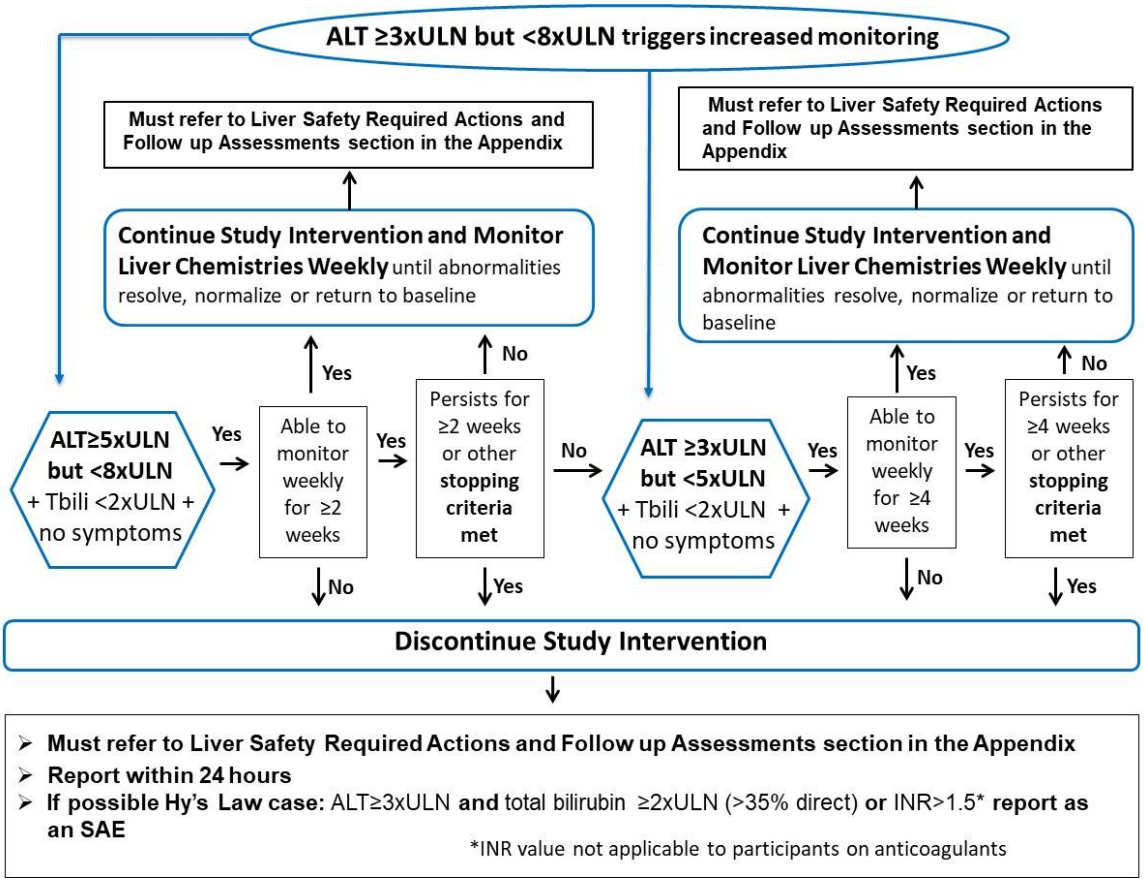
Algorithm A: Phase 3 Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm



Abbreviations: ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal

Refer to Section 10.6 for required Liver Safety Actions and Follow up Assessments.

Algorithm B：Phase 3 Liver Chemistry Increased Monitoring Algorithm with Continued Study Intervention for Participants with ALT ≥3xULN but <8xULN



Abbreviations: ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal, Tbili = Total bilirubin.

Refer to Section 10.6 for required Liver Safety Actions and Follow up Assessments.

7.1.2. QTc Stopping Criteria

Adult Participant

- If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using Bazett's formula [QTcB] or Fridericia's formula [QTcF]) after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.
- A participant who meets the bulleted criteria based on the average of triplicate ECG readings will be withdrawn from study intervention:
  - QTc > 500 msec OR Uncorrected QT > 600 msec
  - Change from baseline of QTc > 60 msec

For patients 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 – 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. (Note: Ideally, all ECGs for a participant should be performed with the same ECG machine.)
    - 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. Other nonprotocol-specified ECGs are an exception.
- The QTc should be based on the average of triplicate ECG readings obtained over a brief (e.g., 5- to 10-minute) recording period.

Participant ≥12 to <18 years of age

For any participant ≥12 to <18 years of age, if the participant has an abnormal ECG reading during the study treatment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed.

7.1.3. Renal Stopping and Monitoring Criteria

- If baseline creatinine clearance (CrCl) <45 ml/min, stop study treatment immediately and ensure prompt clinical assessment including repeat labs
- If baseline CrCl 45 to < 60 ml/min, advise that the On Therapy visit is expedited so that participants undergo prompt clinical assessment. Evaluation should include on therapy labs and an assessment of clinical response and adverse effects to treatment to weigh the potential benefits and concerns with continuing or discontinuing treatment. If the patient is clinically well, study treatment can be continued or if there are concerns, study treatment can be discontinued at investigator's discretion when this is felt to be in the best interest of the participant. The following factors should be considered:
    - All patients to remain in the study for safety follow-up
    - All patients to have labs including CrCl repeated at the TOC visit as per study protocol

7.1.4. Rechallenge

7.1.4.1. Study Intervention Restart or Rechallenge after liver stopping criteria met

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

7.1.5. Gastrointestinal Evaluation Criteria

If a participant meets the criteria in 10.7, *Clostridioides difficile* toxin testing should be conducted and the specific eCRF page completed, then reported as AE if positive for the testing. *Clostridioides difficile* infection or colitis is considered an AE of special interest (Section 8.3.7).

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
    - Reasons for study withdrawal include:
    - Participant lost to follow-up
    - Participant withdrew consent
    - Termination of the study by GSK
    - Investigator discretion
- At the time of discontinuing from the study, if possible, an early withdrawal visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from the study intervention and the study at that time.
- 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, she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

The reason for participant withdrawal will be recorded in the eCRF. Participants who are withdrawn from the study should return to the study site and have the microbiological and clinical outcomes assessed at the time of withdrawal (see the SoA in Section 1.3), if data permit, and return all unused study treatment. Data from these participants will be

considered evaluable up to the point at which they are withdrawn, using the same criteria for evaluability as for participants who complete the study.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if 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, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether 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, she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of 10.1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- 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 intervention.
- Adherence to the study design requirements, including those specified in the SoA, 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 timeframe defined in the SoA.
- Prescreening activities may be conducted, including a prescreening informed consent and urine testing, as further detailed in the SRM. The required baseline urine

specimen may be collected as part of an optional prescreening process, if not already part of standard of care, and is further detailed in the SRM. This specimen can be used for the required baseline procedures of the diagnosis of presumptive acute uncomplicated cystitis and pregnancy testing.

- Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- 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 200 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Participants may return to the study site at any time due to AEs or if they are experiencing new or continuing signs and symptoms of acute cystitis. Participants will be assessed and treated per the investigator's judgement. If a participant is switched to a different antimicrobial before or during the TOC Visit, all TOC procedures should be completed before the other antimicrobial is started.
- Each treatment day will be assessed over 24 hours starting with the first dose of study treatment, as further detailed in the SRM.

The study will comprise the following 4 planned study visits:

Note: For all study visits, to minimize the amount of time that participants spend at the clinic, eConsent may be utilized and remote collection of study-related data may be obtained as described in the SRM. Thus, some visit data may be collected through a combination of telemedicine and on-site visits. Collection of information via telemedicine will be performed only where local regulations permit.

- **Baseline (Day 1) Visit:** The Baseline Visit will be performed before dosing on Day 1. Assessments will be performed as shown in the SoA (Section 1.3), including the following:
  - Pretreatment baseline specimens for microbiological testing will be collected, as described in Section 8.1.2 Clinical signs and symptoms of acute cystitis will be recorded, as described in Section 8.1.3.1 and 10.10. CCI [redacted].
  - Following completion of all pretreatment assessments, eligible participants will be randomly assigned to a study treatment, as described in Section 6.3.
  - The first dose of randomly assigned oral study treatment will be administered at the study site. Participants will remain at the study site approximately 2 hours (1.5 to 4 hours) after dosing, during which time all Day 1 posttreatment assessments will be performed (i.e., triplicate ECG and postdose plasma and pooled urine PK sample collection), as shown in Section 1.3. Any AEs or clinically significant changes should be followed accordingly. Subsequent to administration of the first dose at the study site, participants will self-administer doses as outpatients thereafter, beginning with the second dose, excluding the

day of On-therapy Visit. (Note: Each dose should be taken after food consumption and with water.)

- The On-therapy, TOC, and Follow-up Visits should be scheduled before the participant leaves the study site on Day 1 (as per the Schedule of Activities Table in Section 1.3); the planned return day/time should be at the convenience of the participant and also the availability of the study site staff.

