TITLE PAGE

Protocol Title: A Phase III, Randomized, Multicenter, Parallel-Group, Double-Blind, Double-Dummy Study in Adolescent and Adult Female Participants Comparing the Efficacy and Safety of Gepotidacin to Nitrofurantoin in the Treatment of Uncomplicated Urinary Tract Infection (Acute Cystitis)

Protocol Number: 204989 / Amendment 2

Short Title: Phase III, Double-Blind, Parallel-Group, Comparator-Controlled, Efficacy and Safety Study of Gepotidacin in the Treatment of Uncomplicated Urinary Tract Infection (Acute Cystitis); Efficacy of Antibacterial Gepotidacin Evaluated (EAGLE-2)

Compound Number: GSK2140944

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The signed page is a separate document.

Medical Monitor Name and Contact Information can be found in the Study Reference Manual.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 2	03-NOV-2021	TMF-13817543
Amendment 1	06-MAY-2021	2017N318043_01
Original Protocol	12-APR-2019	2017N318043_00

Amendment 2 03-NOV-2021

This global amendment is considered to be substantial.

Overall Rationale for the Amendment: This global amendment added details for an interim analysis to be conducted and managed by an Independent Data Monitoring Committee and sample size impact on the primary analysis population. The primary analysis method was updated from Cochran-Mantel-Haenszel to Miettinen and Nurminen. Other revisions also included updates to the PK Population definition and the exploratory PK/PD objective, and increasing the inclusion window for the onset of acute cystitis clinical signs and symptoms from ≤72 hours to <96 hours. In addition, minor revisions to 3 exclusion criteria were made, unblinding of PPD PK analysts (who have no involvement in study conduct) was described, prescreening activities for consent and urine pregnancy testing were clarified, the potential for home healthcare visits was added, minor revisions were made to allow more site and participant flexibility at the Baseline and On-therapy Visits, and minor updates were made to the Schedule of Events table for the interactive response technology. The amendment also includes additional minor administrative and wording edits.

Section # and Name	Description of Change	Brief Rationale
Synopsis 5.4 Scientific Rationale for Study Design 7.4 Blinding 10.1 Statistical Hypothesis 10.2 Sample Size Determination 10.4.1 General Considerations 10.4.2 Efficacy Analysis 10.5 Interim Analysis 10.6 Data Monitoring Committee or Other Review Board 12.3 Appendix 3: Study Governance Consideration Throughout	Added interim analysis and Independent Data Monitoring Committee details, including updates to the number of evaluable participants needed and sample size determination revisions, as well as applicable revisions to section numbers and content (i.e., additions and deletions) in the statistical section	To allow interim statistical evaluation for efficacy and futility
Synopsis 4 Objectives and Estimands/Endpoints	Revised the secondary objective related to therapeutic response	Consistency between primary and secondary endpoint
Synopsis 5.2 Number of Participants 10.2 Sample Size Determination 10.5 Interim Analysis	Revised description of the number of participants in the primary analysis population based on interim analysis considerations and clarified that the number of randomized participants may vary based on evaluability rate and review of qualifying uropathogens	Updated for clarification related to the interim analysis on the primary analysis population
2 Schedule of Activities	Divided the “Interactive response technology” row in to 2 separate rows specific for the screening and randomization modules	To align with how the interactive response is being used at study sites and to more closely follow the expected order of procedures

Section # and Name	Description of Change	Brief Rationale
2 Schedule of Activities 9 Study Assessments and Procedures	Clarified prescreening activities that may occur	Consistency with the Study Reference Manual
2 Schedule of Activities 5.1 Overall Design 12.5.2 Study Procedures During the COVID-19 Pandemic	Added text to allow potential home healthcare visits. Such visits will be limited to where applicable regulations and infrastructure allow.	To support study feasibility
3.3.1 Risk Assessment	Minor text clarifications for clinical QTc effects and added relevant exposures for nonclinical embryofetal effects	Consistency with currently known safety data
4 Objectives and Estimands/Endpoints	Revised the exploratory PK/PD endpoint Re-defined the PK intercurrent event as first dose to On-therapy Visit	Alignment with the planned analysis
6.1 Inclusion Criteria #2	Revised the criterion to allow the onset of clinical signs and symptoms of acute cystitis within <96 hours prior to study entry	To support study enrollment
6.2 Exclusion Criteria #2	Edited to include “uncontrolled” before high blood pressure	Text clarification
6.2 Exclusion Criteria #23	Added details to the exclusion note for ECG exclusion	To support consistency in ECG measurements
6.2 Exclusion Criteria #30	Revised wording to support a “no” response, which is in line with this being an exclusion criterion	Text clarification
7.4 Blinding	Added text to describe the unblinding of PPD PK analysts	To support ongoing PK model development and refinement
9 Study Assessments and Procedures	Removed the requirement for participants to remain at the site for approximately 1 to 2 hours after dosing at the Baseline Visit; however, retained text indicating that posttreatment assessments still need to be completed	To support site flexibility for study conduct

Section # and Name	Description of Change	Brief Rationale
9 Study Assessments and Procedures	Clarified options for the PK sample collection with respect to dose administration for the On-therapy Visit	To support site and participant flexibility
9.1.2.1 Microbiological Outcome and Response 9.1.3.1 Clinical Signs and Symptom Scores, Clinical Outcomes, and Clinical Response	Removed footnote from tables with regard to comparing the date and time of other systemic antimicrobials received with the date and time of On-therapy Visit	Updated as “time” will not be used
10.1 Statistical Hypothesis	Clarified null and alternative hypotheses for superiority testing	Clarification of the planned analysis
10.3 Populations for Analyses	Revised the definition of the PK Population	Consistency with the reporting and analysis plan
10.4.2 Efficacy Analysis	Revised the primary analysis to be performed using the Miettinen and Nurminen method instead of the Cochran-Mantel-Haenszel method	Consistency with the reporting and analysis plan
12.3 Appendix 3 Study Governance Considerations	Clarified that, in countries where certain responsibilities reside with the sponsor instead of the investigator, GSK or its designee will be responsible for those activities	Incorporation of the 26-May-2021 site clarification letter
Throughout	Minor editorial and document formatting revisions	Minor, therefore, have not been summarized

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1. SYNOPSIS

Protocol Title: A Phase III, Randomized, Multicenter, Parallel-Group, Double-Blind, Double-Dummy Study in Adolescent and Adult Female Participants Comparing the Efficacy and Safety of Gepotidacin to Nitrofurantoin in the Treatment of Uncomplicated Urinary Tract Infection (Acute Cystitis)

Short Title: Phase III, Double-Blind, Parallel-Group, Comparator-Controlled, Efficacy and Safety Study of Gepotidacin in the Treatment of Uncomplicated Urinary Tract Infection (Acute Cystitis); Efficacy of Antibacterial Gepotidacin Evaluated (EAGLE-2)

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 cystitis per year. In addition, one third of all female adolescents and women experience more than 1 episode of acute cystitis, requiring antimicrobial therapy, by the age of 24 years. The predominant uropathogen isolated in community-acquired UTIs is *Escherichia coli* (75% to 90%) followed by *Staphylococcus saprophyticus* (5% to 15%). 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. 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 *Enterococcus faecalis*. This Phase III study aims to evaluate the therapeutic response (combined microbiological and clinical efficacy per participant) of oral gepotidacin compared to oral nitrofurantoin for acute cystitis in adolescent and adult female participants.

Objectives and Estimands/Endpoints:

Objectives	Endpoints
Primary • To assess the combined clinical and microbiological efficacy of gepotidacin compared to nitrofurantoin, at the Test-of-Cure (TOC) Visit, in female participants with acute cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin	• Therapeutic response (combined per-participant microbiological and clinical response) at the TOC Visit

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

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

Primary Estimand

The primary clinical question of interest is: What is the treatment effect on the therapeutic response after 5 days of treatment with gepotidacin 1500 mg twice daily compared to 5 days of treatment with nitrofurantoin 100 mg twice daily in participants with acute cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin, regardless of treatment discontinuation for any reason. Receipt of systemic antimicrobials will impact the endpoint definition (see Section 9.1.2.1 and Section 9.1.3.1.

The primary estimand is described by the following attributes:

- Population: Female participants with acute cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin.
- Treatment condition: Gepotidacin 1500 mg twice daily for 5 days versus nitrofurantoin 100 mg twice daily for 5 days, regardless of adherence.
- Variable: Therapeutic response (combined per-participant microbiological and clinical response) at the 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: Absolute difference in the therapeutic success rate in the gepotidacin and nitrofurantoin treatment groups.
- 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 9.1.2.1 and Section 9.1.3.1) and will be counted as therapeutic failures.

Rationale for Estimand:

Interest 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 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.

Secondary Estimands:

The secondary clinical questions of interest are: What is the treatment effect on each of the secondary efficacy endpoints after 5 days of treatment with gepotidacin 1500 mg twice daily compared to 5 days of treatment with nitrofurantoin 100 mg twice daily in participants with acute cystitis (clinical endpoints) and in participants with acute cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin (therapeutic, clinical, and microbiological endpoints), regardless of treatment discontinuation for any reason. Receipt of systemic antimicrobials impacts the endpoint definition (see Section 9.1.2.1 and Section 9.1.3.1).

For each of the secondary endpoints the estimand will follow a similar approach to the estimand for the primary endpoint and will use the same strategies for the ICEs. The exception is the summary measure for the outcome endpoints. These endpoints are descriptively summarized; therefore, the summary measure will be the percentage in each clinical and microbiological outcome category in the gepotidacin and nitrofurantoin arms separately (as no direct comparison between treatment groups will be made) (see Section 9.1.2.1 and Section 9.1.3.1 for endpoint definitions).

The safety endpoint will use a treatment policy strategy of the ICE of withdrawal from treatment as the safety will be assessed at all postbaseline assessments irrespective of whether the participant completed the treatment.

See Table 2 for the components of estimand for the secondary endpoints.

Overall Design:

- Study 204989 is a Phase III, randomized, multicenter, parallel-group, double-blind, double-dummy, comparator-controlled, noninferiority study in adolescent and adult female participants comparing the efficacy and safety of oral gepotidacin to oral nitrofurantoin in the treatment of uncomplicated UTI (acute cystitis).
- Participants will be stratified by age category and acute cystitis recurrence and will be randomly assigned in a 1:1 ratio to receive either oral gepotidacin or oral nitrofurantoin.
- Appropriate safety, efficacy, 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. Pharmacokinetic samples will be collected at the On-therapy Visit. 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, regardless of treatment discontinuation.

Number of Participants:

The study is planned to enroll approximately 2500 participants to fulfill the maximum target sample size of approximately 884 participants in the primary analysis micro-ITT NTF-S Population. The final number of randomized participants may vary based on the evaluability rate and review of qualifying uropathogens by an unblinded Statistical Data Analysis Center.

Treatment Groups and Duration:

- Participants will receive 1 of the following treatments:
  - Gepotidacin: 1500 mg administered orally twice daily for 5 days (Note: Each dose should be taken after food consumption and with water to assist with tolerability.)
  - Nitrofurantoin: 100 mg administered orally twice daily for 5 days (Note: Each dose 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 or Other Committee: Yes; this study will include an Independent Data Monitoring Committee for interim analysis purposes, a GlaxoSmithKline Safety Review Team will monitor blinded safety data, and a Microbiology Review Team will monitor blinded microbiological data instream.

2. SCHEDULE OF ACTIVITIES

Table 1 Schedule of Activities

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

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

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

a. For all study visits, to minimize the amount of time that participants spend at the clinic, eConsent may be utilized and remote collection of study-related data may be obtained as described in the Study Reference Manual. Thus, some visit data may be collected through a combination of telemedicine and on-site visits. Collection of information via telemedicine will be performed only where local regulations permit. Prescreening activities may also be conducted, including a prescreening informed consent and urine testing, as detailed in Section 9 and the Study Reference Manual.
b. For the On-therapy (Day 2 to 4) Visit: Participants will be instructed to return to the study site within 1 to 3 days postrandomization. Each treatment day will be assessed over 24 hours starting with the first dose of study treatment, as further detailed in the Study Reference Manual. For the TOC (Day 10 to 13) Visit: Participants will be instructed to return to the study site 5 to 8 days after completion of study treatment.
c. At the TOC Visit, the physical examination may be symptom directed and is only required if indicated for a specific participant.
d. Individual clinical signs and symptoms scores of acute cystitis will be recorded by a study physician or otherwise appropriately medically trained staff based on participant interview and using the scoring system in Appendix 6. The same scorer will be used at all assessment time points for each participant, on all occasions, whenever possible.

CCI [redacted]

f. Based on confirmation of nitrite or pyuria (>15 WBC/HPF or the presence of 3+/large leukocyte esterase) from a pretreatment clean-catch midstream urine sample per local laboratory procedures.
g. Participants will provide a clean-catch midstream urine sample at each visit for Gram stain, quantitative bacteriology culture, and in vitro antimicrobial susceptibility testing by a designated laboratory(ies). Refer to the laboratory manual.
h. A bacteriology urine sample will be collected at the On-therapy Visit, as further detailed in the Study Reference Manual.
i. See Section 6.2 for electrocardiogram exclusion criterion for participants aged ≥12 to <18 years. For additional details see Section 8.1.2 and Section 9.4.3.
j. Take measurement of temperature, blood pressure, and pulse rate.
k. If serology testing was performed within 3 months prior to the first dose of study treatment and the results were **positive**, testing at Baseline **is not required**. If testing was performed within 3 months and any result was **negative**, testing at Baseline **is required**.
l. For women of childbearing potential, a negative high sensitivity urine pregnancy test is sufficient for eligibility. See Appendix 2 for Baseline urine test sensitivity requirements and associated contraception requirements. Pregnancy testing should also be performed after Dose 4 and before Dose 8 as specified in Appendix 2.

CCI [redacted]

n. Participants will receive oral study treatment twice daily for 5 days under double-blind, double-dummy conditions. The first oral dose will be administered at the study site during the Baseline Visit; participants will self-administer as outpatients thereafter. Each dose should be taken after food consumption and with water.
o. Participants should continue taking study treatment per their planned dosing schedule. If at all possible, the appointment time of the On-therapy Visit should be approximately 1 to 2 hours after the participant's most recent dose is expected to be taken. See the Study Reference Manual for additional details.
p. Record serious adverse events from the time of consent/assent in order to fulfill international regulatory requirements.
q. Record adverse events from the time of the first dose of study treatment.
r. At the On-therapy Visit, PK samples will be collected, as further detailed in Section 9 and the Study Reference Manual.
s. Determine study treatment compliance by performing pill count.
t. Confirm return day/time for the On-therapy, TOC, and Follow-up Visits. Refer to footnote o for scheduling the On-therapy Visit.
u. Previsit reminder: Study site staff will contact the participant 24±4 hours before the scheduled On-therapy, TOC, and Follow-up Visits.
v. Collect sample only if the participant has a signed consent/assent specific for this purpose. The Baseline Visit is the recommended time to collect the sample, but it can be collected at any time during the study.

3. INTRODUCTION

Gepotidacin (GSK2140944), a novel triazaacenaphthylene bacterial type II topoisomerase inhibitor, is being developed for the treatment of uncomplicated urinary tract infections (UTIs; acute cystitis). Gepotidacin 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 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.

3.1. Study Rationale

This study is being conducted based on the need to identify new and effective oral antibiotic treatment options for acute cystitis, as such therapies are becoming limited due to the increase of multidrug-resistant (MDR) pathogens and extended-spectrum β-lactamase (ESBL)-producing Enterobacterales pathogens, which are impacting the efficacy of currently available oral antibacterial treatment options (see Section 3.2). Two Phase II studies have been conducted and the results demonstrated that gepotidacin was efficacious in the treatment of uncomplicated urogenital gonorrhea and acute bacterial skin and skin structure infections (ABSSSIs) (see Section 5.3.3 in the investigator's brochure [IB] for details. In addition, a Phase IIa pharmacokinetic (PK) study (206899) was recently conducted in 22 participants with acute cystitis that also included exploratory clinical and microbiological efficacy objectives. All 22 participants were evaluable 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 ($<10^3$ 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.

This study (204989) aims to evaluate the therapeutic response (combined microbiological and clinical efficacy per participant) of oral gepotidacin compared to oral nitrofurantoin for acute cystitis in adolescent and adult female participants.

3.2. Background

Urinary tract infections are very common, with approximately 11% of women >18 years of age experiencing at least 1 episode of acute cystitis per year [Foxman, 2000]. Of these, half will experience more than 1 recurrent episode over their lifetime [Foxman, 2000]. The peak incidence of acute cystitis occurs in young, sexually active women ages 18 to 29 years [Fihn, 2003]. The predominant 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 cystitis [Stamm, 1993; Talan, 2000; Foxman, 2010].

Multidrug resistance, which is typically associated with nosocomial infections, has now emerged at the community level and has made treatment approaches for UTIs more difficult [Hooton, 2012; Flamm, 2014; Sanchez, 2016]. This has led to increasing patient morbidity, increasing costs due to reassessment and retreatment, higher rates of hospitalization, and increased use of broad-spectrum antibiotics [Foxman, 2002; Gupta, 2011a; Hooton, 2012]. Furthermore, ESBL-producing *Enterobacteriaceae* (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]. One reason for this serious threat level is the growing rise in the MDR *E. coli* sequence type (ST)-131 clone [Johnson, 2012; Nicolas-Chanoine, 2014]. Spread of this ST-131 clone has led to UTIs and blood stream infections caused by MDR *E. coli* worldwide [Peirano, 2010]. The availability of oral antimicrobials that are effective against ESBLs is limited and, for some outpatient infections, no oral options remain.

An in vitro evaluation of antimicrobial resistance of urinary *E. coli* isolates (n=12,253,679) among US outpatients between 2000 and 2010 was conducted using The Surveillance Network and found significant increases in the percentage of *E. coli* that were resistant to ciprofloxacin (3% to 17.1%) and trimethoprim-sulfamethoxazole (TMP-SXT) (17.9% to 24.2%), whereas there were minimal changes in the percentage of resistance to nitrofurantoin (0.8% to 1.6%) and ceftriaxone (0.2% to 2.3%) over time [Sanchez, 2012]. Another surveillance study, which looked at US susceptibility patterns and ESBL rates of *E. coli* from UTIs, showed an increase in ESBL rates from 7.8% to 18.3% ($p<0.0001$) from 2010 to 2014 [Lob, 2016]. The expansion of ESBL-producing *E. coli*, which are usually co-resistant to TMP-SXT and fluoroquinolones, is of urgent concern globally as well [Oteo, 2010]. Recent global surveillance data of *E. coli* showed high resistance rates to third-generation cephalosporins and fluoroquinolones in all 6 WHO regions [WHO, 2014]. An evaluation of the prevalence and susceptibility of acute cystitis pathogens in 9 European countries and Brazil from 2003 to 2006 showed that >10% of *E. coli* strains were MDR and 1.7% were ESBL producers [Schito, 2009]. A separate study in Brazil reported a prevalence of 7.6% ESBL-producing 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 cystitis now recommend first-line antibiotic treatment with nitrofurantoin, TMP-SXT, fosfomycin, or pivmecillinam, assuming the drug is available and the patient does not have a concerning allergy history or tolerance issues [Gupta, 2011b]. Trimethoprim-sulfamethoxazole should not be used as a first-line treatment if the prevalence of resistance exceeds the 20% threshold or if TMP-SXT was used for treatment of a UTI in the previous 3 months. If any of these are concerns for a patient, then fluoroquinolones or β-lactams are recommended.

Gepotidacin is a first-in-class, novel triazaacenaphthylene antibacterial that has demonstrated in vitro activity against uropathogens including *E. coli* (see Section 4.2.1.2 of the IB for details) and provides high and sustained urine concentrations for the treatment of UTIs. With its unique ability to selectively inhibit bacterial DNA replication by a means not utilized by any currently approved human therapeutic agent, gepotidacin warrants further study as a potential opportunity to address an unmet medical need by providing a new and effective oral treatment option for acute cystitis.

A detailed description of the chemistry, pharmacology, efficacy, and safety of gepotidacin is provided in the IB. Details on the active comparator in this study, nitrofurantoin, may be found in the locally approved prescribing information.

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of gepotidacin and nitrofurantoin may be found in the IB and the locally approved prescribing information, respectively.

3.3.1. 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 Section 5.2.6 and Section 6 of the IB). In Phase I and II 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).	See Section 6.2 for excluded cardiac conditions. Close monitoring of clinical parameters and AEs (Section 2) will be conducted, and treatment monitoring and evaluation criteria (Section 8.1.2) will be utilized to mitigate cardiovascular effects. Participants taking medications known to increase QT or potent CYP3A4 inhibitors will be excluded (see Section 7.7.2). See also the Renal and Hepatic sections within this table below.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Gastrointestinal Effects Based on nonclinical data, gastrointestinal effects were mild ulceration of the nonglandular mucosa and minimal erosion and/or mural inflammation of the glandular mucosa in stomach (rat, oral study); moderate cecal ulceration and minimal colonic erosion (rat, IV study); and vomiting (dog). Lower gastrointestinal effects (soft stools, flatulence, and diarrhea) are among the most common AEs reported in gepotidacin clinical studies. Nausea and vomiting AEs have also been commonly observed in gepotidacin clinical studies.	See also the Acetylcholinesterase Inhibition section within this table below. *Clostridium difficile*-associated diarrhea has been observed in clinical trials with gepotidacin.	See Section 6.2 for excluded medical conditions. Close monitoring of clinical parameters and AEs (Section 2) will be conducted to mitigate and assess gastrointestinal effects. Suspected *C. difficile* infection will be managed according to a prespecified algorithm provided in Appendix 1.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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, 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 6.2 for excluded medical conditions and Section 7.7.2, Prohibited Medications and Nondrug Therapies, for prohibited medications. Close monitoring of clinical parameters and AEs will be conducted to assess effects potentially related to acetylcholinesterase inhibition (Section 2).
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. A substantial increase in Cmax and AUC and decrease in clearance was observed in volunteer participants with severe hepatic impairment.	Participants with severe hepatic impairment are excluded from Phase III trials. See Section 6.2 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
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 6.2 for excluded medical conditions. Monitoring criteria have been implemented.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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 exposures (65 µg.h/mL in rat and 35 µg.h/mL in mouse).	There are no data on the use of gepotidacin in pregnant women.	Gepotidacin is contraindicated in pregnant or nursing mothers and women of childbearing potential who are not employing adequate contraceptive measures. See Appendix 2 for contraceptive measures and for required pregnancy testing.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Other		
Nitrofurantoin	The most frequent AEs possibly or probably related to oral nitrofurantoin treatment are nausea (8%), 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 anemia, diabetes mellitus, electrolyte imbalance, vitamin B deficiency, and debilitating disease. Nitrofurantoin has induced the occurrence of hemolytic anemia of the primaquine-sensitivity	Close monitoring of clinical parameters and AEs (Section 2) will be conducted, and treatment monitoring and evaluation criteria (Section 8.1.2) 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 6.2). Participants with a history of sensitivity to nitrofurantoin, or components thereof, will not be allowed to enroll in the study (Section 6.2). 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 7.7.2).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	type, which appear to be linked to a glucose-6-phosphate dehydrogenase deficiency in the red blood cells of the affected patients. 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. Refer to locally approved nitrofurantoin prescribing information for specific details relating to nitrofurantoin.	Suspected *C. difficile* infection will be managed according to a prespecified algorithm provided in Appendix 1. Precautions related to nitrofurantoin are summarized in detail in the Study Reference Manual.

bpm=beats per minute; AE=adverse event; ALT=alanine aminotransferase; AUC=area under the drug concentration-time 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.

3.3.2. Benefit Assessment

Acute 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. Gepotidacin is active in vitro and in vivo against the key causative pathogen in acute 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 cystitis.

The active comparator in this study is nitrofurantoin, a marketed antibiotic for the treatment of acute uncomplicated UTIs (acute cystitis) caused by susceptible strains of *E. coli* or *S. saprophyticus* (refer to locally approved nitrofurantoin prescribing information). Participants randomly assigned to this treatment group are also expected to experience treatment benefits. It is expected that gepotidacin will have a similar efficacy profile to nitrofurantoin.

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

3.3.3. Overall Benefit:Risk Conclusion

Antimicrobial resistance among uropathogens causing acute cystitis has increased in the past decades [Gupta, 2011b; Sanchez, 2016]. However, even in the face of increasing drug resistance to existing agents, few new antibiotics 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 efficacious treatment of uncomplicated urogenital gonorrhea and ABSSSIs, and the cumulative safety results from Phase I and Phase II studies with oral gepotidacin treatment, this study will test whether gepotidacin is noninferior to the current recommended treatment and thus represents a potential new treatment option for acute cystitis.

None of the potential or identified risks seen to date in participants dosed with gepotidacin preclude further clinical development. Mitigation strategies have been implemented to promptly identify and appropriately address risks in order to protect participant safety and to better characterize the safety profile of the study treatments (Section 3.3.1). Furthermore, a GlaxoSmithKline (GSK) Safety Review Team (SRT) will monitor blinded safety data instream (see Appendix 3). Careful safety monitoring should also identify any emerging safety issues for gepotidacin and contribute to the benefit-risk profile of 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 cystitis.

4. OBJECTIVES AND ESTIMANDS/ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the combined clinical and microbiological efficacy of gepotidacin compared to nitrofurantoin, at the Test-of-Cure (TOC) Visit, in female participants with acute cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin	• Therapeutic response (combined per-participant microbiological and clinical response) at the TOC Visit
Secondary	
• To assess the clinical efficacy of gepotidacin compared to nitrofurantoin, at the TOC and Follow-up Visits, in female participants with acute cystitis	• Clinical outcome and response at the TOC and Follow-up Visits
• To assess the clinical efficacy of gepotidacin compared to nitrofurantoin, at the TOC and Follow-up Visits, in female participants with acute cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin	• Clinical outcome and response at the TOC and Follow-up Visits
• To assess the microbiological efficacy of gepotidacin compared to nitrofurantoin, at the TOC and Follow-up Visits, in female participants with acute cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin	• Microbiological outcome and response at the TOC and Follow-up Visits

Objectives	Endpoints
Secondary continued	
• To assess the combined clinical and microbiological efficacy of gepotidacin compared to nitrofurantoin, at the Follow-up Visit, in female participants with acute cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin	• Therapeutic response (combined per-participant microbiological and clinical response) at the Follow-up Visit
• To determine the plasma and urine pharmacokinetic (PK) concentrations of gepotidacin in female participants with acute cystitis	• Gepotidacin plasma and urine concentrations
• To assess the safety and tolerability of gepotidacin compared to nitrofurantoin in female participants with acute cystitis	• Treatment-emergent adverse events and serious adverse events and change from baseline results for clinical laboratory tests and vital sign measurements
CCI [redacted]	

Objectives	Endpoints
CCI	

Primary Estimand

The primary clinical question of interest is: What is the treatment effect on the therapeutic response after 5 days of treatment with gepotidacin 1500 mg twice daily compared to 5 days of treatment with nitrofurantoin 100 mg twice daily in participants with acute cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin, regardless of treatment discontinuation for any reason. Receipt of systemic antimicrobials will impact the endpoint definition (see Section 9.1.2.1 and Section 9.1.3.1).

The primary estimand is described by the following attributes:

- Population: Female participants with acute cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin.
- Treatment condition: Gepotidacin 1500 mg twice daily for 5 days versus nitrofurantoin 100 mg twice daily for 5 days, regardless of adherence.
- Variable: Therapeutic response (combined per-participant microbiological and clinical response) at the 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: Absolute difference in the therapeutic success rate in the gepotidacin and nitrofurantoin treatment groups.
- 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 9.1.2.1 and Section 9.1.3.1) and will be counted as therapeutic failures.

Rationale for Estimand:

Interest 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 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.

Secondary Estimands:

The secondary clinical questions of interest are: What is the treatment effect on each of the secondary efficacy endpoints after 5 days of treatment with gepotidacin 1500 mg twice daily compared to 5 days of treatment with nitrofurantoin 100 mg twice daily in participants with acute cystitis (clinical endpoints) and in participants with acute cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin (therapeutic, clinical, and microbiological endpoints), regardless of treatment discontinuation for any reason. Receipt of systemic antimicrobials impacts the endpoint definition (see Section 9.1.2.1 and Section 9.1.3.1).

For each of the secondary endpoints the estimand will follow a similar approach to the estimand for the primary endpoint and will use the same strategies for the ICEs. The exception is the summary measure for the outcome endpoints. These endpoints are descriptively summarized; therefore, the summary measure will be the percentage in each clinical and microbiological outcome category in the gepotidacin and nitrofurantoin arms separately (as no direct comparison between treatment groups will be made) (see Section 9.1.2.1 and Section 9.1.3.1 for endpoint definitions).

The safety endpoint will use a treatment policy strategy of the ICE of withdrawal from treatment as the safety will be assessed at all postbaseline assessments irrespective of whether the participant completed the treatment.

Components of estimand for all secondary endpoints are listed in Table 2.