- **On-therapy (Day 2 to 4) Visit**: Participants will be instructed to return to the study site 1 to 3 days following study treatment administration at Baseline in order to complete the On-therapy Visit. Assessments will be performed as shown in the SoA (Section 1.3), including the following:
  - The On-therapy Visit will be preceded by a documented reminder contact from the study site to the participant 24 ± 4 hours before the scheduled appointment time per the method (e.g., text message, telephone call, e-mail) confirmed with the study site staff prior to departing the study site on Day 1.
  - At the On-therapy Visit should be scheduled to support completion of the predose plasma & spot urine and postdose plasma & pooled urine PK samples collection, if at all possible:
    - Participants will go to the study site before taking the morning dose, have the PK sample collection performed, and then take the morning dose, while aiming to keep the time of dosing as close as possible to 12 hours after the previous evening dose was taken.
    - Participants will remain at the study site until approximately 2 hours (1.5 to 4 hours) after dosing, during which time all Day 1 posttreatment assessments will be performed (i.e., triplicate ECG and postdose PK sample collection), as shown in Section 1.3.
  - At the On-therapy Visit, whenever it is possible, the participant will have the pregnancy test performed at the study site. If the visit coincides with the 8th dose, the participant will take their next dose of study treatment at the study site after negative pregnancy test results are confirmed.
  - Before the On-therapy Visit, if the requirement for the single pregnancy test to be done between dose 4 and dose 8 cannot be done at the study site due to availability of open clinic hours and the investigator considers the participant reliable to accurately perform the study-provided pregnancy test at home will be instructed to do so. If the pregnancy test is negative, those participants will be instructed to take their next dose of study treatment at home via text or by study site staff before going to the study site for their On-therapy Visit.

    Note: The On-therapy Visit should be scheduled to support completion of the postdose PK sample collection and ECG within the protocol-defined window. Also, in WOCBP, the high sensitivity pregnancy test must be performed and show negative results at the latest before Dose 8 of study treatment is taken.
  - Specimens for microbiological testing will be collected, as described in Section 8.1. Clinical signs and symptoms of acute cystitis will be recorded, as described

in Section 8.1.3.1 and 10.10. CCI [redacted]

- Pregnancy testing, as required, after Dose 4 and before Dose 8. Refer to Section 8.2.5 for details.

- **TOC (Day 10 to 13) Visit**: Participants will be instructed to return to the study site 5 to 8 days after completion of study treatment in order to complete the TOC Visit. Assessments will be performed as shown in the SoA (Section 1.3), including the following:
  - The TOC Visit will be preceded by a documented reminder contact from the study site to the participant 24 ± 4 hours before the scheduled appointment time per the method (e.g., text message, telephone call, e-mail) confirmed with the study site staff prior to departing the study site on Day 1.
  - Specimens for microbiological testing will be collected, as described in Section 8.1. Clinical signs and symptoms of acute cystitis will be recorded, as described in Section 8.1.3.1 and 10.10. Investigator assessment of clinical response will be documented per the definitions described in Section 8.1.3.2and 10.11. CCI [redacted]
- **Follow-up (Day 28±3) Visit**: Participants will be instructed to return to the study site on Day 28 (±3) in order to complete the Follow-up Visit. Assessments will be performed as shown in Section 1.3, including the following:
  - The Follow-up Visit will be preceded by a documented reminder contact from the study site to the participant 24 ±4 hours before the scheduled appointment time per the method (e.g., text message, telephone call, e-mail) confirmed with the study site staff prior to departing the study site on Day 1.
  - Specimens for microbiological testing will be collected, as described in Section 8.1. Clinical signs and symptoms of acute cystitis will be recorded, as described in Section 8.1.3.1 and 10.10. Investigator assessment of clinical response will be documented per the definitions described in Section 8.1.3.2 and 10.11. CCI [redacted]
  - Participants experiencing signs and symptoms suggestive of infection recurrence or relapse will be assessed and treated per the investigator's judgement.

8.1. Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA (Section 1.3).

8.1.1. 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 8.1.2.1) and a "clinical success" (see Section 8.1.3.1). 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 the TOC and Follow-up Visits.

Therapeutic response at TOC is the primary efficacy endpoint.

8.1.2. Bacteriology Samples

At the Baseline Visit, a pretreatment, clean-catch midstream urine sample must be obtained from all randomized participants for Gram stain, quantitative bacteriological culture, and in vitro antimicrobial susceptibility testing at a designated central laboratory(ies). For inclusion in the micro-ITT Population, a baseline qualifying bacterial uropathogen is required as defined in Section 10.8; for inclusion in the micro-ITT NTF-S Population, the baseline qualifying uropathogen must also be susceptible to nitrofurantoin. At the On-therapy, TOC, and Follow-up Visits, a clean-catch midstream urine sample will be obtained and sent to a designated central laboratory(ies) 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 central laboratory(ies). Additional tests, as needed, to further characterize recovered isolates will also be performed by a designated central laboratory(ies). 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.

8.1.2.1. Microbiological Outcome and Response

Only those participants who have a qualifying bacterial uropathogen (defined in Section 10.8) identified at Baseline will be evaluated for microbiological outcome and response by baseline qualifying uropathogen for the primary efficacy endpoint. The microbiological outcome and response to study treatment will be determined programmatically for each participant/uropathogen prior to breaking of the study blind.

The microbiological outcome by baseline qualifying uropathogen is determined by comparing the baseline culture results to the culture results at each subsequent visit (see Table 4, Table 5, and Table 6 for baseline qualifying uropathogen outcomes). The corresponding microbiological response (success or failure) “by uropathogen” is then assigned, as shown in Table 5 and Table 6. Participant-level microbiological response is a measure of the combined “by uropathogen” response(s). Participant-level microbiological success refers to participants who have been deemed a “microbiological success” for all of their “by uropathogen” microbiological responses. All other combinations (other than all “microbiological successes”) are deemed failures for participant-level microbiological response. The participant-level microbiological outcome and response definitions are provided in Table 7.

Microbiological outcome criteria for new qualifying uropathogens (i.e., uropathogens not identified at Baseline) are defined by visit in

Table 8, Table 9, and Table 10.

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

Defining Criteria	Outcome
A quantitative urine culture taken at the On-therapy Visit shows that the qualifying bacterial uropathogen recovered at Baseline is reduced to $<10^3$ CFU/mL, without the participant receiving other systemic antimicrobials before the On-therapy Visit	Microbiological eradication
A quantitative urine culture taken at the On-therapy Visit shows that the qualifying bacterial uropathogen recovered at Baseline grows $\geq 10^3$ CFU/mL, without the participant receiving other systemic antimicrobials before the On-therapy Visit	Microbiological persistence
The On-therapy urine culture result is missing, or The participant received other systemic antimicrobials before the Ontherapy Visit	Unable to determine

CFU=colony-forming units.

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

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

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

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

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

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

Table 7 Participant-Level Microbiological Outcome and Response Definitions per Study Visit

Defining Criteria at the On-Therapy Visit	Outcome	Response
All qualifying baseline uropathogens have a microbiological outcome of eradication at On-therapy	Microbiological eradication	NA
At least one qualifying baseline uropathogen has an outcome of persistence at On-therapy	Microbiological persistence	NA
All qualifying baseline uropathogen outcomes are unable to determine at On-therapy	Unable to determine	NA
Defining Criteria at the TOC Visit	**Outcome**	**Response**
All qualifying baseline uropathogens have a microbiological outcome of eradication at TOC	Microbiological eradication	Microbiological success
At least one qualifying baseline uropathogen has an outcome of persistence at TOC	Microbiological persistence	Microbiological failure
At least one qualifying baseline uropathogen has an outcome of recurrence and none have an outcome of persistence at TOC	Microbiological recurrence	Microbiological failure
All qualifying baseline uropathogen outcomes are unable to determine at TOC	Unable to determine	Microbiological failure
Defining Criteria at the Follow-up Visit	**Outcome**	**Response**
All qualifying baseline uropathogens have a microbiological outcome of sustained eradication at Follow-up	Sustained microbiological eradication	Microbiological success
At least one qualifying baseline uropathogen has an outcome of recurrence and none have an outcome of persistence at Follow-up	Microbiological recurrence	Microbiological failure
At least one qualifying baseline uropathogen has an outcome of persistence at Follow-up	Microbiological persistence	Microbiological failure
At least one qualifying baseline uropathogen has an outcome of delayed eradication and none have an outcome of persistence or recurrence at Follow-up	Delayed microbiological eradication	Microbiological failure
All qualifying baseline uropathogen outcomes are unable to determine at Follow-up	Unable to determine	Microbiological failure

NA=Not applicable; TOC=Test-of-Cure.

Table 8 Microbiological Outcome by New Qualifying Uropathogen at the On-Therapy Visit

Defining Criteria	Outcome
A new qualifying bacterial uropathogen, not identified at Baseline, is documented by quantitative urine culture at the On-therapy Visit	New uropathogen

Table 9 Microbiological Outcome by New Qualifying Uropathogen at the Test-of-Cure Visit

Defining Criteria	Outcome
A new qualifying bacterial uropathogen, not identified at Baseline, is documented by quantitative urine culture at the Test-of-Cure Visit in a participant who did not achieve a clinical outcome of clinical resolution at the Test-of-Cure Visit	New infection
A new qualifying bacterial uropathogen, not identified at Baseline, is documented by quantitative urine culture at the Test-of-Cure Visit in a participant who did achieve a clinical outcome of clinical resolution at the Test-of-Cure Visit	Colonization

Table 10 Microbiological Outcome by New Qualifying Uropathogen at the Follow-up Visit

Defining Criteria	Outcome
A new qualifying bacterial uropathogen, not identified at Baseline, is documented by quantitative urine culture at the Follow-up Visit in a participant who did not achieve a clinical resolution at the Follow-up Visit	New infection
A new qualifying bacterial uropathogen, not identified at Baseline, is documented by quantitative urine culture at the Follow-up Visit in a participant who did achieve a clinical resolution at the Follow-up Visit	Colonization

8.1.3. Clinical Evaluation

8.1.3.1. Clinical Signs and Symptom Scores, Clinical Outcomes, and Clinical Response

Clinical signs and symptoms of acute cystitis will be recorded based on participant interview per the SoA (Section 1.3) using the scoring system and instructions in 10.10. 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 defined 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.