Table 2 Estimand for the Secondary Endpoints

Secondary Endpoint	Population	Treatment Condition	Variable	Summary Measure	Intercurrent Event
Clinical response at the TOC and Follow-up Visits	Female participants with acute cystitis	Gepotidacin 1500 mg BID for 5 days versus nitrofurantoin 100 mg BID for 5 days, regardless of adherence	See Table 11 and Table 12	Absolute difference in the clinical success rate in the gepotidacin and nitrofurantoin treatment groups	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antimicrobials – composite strategy
Clinical outcome at the TOC and Follow-up Visits	Female participants with acute cystitis	Gepotidacin 1500 mg BID for 5 days versus nitrofurantoin 100 mg BID for 5 days, regardless of adherence	See Table 11 and Table 12	Percentage of participants in each outcome category in the gepotidacin and nitrofurantoin arms separately	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antimicrobials – composite strategy
Clinical response at the TOC and Follow-up Visits	Female participants with acute 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	See Table 6	Absolute difference in the clinical success rate in the gepotidacin and nitrofurantoin treatment groups	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antimicrobials – composite strategy
Clinical outcome at the TOC and Follow-up Visits	Female participants with acute 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	See Table 6	Percentage of participants in each outcome category in the gepotidacin and nitrofurantoin arms separately	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antimicrobials – composite strategy

Secondary Endpoint	Population	Treatment Condition	Variable	Summary Measure	Intercurrent Event
Microbiological response at the TOC and Follow-up Visits	Female participants with acute 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	See Table 6	Absolute difference in the microbiological success rate in the gepotidacin and nitrofurantoin treatment groups	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antimicrobials – composite strategy
Microbiological outcome at the Follow-up Visit	Female participants with acute 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	See Table 6	Percentage of participants in each outcome category in the gepotidacin and nitrofurantoin arms separately	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antimicrobials – composite strategy
Therapeutic response at the Follow-up Visit	Female participants with acute 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	See Table 6 and Table 12	Absolute difference in the therapeutic success rate in the gepotidacin and nitrofurantoin treatment groups	Study treatment discontinuation (due to any reason) – treatment policy Use of systemic antimicrobials – composite strategy
Pharmacokinetic	Female participants with acute cystitis	Gepotidacin 1500 mg BID for 5 days	Refer to the reporting and analysis plan	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)

Secondary Endpoint	Population	Treatment Condition	Variable	Summary Measure	Intercurrent Event
Safety	Female participants with acute cystitis	Gepotidacin 1500 mg BID for 5 days versus nitrofurantoin 100 mg BID for 5 days, regardless of adherence	TEAEs, SAEs, as well as change from baseline results for clinical laboratory tests and vital sign measurements	Summary statistics (appropriate for each type of endpoint) in the gepotidacin and nitrofurantoin arms separately	Study treatment discontinuation (due to any reason) – treatment policy

BID=twice daily; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TOC=Test-of-Cure.

5. STUDY DESIGN

5.1. Overall Design

- Study 204989 is a Phase III, randomized, multicenter, parallel-group, double-blind, double-dummy, comparator-controlled, noninferiority study in adolescent and adult female participants comparing the efficacy and safety of oral gepotidacin to oral nitrofurantoin in the treatment of uncomplicated UTI (acute cystitis).
- Participants will be stratified by age category (<18 years, ≥18 to 50 years, or >50 years) and acute cystitis recurrence (nonrecurrent infection or recurrent infection, defined as a confirmed infection [not including the current infection in the calculation] with at least 1 prior episode within the past 3 months, at least 2 prior episodes within the past 6 months, or at least 3 prior episodes within the past 12 months before study entry) and will be randomly assigned in a 1:1 ratio to receive 1 of the following study treatments:
    - Gepotidacin: 1500 mg administered orally twice daily (BID) for 5 days (Note: Each dose should be taken after food consumption and with water to assist with tolerability.)
    - Nitrofurantoin: 100 mg administered orally BID for 5 days (Note: Each dose should be taken after food consumption and with water.)
- Appropriate safety, efficacy, 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. Pharmacokinetic samples will be collected at the On-therapy Visit. 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., $\geq 10^5$ colony-forming units/mL (CFU/mL); defined in Appendix 4] 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. The TOC Visit is 10 to 13 days after randomization, which is also 5 to 8 days after completion of study treatment.
- 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 antibiotic before or during the TOC Visit, all TOC procedures should be completed before the other antibiotic is started.

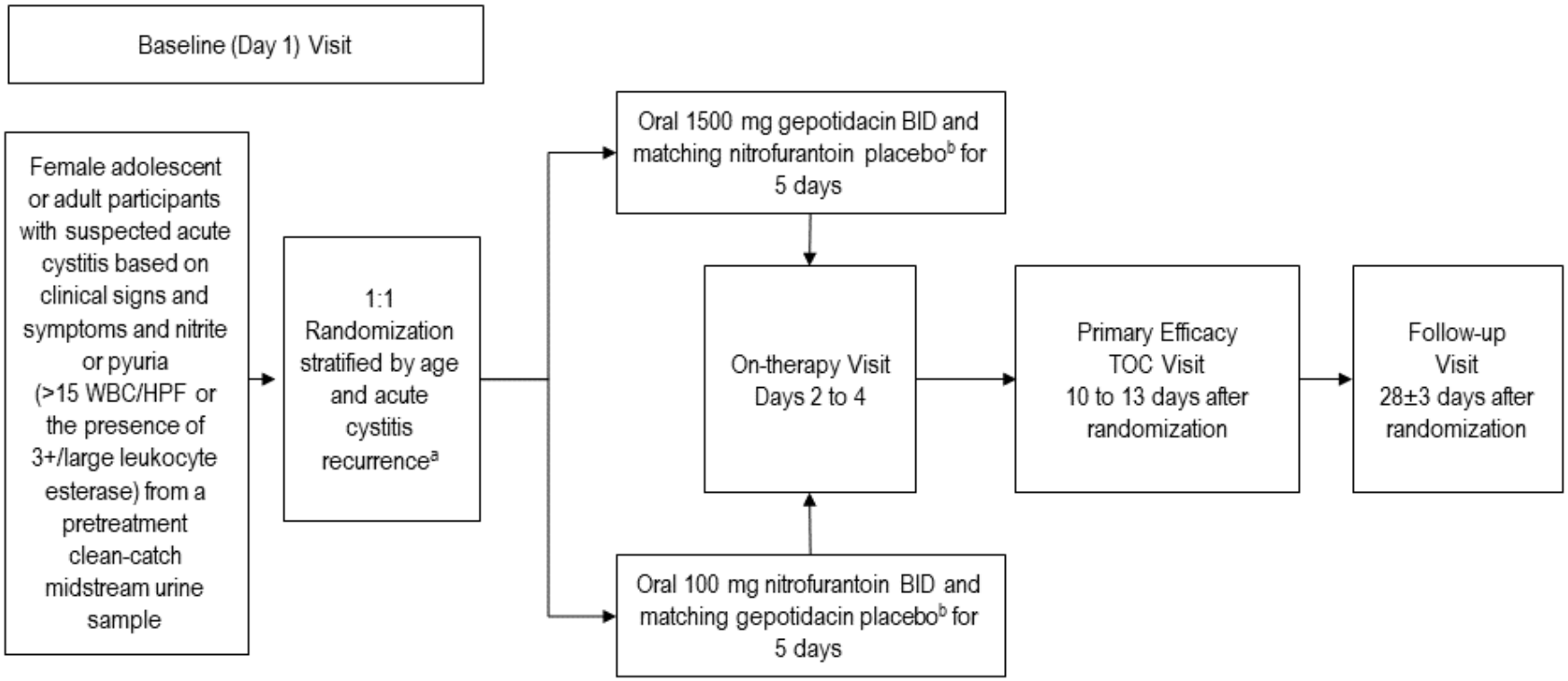
- Participants with a concomitant fungal infection can only be treated with topical antifungals per local standard of care.
- Participants will return to the study site on Day 28 (±3) for a Follow-up Visit. Participants experiencing signs and symptoms suggestive of infection recurrence or relapse will be assessed and treated per the investigator's judgement.
- The duration of study participation is approximately 28 days with 4 planned study visits (see Section 9 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.

Refer to Appendix 5 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.

Figure 1 Study Design Schematic



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

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

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

5.2. Number of Participants

The study is planned to enroll approximately 2500 participants to fulfill the maximum target sample size of approximately 884 participants in the primary analysis micro-ITT NTF-S Population. The final number of randomized participants may vary based on the evaluability rate and review of qualifying uropathogens by an unblinded Statistical Data Analysis Center (SDAC).

5.3. Participant and Study Completion

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

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

5.4. Scientific Rationale for Study Design

The study design is 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. The primary efficacy endpoint will be the therapeutic response (combined per-participant microbiological and clinical response) at the TOC Visit (i.e., 10 to 13 days after randomization, which is also 5 to 8 days after completion of study treatment) in participants who have a qualifying bacterial uropathogen at Baseline. Although the guidances differ in their criteria for defining qualifying uropathogens, this study has been designed with the qualifying uropathogen criteria defined in Appendix 4 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). CCI [redacted]

Nitrofurantoin has been selected as the active comparator in this study. Nitrofurantoin is an approved treatment that is indicated for the treatment of acute uncomplicated UTI (acute cystitis) caused by susceptible strains of *E. coli* or *S. saprophyticus* (refer to locally approved prescribing information). It is globally available in most regions and is a recommended oral first-line treatment for acute cystitis per current US, UK, and European Association of Urology guidelines [Gupta, 2011b; NICE, 2019; EAU, 2017]. Both gepotidacin and nitrofurantoin will be administered BID for a treatment duration of 5 days. As described in Section 5.5, the dose of each study treatment and the 5-day

duration were selected to provide efficacious treatment for acute cystitis and is in alignment with current clinical practice. Having the same dose regimen will also support double-blind dose administration. A noninferiority margin of 10% has been selected for this study [DHHS, 2019].

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 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 local country/national regulatory guidelines 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 Appendix 3). 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.

A separate Phase IIa study (206899) to evaluate the pharmacokinetics in participants with acute cystitis was conducted. This additional study allowed serial PK collections and evaluation of systemic and urinary exposures in this population; thus, only sparse plasma and urine sample collection for PK analysis has been included in this Phase III protocol.

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 instream, while 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. In addition, an Independent Data Monitoring Committee (IDMC) will manage the interim analysis (IA) as described in Section 10.5.

5.5. Dose Justification

The oral gepotidacin dose in this study is 1500 mg BID (total daily dose of 3000 mg) for 5 days. A 5-day dosing duration is in alignment with current treatment guidelines for efficacious antibacterial treatment of uncomplicated acute cystitis in women, which typically ranges from 3 to 7 days [Gupta, 2011b; NICE, 2019; EAU, 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 Section 5 of the 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 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 uncomplicated UTIs, 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).

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

Additionally, an in vitro study to determine the PK/PD characteristics of gepotidacin against *E. coli* (dose-fractionation and dose-ranging studies) indicate that AUC/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* 13441, as determined in this study.

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 [AUC24h]=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 AUC12h=2256 µg.h/mL; thus, AUC24h=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 steady-state PK and qualifying Enterobacterales uropathogens who were microbiological successes at TOC, plasma *f*AUC24h/MIC values ranged from 7 to 90.5 and urine AUC24h/MICs ranged from 1292 to 121,698. The participant with the lowest plasma *f*AUC24h/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.

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 uncomplicated UTI 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 cystitis.

In addition, a PK evaluation (Study 209611) in healthy adult and adolescent participants has been completed (see Section 5 of 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. This oral dose and duration of nitrofurantoin is within the prescribed labeling recommendations, which is 100 mg BID for up to 7 days for adults and pediatric patients over 12 years of age (refer to locally approved prescribing information). The labeled 7-day 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 uncomplicated acute cystitis in women [Gupta, 2007] and a treatment duration of <7 days for nitrofurantoin is in alignment with current treatment guidelines [Gupta, 2011b; NICE, 2019; EAU, 2017].

6. STUDY POPULATION

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

6.1. Inclusion Criteria

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

Age and Weight

1. The participant is ≥12 years of age 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 enroll in the study, study sites must follow their institutional ethics committee and local country/national regulatory guidelines 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 Appendix 6).
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

4. The participant is female. 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 Appendix 2.

Informed Consent

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

6.2. Exclusion Criteria

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

Medical Conditions and History

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 has a history of sensitivity to the study treatments, or components thereof, or a history of a drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates her participation.
4. The participant is immunocompromised or has altered immune defenses that may predispose the participant to a higher risk of treatment failure and/or complications (e.g., 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.
5. 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).
6. The participant has a known glucose-6-phosphate dehydrogenase deficiency.
7. The participant, in the judgment of the investigator, would not be able or willing to comply with the protocol or complete study follow-up.
8. The participant has a serious underlying disease that could be imminently life-threatening, or the participant is unlikely to survive for the duration of the study period.

Urinary Tract Infection/Renal/Urogenital Exclusions

9. The participant has acute cystitis that is known or suspected to be due to fungal, parasitic, or viral pathogens; or known or suspected to be due to *Pseudomonas aeruginosa* or Enterobacterales (other than *E. coli*) as the contributing pathogen.
10. The participant has symptoms known or suspected to be caused by another disease process, such as asymptomatic bacteriuria, overactive bladder, chronic incontinence,

or chronic interstitial cystitis, that may interfere with the clinical efficacy assessments or preclude complete resolution of acute cystitis symptoms.

11. The participant has an anatomical or physiological anomaly that predisposes the participant to UTIs or may be a source of persistent bacterial colonization, including calculi, obstruction or stricture of the urinary tract, primary renal disease (e.g., polycystic renal disease), or neurogenic bladder, or the participant has a history of anatomical or functional abnormalities of the urinary tract (e.g., chronic vesico-ureteral reflux, detrusor insufficiency).
12. The participant has an indwelling catheter, nephrostomy, ureter stent, or other foreign material in the urinary tract.
13. The participant who, in the opinion of the investigator, has an otherwise complicated UTI, an active upper UTI (e.g., pyelonephritis, urosepsis), signs and symptom onset ≥96 hours before study entry, or a temperature ≥101.4°F (≥38°C), flank pain, chills, or any other manifestations suggestive of upper UTI.
14. 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).
15. The participant presents with vaginal discharge at Baseline (e.g., suspected sexually transmitted disease).

Cardiac Exclusions

16. The participant has congenital long QT syndrome or known prolongation of the corrected QT (QTc) interval.
17. The participant has uncompensated heart failure.
18. The participant has severe left ventricular hypertrophy.
19. The participant has a family history of QT prolongation or sudden death.
20. The participant has a recent history of vasovagal syncope or episodes of symptomatic bradycardia or brady arrhythmia within the last 12 months.
21. 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.

Cardiac ECG Exclusions

22. For any participant ≥12 to <18 years of age, the participant has an abnormal electrocardiogram (ECG) reading.

23. 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.

24. The participant has a documented or recent history of uncorrected hypokalemia within the past 3 months

Hepatic Exclusions

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

    Note: Participants with asymptomatic viral hepatitis are eligible for study participation.

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

Prior Antibiotic/Antifungal Use Exclusion

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

Concomitant Medication Use Exclusion

30. The participant plans to use any of the prohibited medications or nondrug therapies from the Baseline Visit through the TOC Visit as detailed in Section 7.7.2.

Prior/Concurrent Clinical Study Experience

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

6.3. Lifestyle Restrictions

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

6.3.1. Meals and Dietary Restrictions

Study treatment should be taken with food (a meal or a snack) (see Section 7.1).