A study physician or otherwise appropriately medically trained staff will determine the individual clinical signs and symptoms scores for acute cystitis (10.10) at the On-therapy, TOC, and Follow up Visits. The same scorer will be used at all assessment time points for each participant, on all occasions, whenever possible. The score will be used to programmatically determine the clinical outcome at the On-therapy Visit (Table 11) and the clinical outcome and response (success or failure) at the TOC Visit (Table 12) and the Follow-up Visit (Table 13).

Table 11 Clinical Outcome at the On-Therapy Visit

Defining Criteria	Outcome[a]
Resolution of signs and symptoms of acute cystitis present at Baseline (and no new signs and symptoms), without the participant receiving other systemic antimicrobials before the On-therapy Visit	Clinical resolution
Improvement in total symptom scores from Baseline, but not complete resolution, without the participant receiving other systemic antimicrobials before the On-therapy Visit	Clinical improvement
Worsening or no change in total symptom scores from Baseline or the participant received other systemic antimicrobials for the current infection prior to or on the date of the On-therapy Visit	Clinical worsening
The Baseline score is missing, or The On-therapy assessment is missing, or The participant received other systemic antimicrobials not for the current infection prior to the assessment (unless clinical worsening outcome criteria were met)	Unable to determine

a. A study physician or otherwise appropriately medically trained staff will determine the individual clinical signs and symptoms scores for acute cystitis (10.10), which will then be used to programmatically determine the clinical outcome. The same scorer will be used at all assessment time points for each participant, on all occasions, whenever possible.

Table 12 Clinical Outcome and Response at the Test-of-Cure Visit

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

TOC = Test-of-Cure

a. A study physician or otherwise appropriately medically trained staff will determine the individual clinical signs and symptoms scores for acute cystitis (10.10), which will then be used to programmatically determine the clinical outcome. The same scorer will be used at all assessment time points for each participant, on all occasions, whenever possible.

Table 13 Clinical Outcome and Response at the Follow-up Visit

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

TOC = Test-of-Cure

a. A study physician or otherwise appropriately medically trained staff will determine the individual clinical signs and symptoms scores for acute cystitis (10.10), which will then be used to programmatically determine the clinical outcome. The same scorer will be used at all assessment time points for each participant, on all occasions, whenever possible.

8.1.3.2. Investigator Assessment of Clinical Response

The clinical signs and symptoms score will be determined for the primary endpoint, as described in Section 8.1.3.1 and 10.10. In addition, for secondary and exploratory purposes, a separate assessment of clinical response will be performed at the TOC and Follow-up Visits, or at the time of early withdrawal (Section 1.3). The investigator will assess the clinical response (clinical success, clinical failure, or indeterminate) for each participant based on the definitions in Section 10.11 and will document the response and reason(s) for clinical failure or indeterminate response, if applicable, in the eCRF. This assessment should be completed after the clinical signs and symptoms score is determined by the same study physician or otherwise appropriately medically trained staff who performed the clinical scoring assessment (Section 8.1.3.1 and 10.10).

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

- A physical examination will be performed at the timepoints indicated in the SoA (Section 1.3) as follows:
  - At Baseline, the examination will include assessments of the respiratory, CV, abdominal, gastrointestinal, neurological, and urogenital systems. Height and weight will also be measured and recorded at the Baseline Visit (before dosing).
  - At the TOC Visits, the physical examination may be symptom directed and is only required if indicated for a specific participant.
- 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.

8.2.2. Vital Signs

- Vital signs will be measured at the time points indicated in the SoA (Section 1.3).
- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse rate.
- 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.

8.2.3. Electrocardiograms

- Tripricate 12-lead ECGs (over an approximate 5- to 10-minute period) will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc

intervals. Refer to Section 7.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

- Ideally, ECGs will be obtained before any vital sign measurements or blood draws scheduled on the same assessment day; however, sites may perform procedures in an order per their standard of care, as long as participants return to a resting state prior to the start of the ECG collections.
- If any additional ECGs are performed during the study (if deemed necessary by the investigator), those may be collected as a single ECG; however, if that initial single reading shows QTc prolongation, then triplicate ECGs should also be performed (see Section 7.1.2).
- If clinically significant changes occur during the study, they will be reported as AEs.
- Electrocardiograms will be reviewed locally by the investigator for safety purposes.

8.2.4. Clinical Safety Laboratory Tests

- See 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, 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 clinically significant 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 tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- If laboratory values from non-protocol specified laboratory tests performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.2.5. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.
- Women of childbearing potential (WOCBP) should only be included after a confirmed menstrual period and a negative urine pregnancy test.

- Pregnancy testing will be performed at Baseline (Day 1) before study treatment administration. The urine pregnancy test at Baseline will determine study contraception and abstinence requirements as follows:
  - Pregnancy testing at Baseline (Day 1) should be performed using the urine test kit provided to the study site (with a high sensitivity of ≤12.5 mIU/mL). Participants with a negative urine pregnancy test result from this test kit may be included in the study with no pretreatment contraception or abstinence requirements. Women of childbearing protentional are not required to be using contraception or to have practiced abstinence within 14 days prior to study entry if the high sensitivity urine pregnancy test results are negative at Baseline (Day 1).

    Note: ***ONLY*** if the study-specific pregnancy kit provided to the study site is unavailable, a standard urine pregnancy test with a sensitivity of 25 mIU/mL may be used as an exception. A participant with a negative urine pregnancy test result from the standard test may be included in the study ***only*** if the participant has used a highly effective contraception method as described in Section 10.4.2 or has practiced abstinence from penile/vaginal intercourse for at least 14 days before receiving study treatment.
- After Dose 4 and before Dose 8, an additional pregnancy test using the urine test kit provided to the study site (with a sensitivity of ≤12.5 mIU/mL) is required to be performed for WOCBP who have not used a highly effective contraception method (in Section 10.4.2) or have not practiced abstinence from penile/vaginal intercourse for at least 14 days prior to the first dose of study treatment. It is preferable for this pregnancy test to be performed at the study site; however, for participants for whom this is not possible, the urine pregnancy kit will be provided to the participant to perform as an outpatient during the defined window. For any participant with a positive pregnancy test result, study treatment must be immediately discontinued.
- A pregnancy test will also be performed at the Test-of-Cure (Day 10 to 13) Visit, 5 to 8 days after the last dose of study treatment.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of adverse events (AEs) or serious adverse events (SAEs) can be found in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording 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 intervention or the study, or that caused the participant to discontinue the study intervention or study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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

- All SAEs will be collected from the start of study intervention until the follow-up visit at the timepoints specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.
- All AEs will be collected from the start of intervention until the follow-up visit at the timepoints specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions not as AEs.
- 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 Section 10.3. 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 information on AEs or SAEs after conclusion of the study participation. 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 intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.
- 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.

8.3.3. 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 non-serious AEs of special interest (as defined in Section 8.3.7), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3.

8.3.4. 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 intervention 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 intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators.
- 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/IEC, if appropriate according to local requirements.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.3.5. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until the follow-up visit.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the female participant pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. 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 in the study will discontinue study intervention.

8.3.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 10.3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

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

8.3.7. Adverse Events of Special Interest

Predefined AEs of special interest for this study are CV events, gastrointestinal events, *C. difficile* infection or colitis events, and AEs related to acetylcholinesterase inhibition (see Section 2.3.1), which will be identified by a prespecified list of coded terms or determined by algorithm, as described in the Statistical Analysis Plan (SAP).

8.4. Pharmacokinetics

Whole blood, spot urine and pooled urine samples (approximately blood 3 mL and urine 1mL, respectively) will be collected for measurement of plasma and urine concentrations of gepotidacin as specified in the SoA (Section 1.3).

- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample collected will be recorded.
  Note: For the pooled urine sample, the volume of complete urination also will be recorded.
- Complete urination is required when collecting a urine sample for bacteriological testing. The time of urination performed is set as the start of the urine pooling and will be recorded.
- At the On-therapy Visit, as the spot urine sample collection coincides with the urine bacteriology sample collection, a single urine sample of adequate volume may be collected and split into separate samples for urine PK and microbiological purposes.
- The date and time of the last dose taken before the PK sample (plasma and urine) collection will be recorded.
  Note: The date and time of the last dose taken at home before hospital visit is also needed for the baseline PK sample collection.
- Samples will be used to evaluate the PK of gepotidacin. Each whole blood sample will be processed into plasma.

- PK Samples will be analysed using an appropriately validated assay method by or under the supervision of the sponsor.
- Intervention concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.5. Pharmacodynamics

Minimum inhibitory concentration values will be included for population PK/PD analyses examining the potential relationship between gepotidacin exposure and clinical and microbiological response at the TOC Visit, if data permit. (The related description is in Section 9.3.5)

8.6. Genetics

In this study, genetics may be evaluated after review by the ethical review committee established by GSK in accordance with Japanese Ethical Guidelines for Bioscience, Medical and Health Research Involving Human Subjects.

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 Section 10.5.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

This section is not applicable.

8.9. Medical Resource Utilization and Health Economics

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[redacted]

9. STATISTICAL CONSIDERATIONS

The statistical analysis plan will be finalized prior to DBL and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1. Statistical Hypotheses

The primary objective is to assess "consistency" with the global study results, this will be compared with the predictive distribution of Japanese participants expected to achieve therapeutic response on the gepotidacin arm at the TOC visit, where the predictive distribution is estimated from the global studies (Studies 204989 and 212390). "Consistency" is defined as:

$$\hat{p}_a > \frac{r_{aj}^{(10\%)}}{n_{aj}}$$

, where:
$\hat{p}_a$: Observed proportion of participants achieving therapeutic success on gepotidacin in this study
n_{aj}: Number of participants in gepotidacin of this study
$r_{aj}^{(10\%)}$: The lower 10th percentile of the cumulative distribution of the prior predictive distribution derived from the global study data for the expected number of participants achieving therapeutic success out of n_{aj} participants.

Therefore, $\frac{r_{aj}^{(10\%)}}{n_{aj}}$ is the threshold response rate that needs to be observed to meet therapeutic success, assuming the response rate is consistent with the global study response rate. The predictive distribution is defined as:

$$r_{aj} \sim \int Binomial(r_{aj}|n_{aj}, p_a) \times Beta(p_a|\alpha = r_{ag}, \beta = n_{ag} - r_{ag}) dp_a$$

, where:
r_{aj}: The expected number of participants achieving therapeutic success in the gepotidacin arm of this study
r_{ag}: The pooled number of participants achieving therapeutic success in the gepotidacin arm across both global studies.
n_{ag}: The pooled number of participants in the gepotidacin arms across both global studies.

The two global studies (204989 and 212390) have almost the same study design and the therapeutic response would be almost the same as well. Therefore, the data will be simply pooled to derive the predictive distribution.

Example:

Assuming 884 participants on the gepotidacin arm and a 76% observed therapeutic response rate in the global studies, there is an approximately 10% probability of observing <= 56 out of 81 responders in this study if the true gepotidacin response rate in this study is consistent with the response rate estimated from the global studies. Therefore, the success rule for gepotidacin is set to require a therapeutic response rate greater than 69.1% (56/81) in order to demonstrate consistency with global results in this example.

The secondary objective is to assess the difference between the therapeutic response of gepotidacin with the nitrofurantoin therapeutic response at the TOC Visit in Japanese female participants with acute uncomplicated cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin. The difference in the therapeutic response rate between gepotidacin and nitrofurantoin will be assessed descriptively.

9.1.1. Multiplicity Adjustment

No multiplicity approaches will be used.

9.2. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Intent-to-Treat (ITT) Population	All participants randomly assigned to study treatment. Participants will be analyzed according to their randomized study treatment.
Microbiological ITT (micro-ITT) Population	All participants randomly assigned to study treatment who receive at least 1 dose of study treatment and have a qualifying baseline uropathogen (defined in 10.8), from a quantitative bacteriological culture of a pretreatment clean-catch midstream urine specimen. Participants will be analyzed according to their randomized study treatment.
Micro-ITT NTF-S Population	All participants in the micro-ITT Population whose baseline qualifying bacterial uropathogens all are susceptible to nitrofurantoin (NTF-S). Participants with missing MIC susceptibility results for any qualifying uropathogens will not be included in the NTF-S subpopulation. Participants will be analyzed according to their randomized study treatment.
Micro-ITT NTF-S (Global Study) Population	All participants from the global studies (Studies 204989 and 212390) in the micro-ITT NTF-S Population defined in individual studies, who are not enrolled into this study but into each of the global studies.

Population	Description
Micro-ITT NTF-S (Entire) Population	All participants from micro-ITT NTF-S Population and micro-ITT NTF-S Population (Global Study) Population. This is the primary analysis population.
Micro-ITT MDR Population	All participants in the micro-ITT Population who have any qualifying baseline bacterial uropathogens that are resistant to two or more classes of antimicrobials. Participants will be analyzed according to their randomized study treatment.
Pharmacokinetic (PK) Population	All randomized participants who receive at least 1 dose of study treatment and have at least 1 nonmissing plasma or urine PK concentration (Non-quantifiable [NQ] values will be considered as non-missing values). This population will be used in the assessment and characterization of plasma and urine concentrations (summary table).
Safety Population	All randomized participants who receive at least 1 dose of study treatment. Participants will be analyzed according to their actual treatment received.

9.3. Statistical Analyses

9.3.1. Primary Estimand Analysis

The primary analysis of the primary estimand will be performed using the micro-ITT NTF-S (Entire) population.

The primary endpoint is therapeutic response (combined per-participant microbiological and clinical response) at the TOC Visit. Therapeutic success refers to participants who have been deemed both a microbiological success and a clinical success (i.e. responders).

The primary treatment effect will be estimated regardless of treatment discontinuation, as per the treatment policy strategy. The ICE of use of other systemic antimicrobial therapy is captured through the definitions of microbiological and clinical response and will be counted as failures (composite strategy). If a participant experiences both ICEs of study treatment discontinuation and use of systemic antimicrobials, then a composite strategy (assigning therapeutic response as a failure) will be used from the point that the relevant systemic antimicrobial was taken. Further details on the primary estimand are provided in Section 3.

The number and proportion of participants achieving a therapeutic success will be presented along with its 95% Exact Clopper Pearson CI at the TOC visit and compared with the threshold for consistency with the global studies (Studies 204989 and 212390). The threshold will be derived with covariate adjustment as follows. For this analysis,

participants who do not return for the TOC Visit or have missing data at the TOC Visit will be treated as failures.

1. Derive the prior for therapeutic success rate in each stratum in EAGLE2/3 studies based on the definition of stratification factor in this study

$$p_k \sim Beta\left(r_{k,global}, n_{k,global} - r_{k,global}\right)$$

, where $n_{k,global}$ and $r_{k,global}$ are the pooled number of participants and therapeutic responders who are assigned to the gepotidacin group of k^{th} stratum in the micro-ITT NTF-S population across both global studies (Studies 204989 and 212390), respectively.

2. Derive the predictive distribution for the number of participants achieving therapeutic success in each stratum

$$r_{k,Japan} \sim Beta\ binomial\left(n_{k,Japan}, \alpha = r_{k,global}, \beta = n_{k,global} - r_{k,global}\right)$$

, where $n_{k,Japan}$ and $r_{k,Japan}$ are the number of participants and therapeutic responders who are assigned to the gepotidacin group of k^{th} stratum in the micro-ITT NTF-S population, respectively.

3. Derive lower 10%tile as a threshold using simulation
   a. Set $j = 1$
   b. Sample $r_{k,Japan}^{(j)}$ from $Beta\ binomial\left(n_{k,Japan}, \alpha = r_{k,global}, \beta = n_{k,global} - r_{k,global}\right)$ for each stratum $(k = 1, \ldots, K)$
   c. Calculate $r_{Japan}^{(j)} = r_{1,Japan}^{(j)} + r_{2,Japan}^{(j)} + \cdots + r_{K,Japan}^{(j)}$ and set $j \leftarrow j + 1$
   d. Repeat the step b and c.
   e. Obtain the lower 10%tile $\left(r_{Japan}^{(10\%)}\right)$ of $r_{Japan}^{(j)}$
   f. Calculate the threshold as $r_{Japan}^{(10\%)}/n_{Japan}$ where n_{Japan} is the number of participants in the gepotidacin group.

Sensitivity analysis on the primary estimand will be done to assess the impact of missing data using a tipping point analysis. Tipping point analysis will vary assumption on the proportion of participants with missing data who achieve therapeutic success on the gepotidacin arm in the Japan study and global studies. For each combination of assumed therapeutic success rate on the gepotidacin arm in Japan study and global studies, the number of additional participants achieving therapeutic success among participants with missing therapeutic response will be imputed by drawing from a binomial distribution. The details will be provided in the SAP.

9.3.2. Secondary Estimand(s) Analysis

9.3.2.1. Therapeutic Response

Therapeutic response (combined per-participant microbiological and clinical response) will be summarized using the micro-ITT NTF-S Population with the exception of the

assessment of therapeutic response of gepotidacin in female participants with acute uncomplicated cystitis who have qualifying uropathogen(s) resistant to “two or more” specific classes of antimicrobials at baseline where the micro-ITT MDR Population will be used. The number and proportion of participants with therapeutic success will be summarized, along with the 95% Exact Clopper Pearson CI, at the TOC Visit by treatment group. The ICE of use of other systemic antimicrobials is captured through the defining criteria of microbiological and clinical response (Section 8.1.2.1 and 8.1.3.1). Participants who do not return for the TOC Visit or have missing data at the TOC Visit will be treated as failures.

The difference in proportions of participants achieving therapeutic success for gepotidacin compared to nitrofurantoin and the 95% CI of the difference will be summarized at TOC Visit. Miettinen-Nurminen (score) confidence limits for the treatment difference will be computed. The MN estimate of the common risk difference and variance is computed by combining the point estimates and variances from the individual strata using MN weights. The estimate uses inverse variance stratum weights to produce MN confidence limits for the stratum risk differences. In addition, supplementary analysis using Bayesian dynamic borrowing will be carried out to estimate the treatment difference in the Japanese population using data from each treatment group of the global studies (Studies 204989 and 212390). Further details will be provided in the SAP.

For the micro-ITT MDR population, the number and proportion of participants with therapeutic success will be presented by treatment group at the TOC Visit along with the 95% Exact Clopper Pearson CI. The ICE of use of other systemic antimicrobials is captured through the defining criteria of microbiological and clinical response (Section 8.1.2.1 and 8.1.3.1).

In addition, Bayesian dynamic borrowing will be used to estimate the treatment difference for therapeutic response in MDR subgroup of the Japanese population using data from each treatment group of the global studies. The details will be provided in the SAP.