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. Participants who are screen failures are allowed to be rescreened for the same infection episode or a subsequent infection episode and participate in the study if they meet all of the inclusion and exclusion criteria. 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, and any serious adverse events (SAEs).

7. TREATMENTS

Study treatment is defined as any investigational treatments, marketed products, or placebo intended to be administered to a study participant according to the study protocol.

7.1. Treatments 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.

Study Treatment Name:	**Gepotidacin**	**Placebo (Matched to Nitrofurantoin)**	**Nitrofurantoin**	**Placebo (Matched to Gepotidacin)**
Dosage 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 Strengths/ Dosage Levels:	2 x 750-mg tablets	Not applicable	1 x 100-mg capsule	Not applicable
Route of Administration:	Oral	Oral	Oral	Oral
Dosing Instructions:	Administer twice daily for 5 days: 1500 mg – 2 tablets (3000 mg total daily dose) Each dose should be taken after food consumption and with water.	Administer twice daily for 5 days: 1 capsule Each dose should be taken after food consumption and with water.	Administer twice daily for 5 days: 100 mg – 1 capsule (200 mg total daily dose) Each dose should be taken after food consumption and with water.	Administer twice daily for 5 days: 2 tablets 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.
Manufacturer:	Patheon Canada (part of Thermo Fisher Scientific)	Almac, LTD (Over-encapsulation by Almac, LTD)	Alvogen (Over-encapsulation by Almac, LTD)	Patheon Canada (part of Thermo Fisher Scientific)

7.2. Dose Modification

The study design does not allow for dose modifications.

7.3. Method of Treatment Assignment

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

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

7.4. Blinding

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, PPD [full service partner]) will know which study treatment a participant is receiving, with the exception of a few select PPD PK analysts to support PK model development and refinement. In order to maintain 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.

Individual participant-level, de-identified, unblinded, and scrambled (i.e., random reassignment of participant identification numbers) drug concentration information will be analyzed prior to unblinding the study. In that case, independent PPD clinical PK analysts (who have no involvement in study conduct) will have access to an unblinded scrambled population PK-specific dataset (e.g., drug concentrations, actual dosing information, demographics, and laboratory details, but no AE or efficacy data) at 1 or more time points (e.g., prior to the interim and/or final analysis) throughout the study for population PK model development and refinement.

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/PPD 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/PPD 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 assignment 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 instream, will remain blinded to participant treatment assignment throughout the study (see Appendix 3). A Microbiology Review Team will monitor blinded pathogen identification and susceptibility data instream 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. Provision will be made for a limited degree of unblinding of a minority of participant sample data should this be viewed as appropriate for planning closure of trial enrollment. Procedures will be described in a separate microbiology sample monitoring plan, and no impact on trial integrity is expected.

The IDMC and SDAC will be unblinded for the IA (Section 10.5). The IDMC details will be described in a separate charter and analysis plan. The GSK and PPD study teams that are operating the study and conducting the final analysis will remain blinded.

GSK's Global Clinical Safety and Pharmacovigilance staff may unblind the treatment 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 treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

7.5. Preparation/Handling/Storage/Accountability

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

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

A Material Safety Data Sheet or equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

7.6. Treatment Compliance

- When participants are dosed at the study site during the Baseline Visit, they will take their study treatment when directed by the investigator or designee, under medical supervision. The date and time of any dose administered at the study site will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.
- When participants self-administer study treatments as outpatients, compliance with gepotidacin, nitrofurantoin placebo, nitrofurantoin, and gepotidacin placebo will be assessed through querying the participant during the study site visits and documented in the source documents and eCRF. A record of the number 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 treatment and compliance records. Treatment start and stop dates, including dates for treatment delays, will also be recorded in the eCRF.

7.7. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving within 30 days prior to the Baseline Visit or receives during the study must be recorded in the eCRF. In addition, any antibiotic 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.

7.7.1. Permitted Medications and Nondrug Therapies

The use of H_1 antihistaminics not associated with QT prolongation is allowed (e.g., loratadine, cetirizine, ebastine, and fexofenadine). The use of topical, nonsystemic antibacterials (e.g., topical clindamycin, neomycin, or polymyxin) and topical, nonsystemic antifungals (e.g., topical clotrimazole, tolnaftate, or ketoconazole) is allowed throughout the study. Please also refer to Appendix 7.

Acetaminophen or paracetamol use is permitted throughout the study as it does not mask symptoms of the disease under study. A list of permitted medications commonly used for nausea, vomiting, pain, and diarrhea per investigator discretion is provided in Appendix 7. As described in Appendix 7, low-dose acetylsalicylic acid (≤100 mg/day) is permitted for the prevention of cardiovascular (CV) disease events.

A further detailed list of medications will be provided in the SRM.

7.7.2. Prohibited Medications and Nondrug Therapies

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

- An investigational product within 30 days or 5 half-lives, whichever is longer, of the Baseline Visit.
- Treatment with other systemic antimicrobials (e.g., oral ciprofloxacin, amoxicillin/clavulanate, cephalexin, or doxycycline) or systemic antifungals (e.g., oral fluconazole, itraconazole, or terbinafine) within 1 week before study entry. Treatment with systemic fluconazole or other systemic antifungals per local standard of care is only allowed after all TOC Visit procedures have been completed.
- Immunosuppressive therapy, including corticosteroid therapy (>40 mg/day prednisolone or equivalent for >1 week, ≥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; additional guidance is provided in Appendix 7. Of note, ondansetron is not allowed from the Baseline Visit to the TOC Visit due to its known TdP risk. Alternative antiemetics that are permitted per investigator discretion are listed in Appendix 7.

  Note: Crediblemeds.org categorizes drugs into 4 categories. The only category for exclusion in this study is the "Known Risk of TdP" category; participants taking drugs that meet criteria of other categories are NOT excluded from participation.
- Strong CYP3A4 inhibitors (a list of strong CYP3A4 inhibitors is provided in the SRM).
- St John's wort or other strong CYP3A4 inducers are not permitted from 14 days before study entry through the TOC Visit (a list is provided in the SRM).
- Prescription, nonprescription, or supplements that may impact UTI clinical or microbiological efficacy outcomes including, but not limited to, *Uva ursi*, D-mannose, cranberry tablets, phenazopyridine, nonsteroidal anti-inflammatory drugs including ibuprofen and cyclooxygenase-2 inhibitors, and uricosuric drugs (e.g., probenecid and sulfinpyrazone). As described in Appendix 7, acetylsalicylic acid (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 other 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.

7.8. Treatment After the End of the Study

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

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

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

Reasons for study treatment discontinuation may include the following:

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

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

The reason for study treatment discontinuation will be recorded in the 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 Table 1).

8.1.1. Liver Chemistry Stopping Criteria

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

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

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

OR

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

Liver safety required actions and follow-up assessments section can be found in Appendix 8.

Figure 2 Phase III Liver Chemistry Stopping and Increased Monitoring Algorithm

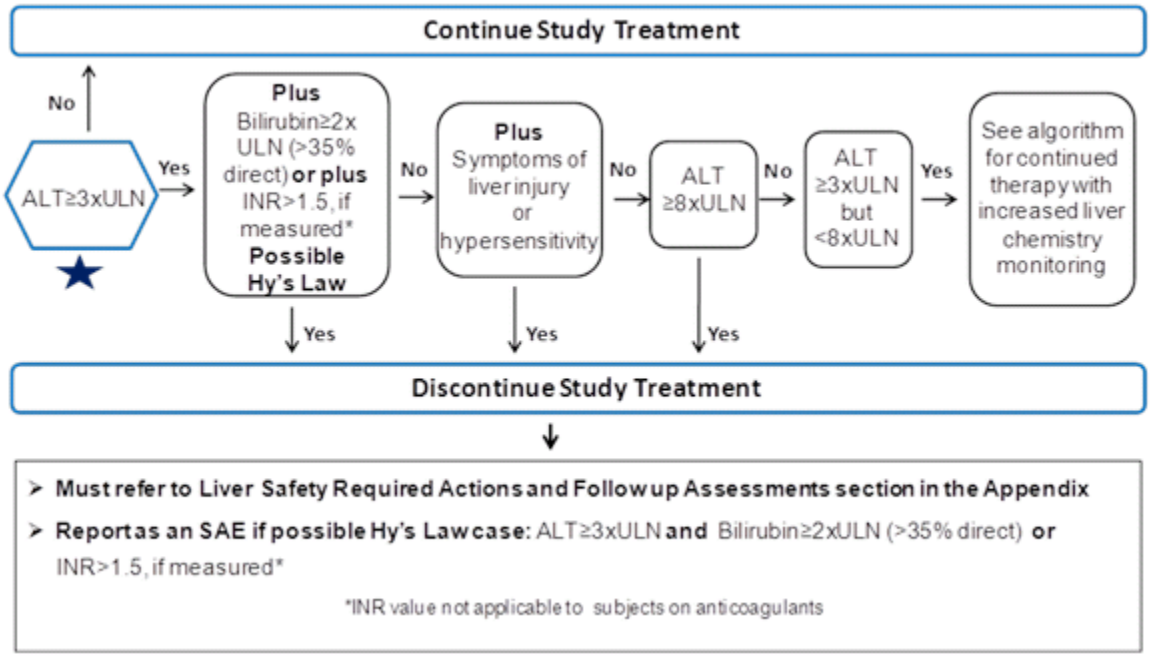
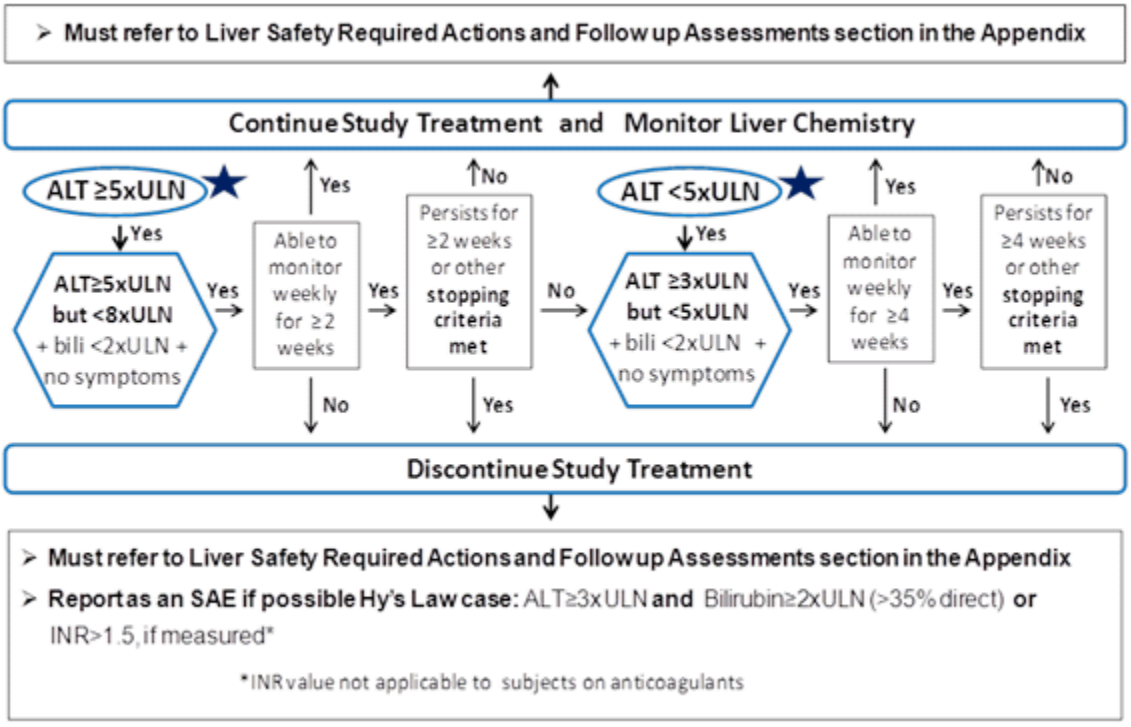


Figure 3 Phase III Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥3 x ULN but <8 x ULN



8.1.2. QTc Stopping Criteria

This protocol only requires an ECG evaluation at the Baseline Visit. Should further ECG monitoring or evaluation be needed for an individual participant, per investigator discretion, the following should be considered:

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

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

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

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

- The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled. (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*. Safety ECGs and other nonprotocol-specified ECGs are an exception.
- The QTc should be based on averaged QTc values of triplicate ECGs obtained over a brief (e.g., 5- to 10-minute) recording period.

8.1.3. Rechallenge

8.1.3.1. Study Treatment Restart or Rechallenge

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

8.1.4. Gastrointestinal Evaluation Criteria

If a participant meets the criteria in Appendix 1, *Clostridium difficile* toxin testing should be conducted and the specific eCRF page completed. *C. difficile* infection or colitis is considered an AE of special interest (Section 9.2.5).

8.2. Withdrawal From the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- Reasons for study withdrawal include:
  - Participant lost to follow-up
  - Participant withdrew consent
  - Termination of the study by GSK
  - Investigator discretion
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he or 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 Schedule of Activities [SoA] in Section 2), 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.

8.3. Lost to Follow-Up

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

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

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

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in Table 1.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in Table 1, is essential and required for study conduct.
- All baseline screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in Table 1.
- 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 cystitis and pregnancy testing.
- 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 antibiotic before or during the TOC Visit, all TOC procedures should be completed before the other antibiotic 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 Table 1, including the following:
  - Pretreatment baseline specimens for microbiological testing will be collected, as described in Section 9.1. Clinical signs and symptoms of acute cystitis will be recorded, as described in Section 9.1.3.1 and Appendix 6. CCI [redacted]
  - Following completion of all pretreatment assessments, eligible participants will be randomly assigned to treatment, as described in Section 7.3.
  - The first dose of randomly assigned oral study treatment will be administered at the study site. After dose administration, Day 1 posttreatment assessments will be performed, as shown in Table 1. 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. (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 2 [Table 1]); the planned return day/time should be at the convenience of the participant and also the availability of the study site staff. If at all possible, the appointment time of the On-therapy Visit should be approximately 1 to 2 hours after the participant's most recent dose is expected to be taken. See the SRM for additional details.
- **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 Table 1, 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, 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: 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.

- The On-therapy Visit should be scheduled to support completion of the postdose PK collection, if at all possible, 1 to 2 hours after the most recent dose is taken. However, the following options are acceptable and should be prearranged with each participant based on personal preference:
    - Participants may take the morning dose as usual, then go to the study clinic for PK sample collection at approximately 1 to 2 hours postdose.
    - Participants may go to the study clinic, take the morning dose at the clinic, and then wait at the clinic for approximately 1 to 2 hours postdose for the PK sample collection to be performed.
    - Participants may go to the study clinic 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.
- Specimens for microbiological testing, as described in Section 9.1, and blood and urine samples for PK analysis, as described in Section 9.5, will be collected. Clinical signs and symptoms of acute cystitis will be recorded, as described in Section 9.1.3.1 and Appendix 6. CCI [redacted]
- Pregnancy testing as required after Dose 4 and before Dose 8. Refer to Appendix 2 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 Table 1, 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 9.1. Clinical signs and symptoms of acute cystitis will be recorded, as described in Section 9.1.3.1 and Appendix 6. CCI [redacted]
- **Follow-up (Day 28±3) Visit**. Participants will be instructed to return to the study site 28 (±3) days postrandomization in order to complete the Follow-up Visit. Assessments will be performed as shown in Table 1, 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 9.1. Clinical signs and symptoms of acute cystitis will be recorded, as described in Section 9.1.3.1 and Appendix 6. CCI [redacted]

CCI [redacted]

- Participants experiencing signs and symptoms suggestive of infection recurrence or relapse will be assessed and treated per the investigator's judgement.

9.1. Efficacy Assessments

9.1.1. Therapeutic Response Evaluation

Therapeutic response (combined per-participant microbiological and clinical response) (success/failure) is a measure of the overall efficacy response. A therapeutic success refers to participants who have been deemed both a "microbiological success" (see Section 9.1.2.1) and a "clinical success" (see Section 9.1.3.1). 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.

9.1.2. 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 laboratory(ies). For inclusion in the micro-ITT Population, a baseline qualifying bacterial uropathogen is required as defined in Appendix 4; 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 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 laboratory(ies). Additional tests, as needed, to further characterize recovered isolates will also be performed by a designated 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.

9.1.2.1. Microbiological Outcome and Response

Only those participants who have a qualifying bacterial uropathogen (defined in Appendix 4) 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 programatically 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 3, Table 4, and Table 5 for baseline qualifying uropathogen outcomes). The corresponding microbiological response (success or failure) "by uropathogen" is then assigned, as shown in Table 4 and Table 5. 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 6.

Microbiological outcome criteria for new qualifying uropathogens (i.e., uropathogens not identified at Baseline) are defined by visit in Table 7, Table 8, and Table 9.

Table 3 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
1) The On-therapy urine culture result is missing, or 2) The participant received other systemic antimicrobials before the On-therapy Visit	Unable to determine

CFU=colony-forming units.

Table 4 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
1) The TOC urine culture result is missing, or 2) The participant received other systemic antimicrobials before the TOC Visit	Unable to determine	Microbiological failure

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

Table 5 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
1) The Follow-up urine culture result is missing, or 2) 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 6 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 7 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 8 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 9 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

9.1.3. Clinical Evaluation

9.1.3.1. 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 2) using the scoring system and instructions in Appendix 6. 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 (Appendix 6) 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 10) and the clinical outcome and response (success or failure) at the TOC Visit (Table 11) and the Follow-up Visit (Table 12).

Table 10 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
1) The Baseline score is missing, or 2) The On-therapy assessment is missing, or 3) 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 (Appendix 6), 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 11 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
1) The Baseline score is missing, or 2) The TOC assessment is missing, or 3) The participant received other systemic antimicrobials not for the current infection 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 (Appendix 6), 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 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 (Appendix 6), 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.

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9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 10.

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

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

- All SAEs will be collected from the signing of the ICF until the Follow-up Visit at the time points specified in the Table 1 (Section 2).
- All AEs will be collected from the start of treatment until the Follow-up Visit at the time points specified in the Table 1 (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the medical history/current medical conditions section of the eCRF and not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstances should this exceed 24 hours, as indicated in Appendix 10. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death,

at any time after a participant has been discharged from the study, and he or she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 10.

9.2.2. Method of Detecting AEs and SAEs

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

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and nonserious AEs of special interest (as defined in Section 9.2.5), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 10.

9.2.4. Regulatory Reporting Requirements for SAEs

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

9.2.5. 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 3.3.1), which will be identified by a prespecified list of coded terms or determined by algorithm, as described in the reporting and analysis plan (RAP). Additional details are provided in Appendix 10.

9.2.6. Cardiovascular and Death Events

For any CV events detailed in Appendix 10 and all deaths, whether or not they are considered SAEs, specific CV and death sections of the eCRF will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-CV death.

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

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

9.2.7. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment and through the Follow-up Visit.
- If a pregnancy is reported, the investigator should inform GSK/PPD within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 2.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

9.3. Treatment of Overdose

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

Occasional incidents of acute overdosage of nitrofurantoin have not resulted in any specific symptoms other than vomiting (refer to locally approved prescribing information). 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 treatment can no longer be detected systemically (at least 72 hours).
3. Obtain a plasma sample for PK analysis within 24 hours from the date of the last dose of study treatment if requested by the medical monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

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

9.4. Safety Assessments

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

9.4.1. Physical Examinations

- A physical examination will be performed at the time points indicated in the SoA (Section 2).
  - At Baseline, the examination will include assessments of the respiratory, CV, abdominal, gastrointestinal, neurological, and urogenital systems. Height and weight will only be measured and recorded at the Baseline Visit (before dosing).
  - At the TOC Visit, 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.

9.4.2. Vital Signs

- Vital signs will be measured at the time points indicated in Table 1.
- Vital signs will be measured in a semi-supine position 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.

9.4.3. Electrocardiograms

- Triplicate 12-lead ECGs (over an approximate 5- to 10-minute period) will be performed at the Baseline Visit using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 8.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- This protocol only requires an ECG evaluation at the Baseline Visit. 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. Subsequent ECGs only need to be triplicate if the initial one is prolonged.

- If clinically significant changes occur during the study, they will be reported as AEs.

9.4.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 11 for the list of clinical laboratory tests to be performed and to Table 1 for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 11, must be conducted in accordance with the laboratory manual and Table 1.

9.5. Pharmacokinetics

- Blood and urine samples for PK analysis of gepotidacin will be collected at the time point indicated in Table 1, with collection options described in Section 9. The actual date and time of the sample collection will be recorded. The volume of blood required for the PK sample is approximately 3 mL.
- At the On-therapy Visit, as the urine PK collection coincides with the urine bacteriology sample collection, a single urine sample of adequate volume may be collected and split into separate samples for PK and microbiological purposes. **Note**: The date and time of the last dose taken before the PK collection will be recorded.
- Processing, storage, and shipping procedures for blood and urine samples are provided in the SRM and/or laboratory manual.

CCI [redacted]

9.7. Genetics

A 6-mL blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is

optional. Participants who do not wish to participate in the genetic research may still participate in the study.

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

Details on processes for collection and shipment and destruction of these samples can be found in Appendix 12.

9.8. Biomarkers

Biomarkers are not evaluated in this study.

9.9. Health Economics or Medical Resource Utilization and Health Economics

CCI [redacted]

10. STATISTICAL CONSIDERATIONS

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

10.1. Statistical Hypothesis

The study is designed to demonstrate that gepotidacin administered orally is noninferior compared to nitrofurantoin administered orally on the primary efficacy endpoint of therapeutic response (combined per-participant microbiological and clinical response) at the TOC Visit in participants with a qualifying bacterial uropathogen at Baseline that is susceptible to nitrofurantoin. Microbiological success is defined as eradication (i.e., 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 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.

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

- H_0: therapeutic success rate of gepotidacin 1500 mg BID – therapeutic success rate of nitrofurantoin 100 mg BID $\leq$ -10.0%
- H_1: therapeutic success rate of gepotidacin 1500 mg BID – therapeutic success rate of nitrofurantoin 100 mg BID >-10.0%

The use of a -10% noninferiority margin in the primary efficacy estimand is in accordance with current FDA guidance [DHHS, 2019; EMA, 2013].

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

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

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

An IA is planned as described in Section 10.5. The study will utilize a group sequential design with 1 IA using Lan-DeMets spending function [Lan, 1983]. The timing of the IA is planned to occur when approximately 60% of the maximum planned participants in the micro-ITT NTF-S Population (N≈884) have achieved the TOC Visit. The stopping boundary for assessing efficacy will use the Pocock stopping rule for efficacy and the O'Brien-Flemming stopping rule for futility. At the time of the IA, the IDMC will perform an unblinded review to confirm that there are sufficient microbiological data for regulatory submission before proceeding to the IA for efficacy and futility. If in any case the microbiological data are not sufficient, the IDMC will instead conduct a futility-only IA. If futility is not declared, the sample size needed for the final analysis will be approximately 768 participants in the micro-ITT NTF-S Population. This will be based on the O'Brien-Flemming stopping boundary for futility. Details on the timing and design selection process are described in Section 10.5.

10.2. Sample Size Determination

10.2.1. Justification of Sample Size

Participants will be randomized to gepotidacin and nitrofurantoin in a 1:1 ratio. Assuming a 76% therapeutic success rate for both nitrofurantoin and gepotidacin, a sample size of approximately 884 participants in the micro-ITT NTF-S Population is required, for a design with 1 IA allowing for stopping the study based on efficacy or futility, to provide approximately 90% power to demonstrate noninferiority in the therapeutic response rate of gepotidacin to nitrofurantoin with a 0.025 one-sided alpha level and a -10.0% noninferiority margin. The minimal response rate difference that would meet the statistical criterion for noninferiority is provided in Table 13.

Table 13 Minimal Response Rate Difference for Efficacy and Futility Interim Analysis

Design	Information Fraction	Micro-ITT NTF-S Sample Size	Minimal Response Rate Difference for Noninferiority
Interim Analysis for Efficacy and Futility	60%	530	-2.2%
	100%	884	-3.6%

Micro-ITT NTF-S=Microbiological Intent-to-Treat Nitrofurantoin-Susceptible.

In case a futility-only IA is conducted, under the same assumption for response rate, significance level, and noninferiority margin, a sample size of 768 participants in the

micro-ITT NTF-S Population will provide approximately 88% power to demonstrate noninferiority. The minimal response rate difference that would meet the statistical criterion for noninferiority is -4.0% for the final analysis.

The study is planned to enroll approximately 2500 participants to ensure a sufficient number of participants in the primary analysis population (i.e., micro-ITT NTF-S Population). If the study proceeds to an efficacy and futility IA, the maximum target sample size (assuming there is a decision to continue the study at the IA) for the primary analysis population will be around 884 participants. If the study proceeds to the futility-only IA, the maximum target sample size (assuming a decision to continue the study at the IA) for the primary analysis population will be approximately 768 participants. The final number of randomized participants may vary based on the evaluability rate and review of qualifying uropathogens by an unblinded SDAC.

Note: "Enrolled" means that a participant's or their legally acceptable representative's agreement to participate in the 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 in the protocol.

10.2.2. Sample Size Sensitivity

Sensitivity of the sample size has been explored considering various therapeutic success rates. Table 14 and Table 15 show the minimum power under various assumptions of "true" therapeutic success rates of gepotidacin and nitrofurantoin under 2 different IA designs, when the IA is conducted at approximately 60% information fraction of the design allowing for efficacy and futility stop at the IA. For all of these cases, the 1-sided type I error is 2.5%, the noninferiority margin is -10%.

Table 14 Power of the Study Under Various Assumptions of the True Therapeutic Success Rates for Efficacy and Futility Group Sequential Design

Therapeutic Success Rate of Nitrofurantoin	Therapeutic Success Rate of Gepotidacin	Total Number of Participants in the Primary Analysis	Number of Participants in the Primary Analysis in the Interim Analysis	Power
76%	76%	884	530	90%
72%	72%	884	530	87%
68%	68%	884	530	84%
64%	64%	884	530	81%
60%	60%	884	530	79%

Table 15 Power of the Study Under Various Assumptions of the True Therapeutic Success Rates for Futility Only Group Sequential Design

Therapeutic Success Rate of Nitrofurantoin	Therapeutic Success Rate of Gepotidacin	Total Number of Participants in the Primary Analysis	Number of Participants in the Primary Analysis in the Interim Analysis	Power
76%	76%	768	530	88%
72%	72%	768	530	85%
68%	68%	768	530	81%
64%	64%	768	530	79%
60%	60%	768	530	77%

10.3. Populations for Analyses

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 Appendix 4), 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. This is the primary analysis population.

Population	Description
Micro-ITT NTF-NS Population	All participants in the micro-ITT Population who have any qualifying baseline bacterial uropathogens that are not susceptible to nitrofurantoin (NTF-NS), defined as resistant to nitrofurantoin, intermediate to nitrofurantoin, or have no interpretation to nitrofurantoin. Participants with missing MIC susceptibility results for all qualifying uropathogens will not be included in the NTF-NS subpopulation. Participants will be analyzed according to their randomized study treatment.
Microbiologically Evaluable (ME) Population	Participants who meet the definition of the micro-ITT Population, follow important components of the study (as specified in the RAP) and have an interpretable quantitative urine culture at the specified visit. Note: Visit-specific ME populations will be defined in the RAP.
ME NTF-S Population	All participants in the ME visit-specific population whose baseline qualifying bacterial uropathogens all are susceptible to nitrofurantoin (NTF-S). Note: Visit-specific ME NTF-S populations will be defined in the RAP.
ME NTF-NS Population	All participants in the ME visit-specific population who have any baseline qualifying bacterial uropathogens that are not susceptible to nitrofurantoin (NTF-NS). Note: Visit-specific ME NTF-NS populations will be defined in the RAP.
Clinically Evaluable (CE) Population	All participants in the ITT Population who follow important components of the study as specified in the RAP. Note: Visit-specific CE populations will be defined in the RAP.
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.
Safety Population	All randomized participants who receive at least 1 dose of study treatment. Participants will be analyzed according to their actual treatment received.

10.4. Statistical Analyses

The RAP will be finalized prior to unblinding and 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, secondary, and exploratory endpoints.

10.4.1. General Considerations

Treatment effect to be estimated for primary and secondary estimands are clinical outcome/response, microbiological outcome/response, and therapeutic response at the designated visits in female participants with acute cystitis (clinical outcome/response) and female participants with acute cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin (clinical outcome/response, microbiological outcome/response, and therapeutic response). Intercurrent events include receiving other systemic antimicrobials and treatment discontinuation; a combination of composite strategy and treatment policy strategy will be implemented to account for the 2 ICEs, respectively. The ICE event strategies determine that (1) treatment effects will be estimated regardless of study treatment discontinuation when the analysis population is the ITT Population or its derivatives; and (2) the definition of a successful response or a positive outcome (clinical resolution and microbiological eradication) precludes the use of other systemic antimicrobials.

Any supplemental analyses will be detailed in the RAP. Any additional analyses or outputs needed as a result of COVID-19 on the study will be detailed in the RAP.

10.4.2. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary analysis of the primary efficacy endpoint will be performed using the micro-ITT NTF-S Population. • The primary treatment effect to be estimated (estimand) is therapeutic response (combined per-participant microbiological and clinical response) at the TOC Visit in female participants with acute cystitis with a qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin. Microbiological success at the TOC Visit is 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 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. 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 4.