9.3.2.2. Clinical Outcome and Response

Clinical outcome and response will be summarized using the micro-ITT NTF-S Population with the exception of the assessment of clinical response and outcome of gepotidacin in female participants with acute uncomplicated cystitis who have qualifying uropathogen(s) resistant to “two or more” specific classes of antimicrobials at baseline where micro-ITT MDR Population will be used. The number and proportion of participants with resolution of signs and symptoms will be presented by treatment group at the TOC Visit. The ICE of use of other systemic antimicrobials is captured through the defining criteria of clinical outcome and response (Section 8.1.3.1). Participants who do not return for the TOC Visit or have missing data at the TOC Visit will be treated as failures.

For the micro-ITT MDR population, the number and proportion of participants with resolution of signs and symptoms will be presented by treatment group at the TOC Visit.

The ICE of use of other systemic antimicrobials is captured through the defining criteria of clinical outcome and response (Section 8.1.3.1).

In addition, Bayesian dynamic borrowing will be used to evaluate the efficacy in MDR subgroup in the Japanese population using the global study data. The details will be provided in the SAP.

9.3.2.3. Microbiological Outcome and Response

Microbiological outcome and response will be summarized using the micro-ITT NTF-S Population with the exception of the assessment of microbiological response and outcome of gepotidacin in female participants with acute uncomplicated cystitis who have qualifying uropathogen(s) resistant to "two or more" specific classes of antimicrobials at baseline where micro-ITT MDR Population will be used. The number and proportion of participants with microbiological success will be presented by treatment group at the TOC Visit. The ICE of use of other systemic antimicrobials is captured through the defining criteria of microbiological outcome and response (Section 8.1.2.1). Participants who do not return for the TOC Visit or have missing data at the TOC Visit will be treated as failures.

For the micro-ITT MDR population, the number and proportion of participants with microbiological success will be presented by treatment group at the TOC Visit. The ICE of use of other systemic antimicrobials is captured through the defining criteria of microbiological outcome and response (Section 8.1.2.1).

In addition, Bayesian dynamic borrowing will be used to evaluate the efficacy in MDR subgroup in the Japanese population using the global study data. The details will be provided in the SAP.

9.3.2.4. Investigator Assessment of Clinical Response

The number and proportion of participants with investigator assessed clinical response of success, failure and indeterminate/missing at the TOC Visit by treatment group based on micro-ITT Population. Reasons for an assessment of failure and indeterminate responses will also be summarized.

The 95% Exact Clopper Pearson CI for the proportion of participants with success will be presented as a binomial proportion for each treatment group.

9.3.3. Exploratory Endpoint(s) Analysis

CCI

[redacted]

CCI

9.3.4. Safety Analysis

All safety analyses will be performed on the Safety Population. All reported AEs will be coded using MedDRA and summarized by system organ class and preferred terms.

The safety estimand will use a treatment policy strategy for the ICE of study treatment discontinuation, as safety will be assessed at all post-baseline assessments irrespective of whether the participant completed the treatment.

Treatment-emergent AE (TEAE) is defined if AE onset date/time is on or after treatment start date/time. The number and proportion 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 maximum intensity.

Adverse events of special interest will include CV, gastrointestinal, and *Clostridioides difficile infection or colitis* events. In addition, AEs associated with acetylcholinesterase inhibition are also considered special interest. As described in the SAP, manual and programmatic reviews of AEs/preferred terms will be used to assess these events.

The severity of specified AEs and laboratory abnormalities will be graded according to the modified DMID toxicity grading system (Section 10.12). Data will be tabulated and reported by absolute grade for Grades 3 and higher, and shift tables, as appropriate.

Change from baseline over time in laboratory parameters, ECGs and vital signs will be summarized with descriptive statistics. The frequency of laboratory abnormality events along with the shift from baseline to the worst-case post-baseline value will be provided. Abnormal liver chemistry results will be determined using increases above the upper limit of normal.

9.3.5. PK and PK/PD analyses

Plasma and urine concentrations for the PK Population will be summarized using descriptive statistics. In addition, gepotidacin plasma concentrations will be analyzed using a population approach to allow for the estimation of gepotidacin exposure in each

participant. A nonlinear mixed-effects model will be used to determine population PK parameters and to identify relevant covariates (e.g., renal function, age, weight, or race).

9.4. Interim Analysis

No formal interim analysis is planned. On the other hand, blinded review for therapeutic, clinical and microbiological response at the TOC visit may be conducted during the study to evaluate if the blinded results have been far from the expected.

9.5. Sample Size Determination

This study is not designed to demonstrate non-inferiority of the gepotidacin to nitrofurantoin but designed to demonstrate consistency of this study with the global studies for therapeutic response of the gepotidacin.

9.5.1. Gepotidacin Sample Size

Approximately 81 participants in the gepotidacin treatment group is considered an appropriate sample size to evaluate consistency between this study and both global studies (Studies 204989 and 212390).

Assuming 81 participants in the micro-ITT NTF-S population on gepotidacin and an observed 76% therapeutic success rate out of 884 participants in the global studies, the therapeutic response in the gepotidacin arm in this study would need to be greater than 69.1% to declare “consistency” with the global studies.

9.5.1.1. Sample Size Sensitivity

Table 14 demonstrates a range of observed therapeutic response rates and the number of participants on the gepotidacin arm in this study against the corresponding consistency thresholds required in this study assuming 884 participants on the gepotidacin arm in both global studies.

Table 14 Gepotidacin Consistency Thresholds for Different Observed Gepotidacin Therapeutic Response Rate in the Global Studies and the Number of Participants on the Gepotidacin arm in this study

Observed Therapeutic Response Rate in the Global Studies	Number of Participants on the Gepotidacin arm in this study						
	75	77	79	81	83	85	87
45%	37.3%	37.7%	38.0%	37.0%	37.3%	37.6%	37.9%
50%	42.7%	42.9%	43.0%	42.0%	42.2%	42.4%	42.5%
55%	46.7%	46.8%	48.1%	48.1%	48.2%	48.2%	48.3%
60%	52.0%	51.9%	53.2%	53.1%	53.0%	52.9%	52.9%
65%	57.3%	57.1%	58.2%	58.0%	57.8%	57.6%	58.6%

Observed Therapeutic Response Rate in the Global Studies	Number of Participants on the Gepotidacin arm in this study						
	75	77	79	81	83	85	87
70%	62.7%	63.6%	63.3%	63.0%	62.7%	63.5%	63.2%
75%	68.0%	68.8%	68.4%	67.9%	68.7%	68.2%	69.0%
80%	73.3%	74.0%	73.4%	74.1%	73.5%	74.1%	74.7%

9.5.2. Nitrofurantoin Sample Size

The sample size on the nitrofurantoin arm is based on the precision estimate of 95%CI for the treatment difference.

The treatment difference between gepotidacin and nitrofurantoin will be assessed descriptively. Table 15 demonstrates a range of observed differences and corresponding 95% CIs assuming a 3:1 randomization (i.e. 81 participants on gepotidacin and 27 on nitrofurantoin in micro-ITT NTF-S population).

Table 15 95% Confidence Intervals for Different Observed Therapeutic Response Rates on the Gepotidacin arm across a Range of Differences in Therapeutic Response Rate in Gepotidacin – Nitrofurantoin assuming a 3:1 randomization.

Observed Gepo TRR	Observed difference of TRR in Gepotidacin from that in Nitrofurantoin and corresponding 95% CI (%)				
	10%	5%	0%	-5%	-10%
45%	(-11.0,31.0)	(-16.4,26.4)	(-21.7,21.7)	(-26.8,16.8)	(-31.7,11.7)
50%	(-11.4,31.4)	(-16.7,26.7)	(-21.8,21.8)	(-26.7,16.7)	(-31.4,11.4)
55%	(-11.7,31.7)	(-16.8,26.8)	(-21.7,21.7)	(-26.4,16.4)	(-31.0,11.0)
60%	(-11.7,31.7)	(-16.6,26.6)	(-21.3,21.3)	(-25.9,15.9)	(-30.3,10.3)
65%	(-11.4,31.4)	(-16.2,26.2)	(-20.8,20.8)	(-25.2,15.2)	(-29.4,9.4)
70%	(-11.0,31.0)	(-15.6,25.6)	(-20.0,20.0)	(-24.1,14.1)	(-28.1,8.1)
75%	(-10.3,30.3)	(-14.7,24.7)	(-18.9,18.9)	(-22.8,12.8)	(-26.4,6.4)
80%	(-9.4,29.4)	(-13.5,23.5)	(-17.4,17.4)	(-21.0,11.0)	(-24.3,4.3)

9.5.3. Proposed Sample Size

Assuming a 36% evaluability rate, approximately 300 participants will be enrolled and randomized to either or nitrofurantoin in a 3:1 ratio to achieve 108 participants in the micro-ITT NTF-S population (i.e. approximately 81 participants on gepotidacin and 27 on nitrofurantoin). Enrolment will continue until the approximate target number of

participants in the micro-ITT NTF-S Population has been reached. This study will be conducted at multiple sites in Japan.

Note: Enrolled means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. 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

  The study will be conducted in accordance with "the Ministerial Ordinance on the Standards for the Conduct of Clinical Trials of Medicinal Products (MHW Notification No.28 dated 27th March, 1997)" and Pharmaceuticals and Medical Devices Act.

  Applicable laws and regulations

- The protocol, protocol amendments, ICF/assent form/eConsent (if applicable), IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC 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.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

  GSK will submit the Clinical Trial Notification (CTN) to the regulatory authorities in accordance with Pharmaceuticals and Medical Devices Act before conclusion of any contract for the conduct of the study with study sites.