Endpoint	Statistical Analysis Methods
	• The population-level effect will be estimated by the difference in percentage response and its 95% CI. 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. • The number and percentage of participants with therapeutic success will be summarized, along with the 95% CI, at the TOC Visit by treatment group. • The testing procedure at the IA and the final analysis involves comparing the noninferiority test statistics with the stopping boundary. Test statistics of the therapeutic success rate difference between the 2 treatment groups for noninferiority (-10% margin) will be calculated using the Miettinen and Nurminen method stratified by age category (<18 years, ≥18 to 50 years, or >50 years) and acute cystitis recurrence (nonrecurrent infection or recurrent infection) [Miettinen, 1985] and compared to the stopping boundaries. If noninferiority is established, test statistics of the success rate difference between the 2 treatment groups for superiority will be calculated using the same method to compare with the stopping boundary for superiority. Details on the testing procedure and stopping boundaries are provided in the IDMC analysis plan. • In the event that a participant is mis-stratified at randomization, the actual stratum will be used instead of the randomized stratum in the primary analysis. • Sensitivity analysis on the primary endpoint will be done with details provided in the RAP. In addition, a tipping point analysis may be performed for the primary estimand, if warranted by the degree of missing data. • Subgroup analysis and supplemental analysis on additional populations for the primary endpoint may be performed with details provided in the RAP. • Handling of protocol deviations will be described in the RAP.

Endpoint	Statistical Analysis Methods
Secondary	Secondary efficacy endpoints for clinical outcome and response will be summarized using the ITT Population and micro-ITT NTF-S Population. Secondary efficacy endpoints for microbiological outcome and response, as well as therapeutic response (combined per-participant microbiological and clinical response), will be summarized using the micro-ITT NTF-S Population. • There will be no multiplicity adjustment for the testing of the secondary endpoints. No formal hypothesis testing will be performed. • The clinical outcome and response (number and percentage of participants with resolution of signs and symptoms) will be summarized by treatment group at the TOC and Follow-up Visits. The ICE of use of other systemic antimicrobials is captured through the defining criteria of clinical outcome and response (Section 9.1.3.1). • The microbiological outcome and response (number and percentage of participants with microbiological success) will be summarized by treatment group at the TOC and Follow-up Visits. The ICE of use of other systemic antimicrobials is captured through the defining criteria of microbiological outcome and response (Section 4). • Therapeutic response (combined per-participant microbiological and clinical response) will be summarized by treatment group at the Follow-up Visit. • Sensitivity analysis on the secondary endpoints, if warranted, will be described in the RAP. • Subgroup analysis by qualifying baseline uropathogen will be done for microbiological outcome and response at relevant visits. Additional subgroup analyses and supplemental analysis on additional populations may be carried out. Details of these analyses will be provided in the RAP.

Endpoint	Statistical Analysis Methods
CCI	[redacted]

10.4.3. Safety Analyses

All safety analyses will be performed on the Safety Population. The severity of AEs and SAEs will be determined by the investigator according to the US National Institute of Allergy and Infectious Diseases Division of Microbiology and Infectious Diseases (DMID) criteria for adult toxicity assessment [DMID, 2007a], with the exception of serum creatinine adolescent laboratory data, which will be assessed using pediatric toxicity criteria [DMID, 2007b] (Appendix 13). All reported AEs will be coded using MedDRA and summarized by system organ class and preferred terms.

Endpoint	Statistical Analysis Methods
Secondary	• The safety endpoint will use a treatment policy strategy for the ICE of withdrawal from treatment, as safety will be assessed at all postbaseline assessments irrespective of whether the participant completed the treatment. • The number and percentage of treatment-emergent AEs, study treatment-related AEs, deaths, SAEs, and AEs leading to study treatment or study withdrawal will be provided. • Treatment-emergent AEs will be summarized by severity.

	• Change from baseline over time in laboratory parameters 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 postbaseline value will be provided. Abnormal liver chemistry results will be determined using increases above the upper limit of normal. Change from baseline values will be summarized with descriptive statistics. • The severity of specified AEs and laboratory abnormalities will be graded according to the modified DMID toxicity grading system (Appendix 13). Data will be tabulated and reported by absolute grade for Grades 3 and higher and shift tables, as appropriate. • Adverse events of special interest will include CV, gastrointestinal, and *C. difficile* infection or colitis events. In addition, AEs associated with acetylcholinesterase inhibition are also considered special interest. As described in the RAP, manual and programmatic reviews of AEs/preferred terms will be used to assess these events. • Baseline ECG results will be provided in a listing.

10.4.4. 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., age, weight, or race). For this analysis, approaches such as pooling the very sparse gepotidacin plasma concentration data obtained from this study with rich data obtained from adult healthy participant Phase I evaluations (e.g., Study BTZ116778) and a Phase IIa PK evaluation in participants with uncomplicated UTI (Study 206899) may be necessary.

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[redacted]

10.5. Interim Analysis

One IA is planned to assess either both efficacy and futility or just futility by the IDMC. The IDMC will meet when approximately 60% of participants in the micro-ITT NTF-S Population have achieved the TOC Visit to evaluate the primary endpoint, identify potential treatment benefit, and make recommendations for continuing or stopping the study, as per the IDMC charter. The IDMC members will include at least 3 independent experts, including an infectious disease specialist, a chairperson with experience chairing IDMC meetings, and a statistician. Details regarding the IDMC process will be described in the IDMC charter.

The SDAC will conduct and provide all unblinded analyses to the IDMC before the meeting is held. Details on the content and structure of the data output will be described in a separate IDMC analysis plan. The GSK and PPD study teams that are operating the study and conducting the final analysis will remain blinded. The IDMC and SDAC will maintain unblinded data in a secure area to ensure the integrity of the data until the study is completed. Details on protecting blind and data integrity will be described in a blinding plan.

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

If the IDMC confirms there is sufficient microbiology data in the gepotidacin arm, an IA with stopping rules for both efficacy and futility will be performed. The nominal significance levels for the interim and final analyses will be determined by the Lan-DeMets spending functions approach [Lan, 1983]. This will be based on the Pocock stopping boundary for efficacy and the O'Brien-Flemming stopping boundary for futility. The futility bounds of this study are nonbinding and are considered guidance rather than strict bounds.

During the course of the IA, the accrual of the study will continue. If efficacy success (i.e., noninferiority) is reached at the IA and the study is stopped early, the IA will be the primary analysis and data collected between the IA data cut and the time when the study is stopped will be considered overrun. Overrun data will be pooled with the IA data to repeat the primary efficacy analysis as sensitivity analysis. If efficacy success is not reached at the IA, the study will continue to the maximum target sample size for the micro-ITT NTF-S Population of approximately 884 participants.

If, at the IA, the IDMC confirms that there is not sufficient microbiology data in the gepotidacin arm, then a futility-only IA will be conducted. The nominal significance levels for the interim and final analyses will be determined by the Lan-DeMets spending functions approach [Lan, 1983]. This will be based on the O'Brien-Flemming stopping boundary for futility. The futility bounds of this study are nonbinding and are considered guidance rather than strict bounds. The stopping boundaries will be calculated under the assumption of an approximate maximum sample size of 768 participants in the micro-ITT NTF-S Population.

Details on timing, microbiological data criteria, design selection, and stopping boundaries for the IA are described in the IDMC charter.

A GSK SRT will review the blinded safety data of this study at regular intervals. Details regarding the SRT process will be available in relevant SRT documents. The SRT will inform the IDMC if any safety signals are identified.

10.6. Data Monitoring Committee or Other Review Board

This study will have an IDMC as described in Section 10.5. In addition, there will be a GSK SRT and Microbiology Review Team. For details on these review teams, refer to Appendix 3.

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CCI [redacted]

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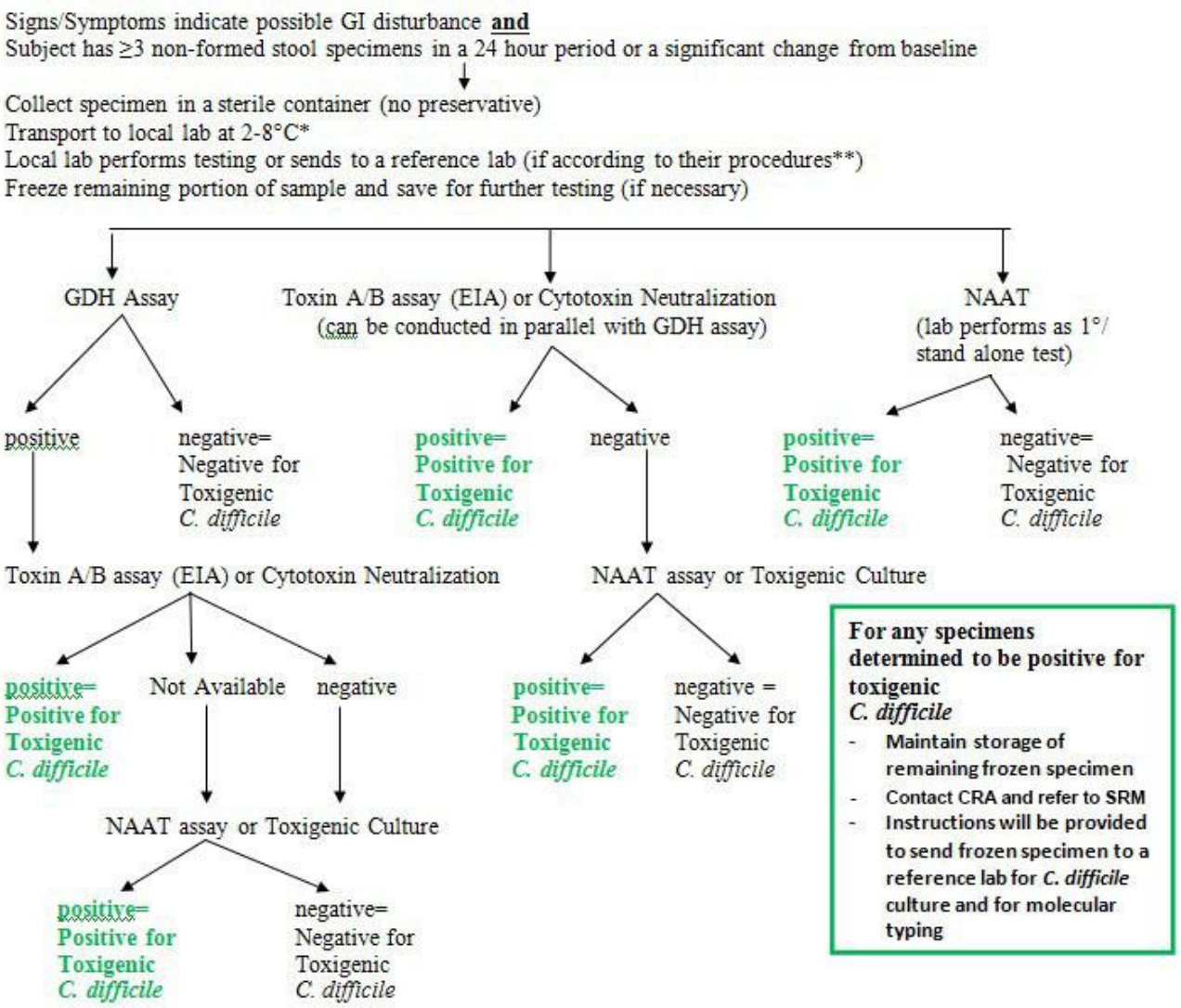
12. APPENDICES

12.1. Appendix 1: *Clostridium 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.

GDH = glutamate dehydrogenase; NAAT = nucleic acid amplification test

CRA = clinical research associate (PPD site monitor); 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 Clostridium difficile-associated diarrhea definition; consideration should be given to diarrhea occurring in this early time frame to be suggestive of a cholinergic effect.

12.2. Appendix 2: Contraceptive Guidance and Collection of Pregnancy Information

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

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

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal 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.

Pregnancy Testing

- 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 (FIRST RESPONSE Early Result Pregnancy Test with a high sensitivity of ≤6.3 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 Table 16 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 (FIRST RESPONSE Early Result Pregnancy Test with a sensitivity of ≤6.3 mIU/mL) is required to be performed for WOCBP who have not used a highly effective contraception method (Table 16) 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.

Contraception Guidance

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

As described in Section 6.3, participants will be requested to abstain from sexual activity from the Baseline Visit through the TOC Visit to prevent possible re-infection.

Table 16 Highly Effective Contraceptive Methods

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

WOCBP=woman of childbearing potential.

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

b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method.

Collection of Pregnancy Information

Female participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GlaxoSmithKline (GSK)/PPD within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on participant and neonate, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event (AE) or serious AE (SAE), any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a poststudy pregnancy that is considered reasonably related to the study treatment by the investigator will be reported to GSK/PPD as described in Appendix 10. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will discontinue study treatment.

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable International Council on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, informed consent form (ICF)/assent form/eConsent (if applicable), investigator's brochure, and other relevant documents (e.g., advertisements) must be submitted to an institutional review board/independent ethics committee (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.
- 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/IEC*
    - Notifying the IRB/IEC of serious adverse events (SAEs) 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 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

***Note**: In countries where the responsibility to perform these submissions and notifications resides with the sponsor rather than the investigator, GSK or their designee PPD (as described in the applicable powers of attorney) will take these responsibilities.

Financial Disclosure

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

Informed Consent/Assent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent and/or eConsent (if applicable) that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study site.
- 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 informed 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 the participant's 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).

Data Protection

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

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 quality lead.

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.

Procedures will be described in a separate microbiology sample monitoring plan.

An Independent Data Monitoring Committee will manage the interim analysis, with details provided in a separate charter and analysis plan.

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

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 study site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK policy.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed case report forms (CRFs) or electronic CRFs (eCRFs) unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Detailed information about study data collection and management process can be found in the Data Validation Manual.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized study site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, 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/equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

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

Study and Site Closure

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

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

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

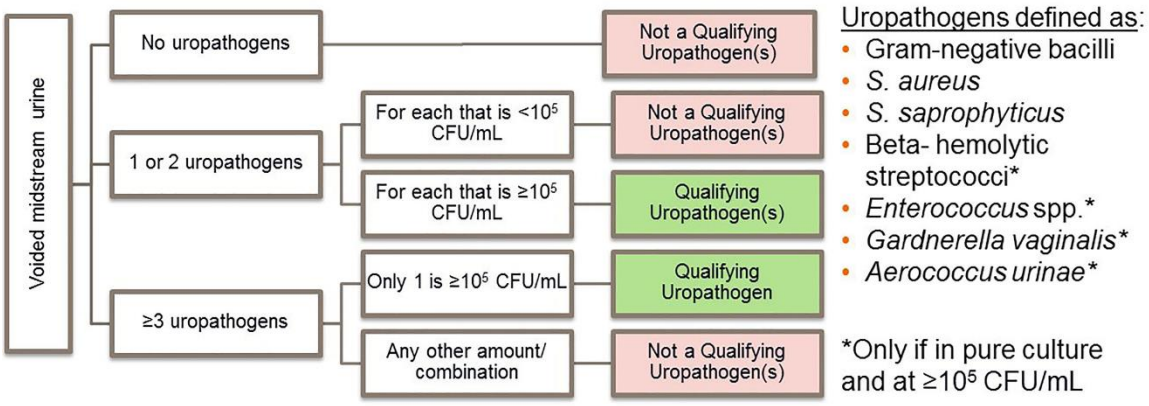
- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

12.4. Appendix 4: Algorithm for Determining Qualifying Uropathogens

In addition to other criteria indicated in Section 10.3, to be included in the micro-ITT Population, participants must have a qualifying bacterial uropathogen (defined in Figure 4) 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 instream to ensure sufficient and balanced enrollment of participants with uropathogens resistant to specific microbiological classes. Please refer to the RAP for specific details.

The algorithm for determining qualifying uropathogens based on microbiology laboratory quantitative culture results is provided in Figure 4, with additional algorithm details provided in the RAP.

Figure 4 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 RAP, as applicable.

References

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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.

12.5. Appendix 5: COVID-19 Protocol Information

12.5.1. 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.

12.5.2. 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/PPD 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/PPD 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/PPD.

12.6. Appendix 6: 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

CCI

[redacted]

12.7. Appendix 7: Additional Guidance on Permitted and Prohibited Medications and Crediblemeds.org

For quick reference, a list of some common concomitant medications that are permitted for participants to take during the study for nausea, vomiting, pain, diarrhea, etc. per investigator discretion is provided below. A list of some of the commonly used medications that are prohibited is also provided in this appendix. Lastly, a topline overview of how to use crediblemeds.org is also provided.

A further detailed list of medications will be provided in the Study Reference Manual.

List of Concomitant Medications Permitted During the Study:

Generic Name[a]	**Common Therapeutic Use(s)**
Acetylsalicylic acid	***Only*** allowed for the prevention of cardiovascular disease events at a low dose of ≤100 mg/day
Dolasetron	Nausea, vomiting
Granisetron	Nausea, vomiting
Metoclopramide	Nausea, vomiting
Palonosetron	Nausea, vomiting
Promethazine	Nausea, vomiting
Tropisetron (Only on Non-US markets)	Nausea, vomiting
Acetaminophen or paracetamol	Pain, fever
Tramadol	Pain
Hydrocodone ER	Pain, severe
Loperamide	Diarrhea
Cetirizine	Antihistamine (H_1)
Ebastine	Antihistamine (H_1)
Fexofenadine	Antihistamine (H_1)
Loratadine	Antihistamine (H_1)
Clindamycin	Antibiotic – ***topical, nonsystemic only***
Neomycin	Antibiotic – ***topical, nonsystemic only***
Polymyxin	Antibiotic – ***topical, nonsystemic only***
Clotrimazole	Antifungal – ***topical, nonsystemic only***
Tolnaftate	Antifungal – ***topical, nonsystemic only***
Ketoconazole	Antifungal – ***topical, nonsystemic only***

ER=extended release; US=United States.

a. Check within each local country to assess if other generic names apply.

Note: See also Section 7.7.1 for other permitted medications.

List of Prohibited Concomitant Medications:

Generic Name or Category[a]	**Common Therapeutic Use(s)**
Ondansetron	Nausea, vomiting
Acetylsalicylic acid (doses >100 mg/day)	Pain, other
Celecoxib	Pain
Diclofenac	Pain
Diflunisal	Pain
Etodolac	Pain
Ibuprofen	Pain, fever
Indomethacin	Pain
Ketoprofen	Pain
Ketorolac	Pain
Nabumetone	Pain
Naproxen	Pain
Oxaprozin	Pain
Phenazopyridine	Pain (urinary tract)
Piroxicam	Pain
Rofecoxib	Pain
Salsalate	Pain
Sulindac	Pain
Tolmetin	Pain
Valdecoxib	Pain
Other investigational products	Various
Systemic antibiotics (e.g., ciprofloxacin, amoxicillin/clavulanate, cephalexin, doxycycline)	Antibiotic – ***all systemic***
Systemic antifungals (e.g., itraconazole, fluconazole, terbinafine)	Antifungal – ***all systemic***
Prednisolone or equivalent (refer to Section 7.7.2 for details)	Immunosuppressive therapy
Strong CYP3A4 inhibitors and strong CYP3A4 inducers	See Study Reference Manual
St John's wort	Herbal, various
Uva ursi	Herbal, various
D-mannose	Nutritional supplement, various
Cranberry supplements	Nutritional supplement, various
Probenecid	Uric acid reducer
Sulfinpyrazone	Uric acid reducer
Magnesium trisilicate	Antacid (common ingredient)
Succinylcholine and other nondepolarizing paralytic agents	Muscle relaxation, muscle paralysis

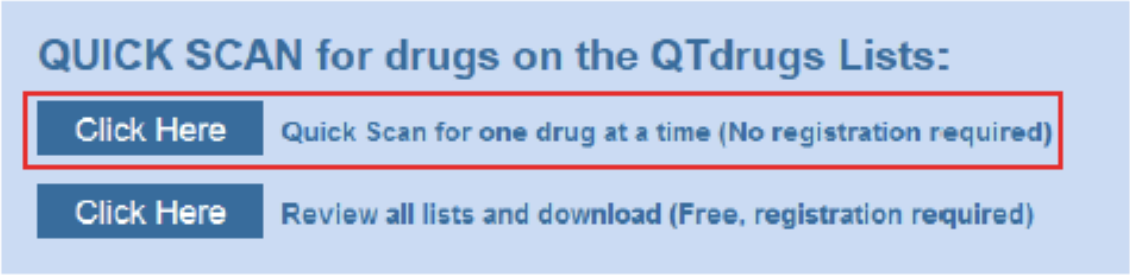
CYP3A4=cytochrome P450 enzyme 3A4; NSAIDS=nonsteroidal anti-inflammatory medications.
a. Check within each local country to assess if other generic names apply.
Note: See also Section 7.7.2 for other prohibited medications and details for the when these medications are prohibited. All NSAIDS are prohibited; this list may not be an exhaustive list of all NSAIDS available globally.

Crediblemeds.org Instructions

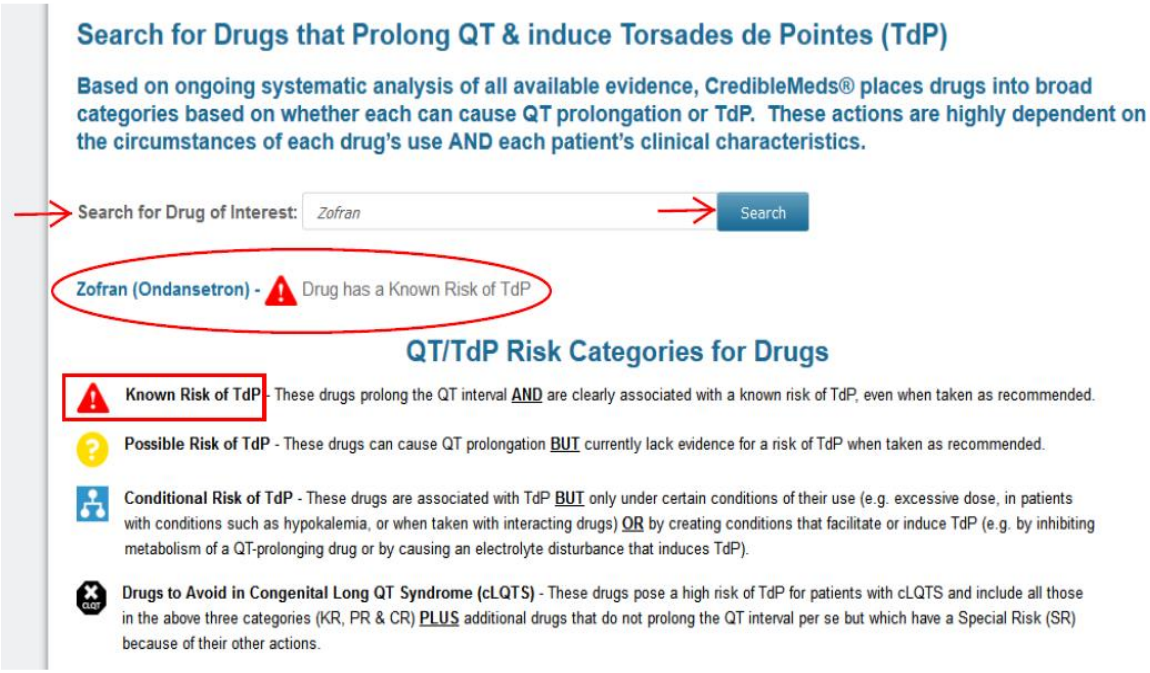
Instructions for accessing www.crediblemeds.org and searching for an exclusionary drug due to its "Known Risk of Torsades de Pointes (TdP)" category are summarized below.

To access www.crediblemeds.org, copy and paste this link into the internet search bar: https://www.crediblemeds.org/

On the main home page, there are 2 search options available. Choose the first option to search for 1 drug at a time, which does not require registration.



Choosing that option brings you to a screen that allows for you to enter a generic or brand drug name and choose Search. If it has a Known Risk of TdP (i.e., is a prohibited exclusionary medication), it will show a red triangle with an exclamation point as shown here:



Always check the www.crediblemeds.org website for the most up-to-date information on drugs with a Known Risk of TdP for participant safety.

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

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

Phase III 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 ≥8 x ULN</td></tr>
<tr><td>ALT Increase</td><td>ALT ≥5 x ULN but <8 x ULN persists for ≥2 weeks
ALT ≥3 x ULN but <5 x ULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[a,b]</td><td>ALT ≥3 x ULN and bilirubin ≥2 x ULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[b]</td><td>ALT ≥3 x ULN and INR >1.5, if INR measured</td></tr>
<tr><td>Cannot Monitor</td><td>ALT ≥5 x ULN but <8 x ULN and cannot be monitored weekly for ≥2 weeks
ALT ≥3 x ULN but <5 x ULN and cannot be monitored weekly for ≥4 weeks</td></tr>
<tr><td>Symptomatic[c]</td><td>ALT ≥3 x ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="2">Required Actions and Follow-up Assessments</th></tr>
<tr><th>Actions</th><th>Follow-up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK/PPD within 24 hours
• Complete the liver event eCRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[b]
• Perform liver event follow-up assessments
• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below)
• Do not restart/rechallenge participant with study treatment
• If restart/rechallenge not allowed or not granted, permanently discontinue study treatment and continue participant in the</td><td>• Viral hepatitis serology[d]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen), quantitative hepatitis B DNA, and hepatitis delta antibody[e]
• Obtain blood sample for PK analysis, within 24 hours after last dose[f]
• Serum creatine phosphokinase and lactate dehydrogenase</td></tr>
</table>

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

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

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

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

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

Phase III liver chemistry increased monitoring criteria with continued therapy

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

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

References

James LP, Letzig L, Simpson PM, et al. Pharmacokinetics of acetaminophen-protein adducts in adults with acetaminophen overdose and acute liver failure. Drug Metab Dispos. 2009;37:1779-1784.

Le Gal F, Gordien E, Affolabi D, 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;43:2363-2369.

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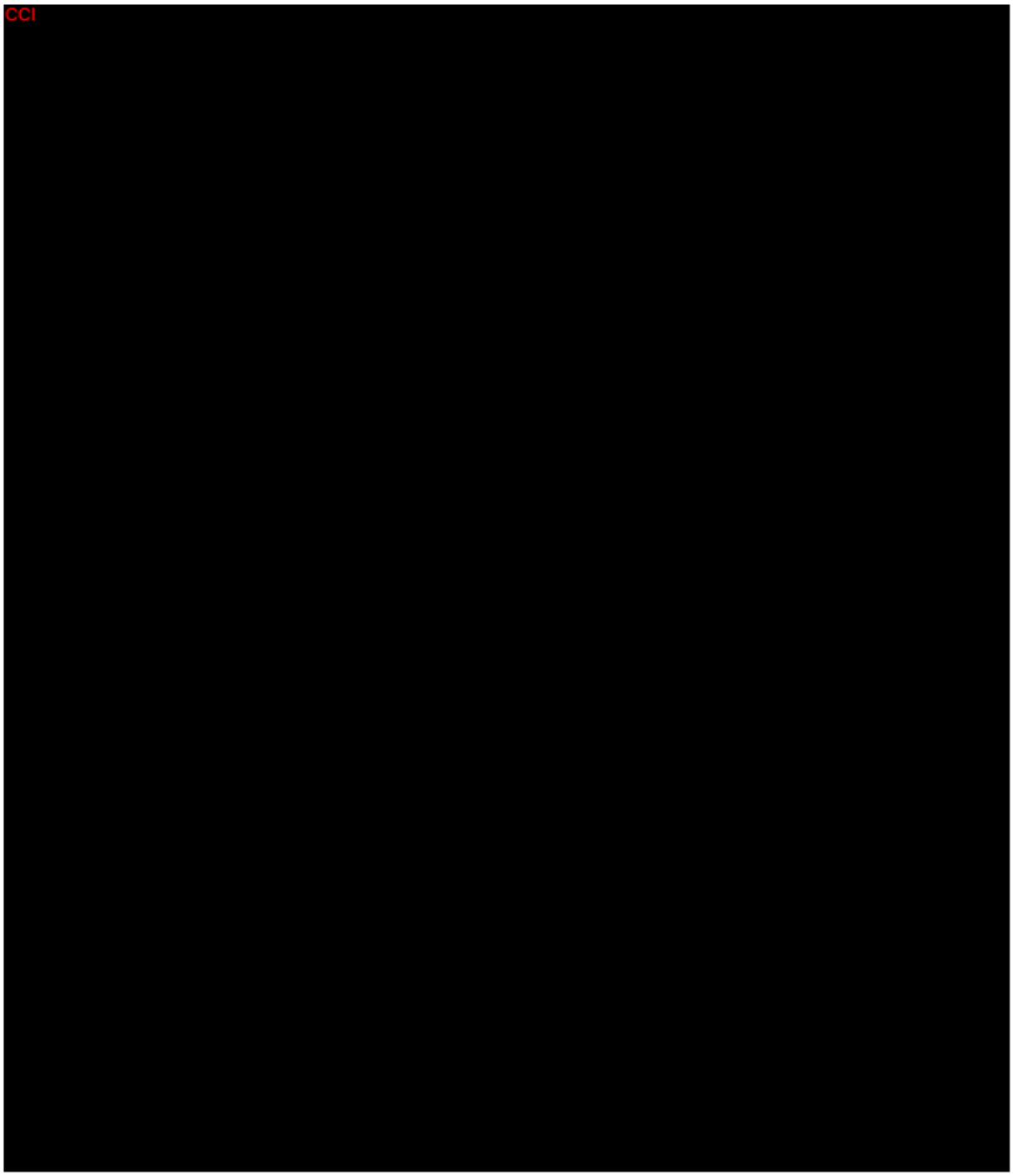

12.10. Appendix 10: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of Adverse Event

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

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of an SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life threatening The term "life threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d.	**Results in persistent disability/incapacity** • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e.	**Is a congenital anomaly/birth defect**
f.	**Other situations:** • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Cardiovascular Adverse Events of Special Interest and Cases of *Clostridium Difficile*

Investigators will be required to fill out the specific event page of the electronic case report form (eCRF) for the following cardiovascular AEs and SAEs, and for cases of *Clostridium difficile*:

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

Recording AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the eCRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GlaxoSmithKline (GSK)/PPD in lieu of completion of the GSK/PPD AE/SAE eCRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
• The severity of AEs and SAEs will be determined by the investigator according to the US National Institute of Allergy and Infectious Diseases Division of Microbiology and Infectious Diseases criteria for adult toxicity assessment [DMIDDMID, 2007a], with the exception of serum creatinine adolescent laboratory data, which will be assessed using pediatric toxicity criteria [DMID, 2007b] (Appendix 13). An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
Assessment of Causality
• The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The investigator will also consult the investigator's brochure 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/PPD. 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/PPD**.**
- 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 completed eCRF.
- The investigator will submit any updated SAE data to GSK/PPD within 24 hours of receipt of the information.