10.1.2. 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.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risk and benefits, to the participant or their 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 and/or eConsent (if applicable) that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protect requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent and/or eConsent (if applicable) 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)/eConsent during their participation in the study.
- A copy of the ICF(s)/eConsent must be provided to the participant or their legally authorized representative.
- Adolescent participants should be asked for their written assent or eConsent (if applicable) to participate in the study.
- As applicable, the IRB/IEC will be consulted before assent form development for guidance around age-appropriate groupings and any specific IRB/IEC requirements or local laws for conducting and documenting assent.
- Participants who are rescreened are required to sign a new ICF or provide eConsent (if applicable).
- If follow-up information from a treating physician or other licensed medical practitioner is required for a medical device incident with an AE/SAE involving an associated person(s), the Associated Person Safety Reporting Information and Authorization Letter must be signed by the associated person to obtain consent.

GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about gepotidacin or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have gepotidacin approved for medical use or approved for payment coverage.

10.1.4. 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 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 who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

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

A Microbiology Review Team will monitor blinded uropathogen identification and susceptibility data instream, including the enrollment rate of participants with a qualifying bacterial uropathogen at Baseline and the resistance profile of uropathogens.

Written documentation regarding key decisions made by the review teams/committee will be promptly distributed to participating investigators and IRB/IECs.

10.1.6. 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 all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their patients' received. The investigator(s) is/are encouraged to share the summary results with the study subjects, as appropriate.
- Under the framework of the SHARE initiative, GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.

- GSK will provide the investigator with the information of the treatment assignments for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized patient-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs 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 CRF.
- Guidance on completion of CRFs will be provided in the electronic data capture system.
- Quality tolerance limits (QTLs) will be pre-defined in the QTL report (field within the TMF) to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan. In addition, refer to Section 10.9 for details regarding allowed revisions to study conduct and/or monitoring due to COVID-19.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Detailed information about study data collection and management process including systems used can be found in the study Data Management Plan.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- 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.

10.1.8. 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 and its origin can be found in the Study Reference Manual.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF 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.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

The first participant enrolled is considered the first act of recruitment and will be the study start date.

Study/Site Termination

GSK or 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:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up

10.1.10. 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.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 16 except where indicated will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 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 16 Protocol-required Safety Laboratory Tests

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[1]	BUN	Potassium	AST/SGOT	Total and direct bilirubin
	Creatinine and creatinine clearance	Sodium	ALT/SGPT	Total protein
	Glucose (non-fasting)	Calcium	Alkaline phosphatase	Albumin
	Chloride	Magnesium	Phosphorus	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, nitrite, and leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Pregnancy testing	• Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2] Note: See Section 8.2.5 for pregnancy test sensitivity requirements and additional pregnancy testing details.			

Other Screening Tests	• Serum or urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serology [HIV antibody, hepatitis B surface antigen (HBsAg), and hepatitis C virus antibody]. If serology testing was performed within 3 months prior to the first dose of study intervention 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. • All study-required laboratory tests will be performed by a central laboratory, with the exception of dipstick urinalysis and urine pregnancy tests which will be performed locally.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN= blood urea nitrogen; 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.

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.1 and Section 10.6 All events of ALT ≥ 3 × upper limit of normal (ULN) and total 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 to GSK in an expedited manner (excluding studies of hepatic impairment or cirrhosis).
2. Local urine testing will be standard for the protocol unless serum testing is required by IRB/IEC.

Investigators must document their review of each laboratory safety report.
Laboratory results that could unblind the study will not be reported to study sites or other blinded personnel until the study has been unblinded.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. 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 intervention, whether or not considered related to the study intervention. • 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 intervention.

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 condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention 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 that 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.

10.3.2. 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, meets one or more of the criteria listed:

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 admitted (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 or significant 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) that 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:** • Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as SAE • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that 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. o Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. 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

10.3.4. Recording and Follow-Up of 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.
- 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 required form.
- 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 investigator will make an assessment of intensity for each AE and SAE reported during the study.

- 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, with the exception of serum creatinine adolescent laboratory data, which be assessed using paediatric toxicity criteria (Section 10.12).

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- 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.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention 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 postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.5. 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) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- 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 site can report this information on a paper SAE form (see next section) or to the medical monitor or SAE coordinator by telephone.

- Contacts for SAE reporting can be found in relevant study user manual located in the Investigator Site File (ISF).

SAE Reporting to GSK via Paper Data Collection Tool

- Secure email transmission of the scanned SAE paper data collection tool is the preferred method to transmit this information to the medical monitor or the SAE coordinator.
- In rare circumstances and in the absence of secure email facilities, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in relevant study user manual located in the ISF.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

Notes:

- 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, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen 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.
- Permanent sterilization methods (for the purpose of this study) include:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
- For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

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

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following (for the purpose of this study):
   a) Documented hysterectomy
   b) Documented bilateral salpingectomy
   c) Documented bilateral oophorectomy

- For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

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

2. 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, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance:

Refer to Section 8.2.5 regarding pregnancy testing for female participants at Baseline (Day 1) and associated pretreatment contraception and abstinence requirements. Female participants who enter the study using contraception must continue to do so throughout the study.

As described in Section 5.3, participants will be requested to abstain from sexual activity from the Baseline Visit through the TOC Visit to prevent possible re-infection.

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c] (not approved in Japan as contraceptive method)
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)[c]
Bilateral tubal occlusion

Azoospermic partner (vasectomized or due to a to medical cause) • *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
• **Highly Effective Methods [b] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • oral • intravaginal (not approved in Japan as contraceptive method) • transdermal (not approved in Japan as contraceptive method) • injectable (not approved in Japan as contraceptive method)
Progestogen-only hormone contraception associated with inhibition of ovulation[c] • oral (not approved in Japan as contraceptive method) • injectable (not approved in Japan as contraceptive method)
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 intervention. 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*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction)

10.5. Appendix 5: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention 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 IRB/IEC 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 gepotidacin and uncomplicated urinary tract infection. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- Additional analyses of DNA samples may be conducted 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 interventions 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 interventions of this class) or uncomplicated urinary tract infections continues but no longer than 15 years after the last subject last visit or other period as per local requirements.

10.6. Appendix 6: Liver Safety: Required Actions and Follow-up Assessments

Phase 3-4 Liver Chemistry Stopping and Increased Monitoring Criteria are designed to assure participant safety and evaluate liver event etiology

Phase 3/4 Liver Chemistry Stopping criteria and Required Follow up Assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td>ALT ≥ 8xULN</td></tr>
<tr><td>ALT Increase</td><td>ALT ≥ 5xULN but <8xULN persists for ≥2 weeks
ALT ≥ 3xULN but <5xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td>ALT ≥ 3xULN and total bilirubin ≥ 2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td>ALT ≥ 3xULN and INR>1.5</td></tr>
<tr><td>Cannot Monitor</td><td>ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks
ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td>ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="2">Required Actions, Monitoring and Follow up Assessments</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study intervention
• Report the event to GSK within 24 hours
• Complete the liver event form and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform follow up assessments as described in the Follow up Assessment column.
• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below)
MONITORING:
If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5:</td><td>• Viral hepatitis serology[4]
• Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, within 24 hours after last dose[5]
• Obtain a serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma glutamyl transferase [GGT], glutamate dehydrogenase [GLDH], and serum albumin.
• Fractionate bilirubin, if total bilirubin ≥2xULN</td></tr>
</table>

• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within **24 hours** • Monitor participant twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For all other stopping criteria (total bilirubin <2xULN and INR ≤1.5):** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline **RESTART/RECHALLENGE** • Do not restart/rechallenge participant with study intervention since not allowed per protocol; continue participant in the study for any protocol specified follow up assessments.	• Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on liver event form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs and other over the counter medications. • Record alcohol use on the liver event alcohol intake form **If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5** obtain the following in addition to the assessments listed above: • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct assay should be conducted (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week (e.g., where the participant has been resident in the clinical unit throughout) • Liver imaging (ultrasound, magnetic resonance, or computed tomography) to evaluate liver disease; complete Liver Imaging form • Liver biopsy may be considered and discussed with local specialist if available, for instance: o In participants when serology raises the possibility of autoimmune hepatitis (AIH) o In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention

	○ In participants with acute or chronic atypical presentation: • If liver biopsy conducted complete liver biopsy form

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

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

3. 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)

4. Includes: hepatitis A Immunoglobulin M (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody. 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. If hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction (PCR) of hepatitis D RNA virus (where needed) [Le Gal, 2005].

5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the PK blood sample draw on the CRF. 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 SRM.

Phase 3/4 Liver Chemistry Increased Monitoring Criteria with Continued Study Intervention

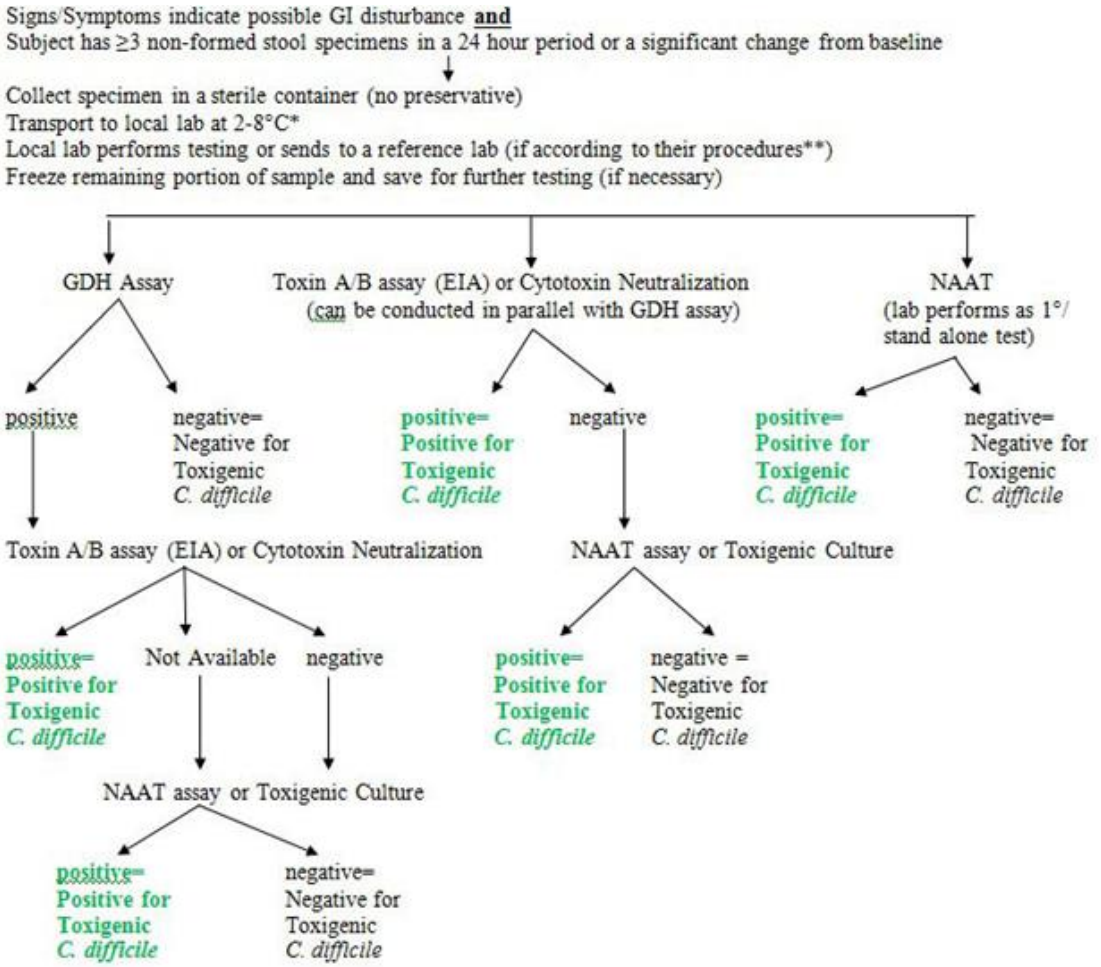
Liver Chemistry Increased Monitoring Criteria and Actions with Continued Study Intervention	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** total bilirubin <2xULN or INR≤1.5 **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** total bilirubin <2xULN or INR≤1.5 **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor within 24 hours of learning of the abnormality to discuss participant safety. • Participant can continue study intervention • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, total bilirubin and INR) until they resolve, stabilise 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 ≥5xULN and <8xULN to ≥3xULN but <5xULN, (total bilirubin <2xULN

	and INR ≤1.5) continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and total bilirubin <2xULN and INR ≤1.5, monitor participants twice monthly until liver chemistries resolve or return to within baseline.

References

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, et al. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. *J Clin Microbiol.* 2005;43(5):2363–2369.

10.7. Appendix 7: *Clostridioides Difficile* Testing Procedure and Algorithm



*If processing and testing cannot be performed within 24 hours, the specimen should be frozen immediately after collection.
**If specimen is sent to a reference laboratory, the procedures to be ordered should follow the same algorithm above.

CRA = clinical research associate; EIA = enzyme immunoassay; GDH = glutamate dehydrogenase; NAAT = nucleic acid amplification test; SRM = Study Reference Manual

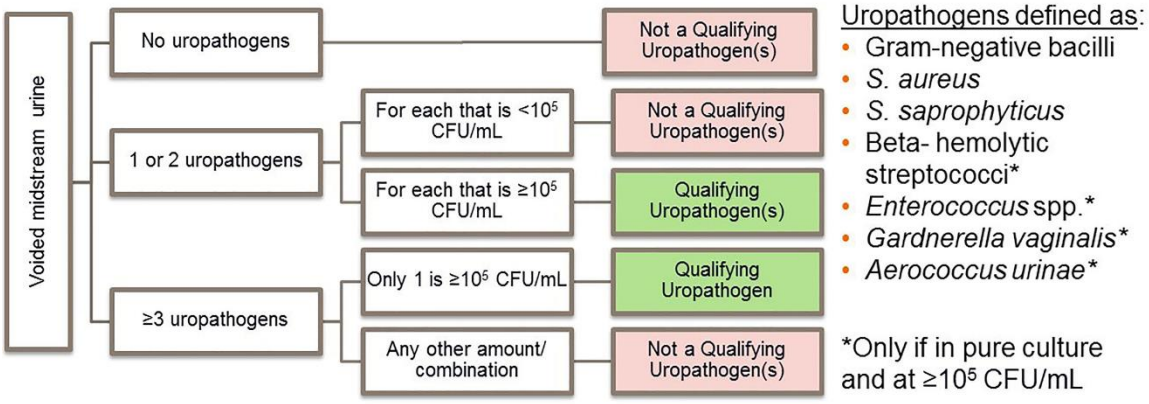
Note: This algorithm is subject to investigator discretion when the clinical presentation and time course of diarrhea (e.g., during or within 12 hours immediately after dosing) do not fit the Clostridioides difficile-associated diarrhea definition; consideration should be given to diarrhea occurring in this early time frame to be suggestive of a cholinergic effect.

10.8. Appendix 8: Algorithm for Determining Qualifying Uropathogens

In addition to other criteria indicated in Section 9.3, to be included in the micro-ITT Population, participants must have a qualifying bacterial uropathogen (defined in Figure 2) at Baseline from a quantitative bacteriology culture of a pretreatment clean-catch midstream urine specimen. For inclusion into the micro-ITT NTF-S Population, all baseline qualifying uropathogen(s) must also be susceptible to nitrofurantoin. Qualifying uropathogen susceptibilities will be monitored in stream to ensure sufficient and balanced enrollment of participants with uropathogens resistant to specific microbiological classes.

The algorithm for determining qualifying uropathogens based on microbiology laboratory quantitative culture results is provided in Figure 2, with additional algorithm details provided in the SAP.

Figure 2 Baseline Algorithm for Determining Qualifying Uropathogens



CFU=colony-forming units.

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

References

McCarter YS, Burd EM, Hall GS, Zervos M. Cumitech 2C, Laboratory diagnosis of urinary tract infections. Coordinating ed., Sharp SE. Washington, DC; ASM Press; 2009.1-26.

Chan WW. Chapter 3.12: Urine cultures. In: Leber AL, editor. Clinical microbiology procedures handbook, 4th ed. Vol 1-3. Washington, DC; ASM Press; 2016.

10.9. Appendix 9: COVID-19 Protocol Information

10.9.1. Overall Rationale for this Appendix

The COVID-19 pandemic may impact the conduct of clinical studies. Challenges may arise from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures.

This appendix outlines measures that may be applicable for any study site impacted by the COVID-19 pandemic. The purpose of the appendix is to provide information on the measures to be taken to protect participants' safety, welfare and rights, and promote data integrity. These measures are expected to be temporary and study sites will be notified of any change to these allowances as the COVID-19 pandemic evolves.

10.9.2. Study Procedures During the COVID-19 Pandemic

During the special circumstances caused by the current COVID-19 pandemic, sites should consider specific public health guidance, the impact of any travel restrictions implemented by local/regional health authorities and local institutions, and individual benefit/risk when making enrollment and treatment decisions for study participants.

Every effort should be made to adhere to protocol-specified assessments for participants on study treatment, including follow-up assessments; however, when not possible, for the duration of these special circumstances, the following measures may be implemented:

- Only where applicable country and local regulations and infrastructure allow, home healthcare (home visits and telemedicine visits) may be performed at the discretion of the investigator and following the participant signing of an informed consent/assent form specific for home healthcare. Specific details will be described in the Study Reference Manual. The participant should be informed of the home healthcare plan and any potential risks associated with home visits and telemedicine. The participant must sign an informed consent form specific to home healthcare.
- For all study visits, to minimize the amount of time that participants spend at the clinic, eConsent may be utilized and remote collection of study-related data may be obtained as described in the Study Reference Manual. Thus, some visit data may be collected through a combination of telemedicine and on-site visits. Collection of information via telemedicine will be performed only where local regulations permit.
- Clinical investigators should document in site/participant/source files how restrictions related to COVID-19 led to changes in study conduct, the duration of those changes, and indicate which trial participants were impacted and how those trial participants were impacted (as per the current local COVID-19 related regulatory guidance).
- Missing protocol-required data/visits due to COVID-19 should be noted in site/participant/source files and recorded as a COVID-19 protocol deviation.

Specifically for data management and monitoring the following will apply:

- If on-site monitoring is no longer permitted, GSK will consider remote Source Data Verification/Source Document Review (SDV/SDR) where permitted by the clinical site/institution. Remote SDV/SDR will be proposed to study sites to meet a participant and/or critical quality need, e.g., to assess participant safety or to ensure data integrity. In case of remote SDV/SDR, GSK will work with the site to ensure participant privacy.
- eCRF/CRF Final or Interim Sign-Off Process: The principal investigator is responsible for ensuring that the data within the eCRF casebook and any other data sources utilized during the study for each study participant is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 4.9.2). The principal investigator may sign/re-sign the eCRF from any computer/location by accessing the validated system using his/her unique eCRF log-in credentials. The principal investigator may delegate this activity to another medically qualified and trained subinvestigator and this must be documented on the Delegation of Responsibilities Log. It is recommended that the principal investigator identifies a subinvestigator as a back-up for eCRF signatures and that appropriate training on the protocol and eCRF requirements is provided and documented.