Reporting of SAE to GSK/PPD

SAE Reporting to GSK/PPD via Electronic Data Collection Tool

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

12.11. Appendix 11: Clinical Laboratory Tests

- The tests detailed in Table 17 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 a response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 17 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet count RBC count Hemoglobin Hematocrit	RBC Indices: MCV MCH	WBC Count With Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[a]	Blood urea nitrogen	Potassium	AST/SGOT	Total and direct bilirubin
	Creatinine	Sodium	ALT/SGPT	Total protein
	Glucose nonfasting	Calcium	Alkaline phosphatase	Albumin
	Chloride	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)			
Other Screening Tests	• Serum or urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines) • Urine hCG pregnancy test (as needed for women of childbearing potential)[b] • Serology (HBsAg, hepatitis C virus antibody, and HIV). If serology testing was performed within 3 months prior to the first dose of study treatment and results were positive, testing at Baseline is not required. If testing was performed within 3 months and any result was negative, testing at Baseline is required.			

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

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

b. See Appendix 2 for urine test requirement details. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or the Institutional Review Board/Independent Ethics Committee.

Laboratory results that could unblind the study will not be reported to study sites or other blinded personnel until the study has been unblinded.

12.12. Appendix 12: Genetics

USE/ANALYSIS OF DNA

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

12.13. Appendix 13: Division of Microbiology and Infectious Diseases Adult Toxicity Tables for Adverse Event Assessment

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

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

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

COMMENTS REGARDING THE USE OF THESE TABLES

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

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

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 pediatric DMID toxicity criteria. The DMID pediatric toxicity table may be accessed at https://www.niaid.nih.gov/sites/default/files/dmidpedtox.pdf.

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

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

CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to 135 mEq/L	123 to 129 mEq/L	116 to 122 mEq/L	<116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146 to 150 mEq/L	151 to 157 mEq/L	158 to 165 mEq/L	>165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 to 3.4 mEq/L	2.5 to 2.9 mEq/L	2.0 to 2.4 mEq/L or intensive replacement therapy of hospitalization required	<2.0 mEq/L or abnormal potassium *with* paresis, ileus, or life-threatening arrhythmia
Hyperkalemia	5.6 to 6.0 mEq/L	6.1 to 6.5 mEq/L	6.6 to 7.0 mEq/L	>7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55 to 64 mg/dL	40 to 54 mg/dL	30 to 39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 to 160 mg/dL	161 to 250 mg/dL	251 to 500 mg/dL	>500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 to 7.8 mg/dL	7.7 to 7.0 mg/dL	6.9 to 6.1 mg/dL	<6.1 mg/dL or abnormal calcium *with* life-threatening arrhythmia or tetany
Hypercalcemia (corrected for albumin)	10.6 to 11.5 mg/dL	11.6 to 12.5 mg/dL	12.6 to 13.5 mg/dL	>13.5 mg/dL or abnormal calcium *with* life-threatening arrhythmia
Hypomagnesemia	1.4 to 1.2 mEq/L	1.1 to 0.9 mEq/L	0.8 to 0.6 mEq/L	<0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 to 2.4 mg/dL	1.5 to 1.9 mg/dL or replacement Rx required	1.0 to 1.4 mg/dL intensive therapy or hospitalization required	<1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 to <1.25 × ULN	1.25 to <1.5 × ULN	1.5 to 1.75 × ULN	>1.75 × ULN
Hyperbilirubinemia (when other liver function tests are in the normal range)	1.1 to <1.5 × ULN	1.5 to <2.0 × ULN	2.0 to 3.0 × ULN	>3.0 × ULN
Blood urea nitrogen	1.25 to 2.5 × ULN	2.6 to 5 × ULN	5.1 to 10 × ULN	>10 × ULN
Hyperuricemia (uric acid)	7.5 to 10.0 mg/dL	10.1 to 12.0 mg/dL	12.1 to 15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1 to 1.5 × ULN	1.6 to 3.0 × ULN	3.1 to 6.0 × ULN	>6 × ULN or dialysis required

Rx=therapy; ULN=upper limit of normal.

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

ULN=upper limit of normal.

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

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

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

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

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

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

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

IV=intravenous.

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

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

ADL=activities of daily living.

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

N/A=not applicable.

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

12.14. Appendix 14: Abbreviations and Trademarks

ABSSSI	acute bacterial skin and skin structure infection
AE	adverse event
CCI	[redacted]
ALT	alanine aminotransferase
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
CDC	Centers for Disease Control and Prevention
CE	Clinically Evaluable
CFU	colony-forming units
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease
CRF	case report form
CV	cardiovascular
CYP3A4	cytochrome P450 enzyme 3A4
DMID	Division of Microbiology and Infectious Diseases
EAGLE	Efficacy of Antibacterial Gepotidacin Evaluated
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
ESBL	extended-spectrum β-lactamase
F	Fahrenheit
*f*AUC/MIC	ratio of the area under the free-drug concentration-time curve to minimum inhibitory concentration over 24 hours
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HPF	high-power field
IA	interim analysis
IB	investigator's brochure
ICE	intercurrent event
ICF	informed consent form
ICH	International Council on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	independent ethics committee
IRB	institutional review board
IRT	interactive response technology
ITT	Intent-to-Treat
IV	intravenous
kg	kilogram
m	meter

MDR	multidrug-resistant
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MIC	minimum inhibitory concentration
micro-ITT	Microbiological Intent-to-Treat
min	minute
mL	milliliter
mm	millimeter
msec	millisecond
NTF	nitrofurantoin
NTF-NS	not susceptible to nitrofurantoin
NTF-S	susceptible to nitrofurantoin
PD	pharmacodynamic
PK	pharmacokinetic
QTc	corrected QT interval
QTcB	QT interval corrected for heart rate according to Bazett
QTcF	QT interval corrected for heart rate according to Fridericia
RAP	reporting and analysis plan
SAE	serious adverse event
SDAC	Statistical Data Analysis Center
SoA	Schedule of Activities
SRM	Study Reference Manual
ST	sequence type
TdP	torsades de pointes
TOC	Test-of-Cure
TMP-SXT	trimethoprim-sulfamethoxazole
µg	microgram
ULN	upper limit of normal
UTI	urinary tract infection
WHO	World Health Organization
WOCBP	woman of childbearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
None

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FIRST RESPONSE
MedDRA

12.15. Appendix 15: Protocol Amendment History

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

Amendment 1 06-MAY-2021

This global amendment is considered to be substantial.

Overall Rationale for the Amendment: CCI [redacted]; indicated study operational allowances with regard to coronavirus disease (COVID-19); incorporated past administrative letters to the sites; added estimand text; removed the pharmacokinetic (PK) sample collection at Baseline; removed the predose requirement for collection of the PK and microbiological samples at the On-therapy Visit; removed the on-site dosing requirement at the On-Therapy Visit; provided minor statistical clarifications to the analysis populations, response and outcomes tables, and accounted for supplementary analysis, which will be detailed in the reporting and analysis plan (RAP); increased the planned total enrollment population; and incorporated updates per the most recent investigator's brochure (IB) version 07. The amendment also includes additional minor administrative and wording edits.

Section # and Name	Description of Change	Brief Rationale
Synopsis 4 Objectives and Estimands/Endpoints Table 2 Estimand for the Secondary Endpoints 10.3.1 General Considerations 10.3.2 Efficacy Analysis 10.3.3 Safety Analyses Throughout	Added estimand text for the primary and secondary endpoints	To meet current ICH guidelines on estimands

Section # and Name	Description of Change	Brief Rationale
Synopsis 4 Objectives and Estimands/Endpoints	For the secondary (updated only in the Synopsis) and exploratory objectives, an additional objective and endpoint were added to each section to examine the clinical response in female participants with acute cystitis with qualifying bacterial uropathogen(s) at Baseline that all are susceptible to nitrofurantoin	Consistency with the primary objective population
Synopsis 10.1.1 Justification of Sample Size	Increased the total enrollment sample size to up to 2500 participants and expanded sample size justification text	To reflect the expected number of participants for full enrollment to support the required number of evaluable participants for the primary analysis and to provide additional sample size details
Schedule of Activities	Removed postdose PK collection at the Baseline Visit; thus, also removed "(peak and trough)" from the secondary PK endpoint	Clinical conduct feasibility
Schedule of Activities 4 Objectives and Estimands/Endpoints 9 Study Assessments and Procedures 9.5 Pharmacokinetics 10.3.4 PK and PK/PD Analyses Throughout	Revised On-therapy Visit procedures as follows: • Removed requirement for participants to take their study treatment at the study site • Removed the predose collection requirement for microbiological and PK samples; thus, also removed "(peak and trough)" from the secondary PK endpoint • Recommended the On-Therapy Visit should ideally be scheduled 1 to 2 hours after the participant's most recent dose of study treatment was taken	Clinical conduct feasibility
Schedule of Activities 6.2 Inclusion Criteria #3	Updated criterion to state "3+/large" rather than "3+/moderate" for the presence of leukocyte esterase	Incorporation of Protocol Administration Letter 1

Section # and Name	Description of Change	Brief Rationale
3.3.1 Risk Assessment 6.2 Exclusion Criteria #5	Added acute porphyria as an example of a risk for the nitrofurantoin comparator and excluded the medical condition for participant enrollment	Incorporation of the letter to sites dated 09-DEC-2019
Section 3.3.1 Risk Assessment 6.2 Exclusion Criteria #21 7.7.2 Prohibited Medications and Nondrug Therapies Section 12.7 Appendix 7	Removed exclusion for strong P-glycoprotein inhibitors	Consistency with the most current Version 07 of the investigator's brochure
6.2 Exclusion Criteria #10	Expanded text to include, "or preclude complete resolution of cystitis symptoms"	Clarification purposes
7.7 Concomitant Therapy	Clarified that any antibiotic use within 6 months of the Baseline Visit should be recorded	To support the study analysis
7.7.1 Permitted Medications and Nondrug Therapies 7.7.2 Prohibited Medications and Nondrug Therapies Section 12.7 Appendix 7	Clarified that low-dose acetylsalicylic acid is permitted as a concomitant medication if taken to prevent cardiovascular disease events	To support study conduct and enrollment for a medication used in a manner that should not have an impact on the efficacy evaluations
7.7.2 Prohibited Medications and Nondrug Therapies Section 12.7 Appendix 7	Added strong CYP3A4 inducers to the prohibited medications	Alignment with preliminary results from a recently completed Phase I study
Schedule of Activities 9.4.1 Physical Examinations	Clarified that the physical examination at the Test-of-Cure Visit may be symptom directed and was only required if indicated for a specific participant	Incorporation of Protocol Administration Letter 3

Section # and Name	Description of Change	Brief Rationale
9.1.2.1 Microbiological Outcome and Response	Minor text clarifications were added to the outcome and response tables, and a new table (Table 6) was added to define participant-level microbiological outcomes and responses	To provide clarification to support the planned statistical analyses and programming details
9.1.3 Clinical Evaluation	Subsections were added for the different clinical evaluations planned for primary and exploratory objectives, minor text clarifications were added to the outcome and response tables	To provide clarification to support the planned statistical analyses and programming details
Synopsis Schedule of Activities 9.1.3.3 Urinary Tract Infection Activity Impairment Assessment	Indicated this assessment should be performed at the end of the study visits and by a different study staff member than the person conducting the clinical symptoms assessment and scoring	To prioritize collection of the primary efficacy clinical measurements with separation from the exploratory clinical measurements
Schedule of Activities 9.1.3.1 Clinical Signs and Symptoms Scores, Clinical Outcomes, and Clinical Response Throughout Section 6 Appendix 6	Clarified that the clinical signs and symptoms scores should be performed by a physician or otherwise appropriately medically trained staff, and that the same scorer should perform the assessment at all time points whenever possible, and clarified additional instructions for the collection of data verbally to support the assessment	Incorporation of Protocol Administrative Letter 3, which will support consistent data collection
CCI [redacted]		

Section # and Name	Description of Change	Brief Rationale
Schedule of Activities Throughout Appendix 5	Added text to allow for eConsent, telemedicine study-related data collection, collection of visit data as a combination of telemedicine and on-site visits, remote source data verification, and eCRF sign-off flexibility for investigators	To support ongoing study conduct from safety and operational perspectives during the COVID-19 pandemic
10.2 Populations for Analyses	Minor clarifications to the description of populations, including updates to analyze per randomized study treatment, where applicable	Consistency with the planned statistical analysis and required outputs
10.3.1 General Considerations	Added text regarding supplemental analysis and additional analysis that may be needed per COVID-19 impact on the study	Consistency with the planned statistical analysis and required outputs
10.3.2 Efficacy Analyses 10.3.3 Safety Analyses	Minor clarifications to the plans for analysis	Consistency with the planned statistical analysis and required outputs
3.3.1 Risk Assessment Throughout	Updates to protocol text, including risk/benefit and dose justification rationale text (i.e., added topline PK and safety results from a study in healthy adult and adolescent participants) per the most current investigator's brochure; no new safety signals were identified or added	Consistency with the most current Version 07 of the investigator's brochure
Appendix 4 Algorithm for Determining Qualifying Uropathogens	Minor clarifications per the current plans for analysis	Consistency with regulatory authority feedback and statistical analysis plans
Throughout	Clarified each treatment day would be assessed over 24 hours, clarified pregnancy testing requirements, and that the On-therapy Visit will occur on "Days 2 to 4"	Incorporation of Protocol Administration Letter 2

Section # and Name	Description of Change	Brief Rationale
Throughout	Revised the in-text definitions of microbiological and clinical success to remove “specific to the disease under study” regarding the use of other systemic antimicrobials	Corrected text to align with the original definitions of success in the endpoint definition tables
Throughout	Updated text to state *Clostridium difficile* and acetylcholinesterase inhibition events are considered adverse events of special interest	To support the planned safety analysis
Throughout	Updated appendices order globally	Consistency with in-text presentation order
Throughout	Minor editorial and document formatting revisions	Minor, therefore, have not been summarized