Essential Document Sign-Off Process: If an investigator is unable to print and sign essential documents such as Protocol/Amendment signature page then e-mail approval can be accepted by replying to the relevant e-mail that is sent by GSK.

10.10. Appendix 10: Clinical Signs and Symptoms Score for Acute Cystitis

Clinical signs and symptoms of acute cystitis will be recorded as follows:

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

CCI

[redacted]


CCI

10.11. Appendix 11: Investigator Assessment of Clinical Response Definitions

For secondary and exploratory purposes, a separate assessment of clinical response will be performed at the TOC and Follow-up Visits, or at the time of early withdrawal (Section 1.3). This assessment should be completed after the clinical signs and symptoms score is determined by the same study physician or otherwise appropriately medically trained staff who performed the clinical scoring assessment (Section 8.1.3.1and 10.10). Clinical response will be assessed and documented in the eCRF according to the clinical response definitions as follows:

Clinical Success

- Sufficient resolution of acute cystitis signs and symptoms such that no additional systemic antimicrobial therapy is required for the current infection

Clinical Failure

Participant meets any one of the criteria below:

- No apparent response to treatment (persistence or progression of any pretreatment clinical signs and symptoms)
- Use of additional systemic antibiotic(s) for the current infection
- Death related to acute cystitis prior to the visit

Indeterminate

Determination of clinical response cannot be made at the visit for any of the following reasons:

- Participant was lost to follow-up and/or the clinical assessment was not undertaken
- Use of confounding systemic antibiotic(s) for another infection
- Death prior to the visit where acute cystitis was clearly noncontributory

10.12. Appendix 12: 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 (DMID) 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.

Note: Adult DMID toxicity criteria will be applied for all laboratory parameters, with the exception of serum creatinine adolescent laboratory data, which will be assessed using paediatric DMID toxicity criteria.

HEMATOLOGY				
	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	9.5 to 10.5 g/dL	8.0 to 9.4 g/dL	6.5 to 7.9 g/dL	<6.5 g/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 µg/mL	41 to 50 µg/mL	51 to 60 µg/dL	>60 µg/dL
Prothrombin Time (PT)	1.01 to 1.25 x ULN	1.26 to 1.5 x ULN	1.51 to 3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APTT)	1.01 to 1.66 x ULN	1.67 to 2.33 x ULN	2.34 to 3 x ULN	>3 x 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 X ULN	1.25 to <1.5 X ULN	1.5 to 1.75 X ULN	>1.75 X ULN
Hyperbilirubinemia (when other liver function tests are in the normal range)	1.1 to <1.5 X ULN	1.5 to <2.0 X ULN	2.0 to 3.0 X ULN	>3.0 X ULN
Blood urea nitrogen	1.25 to 2.5 X ULN	2.6 to 5 X ULN	5.1 to 10 X ULN	>10 X 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 X ULN	1.6 to 3.0 X ULN	3.1 to 6.0 X ULN	>6 X ULN or dialysis required

mEq/L = milliequivalent per litre; Rx = therapy; ULN = upper limit of normal.

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

ULN = upper limit of normal.

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Proteinuria	1+ or 200 mg to 1 g loss/day	2 to 3+ or 1 to 2 g loss/day	4+ or 2 to 3.5 g loss/day	Nephrotic syndrome or >3.5 g 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-power 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; ECG 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; mmHg = millimetre of mercury; IV = intravenous; ECG = 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; FEV1 70 to 80% of peak flow	Requires treatment; normalizes with bronchodilator; FEV1 50 to 70% of peak flow	No normalization with bronchodilator; FEV1 25 to 50% of peak flow; or retractions present	Cyanosis: FEV1 <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 >2 L 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, maculopapular 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 urticaria	Generalized urticaria; 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

10.13. Appendix 13: Abbreviations and Trademarks

ABSSSI	acute bacterial skin and skin structure infection
AE	adverse event
AESI	adverse event of special interest
CCI [redacted]	
AIH	autoimmune hepatitis
ALT	alanine aminotransferase
APTT	Activated Partial Thromboplastin
AST	aspartate aminotransferase
AUC	area under the drug concentration-curve
AUC12h	area under the drug concentration-time curve over 12 hours
AUC24h	area under the drug concentration-time curve over 24 hours
BID	twice daily
BLI	β-Lactamase inhibitor
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CDC	Centers for Disease Control and Prevention
C. difficile	*Clostridioides difficile*
CFR	Code of Federal Regulations
CFU	colony-forming units
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
Cmax	maximum concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease
CPK	creatine phosphokinase
CRA	clinical research associate
CrCl	creatinine clearance
CSR	Clinical Study Report
CTFG	Clinical Trial Facilitation Group
CTN	Clinical Trial Notification
CV	cardiovascular
CYP3A4	cytochrome P450 enzyme 3A4
DAIDS	Division of AIDS
ΔΔQTcF	placebo-corrected change from-baseline in corrected QT interval using the Fridericia formula
DHHS	Department of Health and Human Services
DILI	drug-induced liver injury
DMID	Division of Microbiology and Infectious Diseases
EAGLE-J	Efficacy of Antibacterial Gepotidacin Evaluated in Japan
EAU	European Association of Urology
E. coli	*Escherichia coli*
ECG	electrocardiogram
eCRF	electronic Case Report Form
E. faecalis	*Enterococcus faecalis*
EIA	enzyme immunoassay
EMA	European Medicines Agency
ESBL	extended-spectrum β-lactamase

ESRD	end-stage renal disease
*f*AUC	free-drug concentration-time curve
*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
FEV1	forced expiratory volume in 1 second
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GDH/ GLDH	glutamate dehydrogenase
GGT	gamma glutamyl transferase
GSK	GlaxoSmithKline
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HPF	high-power field
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICE	intercurrent event
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product
INR	international normalised ratio
IRB	Institutional Review Board
IRT	interactive response technology
ISF	Investigator Site File
ITT	Intent-to-Treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
K. pneumoniae	*Klebsiella pneumoniae*
LAM	lactational amenorrhoea method
LDH	lactate dehydrogenase
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MDR	multidrug resistant
MedDRA	Medical Dictionary for Regulatory Activities
mEq/L	milliequivalent per litre
MIC	minimum inhibitory concentration
micro-ITT	Microbiological Intent-to-Treat
Micro-ITT NTF-S	Microbiological Intent-to-Treat Nitrofurantoin-Susceptible
mmHg	millimetre of mercury
MN	Miettinen-Nurminen
MSDS	Material Safety Data Sheet
NA	not applicable
NAAT	nucleic acid amplification test
NIMP	noninvestigational medicinal product
NTF	nitrofurantoin
PD	pharmacodynamic

PK	pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
QID	four times a day
QRS	the series of deflections in an electrocardiogram that represent electrical activity generated by ventricular depolarization prior to contraction of the ventricles
QTc	corrected QT interval
QTcB	QT interval corrected for heart rate according to Bazett's formula
QTcF	QT interval corrected for heart rate according to Fridericia's formula
QTL	Quality tolerance limits
RBC	red blood cell
Rx	therapy
S. saprophyticus	*Staphylococcus saprophyticus*
SAE	serious adverse event
SAP	Statistical Analysis Plan
SDV/SDR	Source Data Verification/Source Document Review
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SoA	Schedule of Activities
SRM	Study Reference Manual
SRT	Safety Review Team
SUSAR	suspected unexpected serious adverse reactions
Tbili	Total bilirubin
TdP	torsades de pointes
TEAE	treatment-emergent adverse event
TOC	Test-of-Cure
TMP-SXT	trimethoprim-sulfamethoxazole
ULN	upper limit of normal
UTI	urinary tract infection
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman of childbearing potential
WONCBP	women of non-childbearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
None

Trademarks not owned by the GlaxoSmithKline group of companies
MedDRA

10.14. Appendix 14: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 01: 12-OCT-2022

Overall Rationale for the Amendment

This amendment included the detailed description about the purpose of unblinding for population PK and PKPD evaluation. The description for the unblinding process of microbiology sample data for closure of trial enrolment was removed. The criteria on the management of enrolled participants in the view of baseline creatinine clearance was added. The adverse event related to acetylcholinesterase inhibition were added, and the description in mitigation strategy for reproductive system effects were edited. The amendment also included the correction of description and/or minor editorial revision in Section 10.2 Clinical Laboratory Test, Section 4.3 Justification for Dose and Section 6.7 Treatment of Overdose.

Section # and Name	Description of Change	Brief Rationale
2.3.1. Risk Assessment	**Added the adverse event related to acetylcholinesterase inhibition and edited the description in mitigation strategy for reproductive system effects**	**To provide additional information of adverse events and clarify the mitigation strategy**
4.3. Justification for Dose	**Corrected the value of gepotidacin Cmax**	**To correct the description**
6.3. Measures to Minimize Bias: Randomization and Blinding	**Included the following expression "Independent representative may be unblinded for draft model development"**	**To provide more detailed information**
6.3. Measures to Minimize Bias: Randomization and Blinding	**Removed the description about a limited degree of unblinding of a minority of participant**	**The unblinding process is not appropriate for this study**

	microbiology sample data for closure of trial enrolment	
6.7. Treatment of Overdose	**Included the description to refer the study reference manual**	**To make reference to the manual**
7.1.3. Renal Stopping and Monitoring Criteria	**Included criteria on the management of enrolled participants who are found to have a baseline creatinine clearance <60 mL/min while on study treatment**	**To provide the criteria for management of participants**
10.2. Appendix 2: Clinical Laboratory Tests	**Corrected the testing parameters and minor editorial revisions**	**To correct the description**

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